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(54) **COMPOSITIONS AND METHODS FOR EPIGENETIC REGULATION OF HBV GENE EXPRESSION**

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(56) **References Cited**

U.S. PATENT DOCUMENTS

5,795,778	A	8/1998	Draper
6,017,756	A	1/2000	Draper
6,453,242	B1	9/2002	Eisenberg et al.
6,534,261	B1	3/2003	Cox, III et al.
7,807,160	B2	10/2010	Presta et al.
7,901,708	B2	3/2011	Maclachlan et al.
8,058,069	B2	11/2011	Yaworski et al.
8,232,257	B2	7/2012	McCaffrey et al.
8,492,359	B2	7/2013	Yaworski et al.
8,642,076	B2	2/2014	Manoharan et al.
8,772,453	B2	7/2014	Paschon et al.
8,822,668	B2	9/2014	Yaworski et al.
8,889,418	B2	11/2014	Zhang et al.
8,906,616	B2	12/2014	Zhang et al.
9,005,654	B2	4/2015	Maclachlan et al.
9,006,417	B2	4/2015	Yaworski et al.
9,023,594	B2	5/2015	Liu et al.
9,023,649	B2	5/2015	Mali et al.
9,260,723	B2	2/2016	Mali et al.
9,301,923	B2	4/2016	Baryza et al.
9,364,435	B2	6/2016	Yaworski et al.
9,404,127	B2	8/2016	Yaworski et al.
9,415,109	B2	8/2016	Kumar et al.
9,487,802	B2	11/2016	Quake et al.
9,518,272	B2	12/2016	Yaworski et al.
9,580,701	B2	2/2017	May et al.
9,593,077	B2	3/2017	Payne et al.
9,650,617	B2	5/2017	May et al.
9,682,139	B2	6/2017	Manoharan et al.
9,688,972	B2	6/2017	May et al.
9,701,623	B2	7/2017	Manoharan et al.
9,771,590	B2	9/2017	Brass et al.
9,771,601	B2	9/2017	May et al.
9,840,702	B2	12/2017	Collingwood et al.
9,868,962	B2	1/2018	May et al.
9,878,042	B2	1/2018	Yaworski et al.
9,885,033	B2	2/2018	Joung et al.
9,932,566	B2	4/2018	Kennedy et al.
9,970,024	B2	5/2018	Church et al.
9,999,673	B2	6/2018	Rajeev et al.
10,059,940	B2	8/2018	Zhong

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0642589	A1	3/1995
EP	1288296	A2	3/2003

(Continued)

OTHER PUBLICATIONS

Davos et al., (Proteins: Structure, Function and Genetics, 2000, vol. 41: 98-107.*

(Continued)

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(57) **ABSTRACT**

This invention relates to compositions, methods, strategies, and treatment modalities related to the epigenetic modification of hepatitis B virus (HBV) genes.

19 Claims, 57 Drawing Sheets

Specification includes a Sequence Listing.

(56) **References Cited**

U.S. PATENT DOCUMENTS

10,137,201 B2 11/2018 Brown et al.
10,266,850 B2 4/2019 Doudna et al.
10,273,501 B2 4/2019 Church et al.
10,286,084 B2 5/2019 Cullen et al.
10,337,001 B2 7/2019 Ryan et al.
10,342,761 B2 7/2019 Bowman et al.
10,369,226 B2 8/2019 Maier et al.
10,378,015 B2 8/2019 Brass et al.
10,435,708 B2 10/2019 Mali et al.
10,519,468 B2 12/2019 May et al.
10,526,590 B2 1/2020 Kennedy et al.
10,544,405 B2 1/2020 Weiss et al.
10,612,044 B2 4/2020 Hatada et al.
10,662,416 B2 5/2020 Jantz et al.
10,696,986 B2 6/2020 Zhang et al.
10,717,990 B2 7/2020 Mali et al.
10,767,175 B2 9/2020 Dellinger et al.
10,767,176 B2 9/2020 Collingwood et al.
10,822,606 B2 11/2020 Huang et al.
10,844,403 B2 11/2020 Joung et al.
10,851,358 B2 12/2020 Jantz et al.
10,900,034 B2 1/2021 Ryan et al.
10,907,150 B2 2/2021 Carlson-Stevermer et al.
10,946,108 B2 3/2021 Zhang et al.
10,954,514 B2 3/2021 Dahlman et al.
10,988,781 B2 4/2021 May et al.
11,001,829 B2 5/2021 Zhang et al.
11,027,025 B2 6/2021 Hoge et al.
11,136,567 B2 10/2021 Behlke et al.
11,141,378 B2 10/2021 Yaworski et al.
11,142,750 B2 10/2021 Smith et al.
11,162,114 B2 11/2021 Crawley et al.
11,180,743 B2 11/2021 Doudna et al.
11,186,849 B2 11/2021 Doudna et al.
11,193,141 B2 12/2021 Dever et al.
11,236,359 B2 2/2022 Mali et al.
11,236,364 B2 2/2022 May et al.
11,268,092 B2 3/2022 Lee et al.
11,274,285 B2 3/2022 Jantz et al.
11,274,302 B2 3/2022 Powell
11,279,928 B2 3/2022 Yin et al.
11,306,305 B2 4/2022 Gagnon et al.
11,306,309 B2 4/2022 Porteus et al.
11,359,211 B2 6/2022 Church et al.
11,365,429 B2 6/2022 Church et al.
11,371,031 B2 6/2022 Doudna et al.
11,377,646 B2 7/2022 Doudna et al.
11,414,657 B2 8/2022 Rahdar et al.
11,441,137 B2 9/2022 Doudna et al.
11,453,864 B2 9/2022 Sontheimer et al.
11,453,866 B2 9/2022 Doudna et al.
11,459,559 B2 10/2022 Collingwood et al.
11,459,588 B2 10/2022 May et al.
11,479,767 B2 10/2022 Smith et al.
11,479,793 B2 10/2022 Jin et al.
11,492,646 B2 11/2022 Dever et al.
11,512,325 B2 11/2022 Church et al.
11,530,398 B2 12/2022 Doudna et al.
11,535,846 B2 12/2022 Porteus et al.
11,535,863 B2 12/2022 Church et al.
11,560,555 B2 1/2023 Oakes et al.
11,578,313 B2 2/2023 Doudna et al.
11,667,903 B2 6/2023 Yeo et al.
12,049,624 B2 7/2024 Huang et al.
2003/0068301 A1 4/2003 Draper et al.
2003/0206887 A1 11/2003 Morrissey et al.
2004/0054156 A1 3/2004 Draper et al.
2004/0127446 A1 7/2004 Blatt et al.
2006/0153826 A1 7/2006 Arnould et al.
2006/0223990 A1 10/2006 Usman et al.
2008/0207539 A1 8/2008 Arbuthnot et al.
2012/0171191 A1 7/2012 Choulika et al.
2012/0297495 A1 11/2012 McCaffrey et al.
2014/0342456 A1 11/2014 Mali et al.
2015/0059010 A1 2/2015 Cigan et al.
2015/0232833 A1 8/2015 Mali et al.
2015/0259704 A1 9/2015 Church et al.
2015/0315557 A1 11/2015 Choulika et al.
2016/0060655 A1 3/2016 Quake et al.
2016/0200779 A1 7/2016 Liu et al.
2016/0201072 A1 7/2016 Cigan et al.
2016/0208288 A1 7/2016 Liu et al.
2016/0273003 A1 9/2016 Duchateau et al.
2016/0298096 A1 10/2016 Charpentier et al.
2016/0317677 A1 11/2016 Bhatia et al.
2016/0355795 A1 12/2016 Ran et al.
2017/0044537 A1 2/2017 Collingwood et al.
2017/0087225 A1 3/2017 Quake
2017/0145394 A1 5/2017 Yeo et al.
2017/0191078 A1 7/2017 Zhang et al.
2017/0219596 A1 8/2017 Tanenbaum et al.
2017/0247690 A1 8/2017 Quake et al.
2017/0247703 A1 8/2017 Sloan et al.
2017/0321214 A1 11/2017 Zhang et al.
2018/0023064 A1 1/2018 Gersbach et al.
2018/0112213 A1 4/2018 Welstead et al.
2018/0142236 A1 5/2018 He et al.
2018/0148719 A1 5/2018 Lee et al.
2018/0179523 A1 6/2018 Collingwood et al.
2018/0187176 A1 7/2018 Behlke et al.
2018/0201921 A1 7/2018 Malcolm
2018/0208914 A1 7/2018 Malcolm et al.
2018/0236103 A1 8/2018 Friedland et al.
2018/0245074 A1 8/2018 Lee et al.
2018/0258411 A1 9/2018 Kadiyala et al.
2019/0010481 A1 1/2019 Joung et al.
2019/0024086 A1 1/2019 Lande et al.
2019/0032049 A1 1/2019 Naldini et al.
2019/0032053 A1 1/2019 Ji et al.
2019/0032088 A1 1/2019 Duchateau et al.
2019/0032090 A1 1/2019 Quake et al.
2019/0040370 A1 2/2019 Yeo et al.
2019/0048338 A1 2/2019 Yin et al.
2019/0071673 A1 3/2019 Malcolm
2019/0127713 A1 5/2019 Gersbach et al.
2019/0233805 A1 8/2019 Segal et al.
2019/0233814 A1 8/2019 Zhang et al.
2019/0233816 A1 8/2019 Langer et al.
2019/0241911 A1 8/2019 Dong et al.
2019/0300908 A1 10/2019 Doudna et al.
2019/0330621 A1 10/2019 Powell
2019/0336617 A1 11/2019 Malcolm
2019/0338315 A1 11/2019 Malcolm et al.
2019/0351070 A1 11/2019 Cullen et al.
2019/0359959 A1 11/2019 Jaenisch et al.
2019/0382751 A1 12/2019 Radhar et al.
2019/0390195 A1 12/2019 Tondera et al.
2020/0087640 A1 3/2020 Doudna et al.
2020/0095586 A1 3/2020 Malcolm
2020/0140896 A1 5/2020 Renaud et al.
2020/0255858 A1 8/2020 Doudna et al.
2020/0263186 A1 8/2020 Barrangou et al.
2020/0299689 A1 9/2020 Lee
2020/0308583 A1 10/2020 Kim et al.
2020/0308599 A1 10/2020 Church et al.
2020/0339980 A1 10/2020 Dellinger et al.
2020/0362369 A1 11/2020 Zhang et al.
2020/0385721 A1 12/2020 Lee et al.
2020/0389425 A1 12/2020 Bhatia et al.
2021/0017508 A1 1/2021 Doudna et al.
2021/0017518 A1 1/2021 Morris et al.
2021/0054371 A1 2/2021 Zhong
2021/0062224 A1 3/2021 Doudna et al.
2021/0079389 A1 3/2021 Ryan et al.
2021/0087568 A1 3/2021 Smith et al.
2021/0123046 A1 4/2021 Huang et al.
2021/0130850 A1 5/2021 Joung et al.
2021/0139870 A1 5/2021 Duchateau
2021/0139891 A1 5/2021 Carlson-Stevermer et al.
2021/0147922 A1 5/2021 Urnov et al.
2021/0180038 A1 6/2021 Jantz et al.
2021/0214724 A1 7/2021 Choudhary et al.
2021/0222164 A1 7/2021 Choudhary et al.
2021/0222165 A1 7/2021 Zhong

(56) **References Cited**

U.S. PATENT DOCUMENTS

2021/0222193	A1	7/2021	Church et al.
2021/0238567	A1	8/2021	Doudna et al.
2021/0254038	A1	8/2021	Doudna et al.
2021/0277392	A1	9/2021	Hubbard et al.
2021/0301271	A1	9/2021	Doudna et al.
2021/0324356	A1	10/2021	Doudna et al.
2021/0324358	A1	10/2021	Doudna et al.
2021/0361779	A1	11/2021	Zhang et al.
2021/0363518	A1	11/2021	Sontheimer et al.
2021/0371847	A1	12/2021	Urnov et al.
2021/0388348	A1	12/2021	Sontheimer et al.
2021/0403888	A1	12/2021	Doudna et al.
2022/0002693	A1	1/2022	Behlke et al.
2022/0010339	A1	1/2022	Zhang et al.
2022/0025408	A1	1/2022	Dever et al.
2022/0056427	A1	2/2022	Smith et al.
2022/0090065	A1	3/2022	Ahn et al.
2022/0111079	A1	4/2022	Hoge et al.
2022/0119809	A1	4/2022	Doyon
2022/0177900	A1	6/2022	Cigan et al.
2022/0195403	A1	6/2022	Wang et al.
2022/0195426	A1	6/2022	Porteus et al.
2022/0195427	A1	6/2022	Porteus et al.
2022/0220508	A1	7/2022	Oakes et al.
2022/0243187	A1	8/2022	Jantz et al.
2022/0290177	A1	9/2022	Malcolm
2022/0306699	A1	9/2022	Stamatoyannopoulos et al.
2022/0340889	A1	10/2022	Doudna et al.
2022/0340934	A1	10/2022	Lee et al.
2022/0372483	A1	11/2022	Alexander et al.
2022/0402862	A1	12/2022	Scully et al.
2023/0002760	A1	1/2023	Welstead et al.
2023/0028178	A1	1/2023	Doudna et al.
2023/0031465	A1	2/2023	Lape et al.
2023/0048681	A1	2/2023	Malcolm
2023/0070861	A1	3/2023	Smekalova et al.
2023/0092393	A1	3/2023	Ryan et al.
2023/0105319	A1	4/2023	Das et al.
2023/0124880	A1	4/2023	Oakes et al.
2023/0132569	A1	5/2023	Sontheimer et al.
2023/0203480	A1	6/2023	Morrissey et al.
2023/0287400	A1	9/2023	Smith et al.
2023/0293645	A1	9/2023	Lee et al.
2024/0023855	A1	1/2024	Patel et al.
2024/0067968	A1	2/2024	Cosgrove et al.
2024/0067969	A1	2/2024	Cosgrove et al.
2024/0076678	A1	3/2024	Maeder et al.
2024/0132855	A1	4/2024	Jaffe et al.
2024/0382622	A1	11/2024	Jaffe et al.
2024/0398950	A1	12/2024	Dumauthioz

FOREIGN PATENT DOCUMENTS

EP	1590468	A2	11/2005
EP	2435560	A2	4/2012
EP	2771468	B1	2/2015
EP	2784162	B1	4/2015
EP	2896697	B1	9/2015
EP	2970208	A2	1/2016
EP	3071695	A2	9/2016
EP	3107999	A2	12/2016
EP	3149170	A1	4/2017
EP	3149171	A1	4/2017
EP	3159407	A1	4/2017
EP	3227447	A1	10/2017
EP	3230452	A1	10/2017
EP	3250691	A1	12/2017
EP	3294880	A1	3/2018
EP	3313989	A1	5/2018
EP	3344771	A1	7/2018
EP	3347464	A1	7/2018
EP	3353309	A1	8/2018
EP	3356527	A1	8/2018
EP	3356528	A1	8/2018
EP	3365447	A1	8/2018
EP	3375877	A1	9/2018
EP	3420077	A1	1/2019
EP	2940140	B1	3/2019
EP	3463406	A1	4/2019
EP	3469084	A1	4/2019
EP	3473720	A1	4/2019
EP	2931891	B1	5/2019
EP	3036327	B1	5/2019
EP	3080261	B1	5/2019
EP	3545085	A1	10/2019
EP	3551757	A1	10/2019
EP	3553174	A1	10/2019
EP	3562942	A1	11/2019
EP	3574093	A1	12/2019
EP	3601568	A1	2/2020
EP	3144390	B1	3/2020
EP	3630975	A1	4/2020
EP	3638792	A1	4/2020
EP	3641785	A1	4/2020
EP	3645721	A1	5/2020
EP	3662061	A1	6/2020
EP	3692154	A1	8/2020
EP	3011031	B1	9/2020
EP	3704239	A1	9/2020
EP	3715461	A2	9/2020
EP	3202899	B1	10/2020
EP	3234133	B1	11/2020
EP	3752632	A1	12/2020
EP	3760719	A1	1/2021
EP	3765616	A1	1/2021
EP	3775187	A1	2/2021
EP	3781704	A1	2/2021
EP	3786296	A1	3/2021
EP	3230451	B1	4/2021
EP	3802828	A1	4/2021
EP	2946015	B1	5/2021
EP	3280803	B1	5/2021
EP	3814370	A2	5/2021
EP	3814493	A1	5/2021
EP	3814524	A1	5/2021
EP	3820503	A1	5/2021
EP	3852911	A2	7/2021
EP	3019619	B1	8/2021
EP	3274454	B1	8/2021
EP	3865586	A1	8/2021
EP	3889260	A1	10/2021
EP	3209783	B1	11/2021
EP	3919505	A1	12/2021
EP	3935156	A1	1/2022
EP	3957734	A1	2/2022
EP	3965832	A1	3/2022
EP	3971287	A1	3/2022
EP	3980533	A1	4/2022
EP	3985115	A1	4/2022
EP	3995584	A1	5/2022
EP	4019635	A1	6/2022
EP	3380613	B1	10/2022
EP	4069729	A1	10/2022
EP	4073249	A1	10/2022
EP	3420093	B1	11/2022
EP	4081533	A1	11/2022
EP	4095246	A1	11/2022
EP	3080259	B1	2/2023
EP	3526323	B1	3/2023
EP	4150091	A2	3/2023
EP	4163374	A1	4/2023
EP	4183876	A1	5/2023
WO	WO-9323569	A1	11/1993
WO	WO-03093473	A1	11/2003
WO	WO-2004067753	A2	8/2004
WO	WO-2005021751	A1	3/2005
WO	WO-2008119000	A1	10/2008
WO	WO-2010136841	A2	12/2010
WO	WO-2010136981	A2	12/2010
WO	WO-2013176772	A1	11/2013
WO	WO-2014093712	A1	6/2014
WO	WO-2014099744	A1	6/2014
WO	WO-2014099750	A2	6/2014
WO	WO-2014113493	A1	7/2014

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	WO-2014144761	A2	9/2014
WO	WO-2014204014	A1	12/2014
WO	WO-2014204729	A1	12/2014
WO	WO-2015006747	A2	1/2015
WO	WO-2015026885	A1	2/2015
WO	WO-2015048690	A1	4/2015
WO	WO-2015071474	A2	5/2015
WO	WO-2015089465	A1	6/2015
WO	WO-2015089473	A1	6/2015
WO	WO-2015095340	A1	6/2015
WO	WO-2015126927	A2	8/2015
WO	WO-2015184259	A1	12/2015
WO	WO-2015184262	A1	12/2015
WO	WO-2015199952	A1	12/2015
WO	WO-2016022866	A1	2/2016
WO	WO-2016049258	A2	3/2016
WO	WO-2016063264	A1	4/2016
WO	WO-2016077321	A1	5/2016
WO	WO-2016081029	A1	5/2016
WO	WO-2016089433	A1	6/2016
WO	WO-2016094867	A1	6/2016
WO	WO-2016094872	A1	6/2016
WO	WO-2016094874	A1	6/2016
WO	WO-2016100951	A2	6/2016
WO	WO-2016123230	A1	8/2016
WO	WO-2016154596	A1	9/2016
WO	WO-2016164356	A1	10/2016
WO	WO-2016186745	A1	11/2016
WO	WO-2016197132	A1	12/2016
WO	WO-2016197133	A1	12/2016
WO	WO-2017004261	A1	1/2017
WO	WO-2017004279	A2	1/2017
WO	WO-2017040511	A1	3/2017
WO	WO-2017044419	A1	3/2017
WO	WO-2017044776	A1	3/2017
WO	WO-2017053713	A1	3/2017
WO	WO-2017053729	A1	3/2017
WO	WO-2017058795	A1	4/2017
WO	WO-2017068377	A1	4/2017
WO	WO-2017070284	A1	4/2017
WO	WO-2017075531	A1	5/2017
WO	WO-2017091630	A1	6/2017
WO	WO-2017106657	A1	6/2017
WO	WO-2017136794	A1	8/2017
WO	WO-2017144630	A1	8/2017
WO	WO-2017147446	A1	8/2017
WO	WO-2017210380	A1	12/2017
WO	WO-2017214460	A1	12/2017
WO	WO-2018005873	A1	1/2018
WO	WO-2018057946	A2	3/2018
WO	WO-2018071849	A2	4/2018
WO	WO-2018081480	A1	5/2018
WO	WO-2018098383	A1	5/2018
WO	WO-2018107028	A1	6/2018
WO	WO-2018118585	A1	6/2018
WO	WO-2018118586	A1	6/2018
WO	WO-2018118587	A1	6/2018
WO	WO-2018125964	A1	7/2018
WO	WO-2018129293	A1	7/2018
WO	WO-2018136396	A2	7/2018
WO	WO-2018140269	A1	8/2018
WO	WO-2018183808	A1	10/2018
WO	WO-2018217981	A1	11/2018
WO	WO-2018232114	A1	12/2018
WO	WO-2018234239	A1	12/2018
WO	WO-2019003193	A1	1/2019
WO	WO-2019027728	A1	2/2019
WO	WO-2019070762	A1	4/2019
WO	WO-2019084664	A1	5/2019
WO	WO-2019089820	A1	5/2019
WO	WO-2019103442	A2	5/2019
WO	WO-2019126037	A1	6/2019
WO	WO-2019147275	A1	8/2019
WO	WO-2019147743	A1	8/2019
WO	WO-2019178428	A1	9/2019
WO	WO-2019183000	A1	9/2019
WO	WO-2019200247	A1	10/2019
WO	WO-2019204661	A1	10/2019
WO	WO-2019204766	A1	10/2019
WO	WO-2019213039	A1	11/2019
WO	WO-2019213062	A1	11/2019
WO	WO-2019213776	A1	11/2019
WO	WO-2019237069	A1	12/2019
WO	WO-2020006126	A1	1/2020
WO	WO-2020006131	A2	1/2020
WO	WO-2020006132	A1	1/2020
WO	WO-2020014577	A1	1/2020
WO	WO-2020023529	A1	1/2020
WO	WO-2020041456	A1	2/2020
WO	WO-2020055941	A1	3/2020
WO	WO-2020061426	A2	3/2020
WO	WO-2020068643	A1	4/2020
WO	WO-2020097360	A1	5/2020
WO	WO-2020181101	A1	9/2020
WO	WO-2020181178	A1	9/2020
WO	WO-2020214003	A1	10/2020
WO	WO-2020231863	A1	11/2020
WO	WO-2020247882	A1	12/2020
WO	WO-2021034373	A1	2/2021
WO	WO-2021113765	A1	6/2021
WO	WO-2021119275	A1	6/2021
WO	WO-2021133829	A1	7/2021
WO	WO-2021216772	A1	10/2021
WO	WO-2021226077	A2	11/2021
WO	WO-2021231606	A2	11/2021
WO	WO-2021247570	A2	12/2021
WO	WO-2022011232	A1	1/2022
WO	WO-2022032397	A1	2/2022
WO	WO-2022055998	A1	3/2022
WO	WO-2022119919	A1	6/2022
WO	WO-2022140572	A1	6/2022
WO	WO-2022140577	A2	6/2022
WO	WO-2022140776	A1	6/2022
WO	WO-2022146654	A1	7/2022
WO	WO-2022148955	A1	7/2022
WO	WO-2022159822	A1	7/2022
WO	WO-2022162247	A1	8/2022
WO	WO-2022182801	A1	9/2022
WO	WO-2022229851	A1	11/2022
WO	WO-2022234519	A1	11/2022
WO	WO-2022236147	A1	11/2022
WO	WO-2022248454	A1	12/2022
WO	WO-2022261292	A1	12/2022
WO	WO-2023004375	A2	1/2023
WO	WO-2023004409	A1	1/2023
WO	WO-2023011638	A1	2/2023
WO	WO-2023039586	A1	3/2023
WO	WO-2023043856	A1	3/2023
WO	WO-2023047338	A1	3/2023
WO	WO-2023250183	A2	12/2023
WO	WO-2023215711	A9	1/2024
WO	WO-2024040254	A2	2/2024
WO	WO-2024064910	A1	3/2024
WO	WO-2024186896	A2	9/2024
WO	WO-2024238700	A1	11/2024

OTHER PUBLICATIONS

Wristlock et al., (Quarterly Reviews of Biophysics 2003, vol. 36 (3): 307-340.*

Kwiatkowski et al., (Biochemistry 38:11643-11650, 1999.*

Kisselev L., (Structure, 2002, vol. 10: 8-9.*

Abraham, et al., The topology of hepatitis B virus pregenomic RNA promotes its replication, J. Virol., 81(21):11577-11584, (2007).

Akalin, A et al., MethylKit: a comprehensive R package for the analysis of genome-wide DNA methylation profiles, Genome Biol., vol. 13, 10 (2012).

Alerasool, N et al., An efficient KRAB domain for CRISPRi applications in human cells, Nature Methods, vol. 17, 11 (2020):1093-1096.

Altinel, et al., Single-Nucleotide Resolution Mapping of Hepatitis B Virus Promoters in Infected Human Livers and Hepatocellular Carcinoma, J Virol., 90(23):10811-10822, (2016).

(56) **References Cited**

OTHER PUBLICATIONS

Amabile, A et al., Inheritable Silencing of Endogenous Genes by Hit-and-Run Targeted Epigenetic Editing, Cell, vol. 167, (2016):219-232.e14.
Bae, S et al., Cas-OFFinder: a fast and versatile algorithm that searches for potential off-target sites of Cas9 RNA-guided endonucleases, Bioinformatics, vol. 30, (2014):1473-1475.
Bartel, M.A et al., Directed evolution of novel adeno-associated viruses for therapeutic gene delivery, Gene Therapy, vol. 19, (2012):694-700.
Batzer, Mark A et al. Enhanced Evolutionary PCR Using Oligonucleotides With Inosine At The 3'-Terminus. Nucleic Acids Research 19(18):5081 (1991).
Bloom, K et al., Inhibition of replication of hepatitis B virus using transcriptional repressors that target the viral Dna, Bmc Infectious Diseases, vol. 19, 1 (2019):802.
Carroll, D., Genome Engineering With Zinc-Finger Nucleases, Genet., vol. 188, 4 (2011):773-782.
Chen, B et al., Dynamic imaging of genomic loci in living human cells by an optimized CRISPR/Cas system, Cell, vol. 155, 7 (2013):1479-1491.
Chen, et al., Detection of hepatitis B virus DNA in hepatocellular carcinoma: methylation of integrated viral Dna, J Virol Methods., 19(3-4):257-263, (1988).
Chen, et al., Translation of the first upstream ORF in the hepatitis B virus pregenomic RNA modulates translation at the core and polymerase initiation codons, Nucleic Acids Res., 33(4):1169-1181, (2005).
Cheng, Q et al., Selective ORgan Targeting (SORT) nanoparticles for tissue specific mRNA delivery and CRISPR/Cas gene editing, Nat Nanotechnol., 15, (2020):313-320.
Christian, M et al., Targeting DNA Double-Strand Breaks with TAL Effector Nucleases, Genetics, vol. 186, 2 (2008):757-761.
Chylinski, K et al., The tracrRNA and Cas9 families of type II CRISPR-Cas immunity systems, RNA Biology, vol. 10, 5 (2013):726-737.
Cullis, Pieter R et al. Lipid Nanoparticle Systems for Enabling Gene Therapies. Molecular Therapy 25(7):1467-1475 (2017).
Dandri, M., Epigenetic modulation in chronic hepatitis B virus infection, Seminars in Immunopathology, vol. 42, 2 (2020): 173-185.
Dillard, S.A et al., Passive, active and endogenous organ-targeted lipid and polymer nanoparticles for delivery of genetic drugs, Nat Rev Mater, vol. 8, 4 (2023):282-300.
Ecco, G et al., KRAB zinc finger proteins, Development, vol. 144, 15 (2017):2719-2729.
Finn, J.D et al., A Single Administration of CRISPR/Cas9 Lipid Nanoparticles Achieves Robust and Persistent In Vivo Genome Editing, Cell Rep., vol. 22, 9 (2018):2227-2235.
Fu, Y. et al., Improving CRISPR-Cas nuclease specificity using truncated guide RNAs, Nat Biotechnol., vol. 32, 3 (2014):279-284.
Galibert, et al., Nucleotide sequence of the hepatitis B virus genome (subtype ayw) cloned in *E. coli*, Nature, 281(5733):646-650, (1979).
Gao, Feng, et al., DNA-guided Genome Editing using the Natronobacterium Gregoryi Argonaute, Nature Biotechnology 34(7):768-773 (2016).
Han, X et al., An ionizable lipid toolbox for RNA delivery, Nat Commun., 12, 7233 (2021).
Hatit, M.Z.C. et al., Species-dependent in vivo mRNA delivery and cellular responses to nanoparticles, Nat Nanotechnol., vol. 17, (2022):310-318.
Hirakawa, M. et al., Gene editing and CRISPR in the clinic: current and future perspectives, Biosci Rep., vol. 40, 4 (2020): BSR20200127.
Hong, X. et al., Epigenetic regulation of hepatitis B virus covalently closed circular DNA: Implications for epigenetic therapy against chronic hepatitis B, Hepatology (Baltimore, Md.), vol. 66, 6 (2017): 2066-2077.
Hou, et al., CpG islands of hepatitis B virus genome isolated from Chinese patients, Gene, 561:261-267, (2015).
Hou, Xucheng, et al., Lipid nanoparticles for mRNA delivery. Nature Reviews Materials 6:1078-1094 (2021).
International Preliminary Report on Patentability issued in PCT/US2021/064913, dated Jun. 13, 2023.
International Search Report and Written Opinion issued in PCT/US2021/064913, mailed Jul. 1, 2022.
International Search Report and Written Opinion issued in PCT/US2023/074931, mailed Feb. 13, 2024.
Isalan, M. et al., A rapid, generally applicable method to engineer zinc fingers illustrated by targeting the HIV-1 promoter, Nat Biotechnol., vol. 19, 7(2001):656-660.
Jain, et al., Comprehensive DNA methylation analysis of hepatitis B virus genome in infected liver tissues, Sci Rep., 5:10478, (2015).
Jinek, M et al., A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity, Science, vol. 337, (2012):816-821.
Joung, J.K. et al., A bacterial two-hybrid selection system for studying protein-DNA and protein-protein interactions, PNAS, vol. 97, (2000):7382-7387.
Joung, J.K. et al., Reply to "Genome editing with modularly assembled zinc-finger nucleases", Nat. Methods, vol. 7, (2010):91-92.
Kasiewicz, L.S. et al., Lipid nanoparticles incorporating a GalNAc ligand enable in vivo liver ANGPTL3 editing in wild-type and somatic LDLR knockout non-human primates, bioRxiv, 2021.
Kazemian, et al., Lipid-Nanoparticle-Based Delivery of CRISPR/Cas9 Genome-Editing Components, Molecular Pharmaceutics, 19(6):1669-1686, (2022).
Kazemian, P. et al., Lipid-Nanoparticle-Based Delivery of CRISPR/Cas9 Genome-Editing Components, Molecular Pharmaceutics, vol. 19, 6 (2022):1669-1686.
Kleinstiver, B.J. et al., Broadening the targeting range of Staphylococcus aureus CRISPR-Cas9 by modifying PAM recognition, Nat. Biotechnol., vol. 33, (2015):1293-1298.
Kleinstiver, B.J. et al., Engineered CRISPR-Cas9 nucleases with altered PAM specificities, Nature vol. 523, 7561(2015):481-485.
Koblan, L.W. et al., Improving cytidine and adenine base editors by expression optimization and ancestral reconstruction, Nat. Biotechnol., vol. 36, 9 (2018):843-848.
Krueger, F. et al., Bismark: A flexible aligner and methylation caller for Bisulfite- Seq applications, Bioinformatics, vol. 27, 11 (2011):1571-1572.
Labun, K et al., CHOPCHOP v3: Expanding the CRISPR web toolbox beyond genome editing, Nucleic Acids Res., vol. 47, (2019):W171-W174.
Ladner, et al., Inducible expression of human hepatitis B virus (HBV) in stably transfected hepatoblastoma cells: a novel system for screening potential inhibitors of HBV replication, Antimicrob. Agents Chemother., 41(8):1715-1720, (1997).
Lam, et al., Optimizing Lipid Nanoparticles for Delivery in Primates, Adv. Materials, 35:2211420, (2023).
Lam, K et al., Unsaturated, Trialkyl Ionizable Lipids are Versatile Lipid-Nanoparticle Components for Therapeutic and Vaccine Applications, Adv.Mater, vol. 35, (2023).
Lambert, S.A. et al., The Human Transcription Factors, Cell, vol. 172, (2018):650-665.
Leibowitz, M. L. et al., Chromothripsis as an on-target consequence of CRISPR-Cas9 genome editing, Nat. Genet., vol. 53, 6 (2021):895-905.
Li, et al., MethPrimer: designing primers for methylation PCRs, Bioinformatics, 18(11):1427-1431, (2005).
Li, T. et al., TAL nucleases (TALNs): hybrid proteins composed of TAL effectors and FokI DNA-cleavage domain, Nucl Acids Res., vol. 39, 1 (2010):359-372.
Li, W. et al., Engineering and Selection of Shuffled AAV Genomes: A New Strategy for Producing Targeted Biological Nanoparticles, Mol Ther., vol. 16, 7 (2008):1252-1260.
Lombardo, A. et al., Gene editing in human stem cells using zinc finger nucleases and integrase-defective lentiviral vector delivery, Nat Biotechnol., vol. 25, 11 (2007):1298-1306.
Londono, J.R. et al., Genetic characterization and epigenetic interference to better understand and fight occult Hepatitis B virus infection, Ph.D. Thesis, (2017).

(56) **References Cited**

OTHER PUBLICATIONS

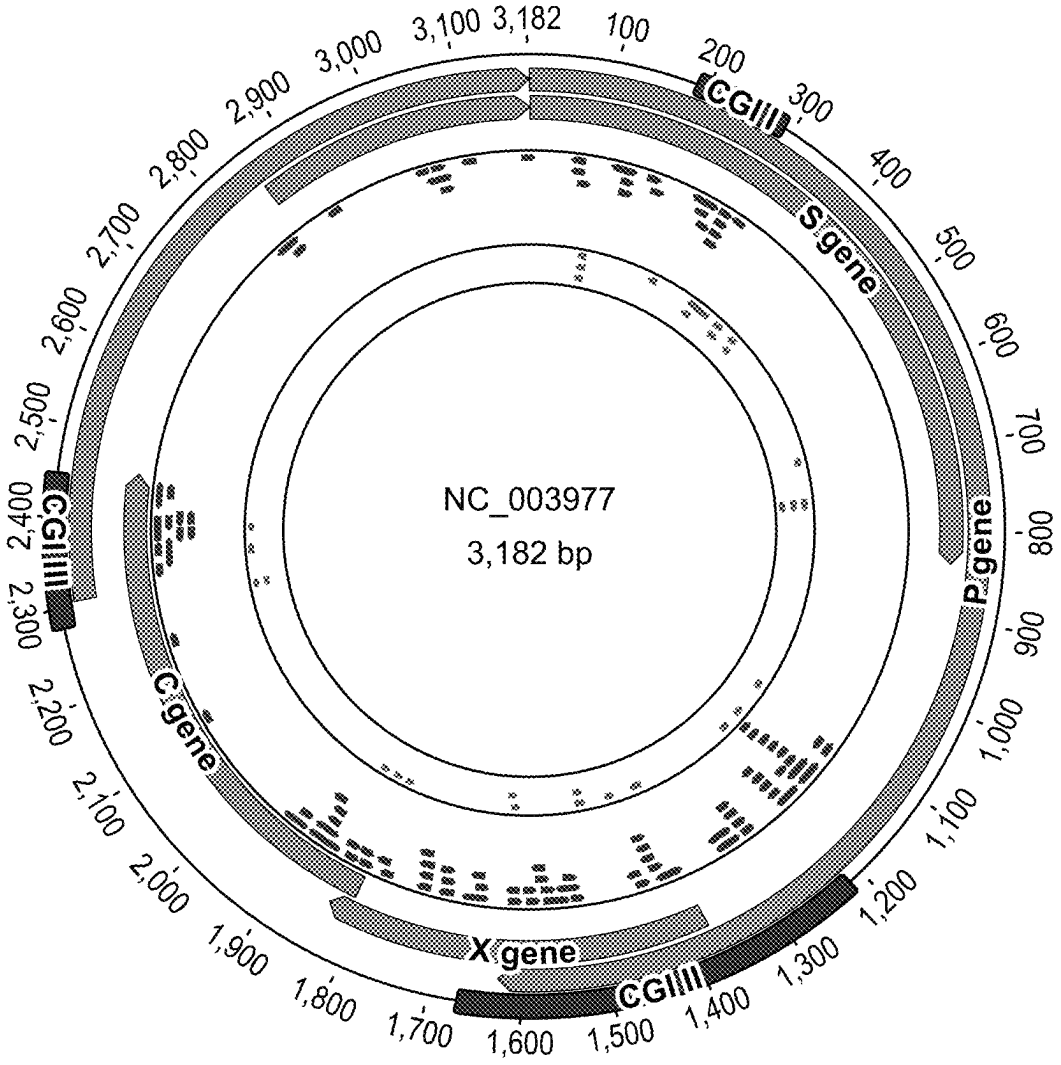
Luck, K. et al., A reference map of the human binary protein interactome, Nature, vol. 580, 7803 (2020):402-408.
Lyko, F., The DNA methyltransferase family: a versatile toolkit for epigenetic regulation, Nat Review, vol. 19, (2018):81-92.
Maeder, M.L. et al., Rapid "open-source" engineering of customized zinc-finger nucleases for highly efficient gene modification, Mol. Cell, vol. 31, (2008):294-301.
McClure, R.F. et al., Production and Titering of Recombinant Adeno-associated Viral Vectors, J Vis Exp., vol. 57, (2011):3378.
Meier-Stephenson, et al., Comprehensive Analysis of Hepatitis B Virus Promoter Region Mutations, Viruses, 10(11):603, (2018).
Micklefield, Jason. Backbone Modification of Nucleic Acids: Synthesis, Structure and Therapeutic Applications. Current Medicinal Chemistry 8(10):1157-1179 (2001).
Miller, et al., Compact organization of the hepatitis B virus genome, Hepatology, 9(2):322-327, (1989).
Miller, J.C. et al., An improved zinc-finger nuclease architecture for highly specific genome editing, Nat Biotechnol., vol. 25, 7 (2007):778-785.
Mitchell, M.J. et al., Engineering precision nanoparticles for drug delivery, Nat Rev Drug Discov., vol. 20, (2021):101-124.
Mitra, B. et al., Host functions used by hepatitis B virus to complete its life cycle: Implications for developing host-targeting agents to treat chronic hepatitis B, Antiviral Research, vol. 158 (2018): 185-198.
Mlambo, T. et al., Designer epigenome modifiers enable robust and sustained gene silencing in clinically relevant human cells, Nucleic Acids Res., vol. 46, 9 (2018):4456-4468.
Moscou, M.J. et al., A Simple Cipher Governs DNA Recognition by TAL Effectors, Science, vol. 326, 5959 (2009):1501.
Mouzannar, et al., The Post-Transcriptional Regulatory Element of Hepatitis B Virus: From Discovery to Therapy, Viruses, 16(4):528, (2024).
Nahmad, A.D. et al., Frequent aneuploidy in primary human T cells after CRISPR-Cas9 cleavage, Nat. Biotechnol., vol. 40, 12 (2022):1807-1813.
No Author, Easl clinical practice guidelines: management of chronic hepatitis B virus infection, J Hepatol., 57:167-185, (2012).
Nuñez, J.K. et al., Genome-wide programmable transcriptional memory by CRISPR-based epigenome editing, Cell, vol. 184, 9 (2021):2503-2519.e17.
Oakes, B.L. et al., CRISPR-Cas9 Circular Permutants as Programmable Scaffolds for Genome Modification, Cell, vol. 176, (2019):254-267.
Ohtsuka, Eiko. et al. An Alternative Approach to Deoxyoligonucleotides as Hybridization Probes by Insertion of Deoxyinosine at Ambiguous Codon Positions. Journal of Biological Chemistry 260(5):2605-2608 (1985).
Paschon, D.E. et al., Diversifying the structure of zinc finger nucleases for high-precision genome editing, Nat. Commun., vol. 10, 1133 (2019).
Paunovska, K. et al., Drug delivery systems for RNA therapeutics, Nat. Rev. Genet., vol. 23, (2022):265-280.
Pausch, Patrick et al. CRISPR-CasΦ from huge phages is a hypercompact genome editor. Science (New York, N.Y.) vol. 369,6501 (2020): 333-337. doi:10.1126/science.abb1400.
Peng, et al., Nonproductive Hepatitis B Virus Covalently Closed Circular DNA Generates HBx-Related Transcripts from the HBx/Enhancer I Region and Acquires Reactivation by Superinfection in Single Cells, J Virol., 97(1):e0171722, (2023).
Potter, M et al., A simplified purification protocol for recombinant adeno-associated virus vectors, Molecular Therapy—Methods & Clinical Development, vol. 1, (2014):14034.
Ray, K.K. et al., Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol, N. Engl. J. Med., vol. 382, 16 (2020):1507-1519.
Rebar, E.J. et al., Zinc Finger Phage: Affinity Selection of Fingers with New DNA-Binding Specificities, Science, vol. 263, (1994):671-673.
Rees, H.A. et al., Analysis and minimization of cellular RNA editing by DNA adenine base editors, Sci. Adv., vol. 5, 1-11 (2019).
Rohner, E. et al., Unlocking the promise of mRNA therapeutics, Nat. Biotechnol., vol. 40, (2022):1586-1600.
Rossolini, Gian Maria et al. Use of Deoxyinosine-containing vVs Degenerate Primers for Polymerase Chain Reaction Based on Ambiguous Sequence Information. Molecular and Cellular Probes 8(2):91-98 (1994).
Schellenberger, V. et al., A recombinant polypeptide extends the in vivo half-life of peptides and proteins in a tunable manner, Nat Biotechnol., vol. 17, 1 (2009):1186-1190.
Singh, P. et al., Silencing hepatitis B virus covalently closed circular DNA: The potential of an epigenetic therapy approach, World Journal of Gastroenterology, vol. 27, 23 (2021): 3182-3207.
Stadelmayer, et al., Full-length 5'RACE identifies all major HBV transcripts in HBV-infected hepatocytes and patient serum, J Hepatol., 73(1):40-51, (2020).
Stadtmauer, E.A. et al., CRISPR- engineered T cells in patients with refractory cancer, Science, vol. 367, (2020):eaba7365.
Sternberg, Samuel H, et al., DNA Interrogation by the CRISPR RNA-Guided Endonuclease Cas9. Nature 507(7490):62-67 (2014).
Su, et al., Improving clinical outcomes of chronic hepatitis B virus infection, Expert Rev Gastroenterol Hepatol, 9:141-154, (2015).
Swarts, D.C. et al., Argonaute of the archaeon Pyrococcus furiosus is a DNA-guided nuclease that targets cognate DNA, Nucl. Acids Res., vol. 43, 10 (2015):5120-5129.
Swarts, D.C. et al., DNA-guided DNA interference by a prokaryotic Argonaute, Nature, vol. 507, 7491 (2014):258-261.
Tombacz, I. et al., Highly efficient CD4+ T cell targeting and genetic recombination using engineered CD4+ cell-homing mRNA-LNPs, Molecular Therapy, 29, 11 (2021):3293-3304.
Turchiano, G. et al., Quantitative evaluation of chromosomal rearrangements in gene-edited human stem cells by CAST-Seq, Cell Stem Cell, vol. 28, 6 (2021): 1136-1147.e5.
Tycko, J. et al., High-Throughput Discovery and Characterization of Human Transcriptional Effectors, Cell, vol. 183, 7 (2020):2020-2035.
U.S. Appl. No. 18/473,990 Office Action dated May 3, 2024.
Vanegas, K.G. et al., Cpf1 enables fast and efficient genome editing in Aspergilli, Fungal Biol Biotechnol., vol. 6, (2019):6.
Vivekanandan, et al., Hepatitis B viral DNA is methylated in liver tissues, J Viral Hepat., 15(2):103-107, (2007).
Ward, P. et al., Chimeric AAV Cap sequences alter gene transduction, Virology, vol. 386, 2 (2009):237-248.
Webber, B.R. et al., Highly efficient multiplex human T cell engineering without double-strand breaks using Cas9 base editors, Nat. Commun., vol. 10, 1 (2019):5222.
Weider, E. et al., Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Single Domain Antibodies Are Potent Inhibitors of Low Density Lipoprotein Receptor Degradation, J Biol Chem., vol. 291, 3 (2016):16659-71.
Wieland, et al., Interferon prevents formation of replication-competent hepatitis B virus RNA-containing nucleocapsids, PNAS, 102(28):9913-9917, (2005).
Wieland, et al., Intrahepatic induction of alpha/beta interferon eliminates viral RNA-containing capsids in hepatitis B virus transgenic mice, J Virol., 74(9):4165-4173, (2000).
Xia, Y. et al., Hepatitis B virus cccDNA: Formation, regulation and therapeutic potential, Antiviral Research, vol. 180 (2020): 104824.
Xirong, L. et al., Hepatitis B virus can be inhibited by DNA methyltransferase 3a via specific zinc-finger-induced methylation of the X promoter, Biochemistry. Biokhimiia, vol. 79, 2 (2014):111-23.
Yin, H. et al., Structure-guided chemical modification of guide RNA enables potent non-viral in vivo genome editing, Nat. Biotechnol., vol. 35, 12 (2017):1179-1187.
Zafra, M.P. et al., Optimized base editors enable efficient editing in cells, organoids and mice. Nat. Biotechnol., vol. 36, 9 (2018):888-896 (2018).
Zhang, et al., Comparative Analysis of CpG Islands among HBV Genotypes, PLOS ONE, 8(2):e56711, (2013).
Zhang, Y. et al., Lipids and Lipid Derivatives for RNA Delivery, Chemical Reviews, 121, 20 (2021).

(56) **References Cited**

OTHER PUBLICATIONS

Low, et al., Hepatitis B virus DNA methylation and its potential role in chronic hepatitis B, Expert Reviews in Molecular Medicine, 25:e11, (2023).
Yuen, et al., Hepatitis B virus infection, Nat Rev Dis Primers, 4(18035), (2018).
Borisova, et al., Structure and expression of the gene of the core antigen of human hepatitis B virus (HBV) in *Escherichia coli* cells, Dokl. Biochem., 279:386-390, (1985) (in Russian—concise explanation of the reference found on p. 88 of specification).
Buti, Maria. et al. Long-term safety and efficacy of nucleo(t) side analogue therapy in hepatitis B. Liver International 38(Suppl. 1):84-89 (2018).
Julio, Rendon Londono. Genetic characterizations and epigenetic interference to better understand and fight occult Hepatitis B virus infection. University of Groningen (pp. 1-280) (2017).
PCT/US2024/029529 International Search Report and Written Opinion dated Oct. 11, 2024.
U.S. Appl. No. 18/473,990 Office Action dated Aug. 22, 2024.
U.S. Appl. No. 18/762,301 Office Action dated Oct. 9, 2024.
Allen, Daniel et al. Using Synthetically Engineered Guide RNAs to Enhance CRISPR Genome Editing Systems in Mammalian Cells. Frontiers in Genome Editing 2:617910, 1-16 (2021).
Bloom, Kristie. et al. Gene Therapy for Chronic HBV-can we Eliminate cccDNA?. Genes 9(4):207, 1-15 (2018).
Brown, Wes et al. Regulating CRISPR/Cas9 Function through Conditional Guide RNA Control. ChemBioChem 22(1):63-72 (2021). Published Online Nov. 17, 2020.
Chen, Qiubing et al. Recent Advances in Chemical Modifications of Guide RNA, mRNA and Donor Template for CRISPR-mediated Genome Editing. Advanced Drug Delivery Reviews 168:246-258 (2021). Published Online Oct. 27, 2020.
Chroma Medicine Presents Data Demonstrating Near-Complete, Durable In Vivo Silencing with Targeted Epigenetic Editors at 2023 ASGCT Annual Meeting. BioSpace, May 18, 2023; [Retrieved on Jan. 20, 2025]. Available at URL:https://www.biospace.com/article/releases/chroma-medicine-presents-data-demonstrating-near-complete-durable-in-vivo-silencing-with-targeted-epigenetic-editors-at-2023-asgct-annual-meeting/ pp. 1-2.
Co-pending U.S. Appl. No. 18/981,846, inventors Friedland; Ari et al., filed on Dec. 16, 2024.
Co-pending U.S. Appl. No. 19/060,404, inventors Jaffe; Aron Brandon et al., filed on Feb. 21, 2025.
Gailhouste, Luc et al. Epigenetic reprogramming promotes the antiviral action of IFN alpha in HBV-infected cells. Cell Death Discovery 7(1):130, 1-11 (2021).
Gait, M J. Oligonucleotide Synthesis: A Practical Approach. IRL Press Limited (1984).
GenBank Accession No. XP_525483 Version No. XP_525483.2 Predicted: DNA (cytosine-5-)-methyltransferase 3-like [Pan troglodytes] pp. 1-2. Record created Sep. 16, 2006. Retrieved Feb. 7, 2025. Retrieved from: https://www.ncbi.nlm.nih.gov/protein/XP_525483.2?report=GenPept.
Hensel, Kai O. et al. Virus-host interplay in hepatitis B virus infection and epigenetic treatment strategies. The FEBS Journal 284(21):3550-3572 (2017).
Jeffries, Matlock A. Epigenetic editing: How cutting-edge targeted epigenetic modification might provide novel avenues for autoimmune disease therapy. Clinical Immunology 196:49-58 (2018).
Li, Fuyang et al. Chimeric DNA methyltransferases target DNA methylation to specific DNA sequences and repress expression of target genes. Nucleic acids research 35(1):100-112 (2007).
Ligat, Gaetan et al. Targeting Viral cccDNA for Cure of Chronic Hepatitis B. Current Hepatology Reports 19(3):235-244 (2020).
Lilley, David. M.J. et al. Dahlberg. Methods in Enzymology; DNA Structure Part A: Synthesis and Physical Analysis of DNA. Academic Press 211:1-5 (1992).
Lu, Juane et al. Types of Nuclear Localization Signals and Mechanisms of Protein Import into the Nucleus. Cell Communication Signal 19(1):60, 1-10 (2021).
Lyer, R P. et al. Modified Oligonucleotides-Synthesis, Properties And Applications. Current Opinion in Molecular Therapeutics 1(3):344-358 (1999).
PCT/US2023/026140 International Search Report and Written Opinion dated Jan. 9, 2024.
Riesenberg, Stephan et al. Improved gRNA Secondary Structures Allow Editing of Target Sites Resistant to CRISPR-Cas9 Cleavage. Nature Communications 13(1):489, 1-8 (2022).
Roe, et al. DNA Isolation and Sequencing: Essential Techniques. John Wiley & Sons, New York 1-4 (1996).
Shapiro, Jenny et al. Chemical Modification of Guide RNAs for Improved CRISPR Activity in CD34+ Human Hematopoietic Stem and Progenitor Cells. CRISPR Guide RNA Design: Methods and Protocols 2162:37-48 (2021).
UniProtKB Accession No. Q99ZW2. CRISPR-associated endonuclease Cas9/Csn1. Record created Jun. 1, 2001. May 30, 2024 at URL: https://www.uniprot.org/uniprotkb/Q99ZW2/entry pp. 1-8.
U.S. Appl. No. 18/762,301 Office Action dated Jan. 13, 2025.
Weitzman, Matthew D. et al. Adeno-associated Virus Biology. Methods in molecular biology (Clifton, N.J.) 807:1-23 (2011).
Zhu, Anjing et al. HBV cccDNA and Its Potential as a Therapeutic Target. Journal of Clinical and Translational Hepatology 7(3):258-262 (2019).

* cited by examiner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3,182 bp

FIGURE 1

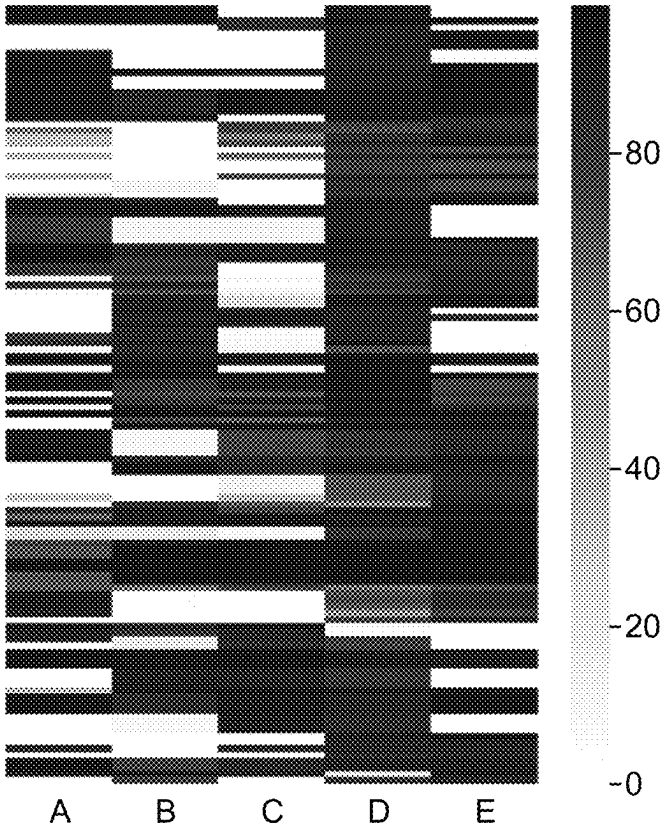


FIGURE 2

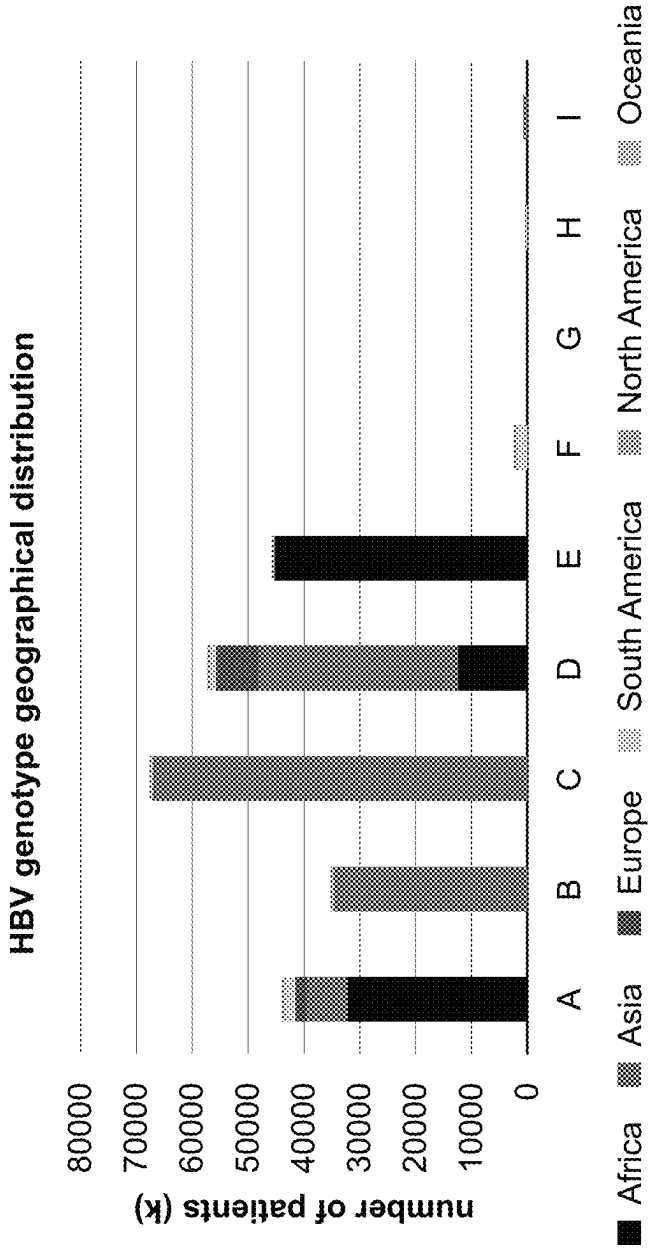

HBV genotype geographical distribution
number of patients (k)
80000
70000
60000
50000
40000
30000
20000
10000
0
A
B
C
D
E
F
G
H
I
Africa
Asia
Europe
South America
North America
Oceania

FIGURE 3

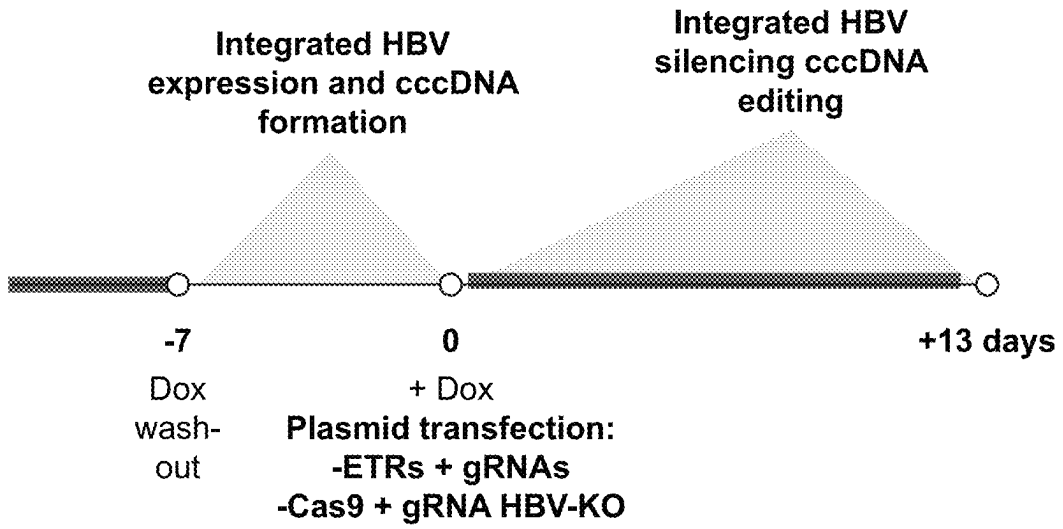


FIGURE 4A

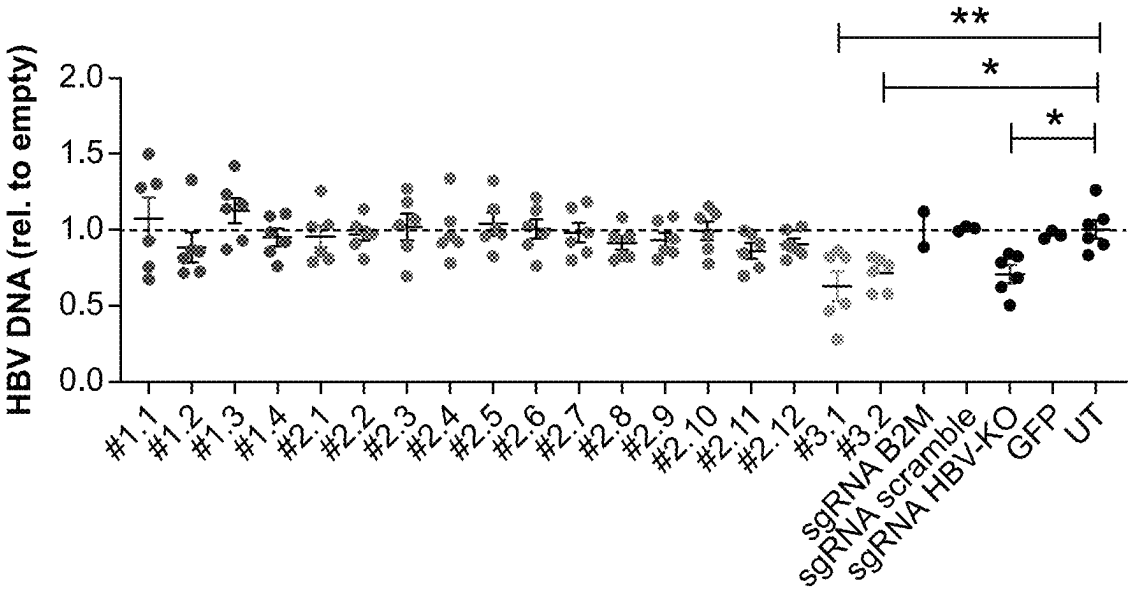


FIGURE 4B

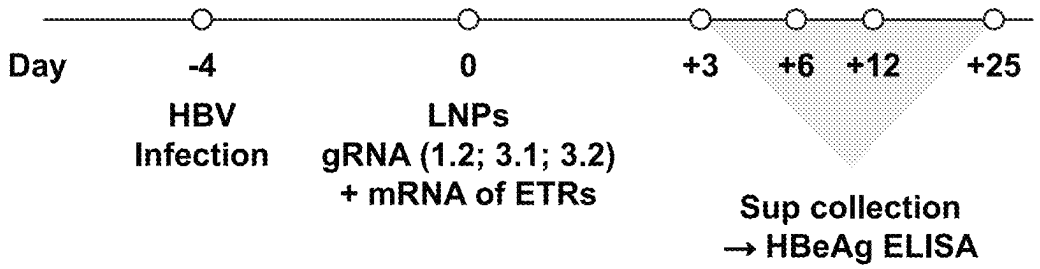


FIGURE 5A

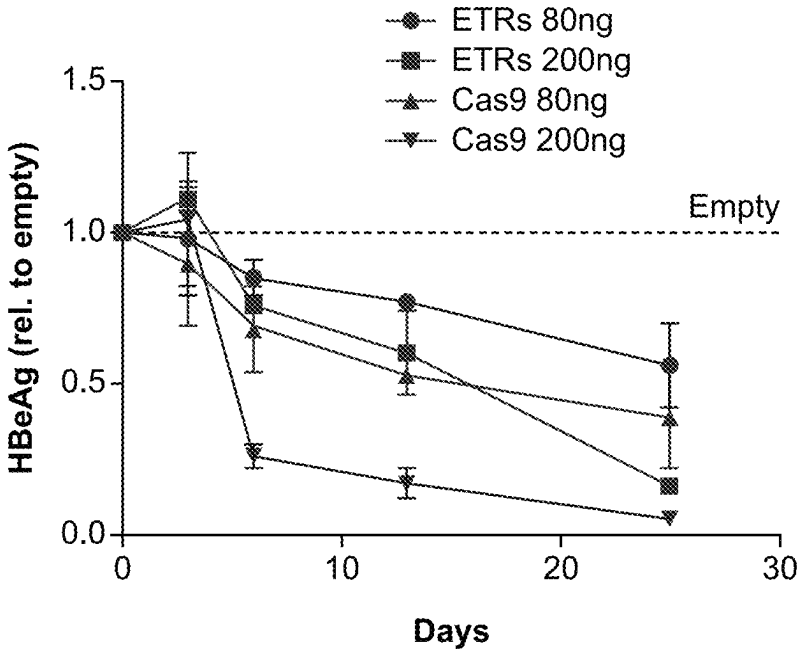


FIGURE 5B

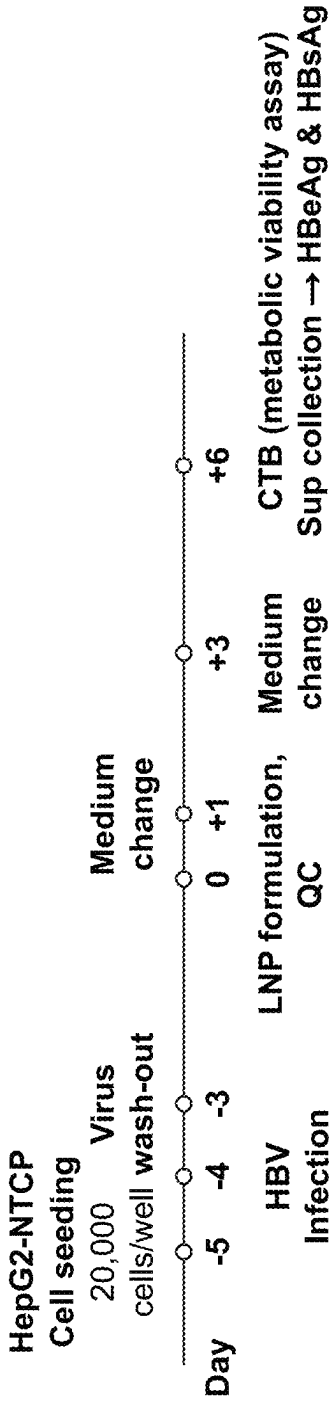

HepG2-NTCP
Cell seeding
20,000
cells/well
Virus
wash-out
Medium
change
Day
-5
-4
-3
0
+1
+3
+6
HBV
Infection
LNP formulation,
QC
and transfection
Medium
change
CTB (metabolic viability assay)
Sup collection → HBeAg & HBsAg
ELISA

FIGURE 6

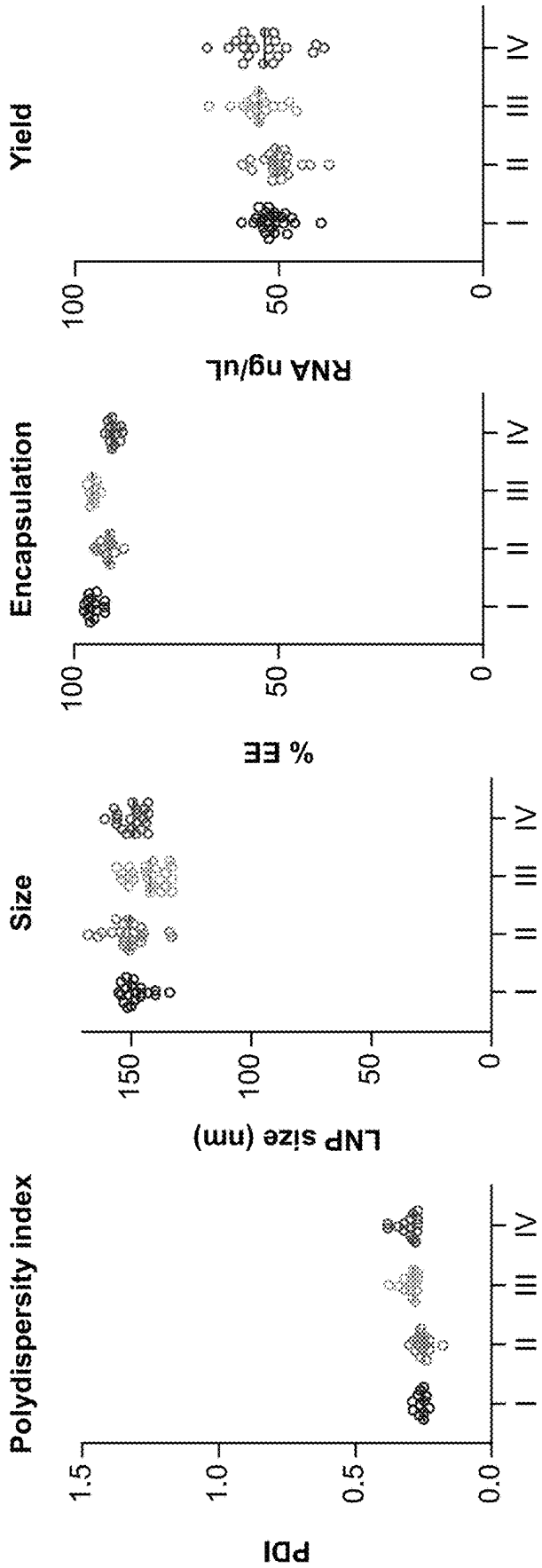

Polydispersity index
PDI
1.5
1.0
0.5
0.0
I
II
III
IV
Size
LNP size (nm)
150
100
50
0
Encapsulation
% EE
Yield
RNA ng/uL

FIGURE 7

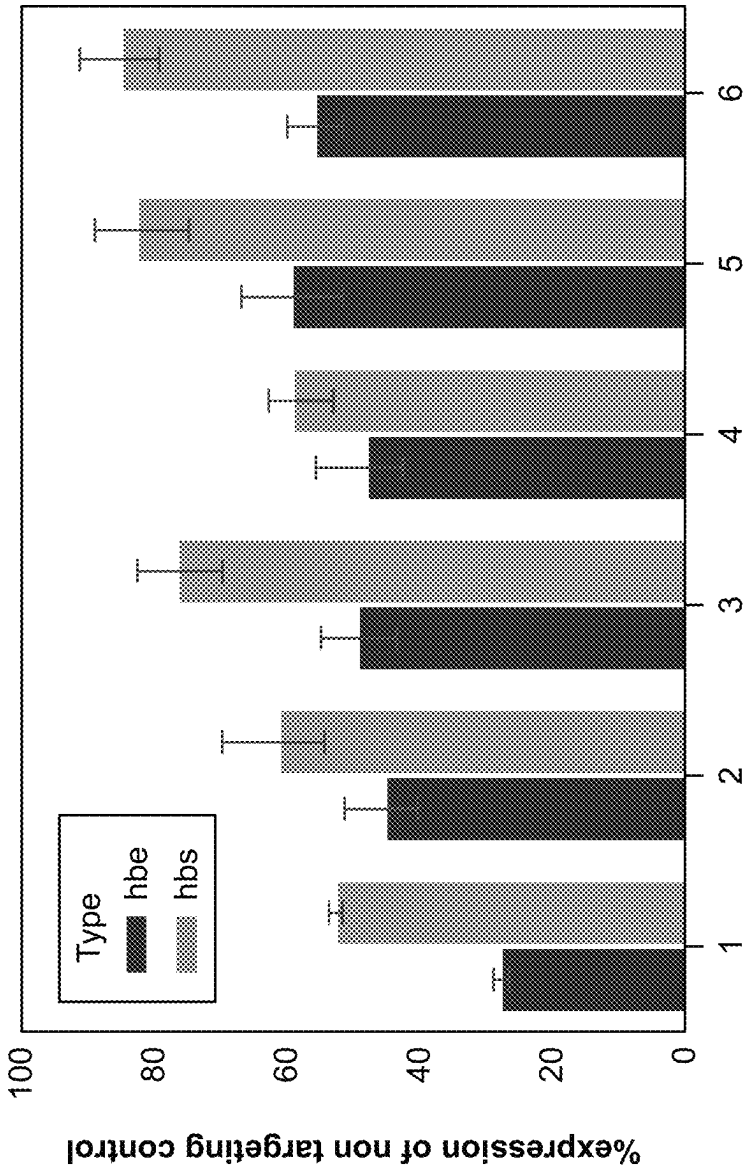

%expression of non targeting control
100
80
60
40
20
0
Type
hbe
hbs
1
2
3
4
5
6

FIGURE 8

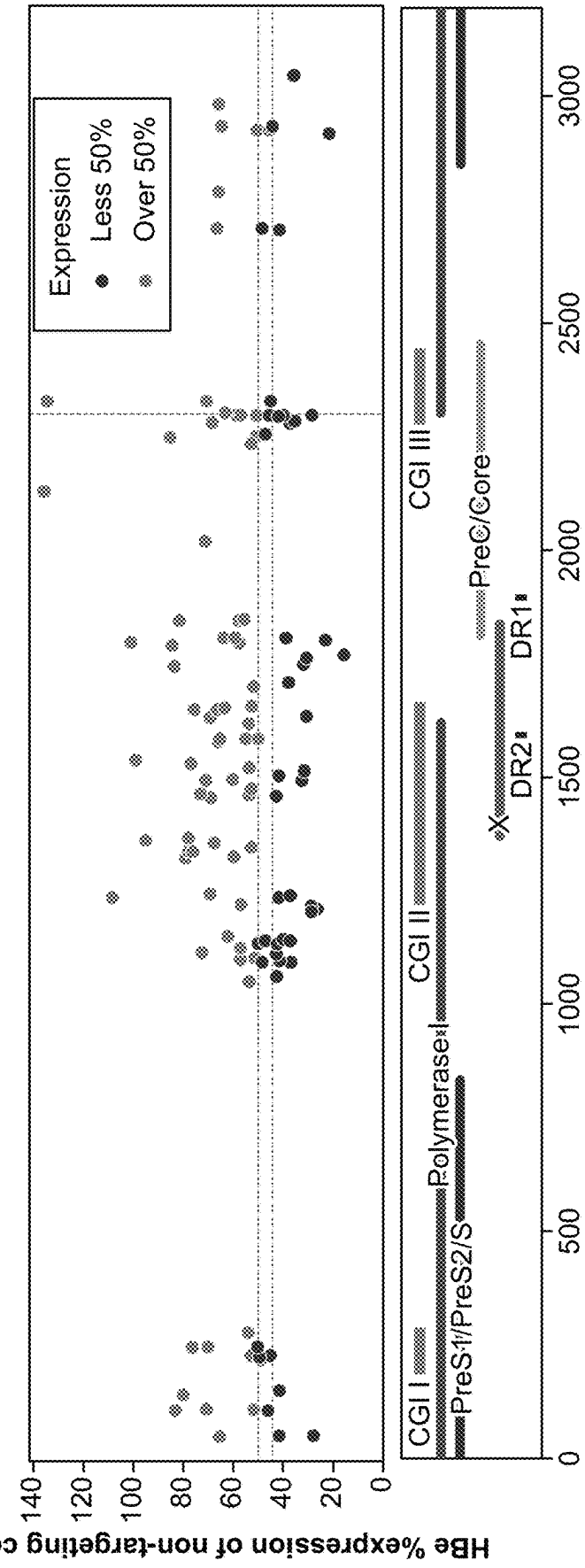

HBe %expression of non-targeting control
140
120
100
80
60
40
20
0
Expression
Less 50%
Over 50%
CGI I
PreS1/PreS2/S
Polymerase
CGI II
X
DR2
DR1
PreC/Core
CGI III
0
500
1000
1500
2000
2500
3000

FIGURE 9

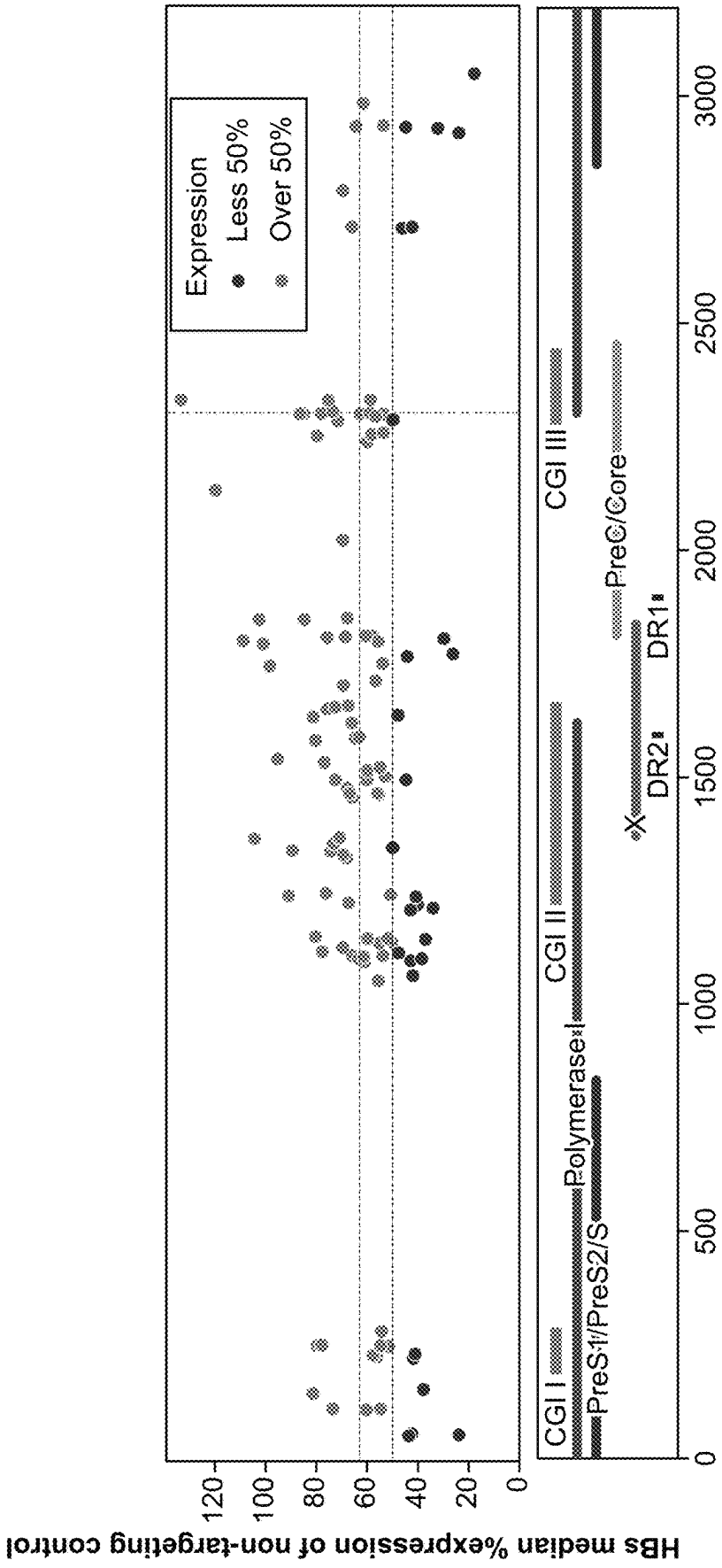

HBs median %expression of non-targeting control
120
100
80
60
40
20
0
Expression
Less 50%
Over 50%
0
500
1000
1500
2000
2500
3000
CGI I
PreS1/PreS2/S
Polymerase
CGI II
X
DR2
DR1
PreC/Core
CGI III

FIGURE 10

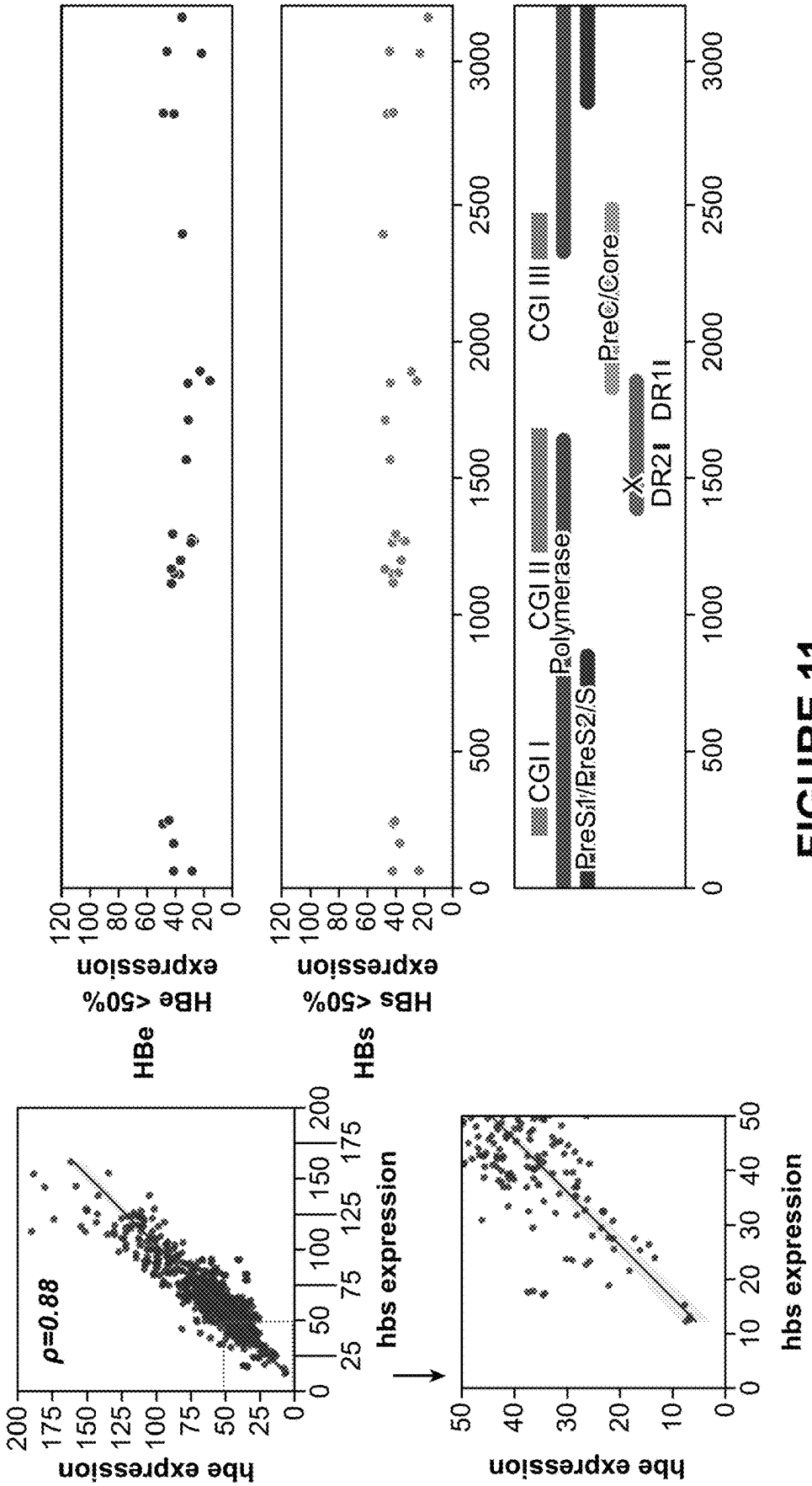

ρ=0.88
hbe expression
hbs expression
HBe
HBe <50% expression
HBs
HBs <50% expression
CGI I
PreS1/PreS2/S
Polymerase
CGI II
X
DR2
DR1
PreC/Core
CGI III

FIGURE 11

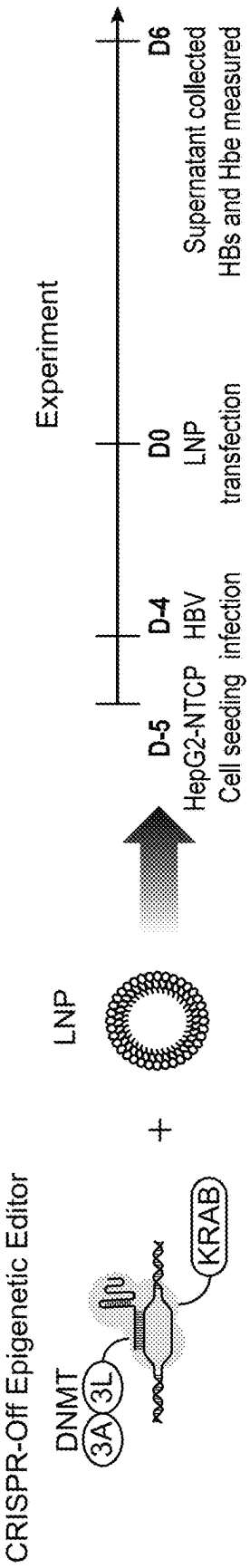


FIGURE 12A

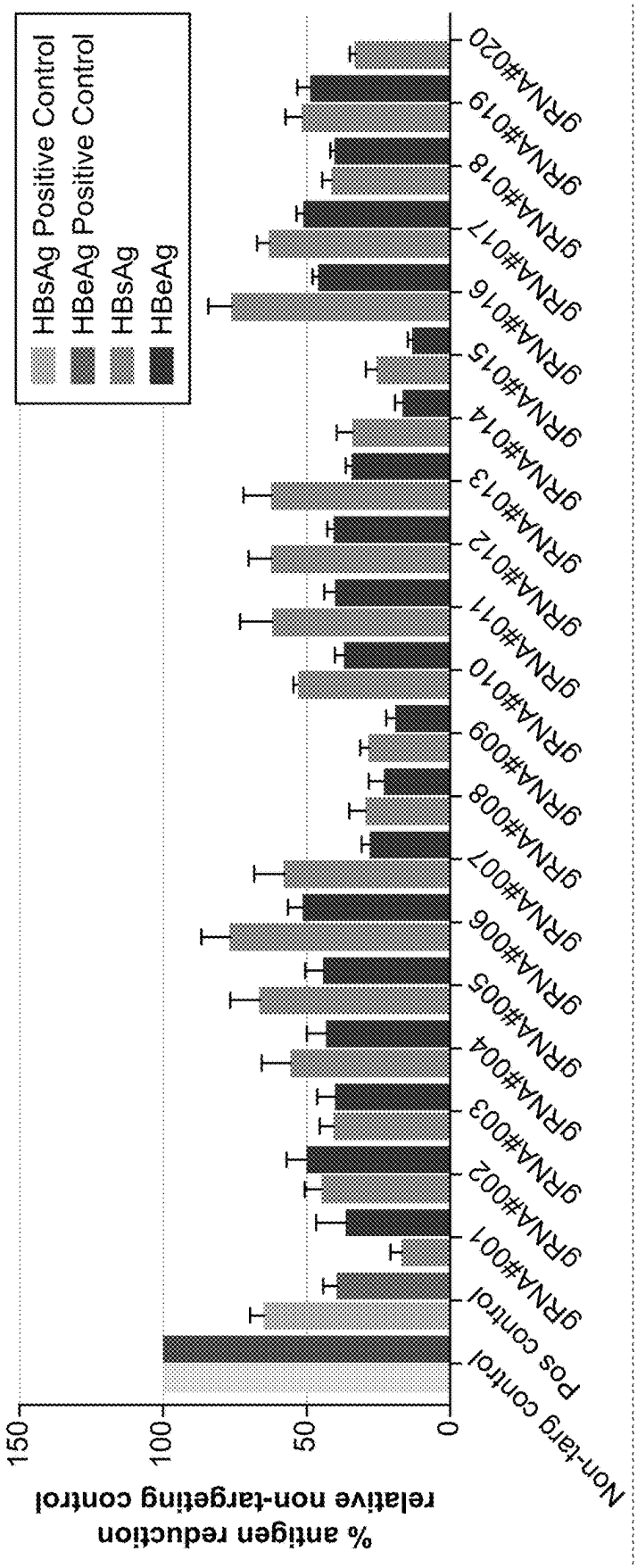


FIGURE 12B

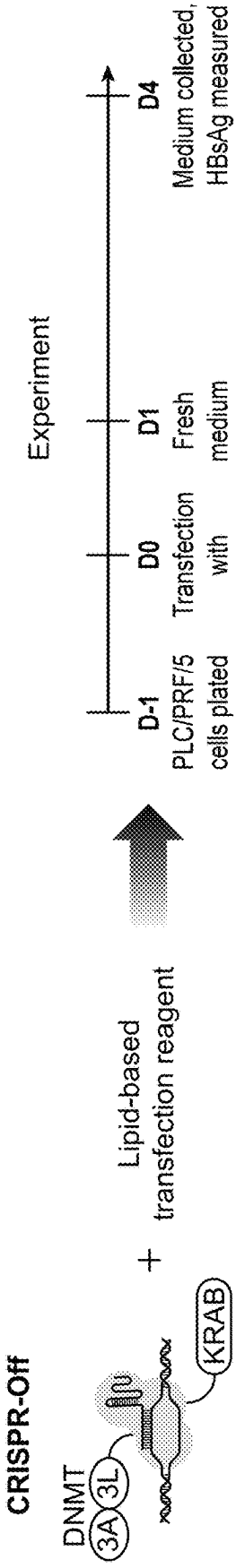


FIGURE 13A

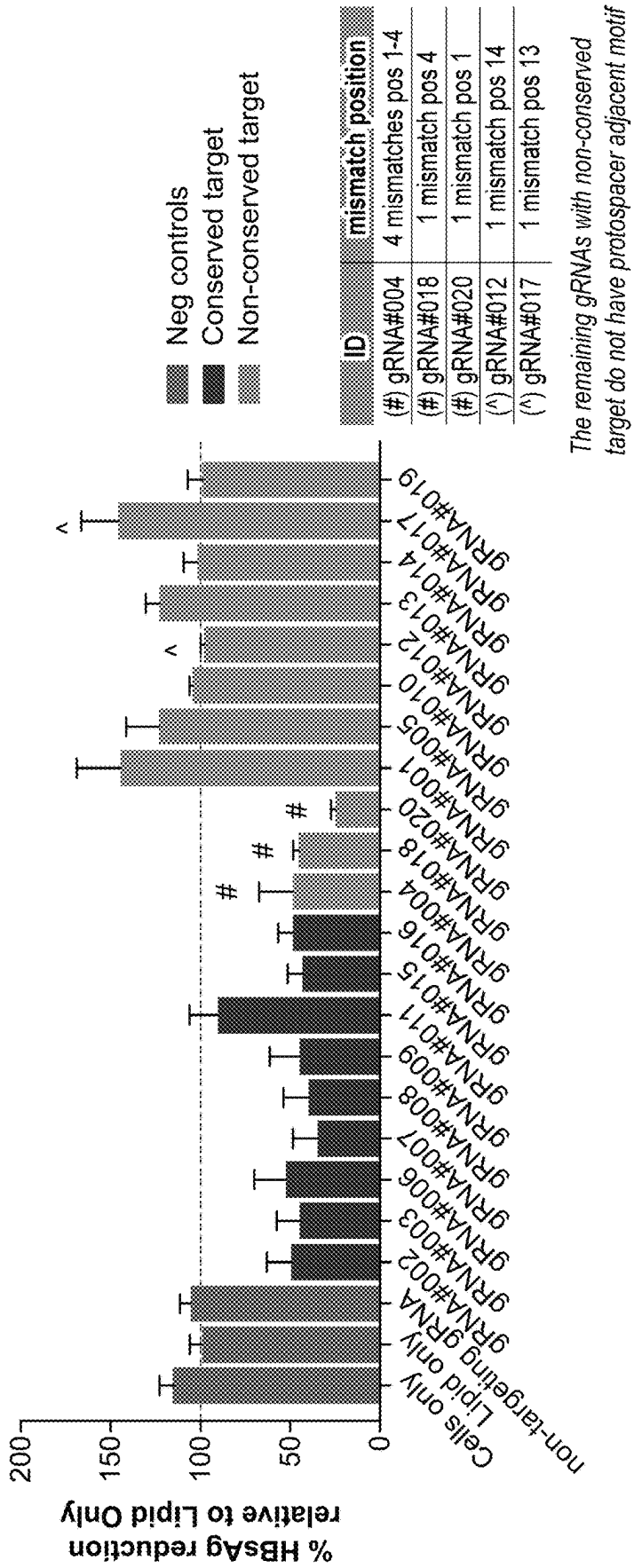


FIGURE 13B

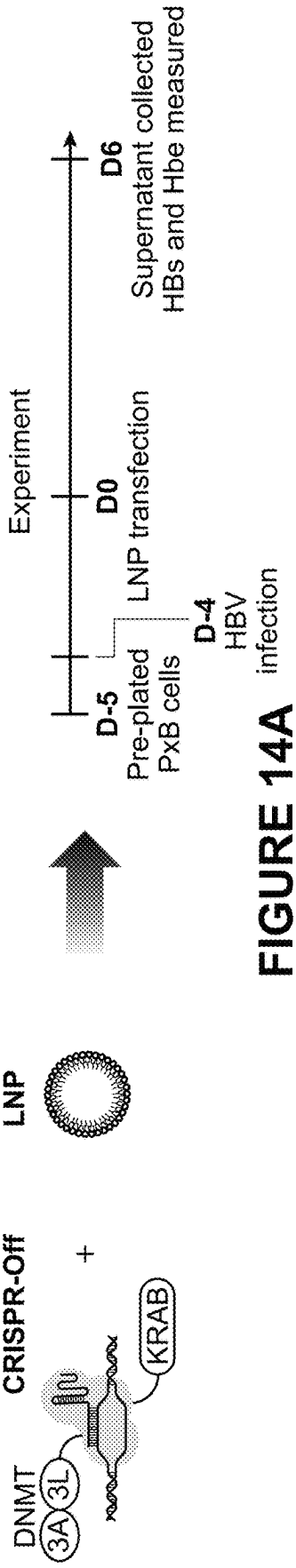


FIGURE 14A

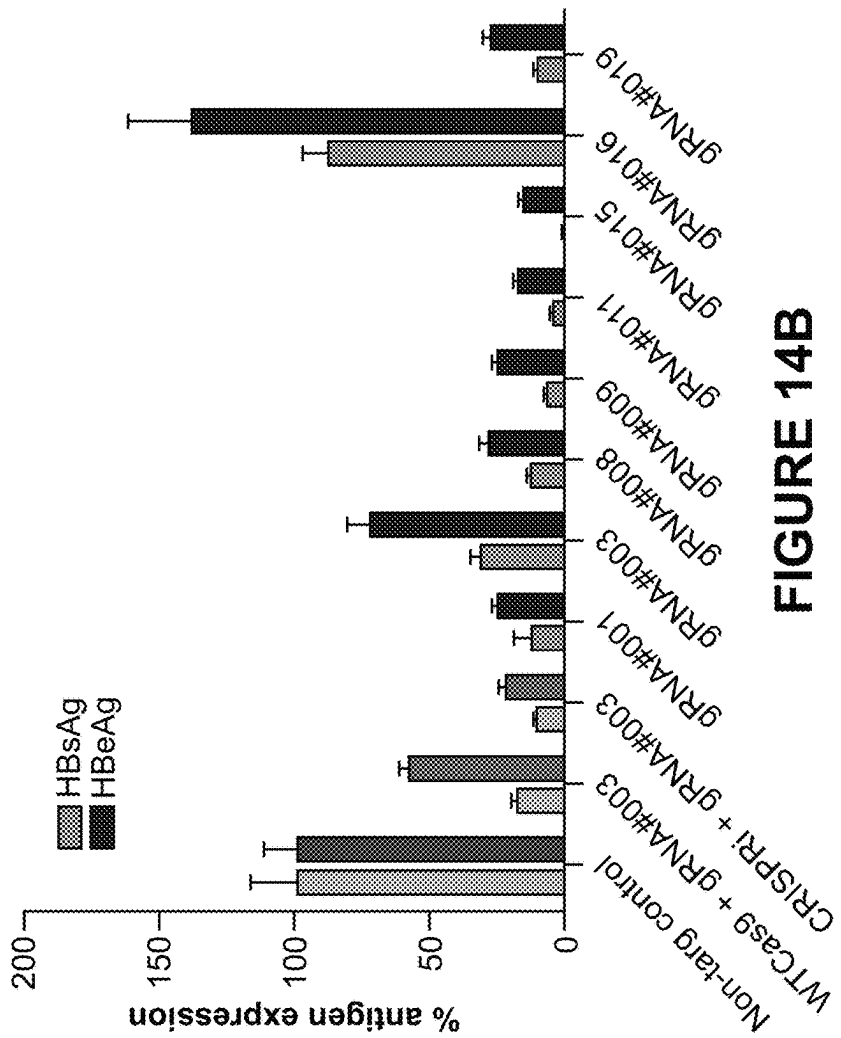


FIGURE 14B

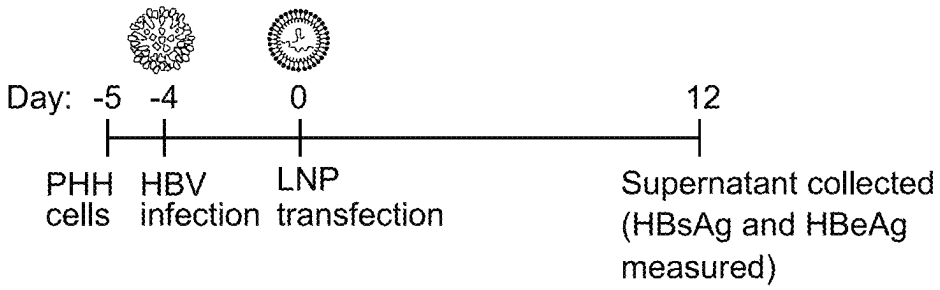


FIGURE 14C

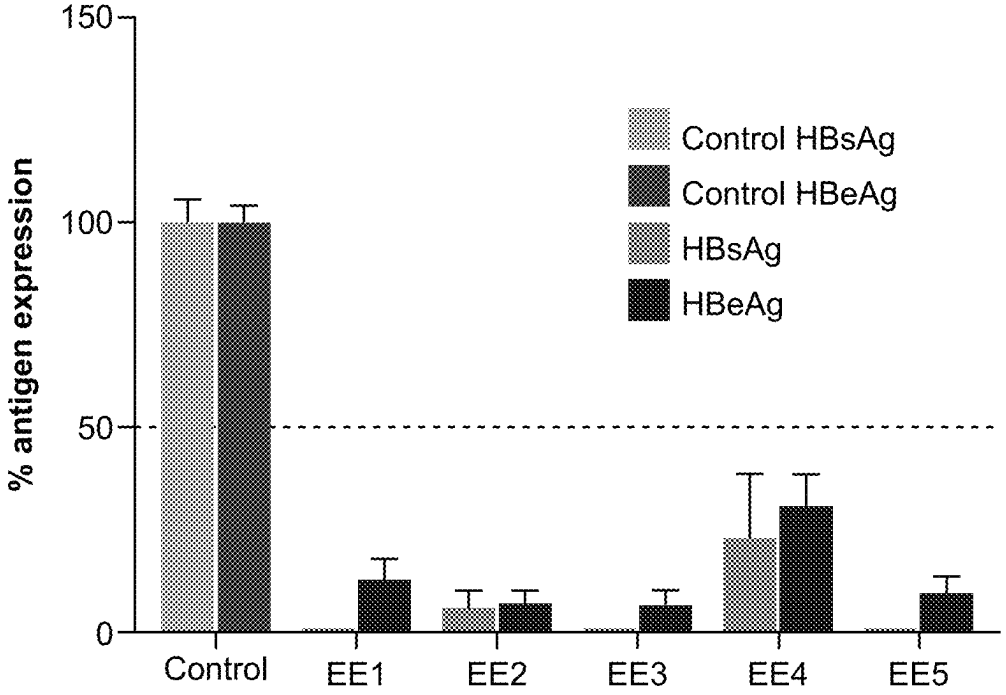
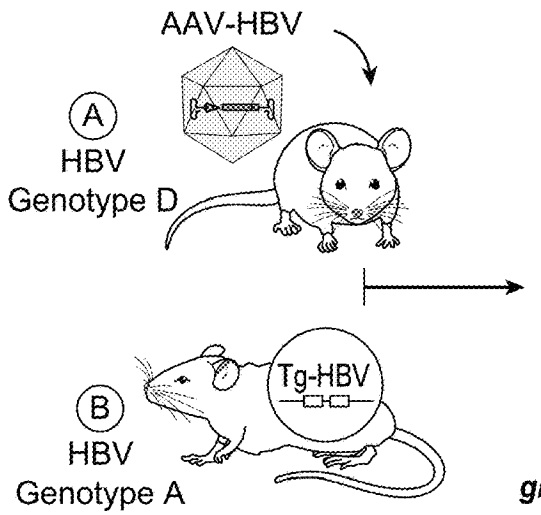


FIGURE 14D



Group	Treatment	Format	N=6 AAV-HBV	N=6 HBV-Tg
1	Vehicle	-	6	6
2	gRNA011	WT-Cas9	6	6
3	gRNA011	CRISPR-Off	6	6
4	gRNA003	CRISPR-Off	6	6
5	gRNA016	CRISPR-Off	6	6
6	gRNA016	3x-ETR	6	6

gRNAs selected from HepG2-NTCP hits, with 100% match in both A and D genotypes

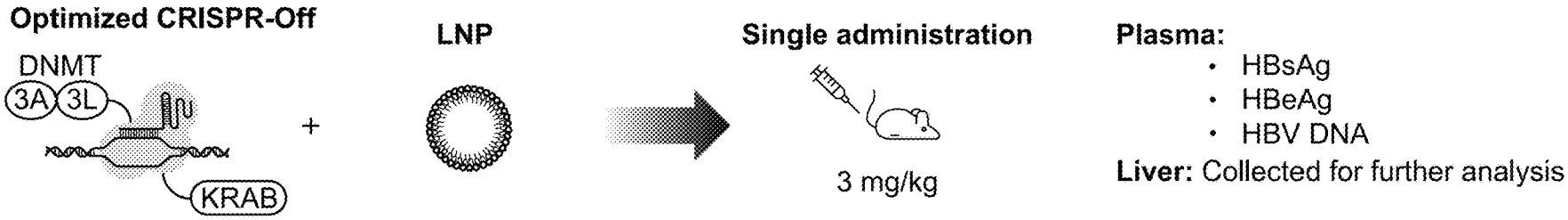


FIGURE 15

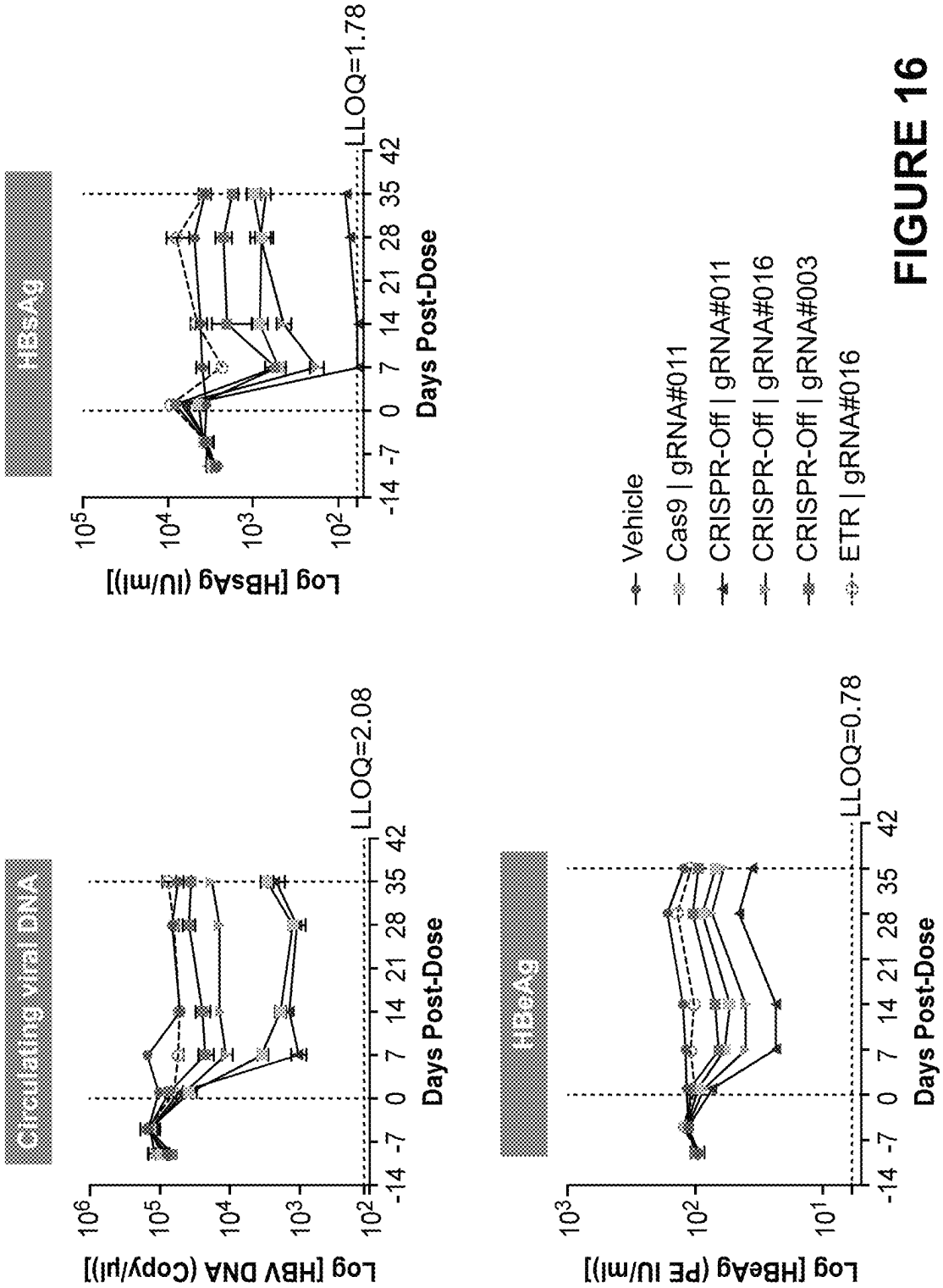

HBsAg
Log [HBsAg (IU/ml)]
10^5
10^4
10^3
10^2
-14 -7 0 7 14 21 28 35 42
Days Post-Dose
LLOQ=1.78
Circulating Viral DNA
Log [HBV DNA (Copy/µl)]
10^6
10^5
10^4
10^3
10^2
-14 -7 0 7 14 21 28 35 42
Days Post-Dose
LLOQ=2.08
HBeAg
Log [HBeAg (PE IU/ml)]
10^3
10^2
10^1
-14 -7 0 7 14 21 28 35 42
Days Post-Dose
LLOQ=0.78
Vehicle
Cas9 | gRNA#011
CRISPR-Off | gRNA#011
CRISPR-Off | gRNA#016
CRISPR-Off | gRNA#003
ETR | gRNA#016

FIGURE 16

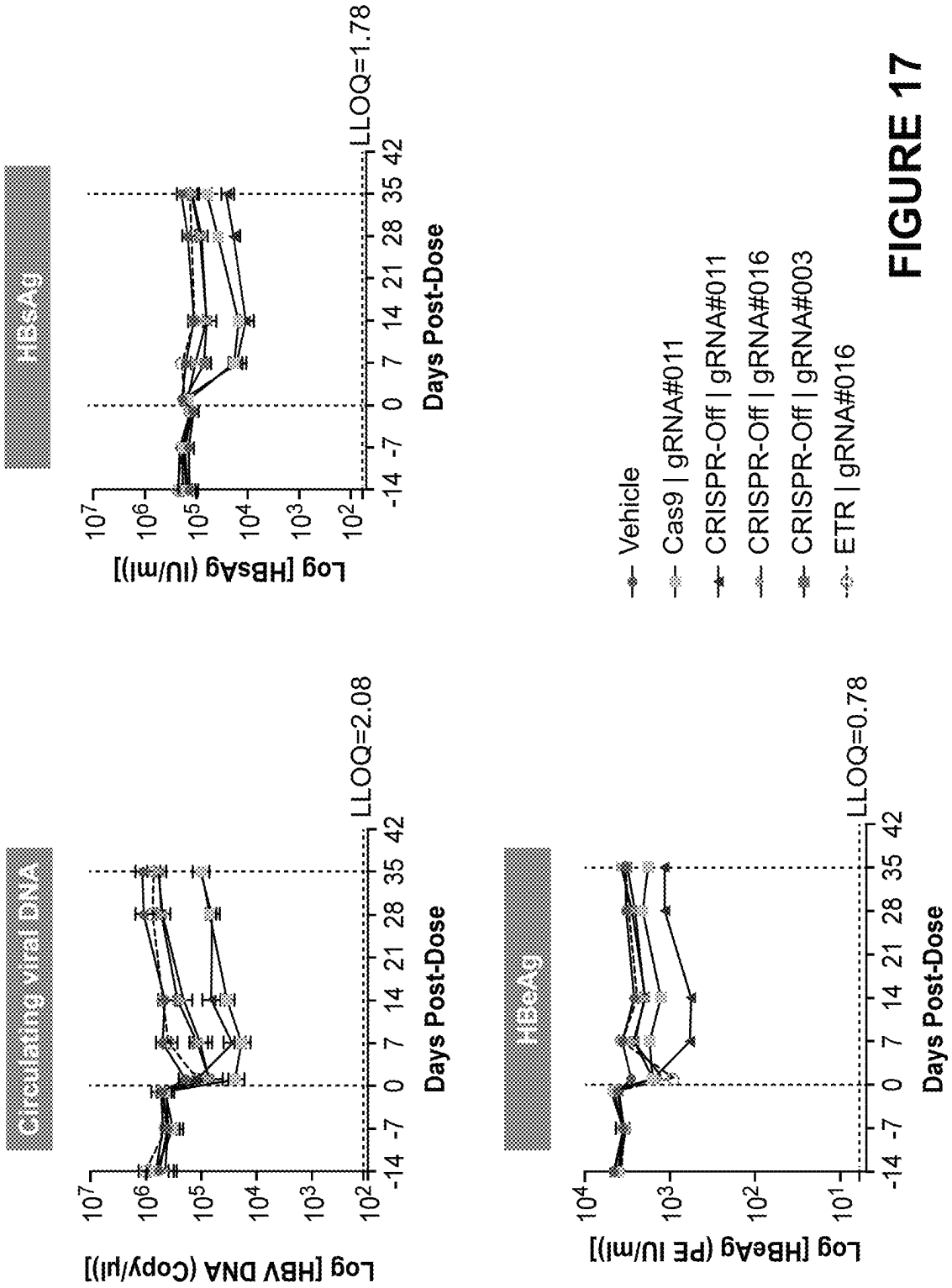

Circulating Viral RNA
Log [HBV DNA (Copy/µl)]
Days Post-Dose
LLOQ=2.08
HBsAg
Log [HBsAg (IU/ml)]
Days Post-Dose
LLOQ=1.78
HBeAg
Log [HBeAg (PE IU/ml)]
Days Post-Dose
LLOQ=0.78
Vehicle
Cas9 | gRNA#011
CRISPR-Off | gRNA#011
CRISPR-Off | gRNA#016
CRISPR-Off | gRNA#003
ETR | gRNA#016

FIGURE 17

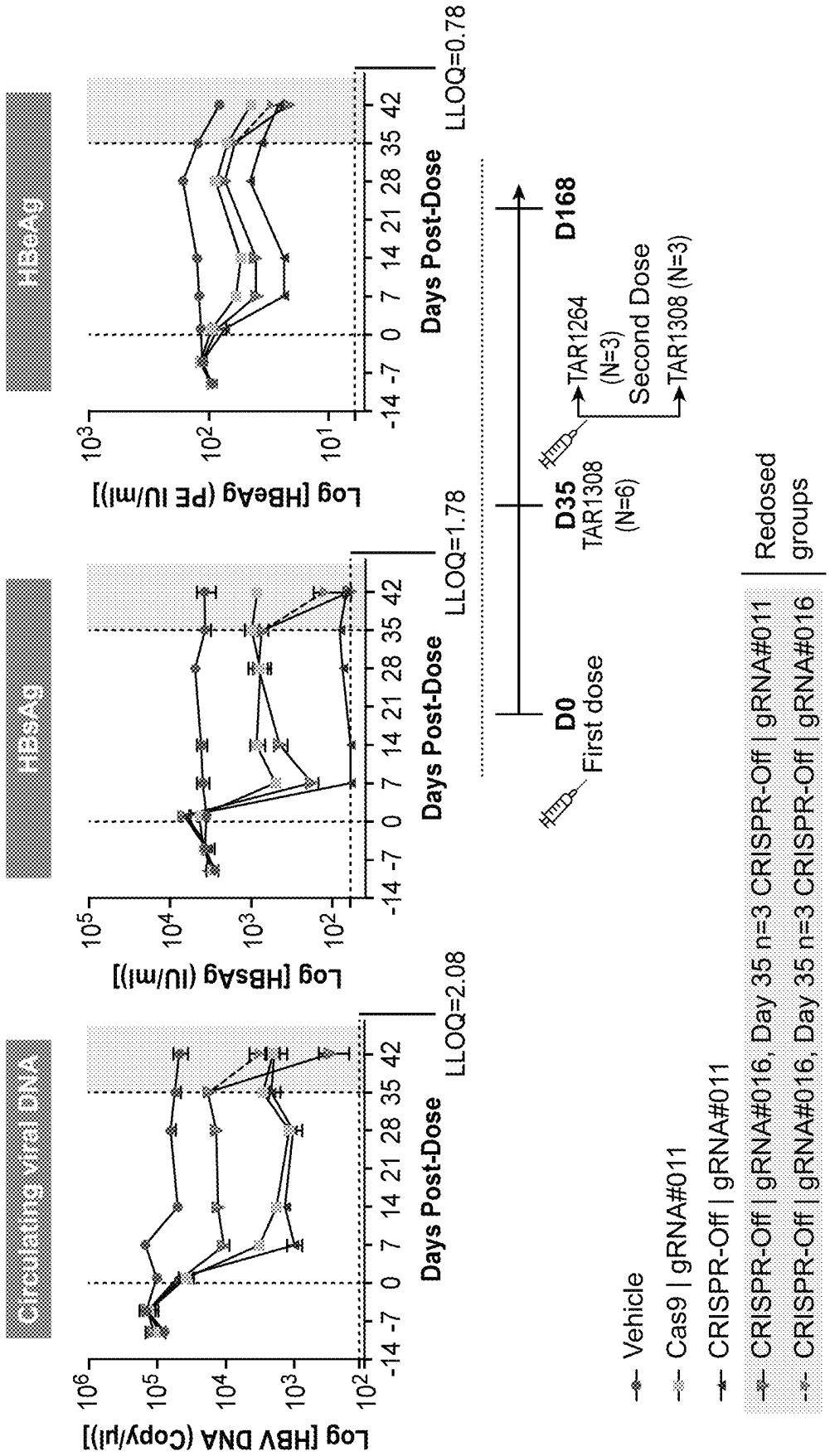

Circulating viral DNA
HBsAg
HBeAg
Log [HBV DNA (Copy/µl)]
Log [HBsAg (IU/ml)]
Log [HBeAg (PE IU/ml)]
Days Post-Dose
LLOQ=2.08
LLOQ=1.78
LLOQ=0.78
D0
First dose
D35
TAR1308
(N=6)
TAR1264
(N=3)
Second Dose
TAR1308 (N=3)
D168
Redosed groups
Vehicle
Cas9 | gRNA#011
CRISPR-Off | gRNA#011
CRISPR-Off | gRNA#016, Day 35 n=3 CRISPR-Off | gRNA#011
CRISPR-Off | gRNA#016, Day 35 n=3 CRISPR-Off | gRNA#016

FIGURE 18A

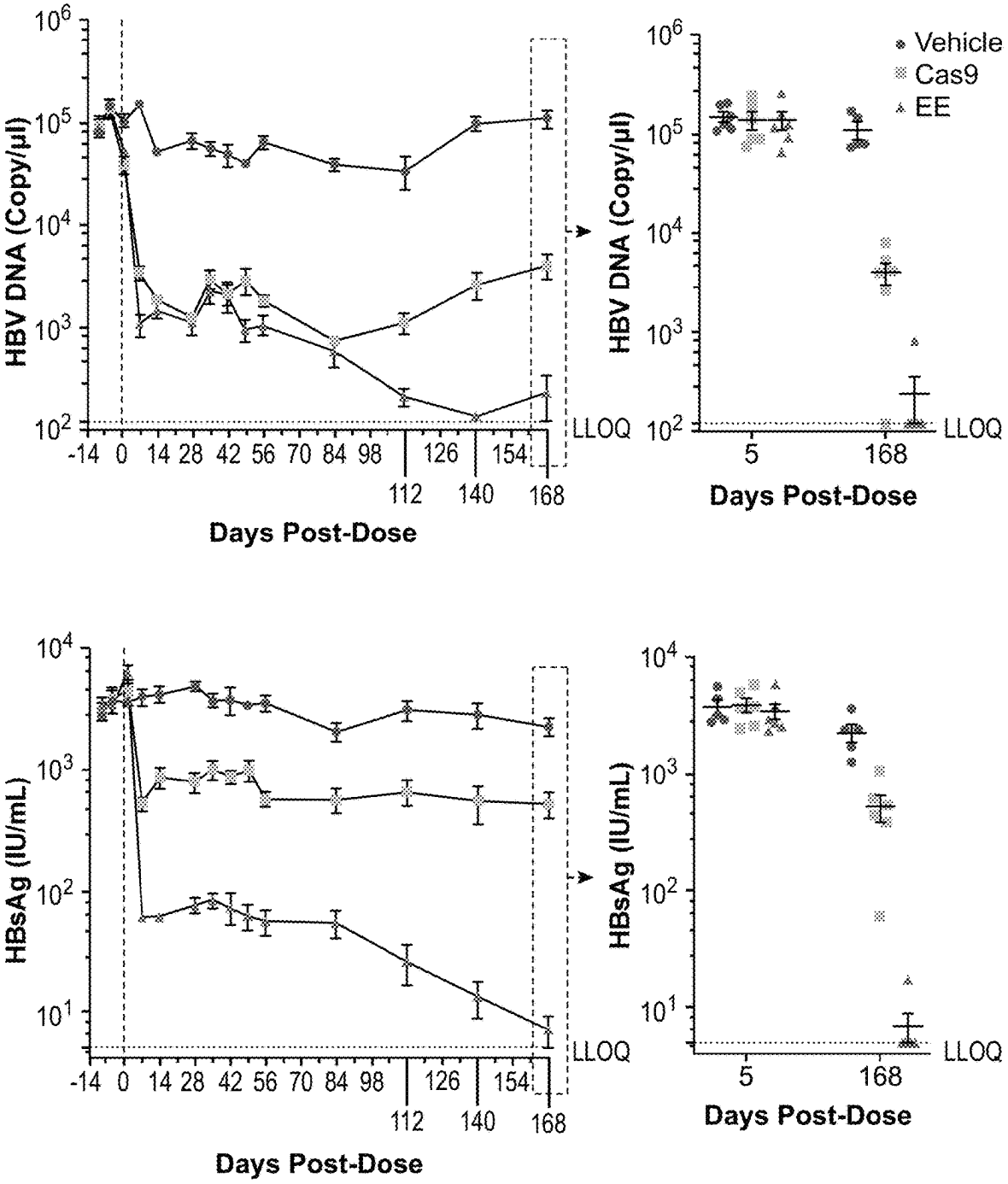

HBV DNA (Copy/µl)
Days Post-Dose
LLOQ
Vehicle
Cas9
EE
HBsAg (IU/mL)

FIGURE 18B

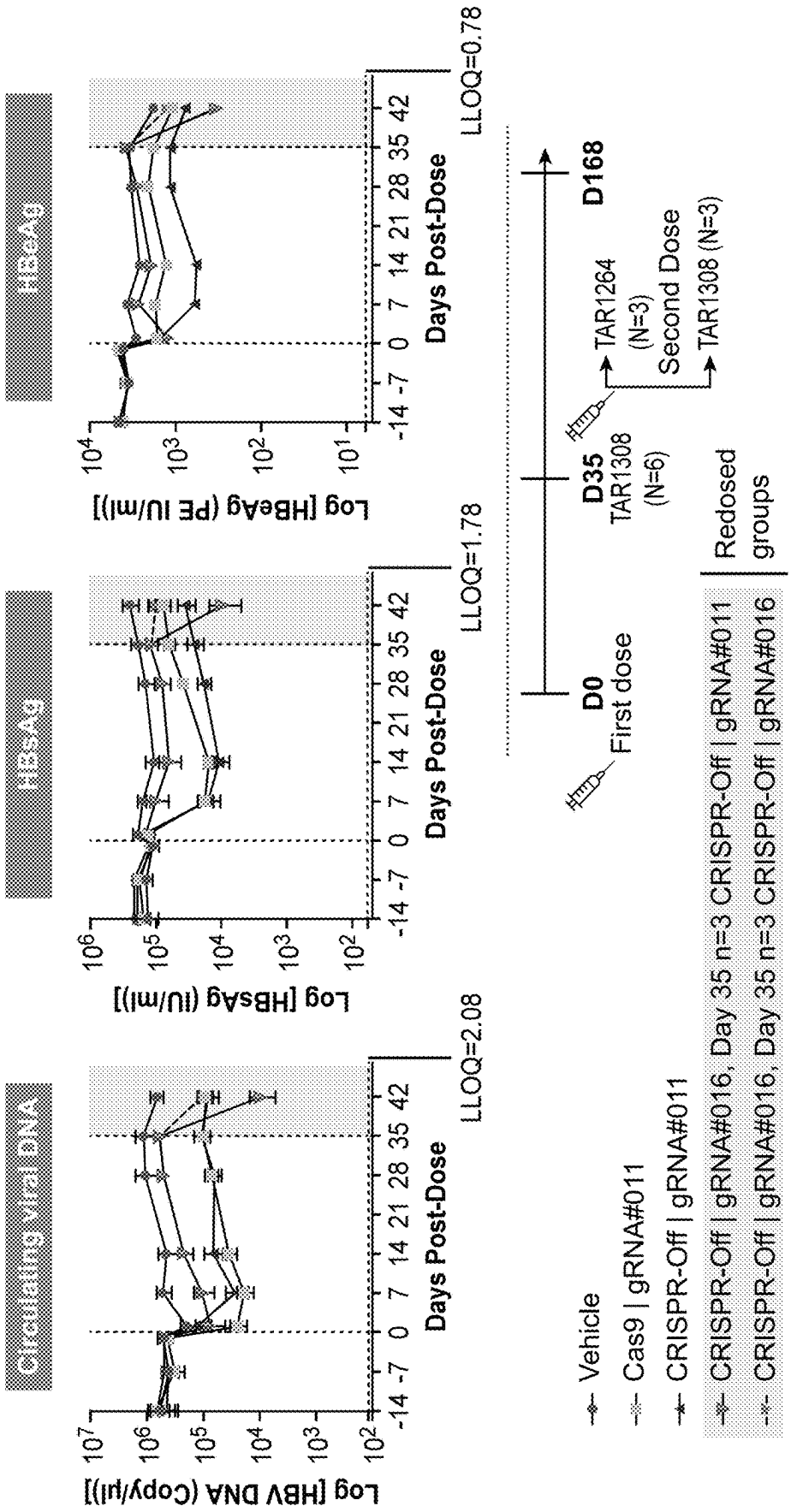

Circulating viral DNA
Log [HBV DNA (Copy/µl)]
LLOQ=2.08
Days Post-Dose
HBsAg
Log [HBsAg (IU/ml)]
LLOQ=1.78
Days Post-Dose
HBeAg
Log [HBeAg (PE IU/ml)]
LLOQ=0.78
Days Post-Dose
D0
First dose
D35
TAR1308
(N=6)
TAR1264
(N=3)
Second Dose
TAR1308 (N=3)
D168
Redosed groups
Vehicle
Cas9 | gRNA#011
CRISPR-Off | gRNA#011
CRISPR-Off | gRNA#016, Day 35 n=3 CRISPR-Off | gRNA#011
CRISPR-Off | gRNA#016, Day 35 n=3 CRISPR-Off | gRNA#016

FIGURE 19

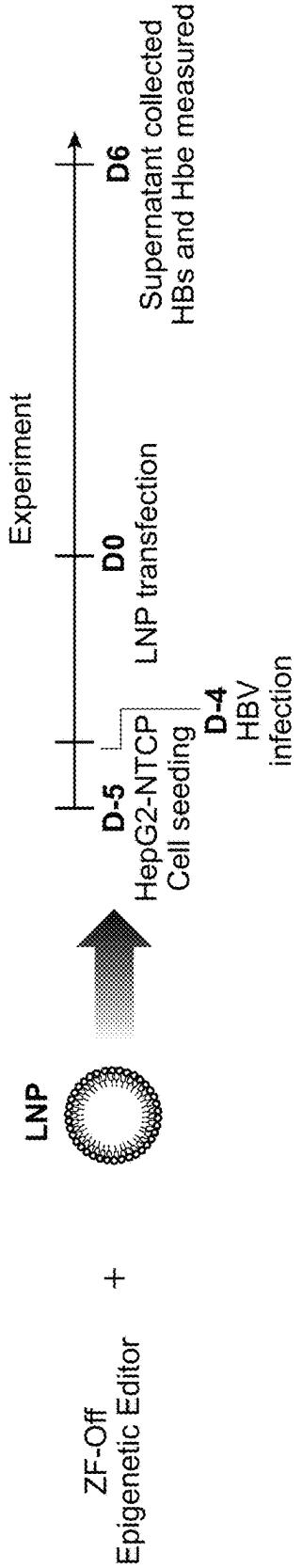


FIGURE 20A

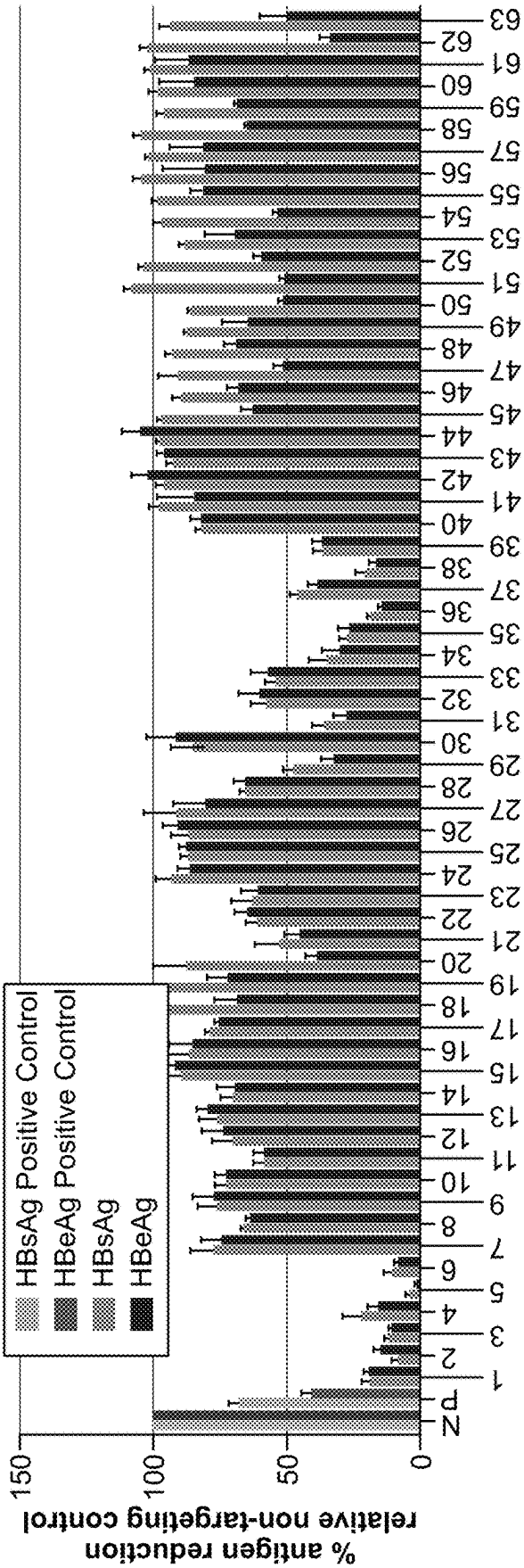


FIGURE 20B

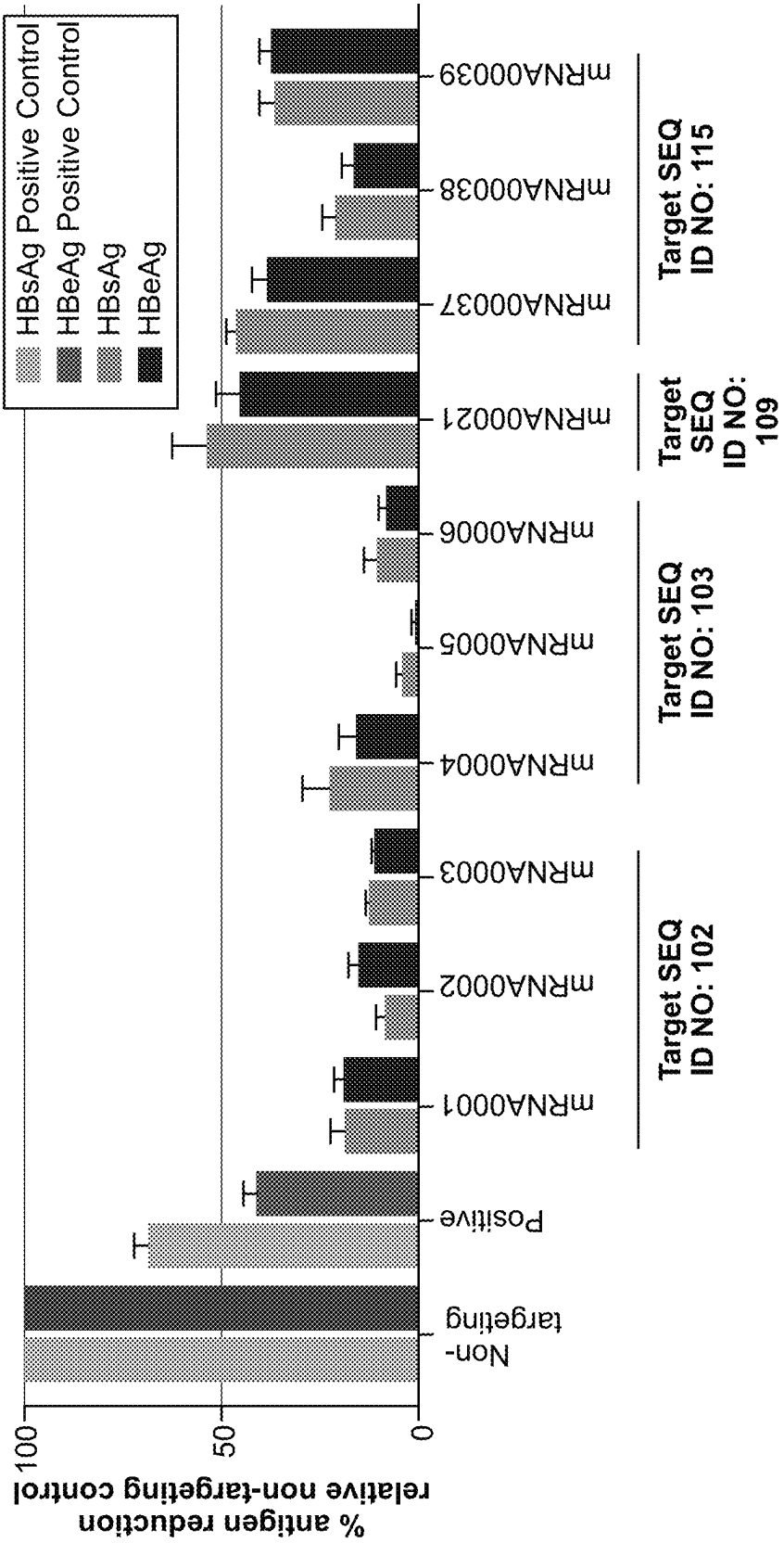

HBsAg Positive Control
HBeAg Positive Control
HBsAg
HBeAg
% antigen reduction relative non-targeting control
100
50
0
Non-targeting
Positive
mRNA00001
mRNA00002
mRNA00003
mRNA00004
mRNA00005
mRNA00006
mRNA00021
mRNA00037
mRNA00038
mRNA00039
Target SEQ ID NO: 102
Target SEQ ID NO: 103
Target SEQ ID NO: 109
Target SEQ ID NO: 115

FIGURE 21A

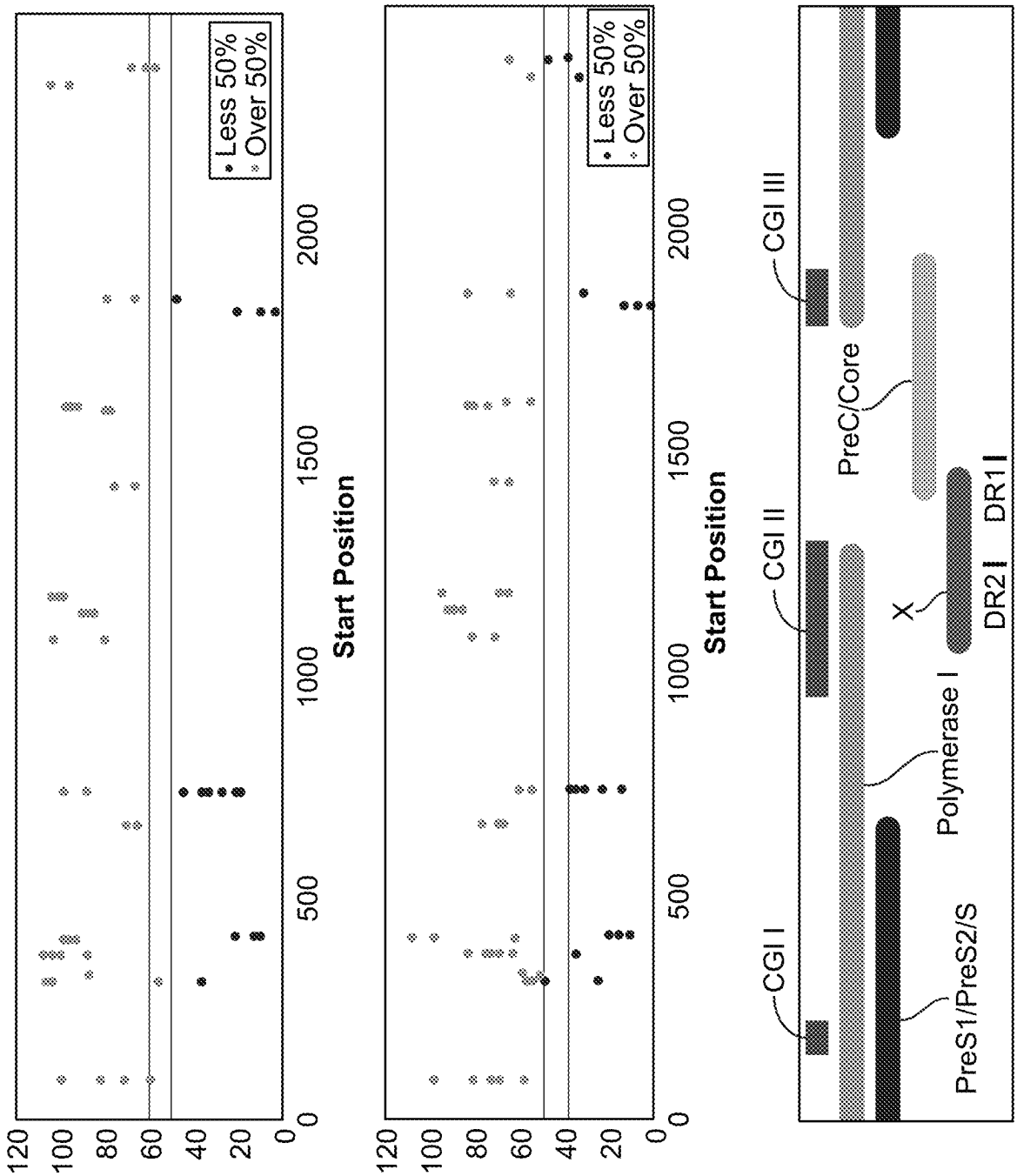

120
100
80
60
40
20
0
0
500
1000
1500
2000
Start Position
Less 50%
Over 50%
120
100
80
60
40
20
0
0
500
1000
1500
2000
Start Position
Less 50%
Over 50%
CGI I
CGI II
CGI III
PreS1/PreS2/S
Polymerase I
X
DR2
DR1
PreC/Core

FIGURE 21B

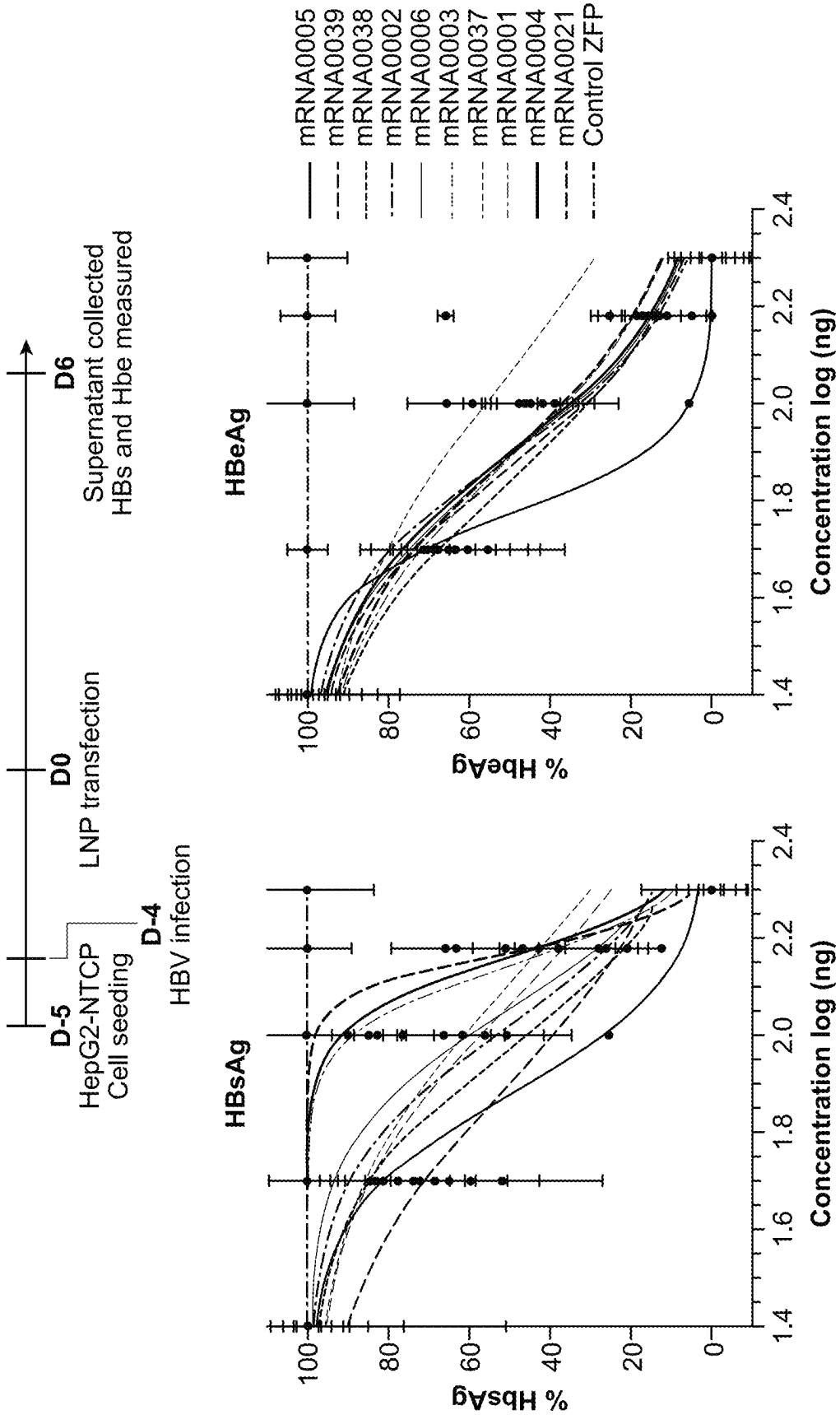

D-5
HepG2-NTCP
Cell seeding
D-4
HBV infection
D0
LNP transfection
D6
Supernatant collected
HBs and Hbe measured
HBsAg
% HbsAg
Concentration log (ng)
HBeAg
% HbeAg
Concentration log (ng)
mRNA0005
mRNA0039
mRNA0038
mRNA0002
mRNA0006
mRNA0003
mRNA0037
mRNA0001
mRNA0004
mRNA0021
Control ZFP

FIGURE 22

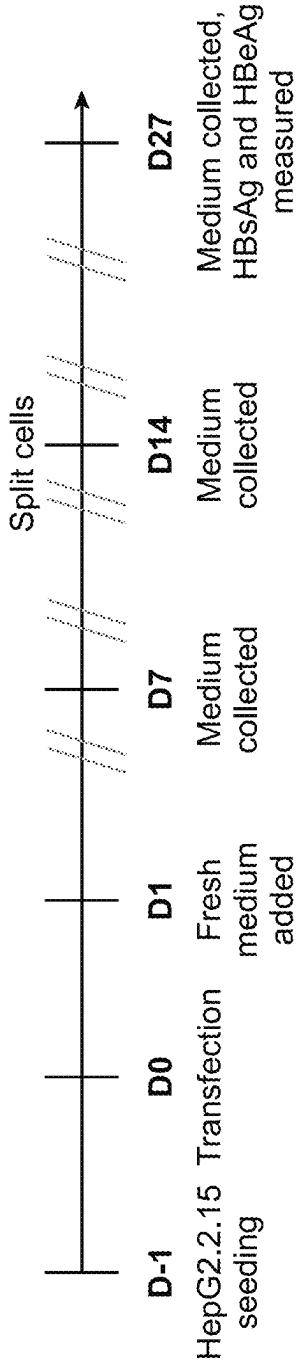


FIGURE 23A

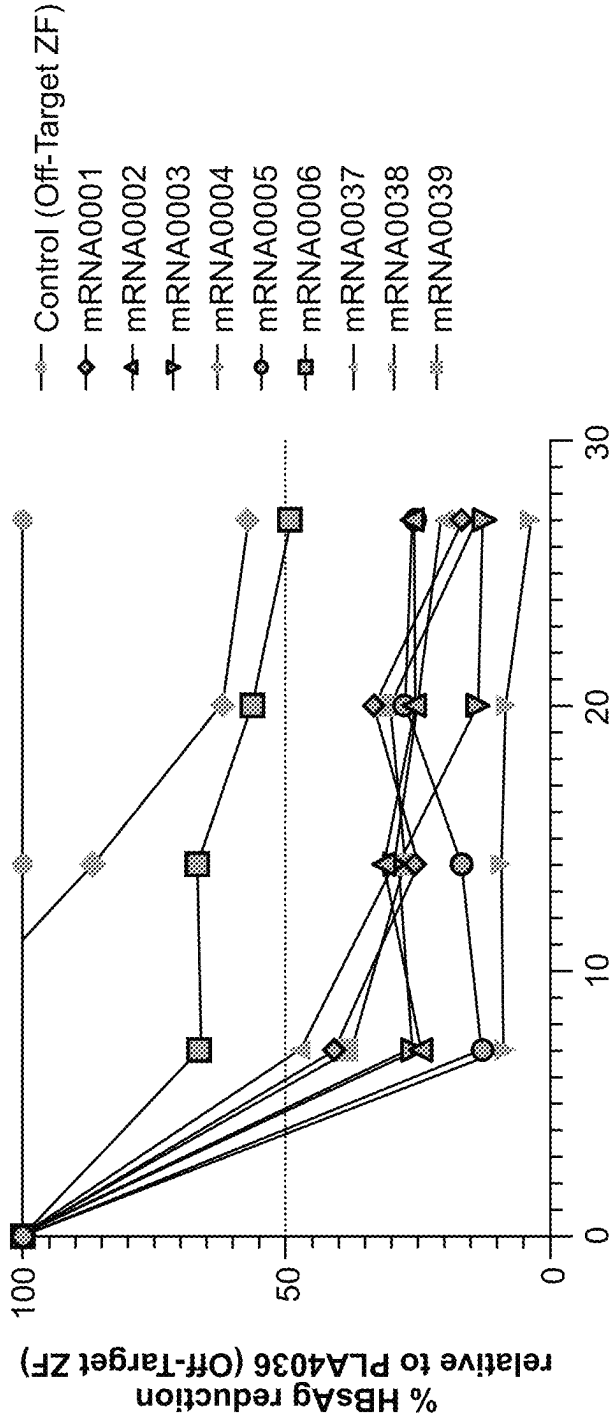


FIGURE 23B

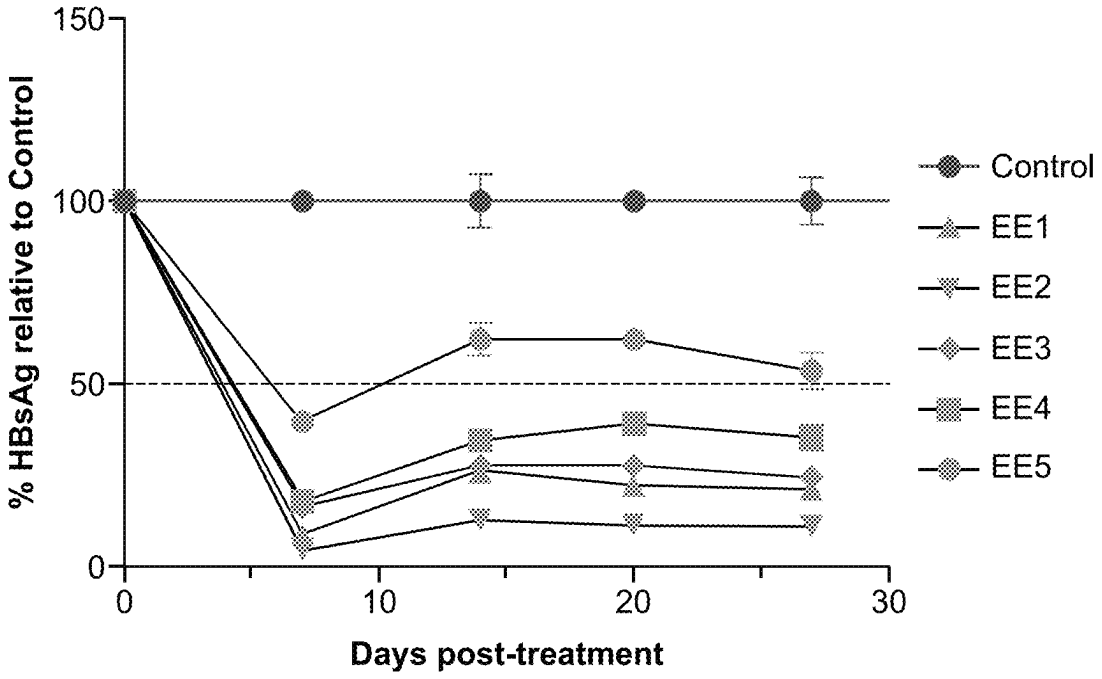

150
100
50
0
% HBsAg relative to Control
0
10
20
30
Days post-treatment
Control
EE1
EE2
EE3
EE4
EE5

FIGURE 23C

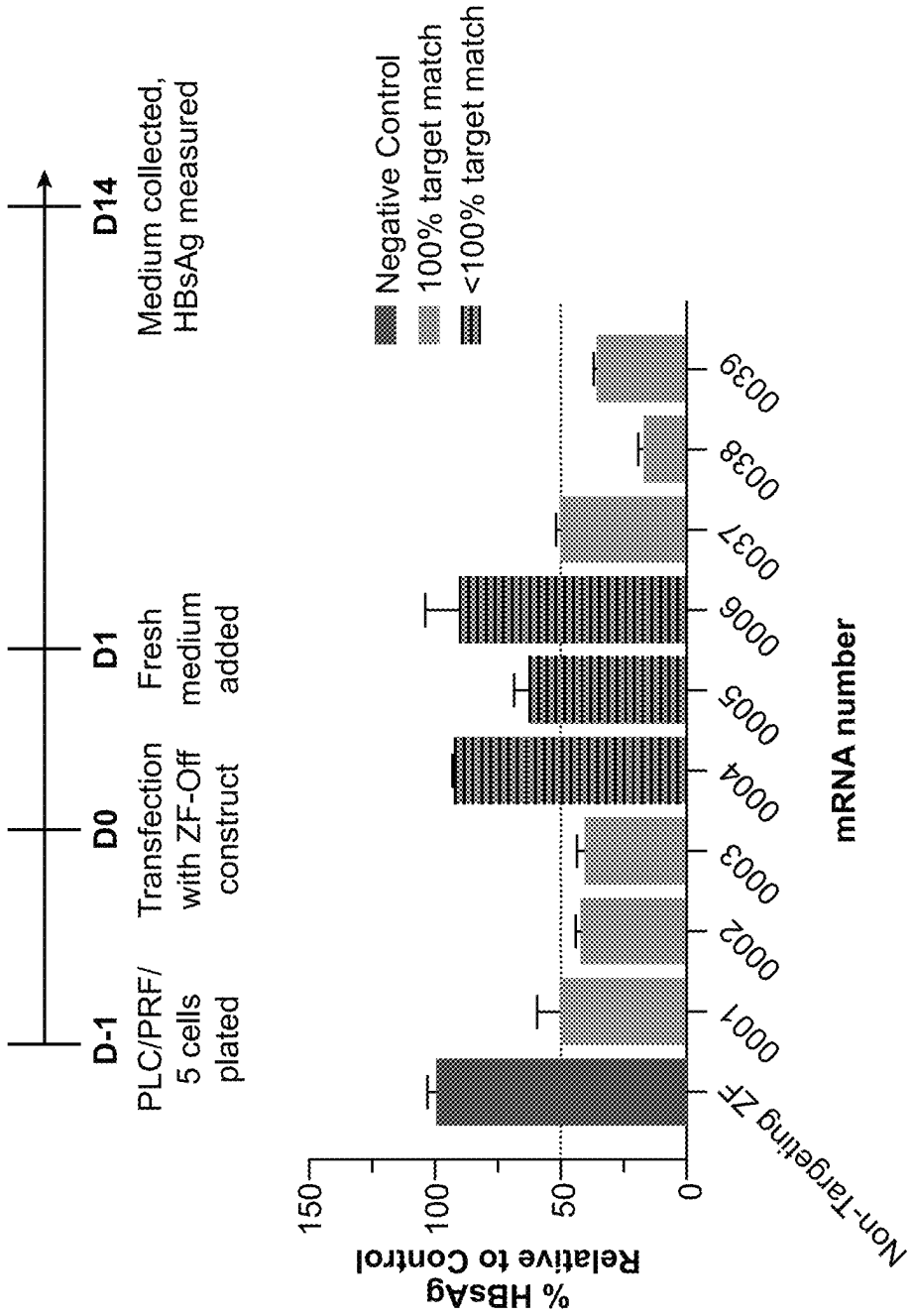

D-1
PLC/PRF/
5 cells
plated
D0
Transfection
with ZF-Off
construct
D1
Fresh
medium
added
D14
Medium collected,
HBsAg measured
Negative Control
100% target match
<100% target match
% HBsAg
Relative to Control
150
100
50
0
Non-Targeting ZF
0001
0002
0003
0004
0005
0006
0037
0038
0039
mRNA number

FIGURE 24

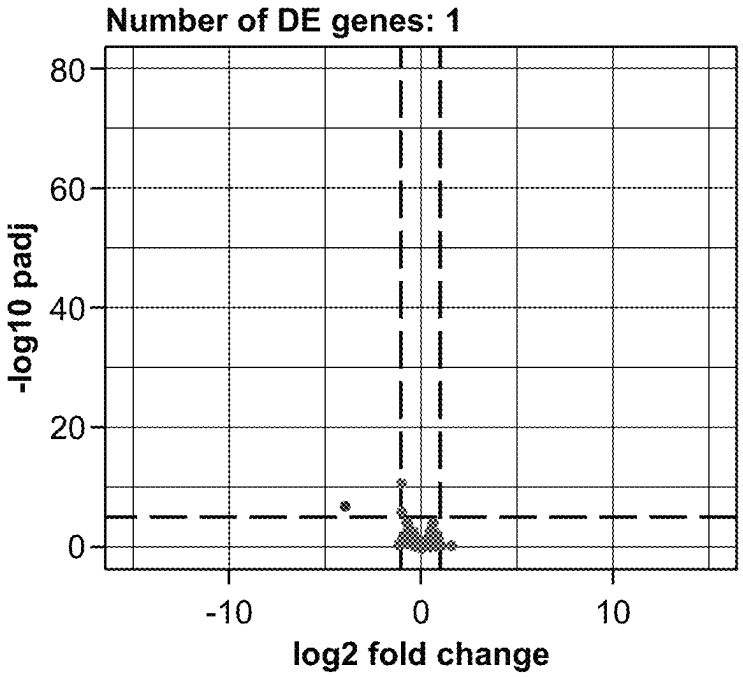

Number of DE genes: 1
80
60
40
20
0
-log10 padj
-10
0
10
log2 fold change

FIGURE 25A

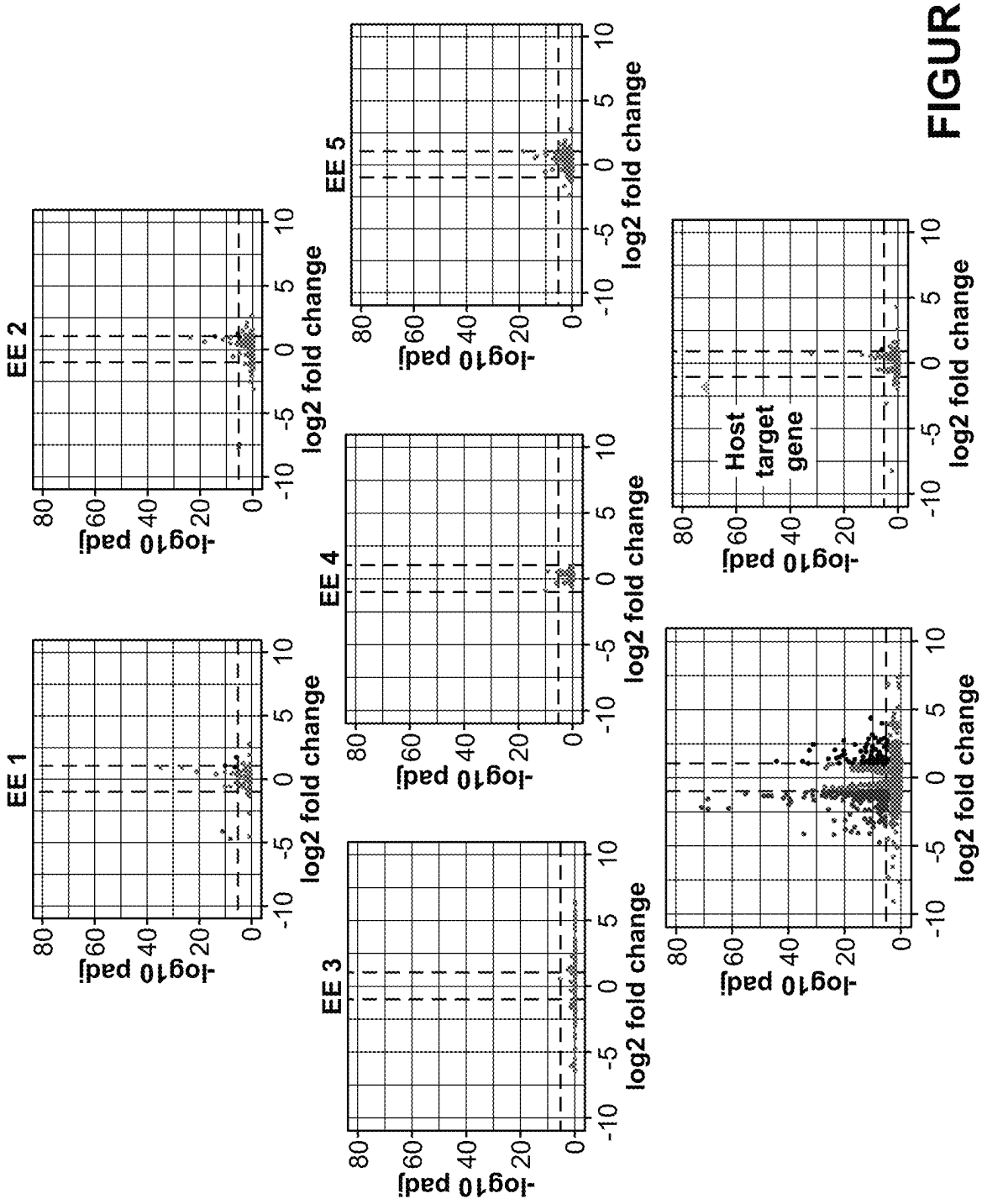

EE 1
EE 2
EE 3
EE 4
EE 5
Host target gene
-log10 padj
log2 fold change
80
60
40
20
0
-10
-5
0
5
10

FIGURE 25B

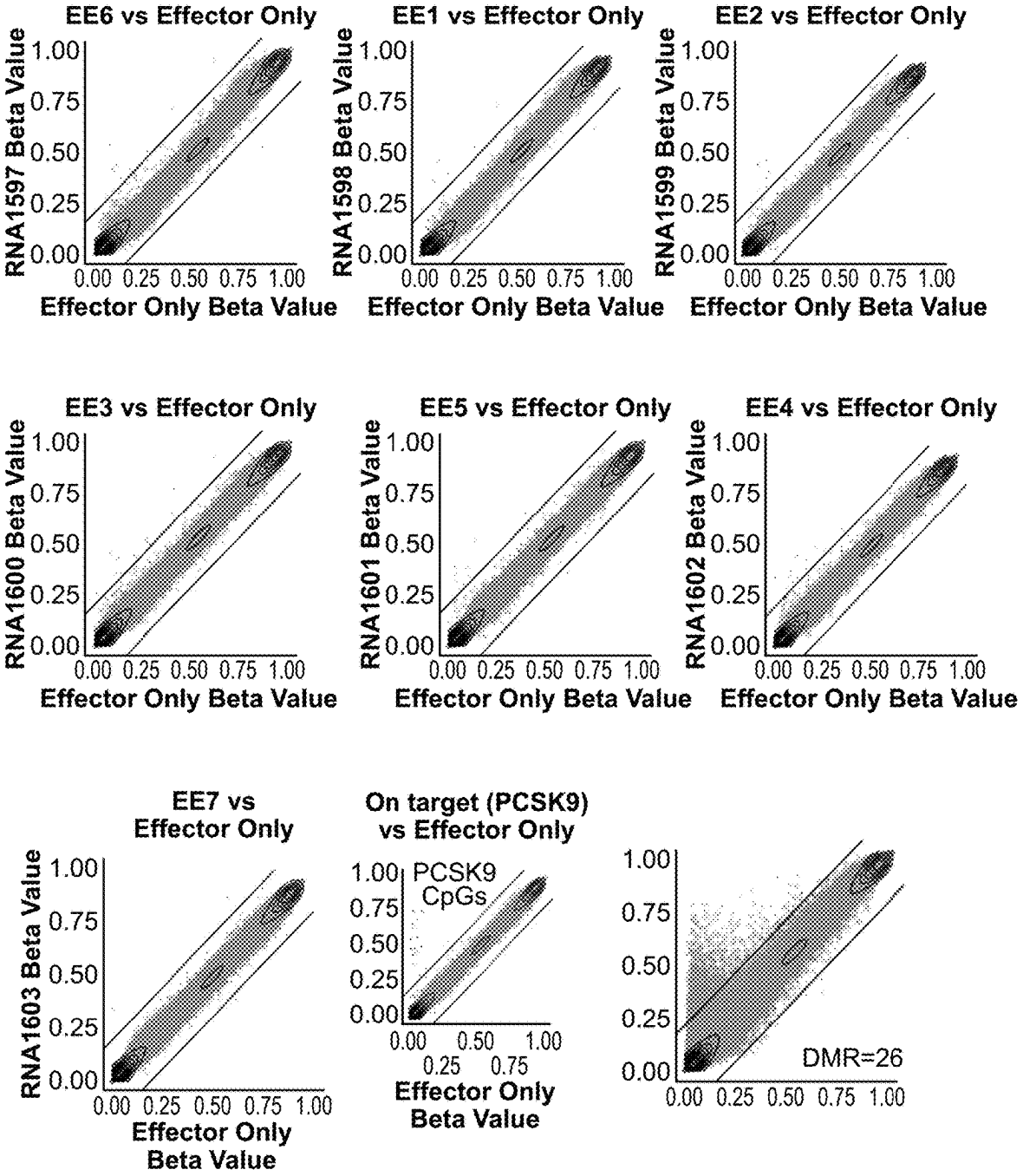

EE6 vs Effector Only
RNA1597 Beta Value
EE1 vs Effector Only
RNA1598 Beta Value
EE2 vs Effector Only
RNA1599 Beta Value
EE3 vs Effector Only
RNA1600 Beta Value
EE5 vs Effector Only
RNA1601 Beta Value
EE4 vs Effector Only
RNA1602 Beta Value
EE7 vs Effector Only
RNA1603 Beta Value
On target (PCSK9) vs Effector Only
PCSK9 CpGs
DMR=26
0.00 0.25 0.50 0.75 1.00
Effector Only Beta Value

FIGURE 25C

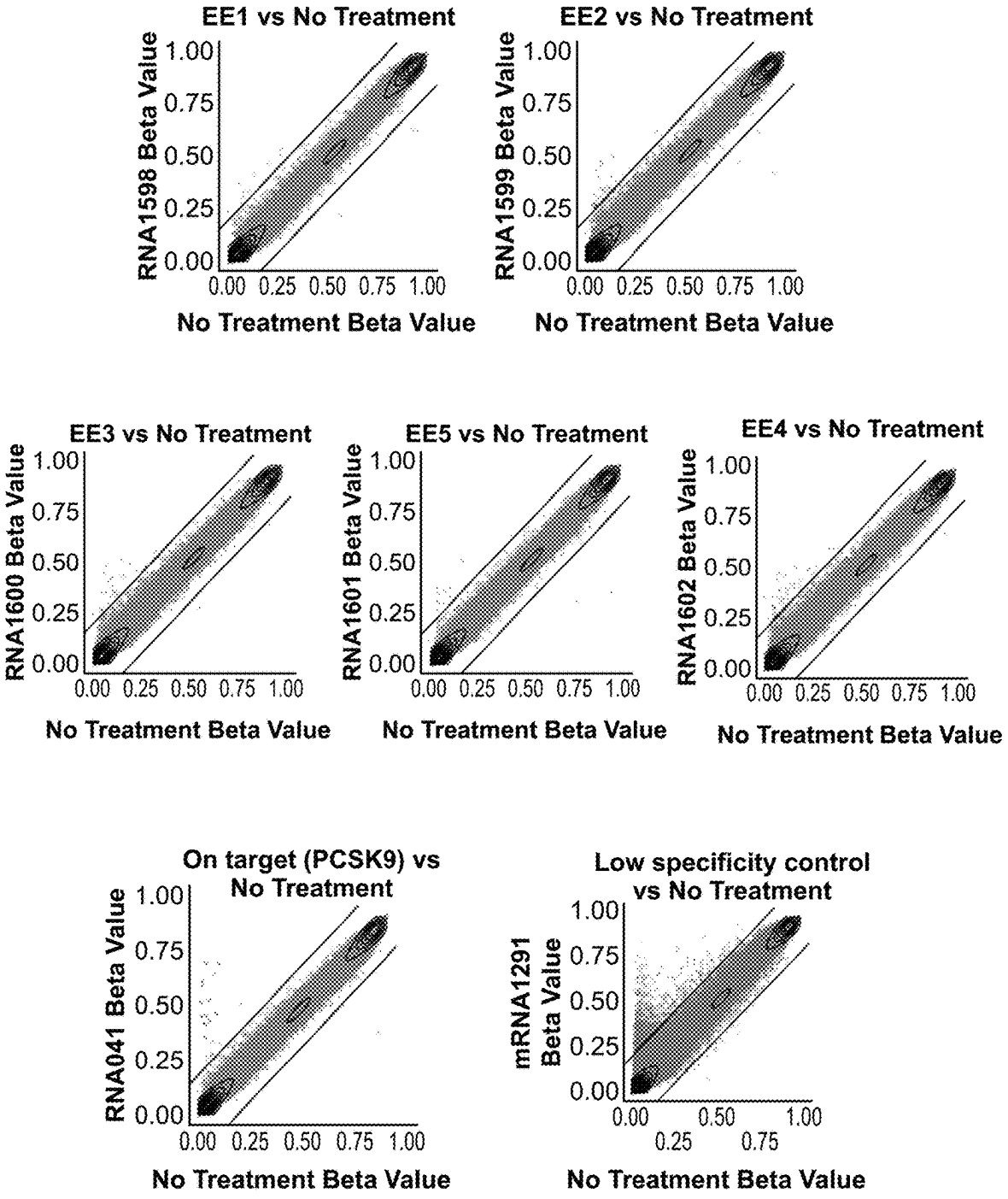

EE1 vs No Treatment
RNA1598 Beta Value
1.00
0.75
0.50
0.25
0.00
0.00 0.25 0.50 0.75 1.00
No Treatment Beta Value
EE2 vs No Treatment
RNA1599 Beta Value
1.00
0.75
0.50
0.25
0.00
0.00 0.25 0.50 0.75 1.00
No Treatment Beta Value
EE3 vs No Treatment
RNA1600 Beta Value
1.00
0.75
0.50
0.25
0.00
0.00 0.25 0.50 0.75 1.00
No Treatment Beta Value
EE5 vs No Treatment
RNA1601 Beta Value
1.00
0.75
0.50
0.25
0.00
0.00 0.25 0.50 0.75 1.00
No Treatment Beta Value
EE4 vs No Treatment
RNA1602 Beta Value
1.00
0.75
0.50
0.25
0.00
0.00 0.25 0.50 0.75 1.00
No Treatment Beta Value
On target (PCSK9) vs
No Treatment
RNA041 Beta Value
1.00
0.75
0.50
0.25
0.00
0.00 0.25 0.50 0.75 1.00
No Treatment Beta Value
Low specificity control
vs No Treatment
mRNA1291
Beta Value
1.00
0.75
0.50
0.25
0.00
0.00 0.50 1.00
0.25 0.75
No Treatment Beta Value

FIGURE 25D

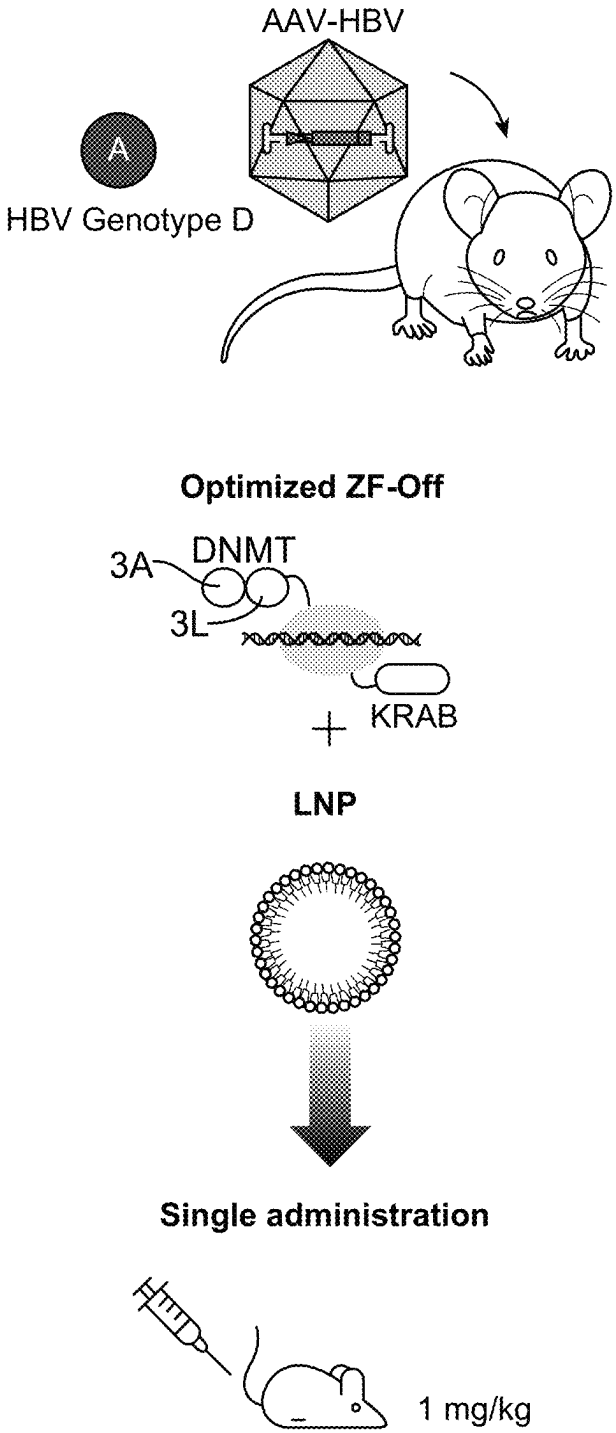

AAV-HBV
A
HBV Genotype D
Optimized ZF-Off
3A
DNMT
3L
KRAB
+
LNP
Single administration
1 mg/kg

FIGURE 26

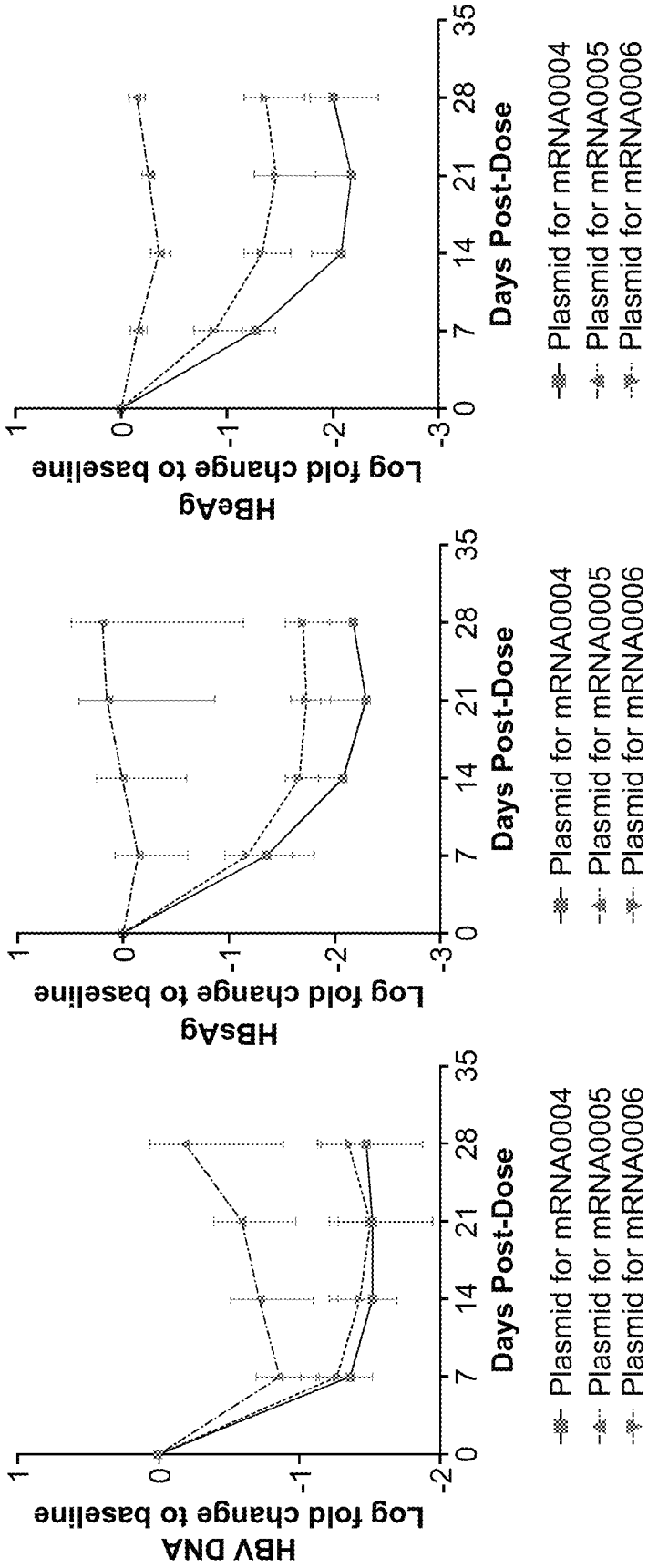

HBV DNA
Log fold change to baseline
1
0
-1
-2
0
7
14
21
28
35
Days Post-Dose
Plasmid for mRNA0004
Plasmid for mRNA0005
Plasmid for mRNA0006
HBsAg
Log fold change to baseline
1
0
-1
-2
-3
0
7
14
21
28
35
Days Post-Dose
Plasmid for mRNA0004
Plasmid for mRNA0005
Plasmid for mRNA0006
HBeAg
Log fold change to baseline
1
0
-1
-2
-3
0
7
14
21
28
35
Days Post-Dose
Plasmid for mRNA0004
Plasmid for mRNA0005
Plasmid for mRNA0006

FIGURE 27

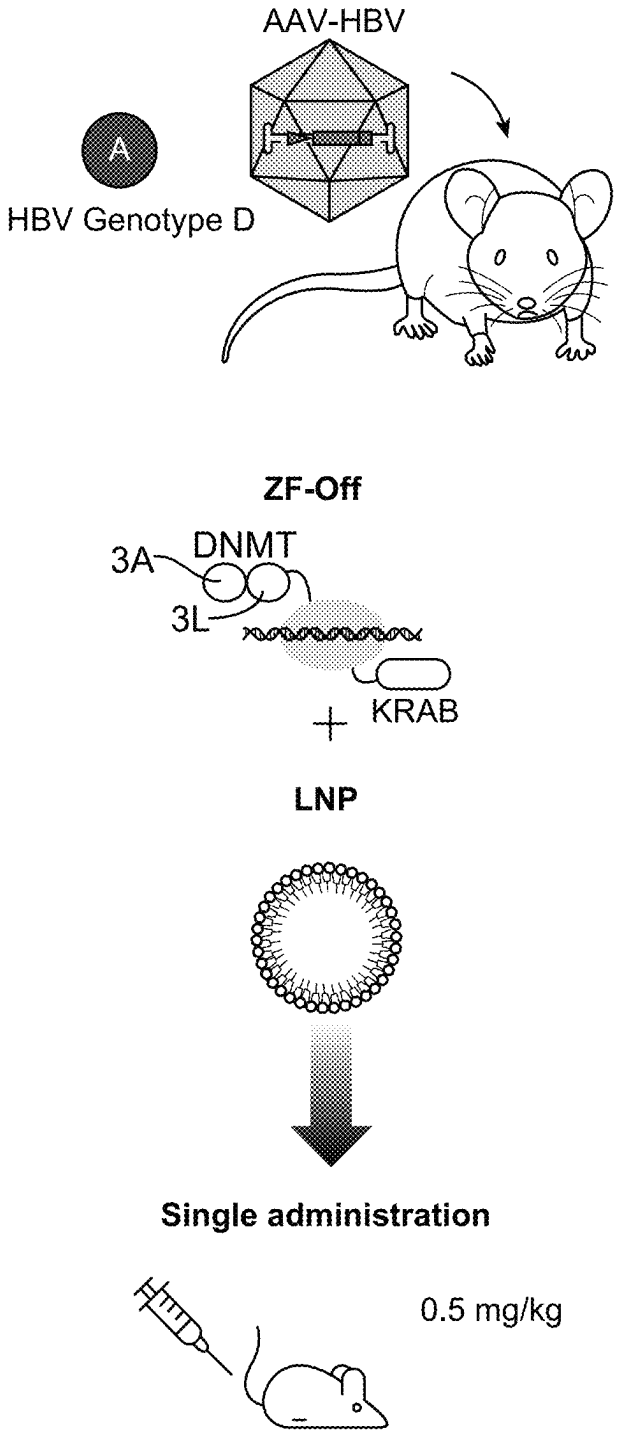

AAV-HBV
A
HBV Genotype D
ZF-Off
3A
DNMT
3L
KRAB
LNP
Single administration
0.5 mg/kg

FIGURE 28

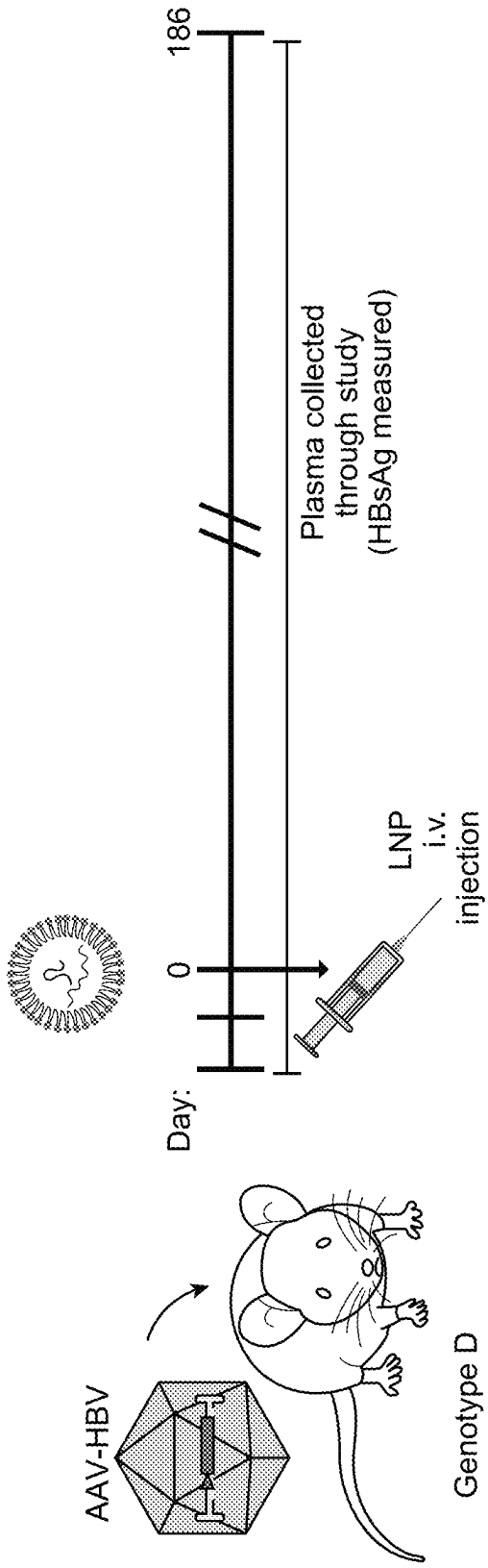

AAV-HBV
Genotype D
Day:
0
186
LNP
i.v.
injection
Plasma collected
through study
(HBsAg measured)

FIGURE 29

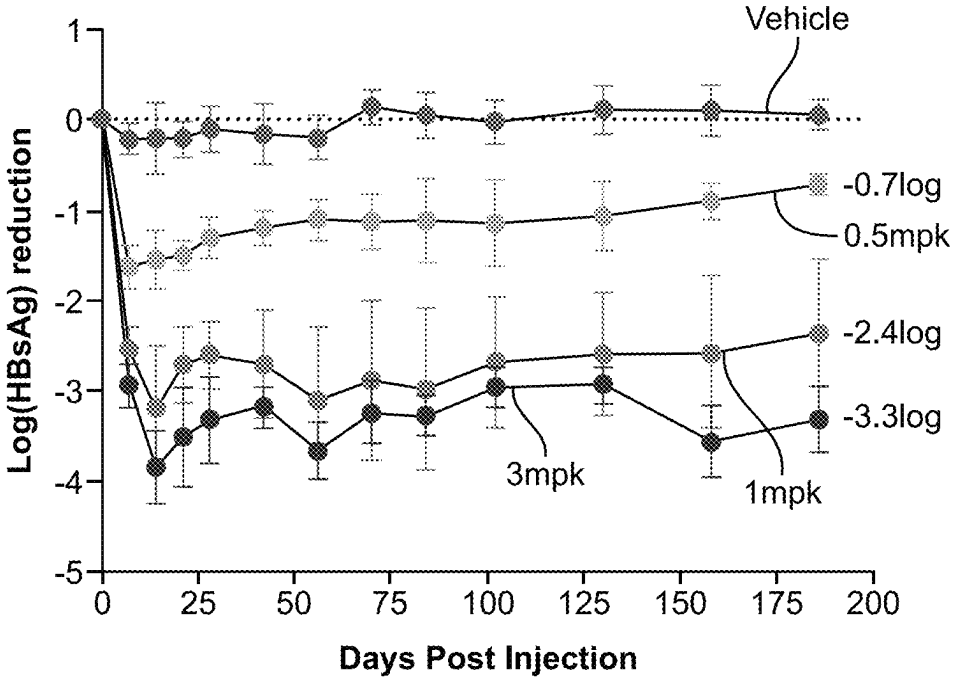

Vehicle
-0.7log
0.5mpk
-2.4log
-3.3log
3mpk
1mpk
Log(HBsAg) reduction
1
0
-1
-2
-3
-4
-5
0
25
50
75
100
125
150
175
200
Days Post Injection

FIGURE 30

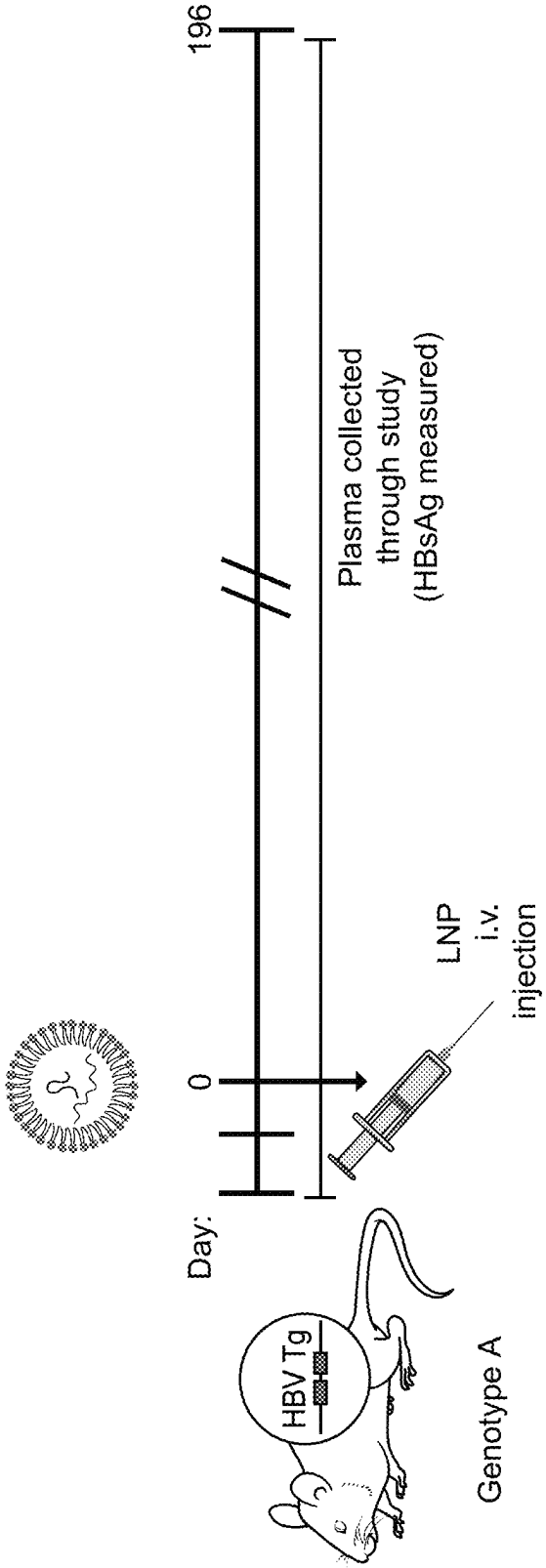

Day:
0
196
HBV Tg
Genotype A
LNP
i.v.
injection
Plasma collected
through study
(HBsAg measured)

FIGURE 31

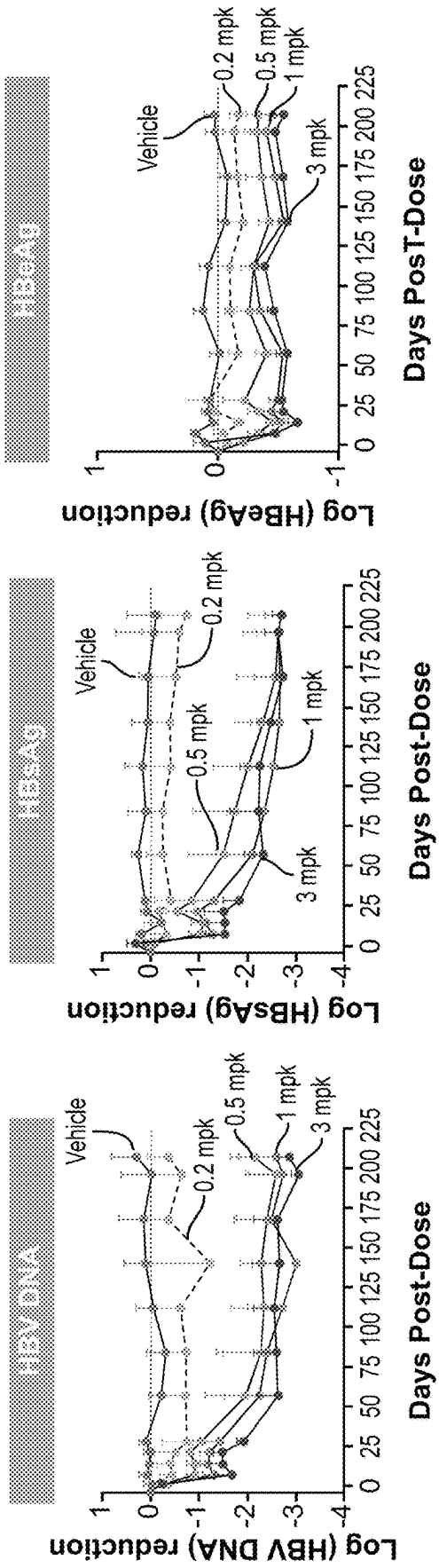

HBV DNA
Log (HBV DNA) reduction
Days Post-Dose
Vehicle
0.2 mpk
0.5 mpk
1 mpk
3 mpk
HBsAg
Log (HBsAg) reduction
Days Post-Dose
Vehicle
0.2 mpk
0.5 mpk
1 mpk
3 mpk
HBeAg
Log (HBeAg) reduction
Days PosT-Dose
Vehicle
0.2 mpk
0.5 mpk
1 mpk
3 mpk

FIGURE 32

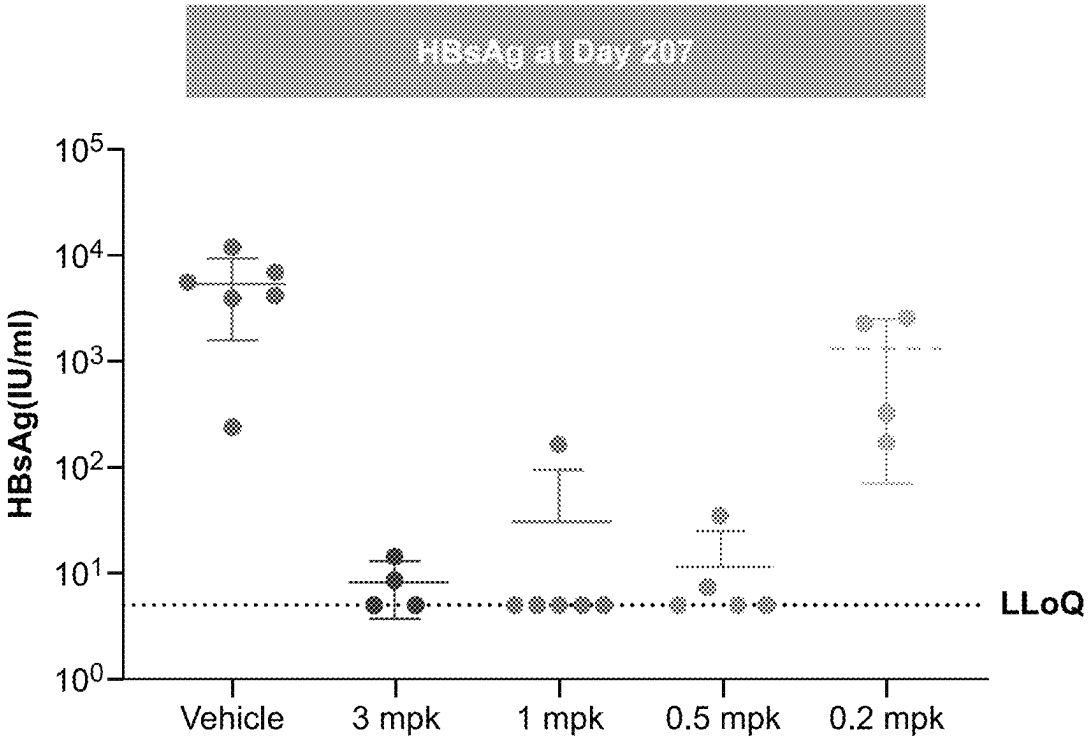
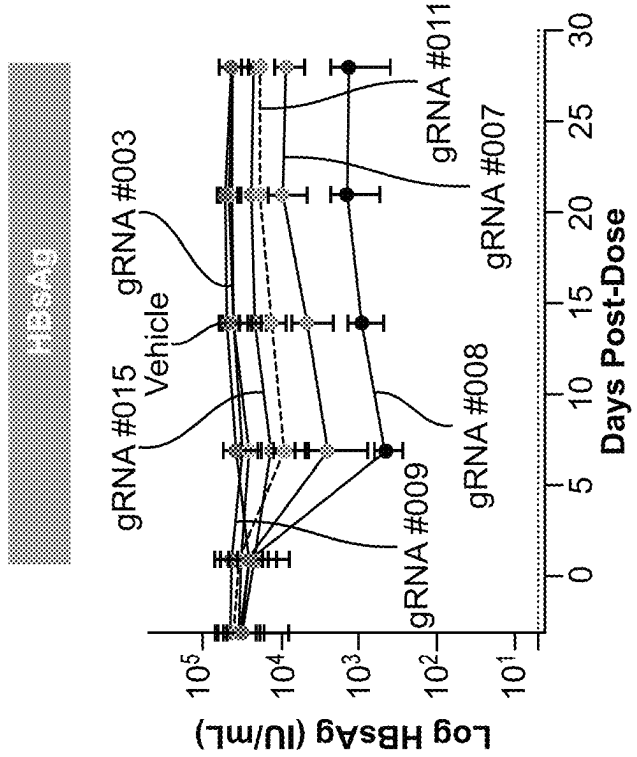

HBsAg at Day 207
HBsAg(IU/ml)
10^5
10^4
10^3
10^2
10^1
10^0
LLoQ
Vehicle
3 mpk
1 mpk
0.5 mpk
0.2 mpk

FIGURE 33


HBsAg
Log HBsAg (IU/mL)
10^5
10^4
10^3
10^2
10^1
0
5
10
15
20
25
30
Days Post-Dose
gRNA #015
Vehicle
gRNA #003
gRNA #009
gRNA #008
gRNA #007
gRNA #011

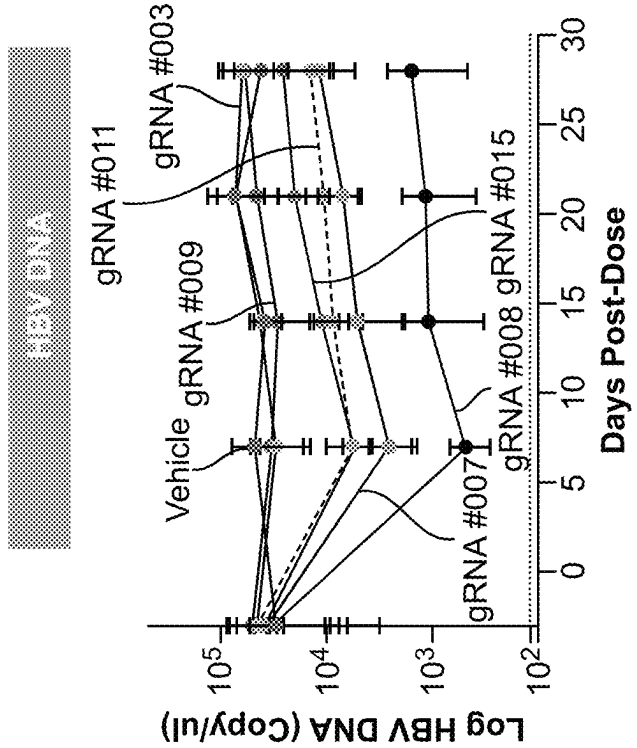
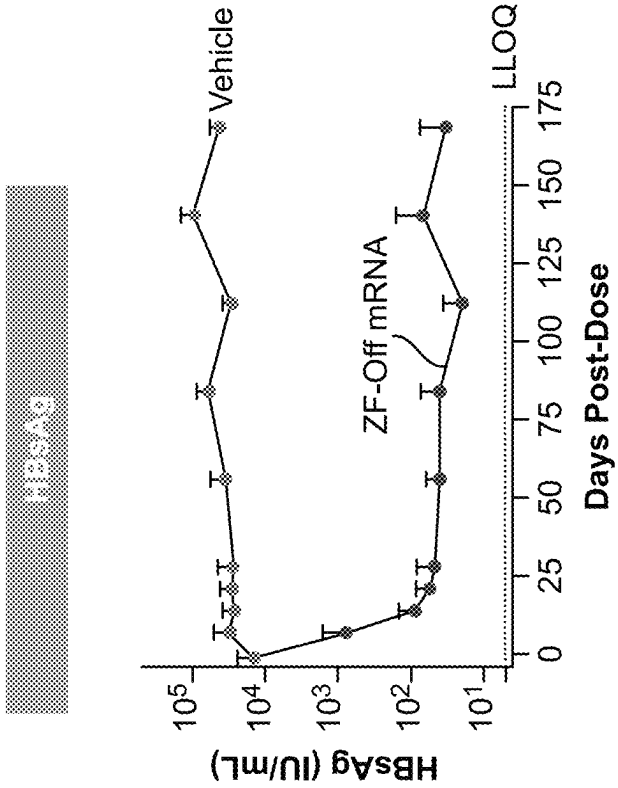

HBV DNA
Log HBV DNA (Copy/ul)
10^5
10^4
10^3
10^2
0
5
10
15
20
25
30
Days Post-Dose
Vehicle
gRNA #009
gRNA #011
gRNA #003
gRNA #007
gRNA #008
gRNA #015

FIGURE 34


HBsAg
HBsAg (IU/mL)
10^5
10^4
10^3
10^2
10^1
Vehicle
ZF-Off mRNA
LLOQ
0
25
50
75
100
125
150
175
Days Post-Dose

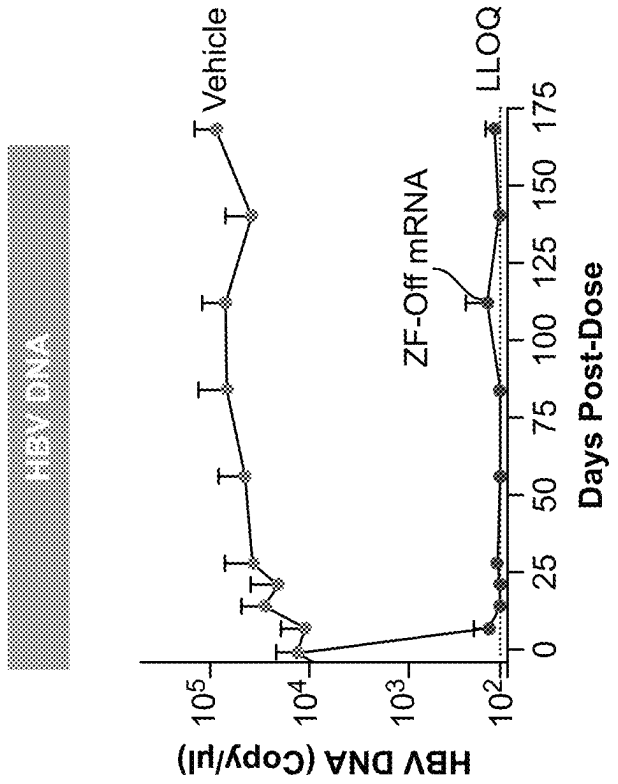

HBV DNA
HBV DNA (Copy/µl)
10^5
10^4
10^3
10^2
Vehicle
ZF-Off mRNA
LLOQ
0
25
50
75
100
125
150
175
Days Post-Dose

FIGURE 35A

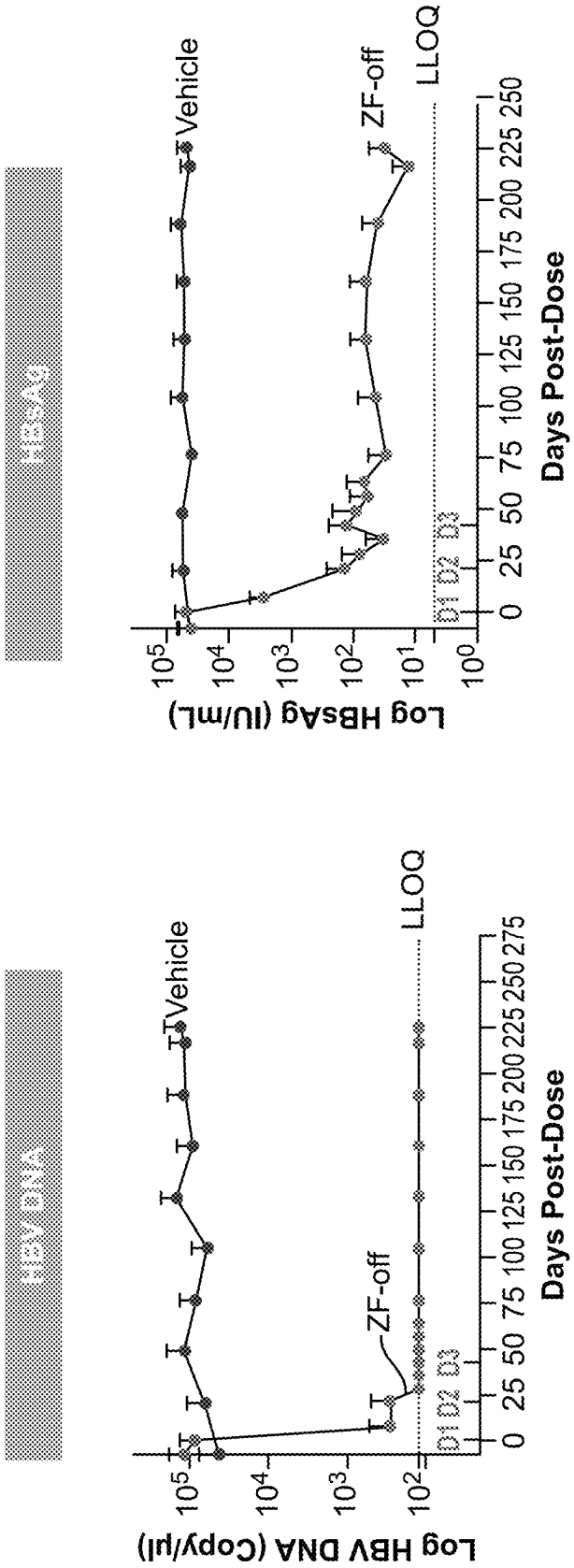
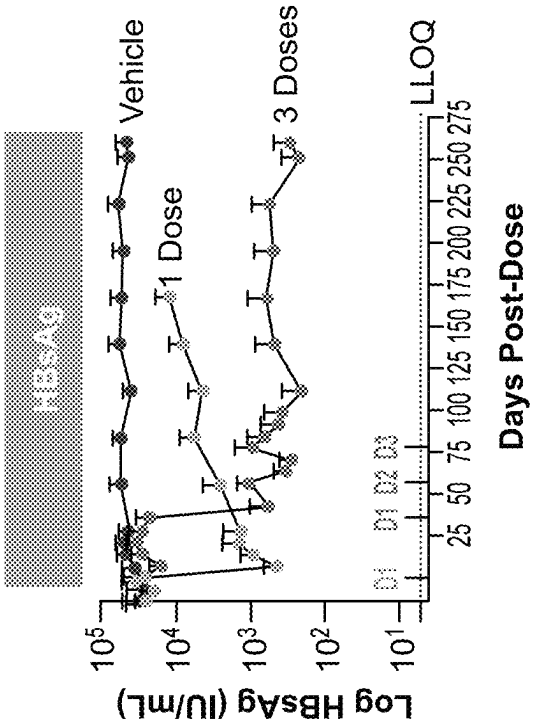
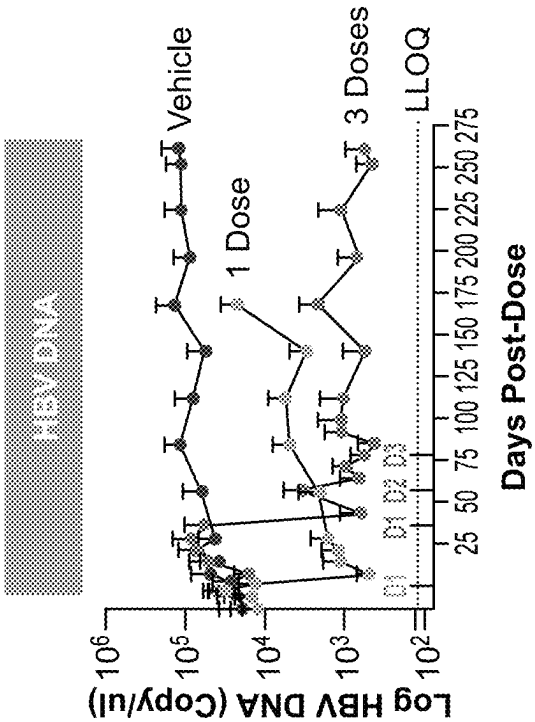

HBsAg
Log HBsAg (IU/mL)
Vehicle
ZF-off
LLOQ
D1 D2 D3
Days Post-Dose
HBV DNA
Log HBV DNA (Copy/µl)
Vehicle
ZF-off
LLOQ
D1 D2 D3
Days Post-Dose

FIGURE 35B


HBsAg
Log HBsAg (IU/mL)
Days Post-Dose
Vehicle
1 Dose
3 Doses
LLOQ
D1 D2 D3


HBV DNA
Log HBV DNA (Copy/ul)
Days Post-Dose
Vehicle
1 Dose
3 Doses
LLOQ
D1 D2 D3

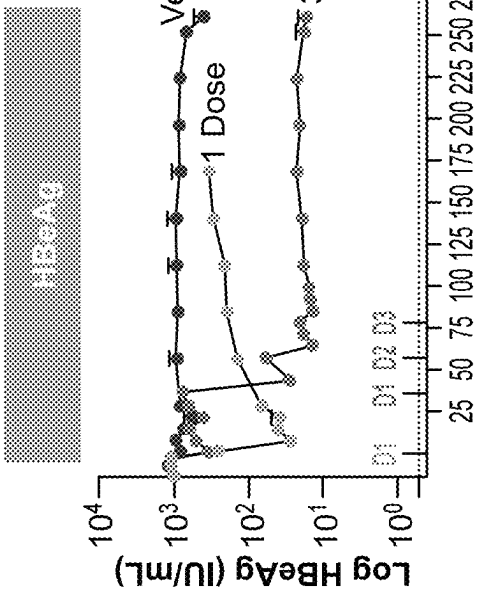
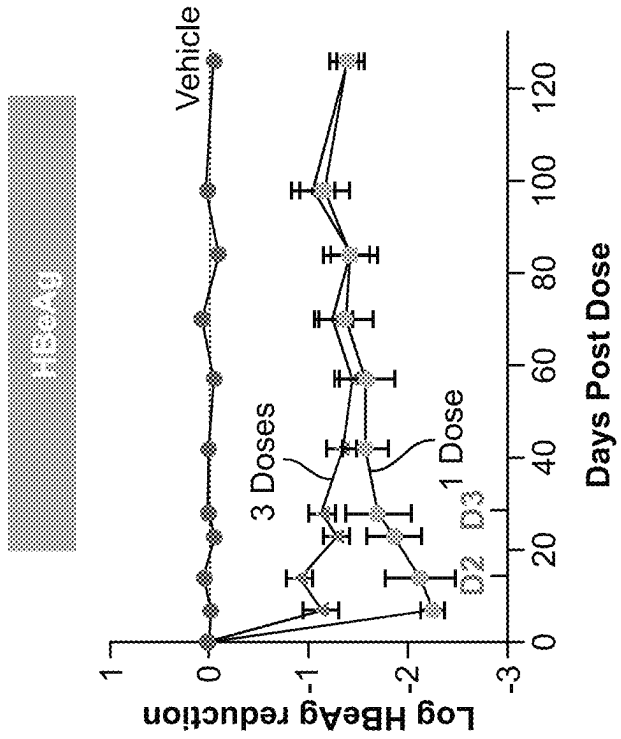

HBeAg
Log HBeAg (IU/mL)
Days Post-Dose
Vehicle
1 Dose
3 Doses
LLOQ
D1 D2 D3

FIGURE 36


HBeAg
Vehicle
3 Doses
1 Dose
D2
D3
Log HBeAg reduction
Days Post Dose
1
0
-1
-2
-3
0
20
40
60
80
100
120

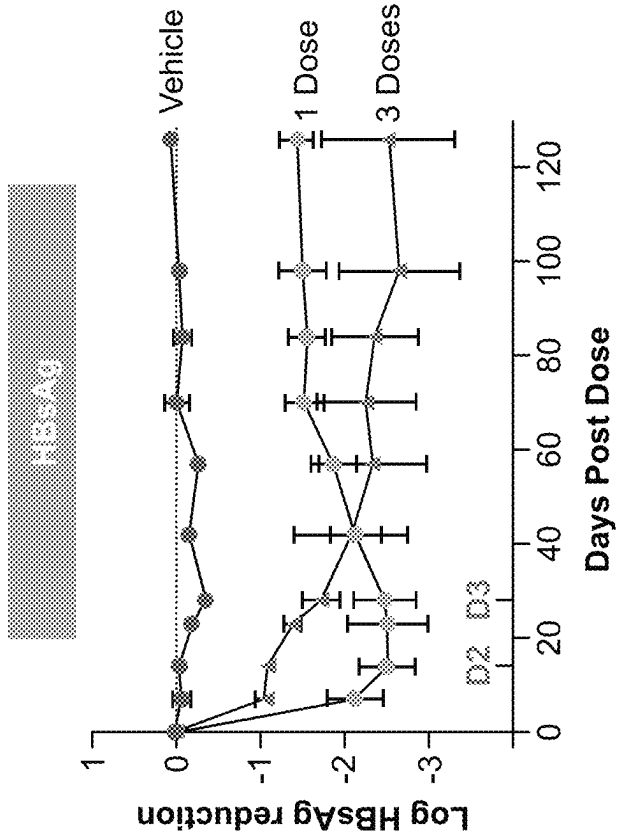

HBsAg
Vehicle
1 Dose
3 Doses
D2
D3
Log HBsAg reduction
Days Post Dose
1
0
-1
-2
-3
0
20
40
60
80
100
120

FIGURE 37

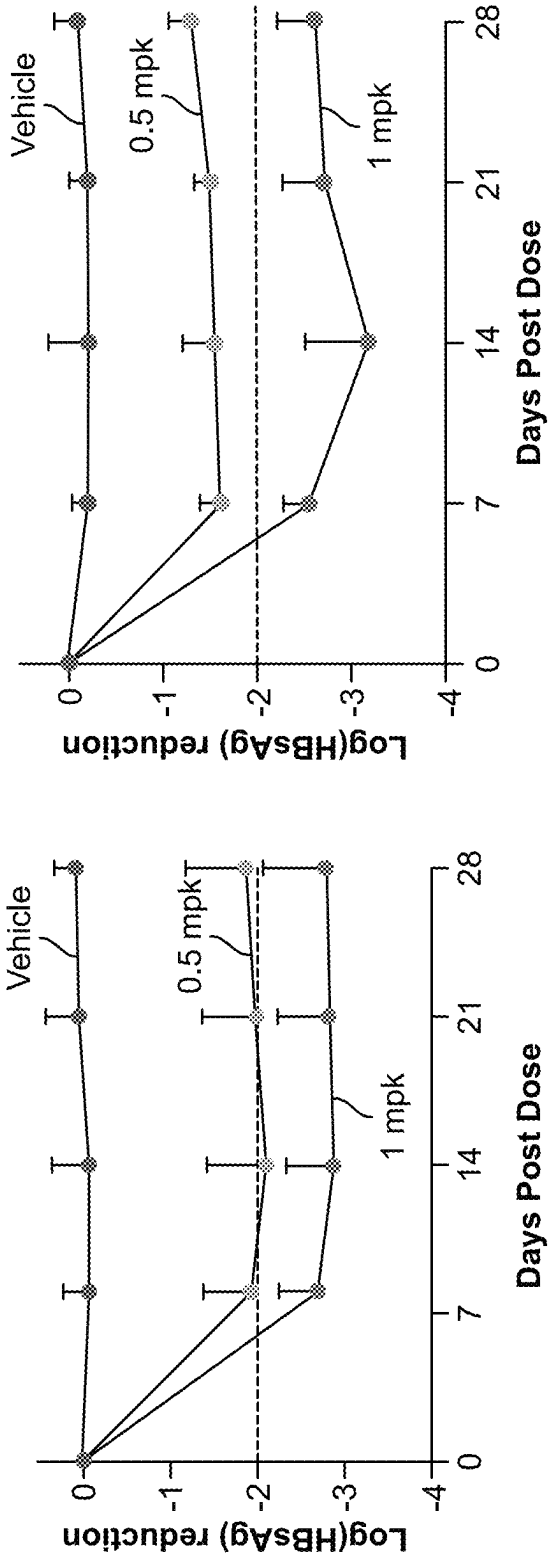

Vehicle
0.5 mpk
1 mpk
Log(HBsAg) reduction
0
-1
-2
-3
-4
0
7
14
21
28
Days Post Dose
Vehicle
0.5 mpk
1 mpk
Log(HBsAg) reduction
0
-1
-2
-3
-4
0
7
14
21
28
Days Post Dose

FIGURE 38

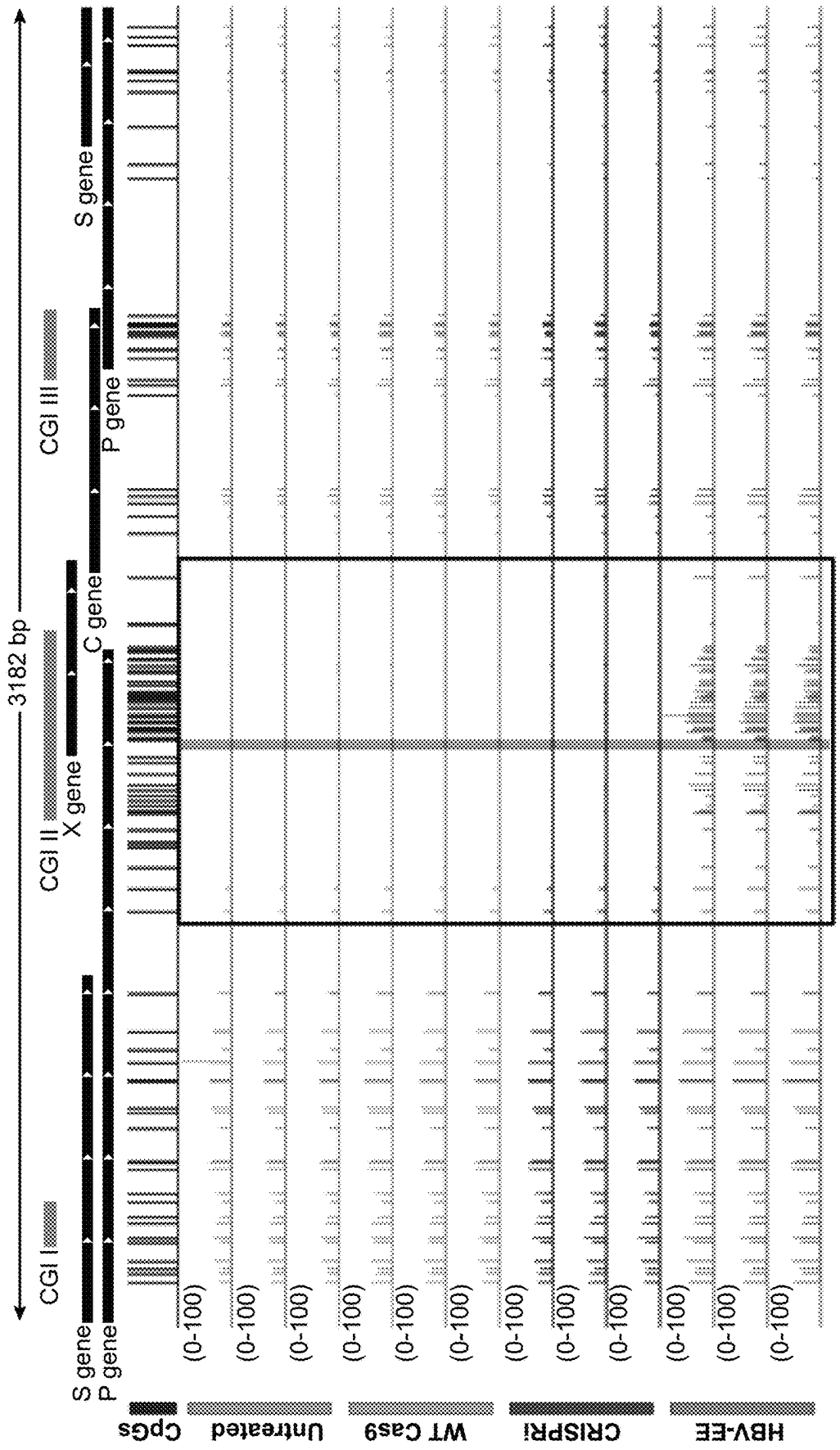

3182 bp
CGI I
CGI II
CGI III
S gene
P gene
X gene
C gene
S gene
P gene
(0-100)
CpGs
Untreated
WT Cas9
CRISPRi
HBV-EE

FIGURE 39A

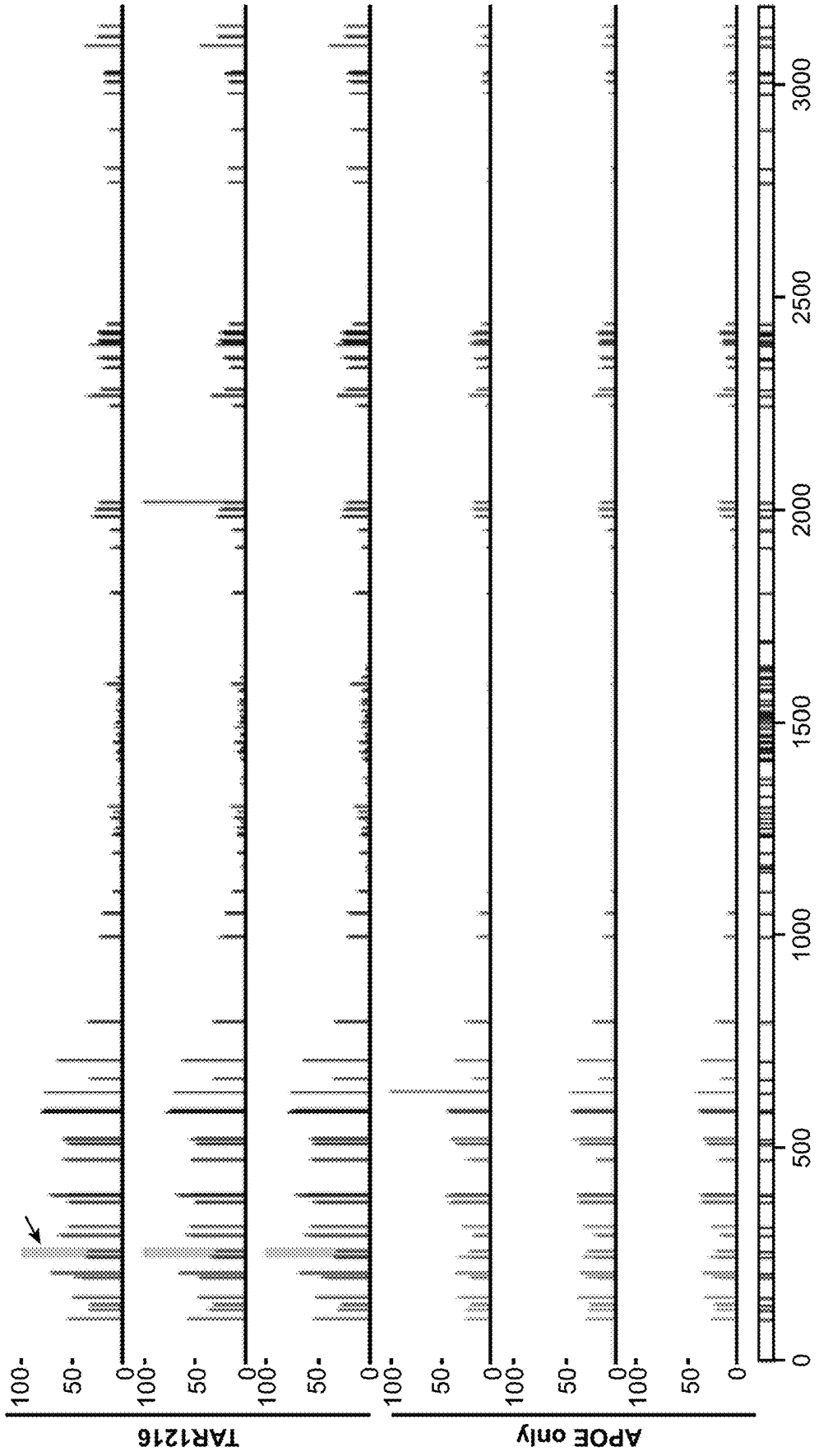


FIGURE 39B

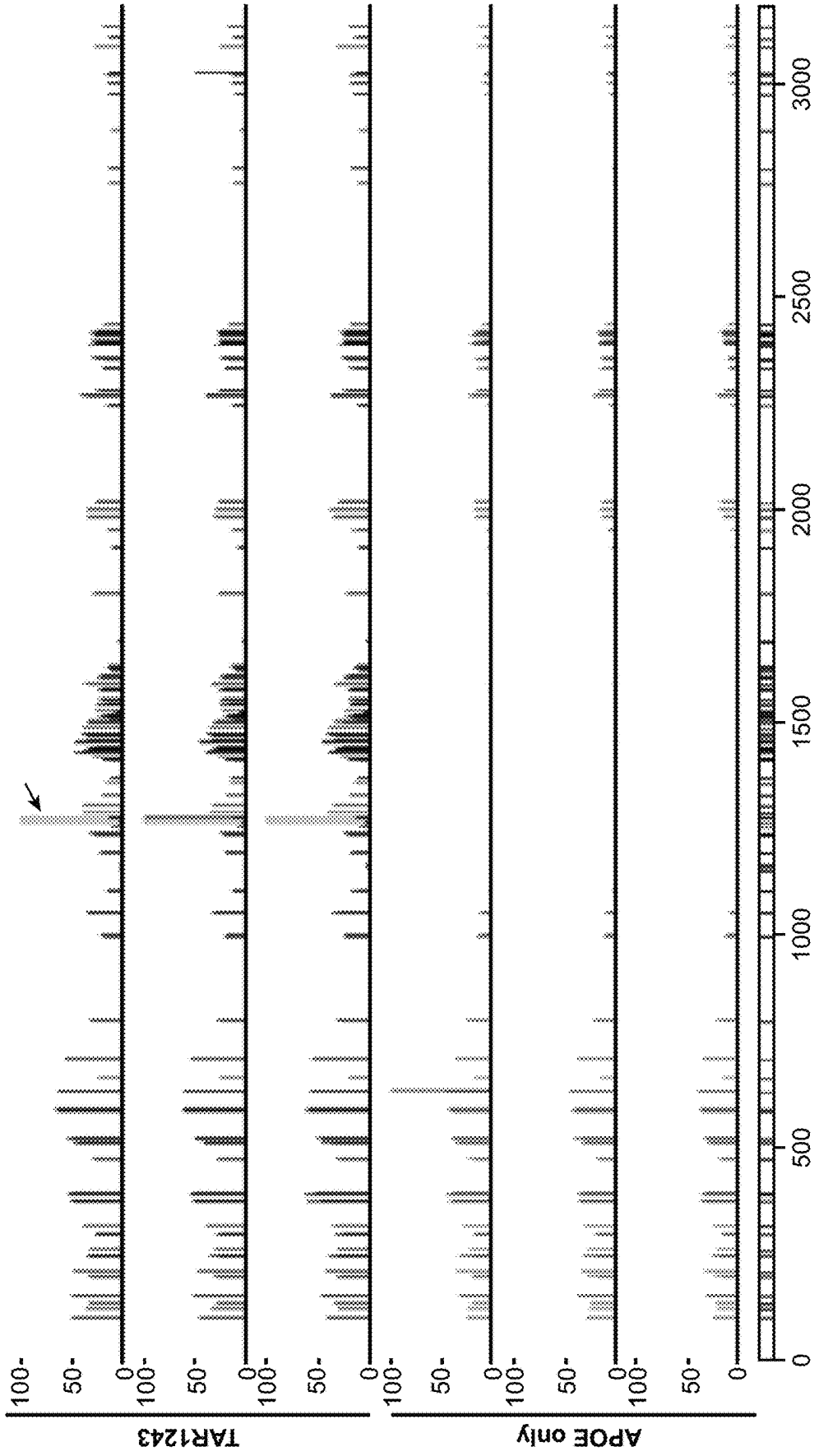


FIGURE 39C

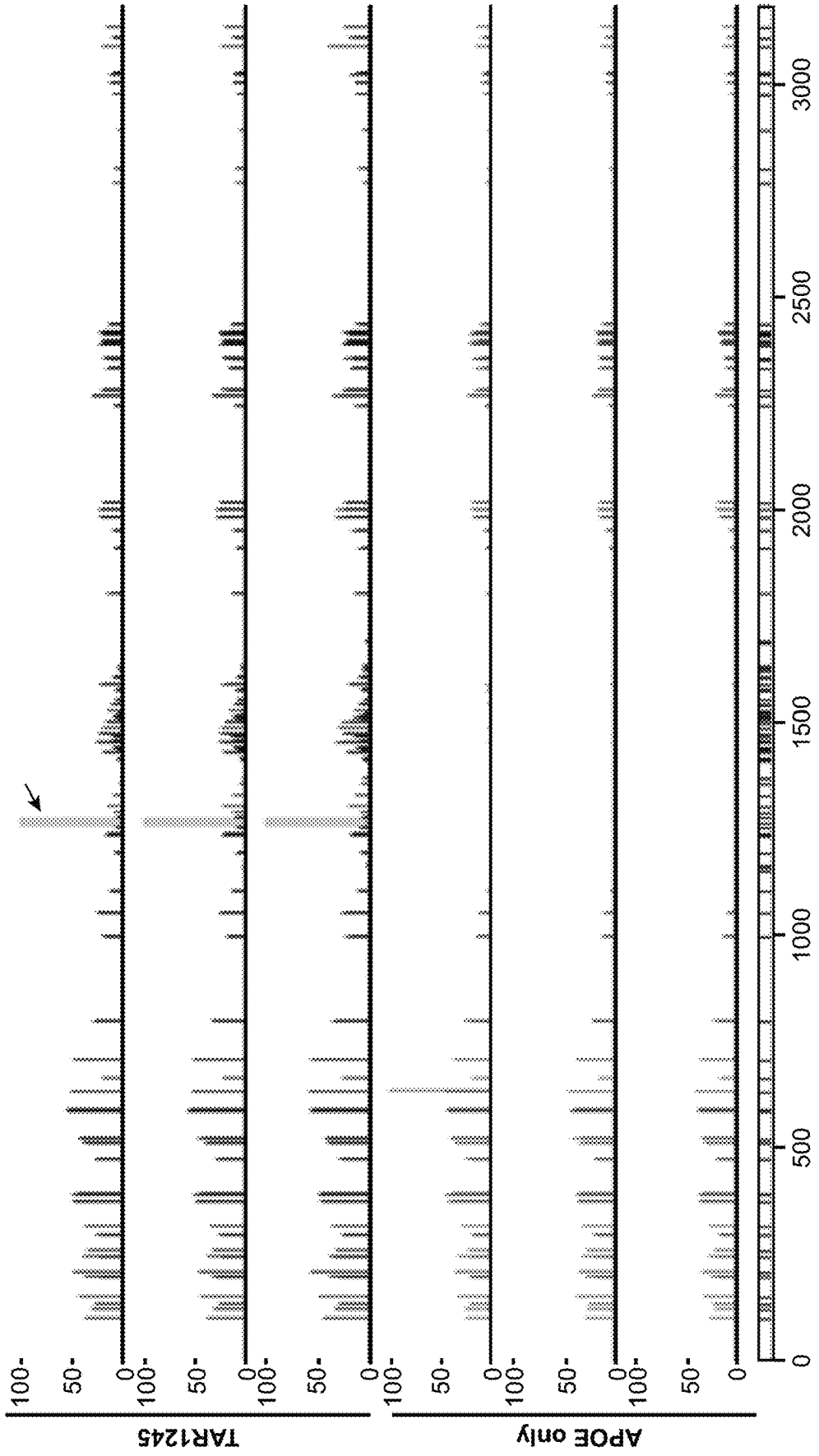


FIGURE 39D

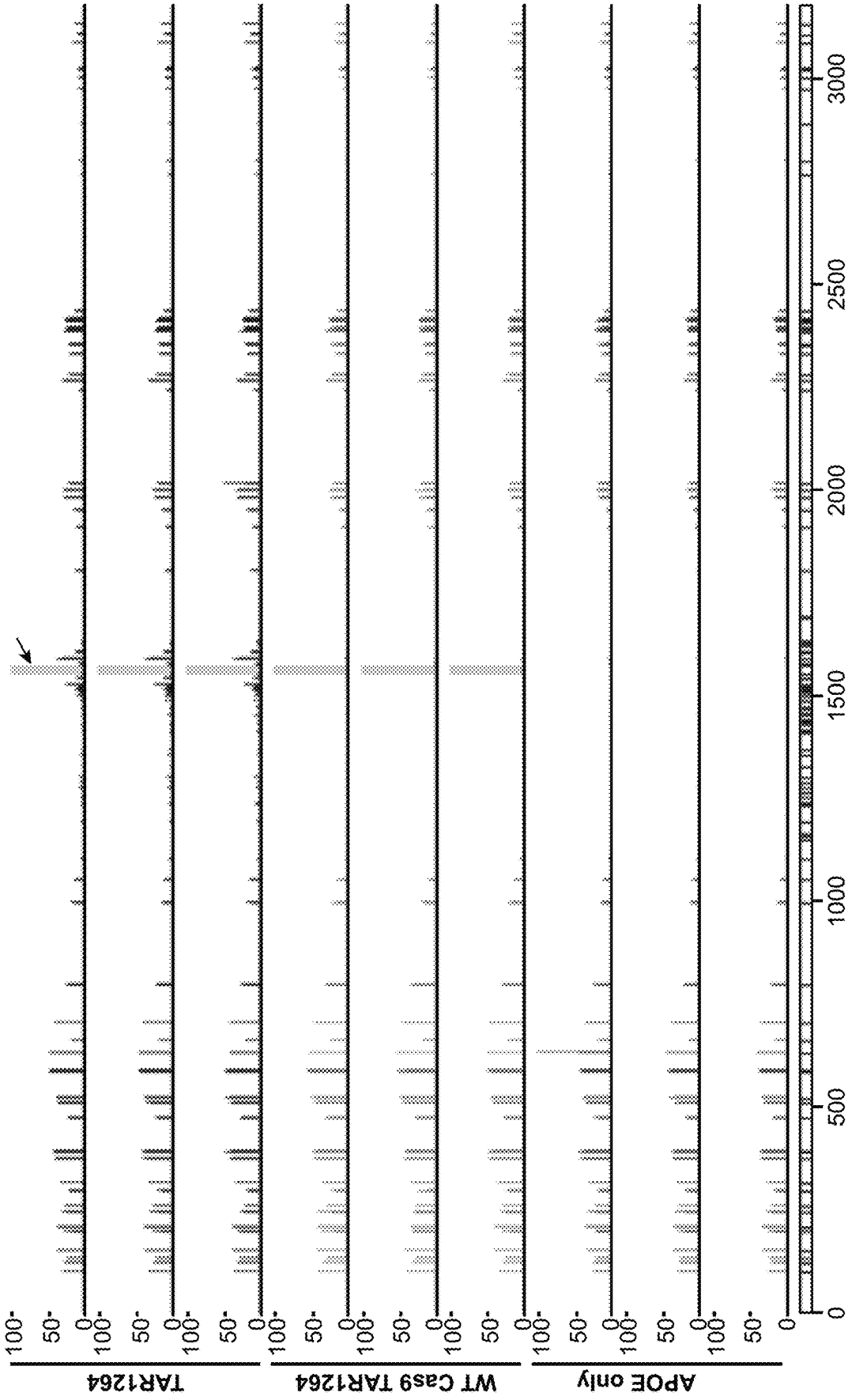

TAR1264
WT Cas9 TAR1264
APOE only
100
50
0
0
500
1000
1500
2000
2500
3000

FIGURE 39E

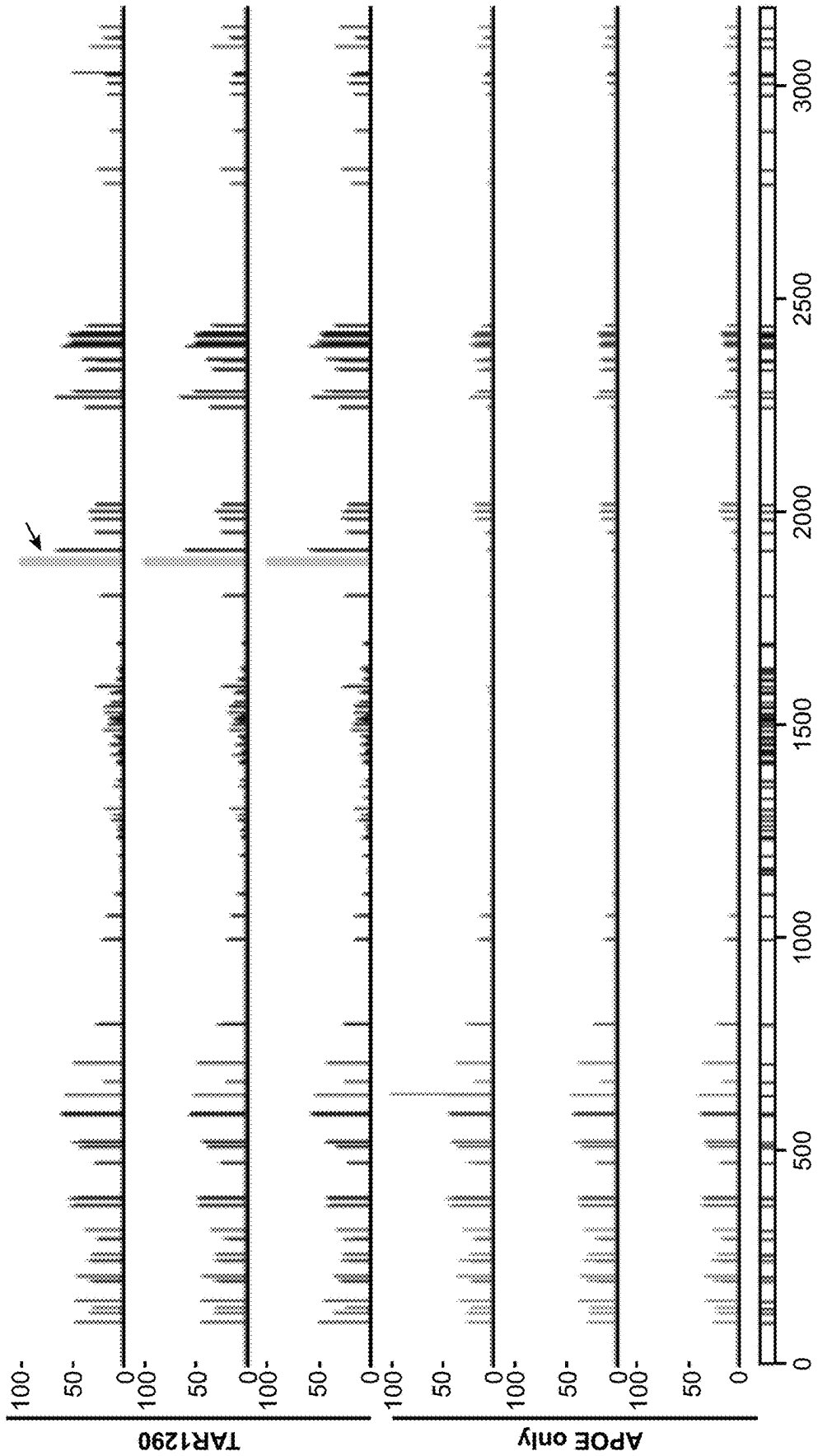


FIGURE 39F

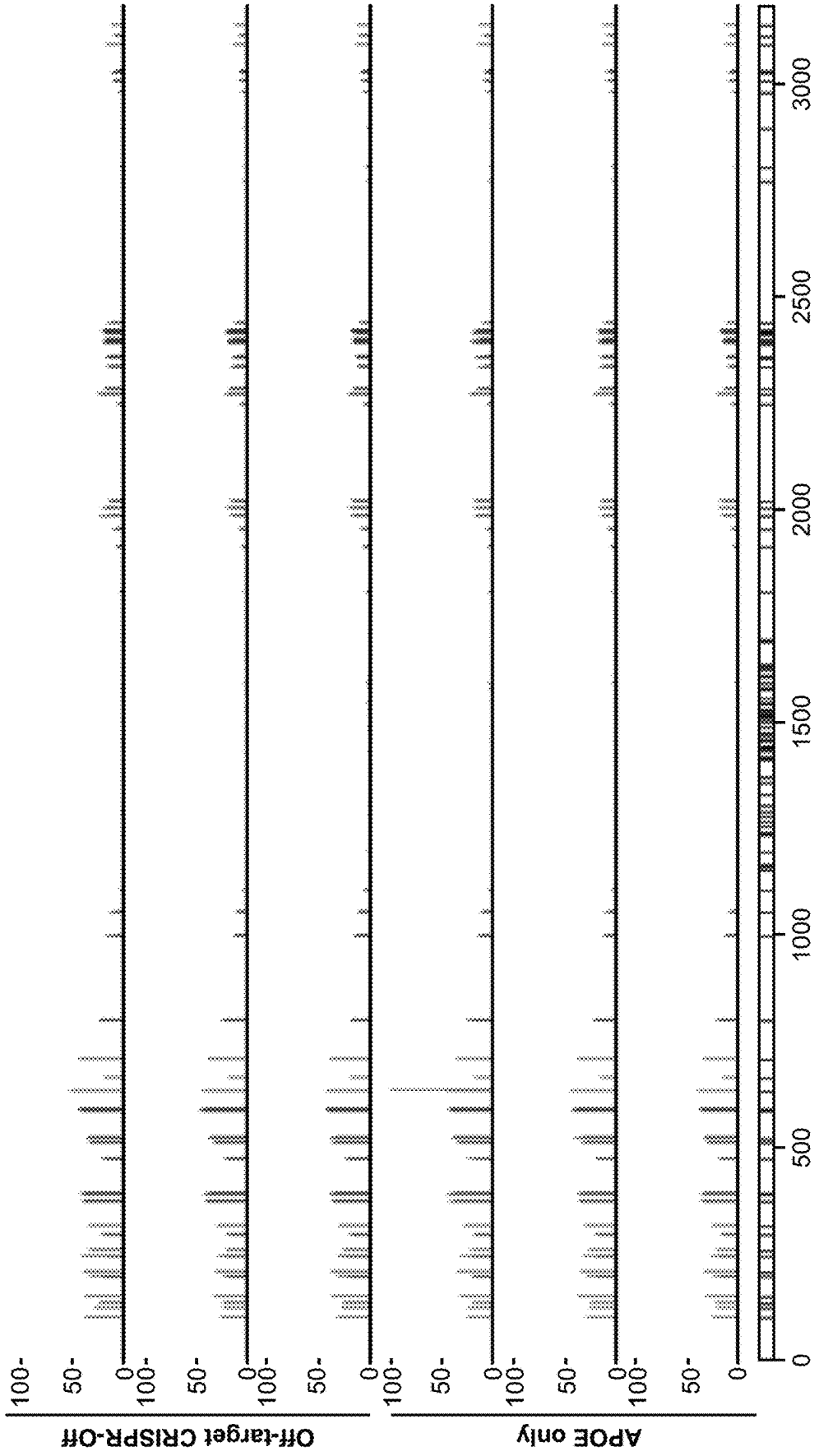

Off-target CRISPR-Off
APOE only
100
50
0
0
500
1000
1500
2000
2500
3000

FIGURE 39G

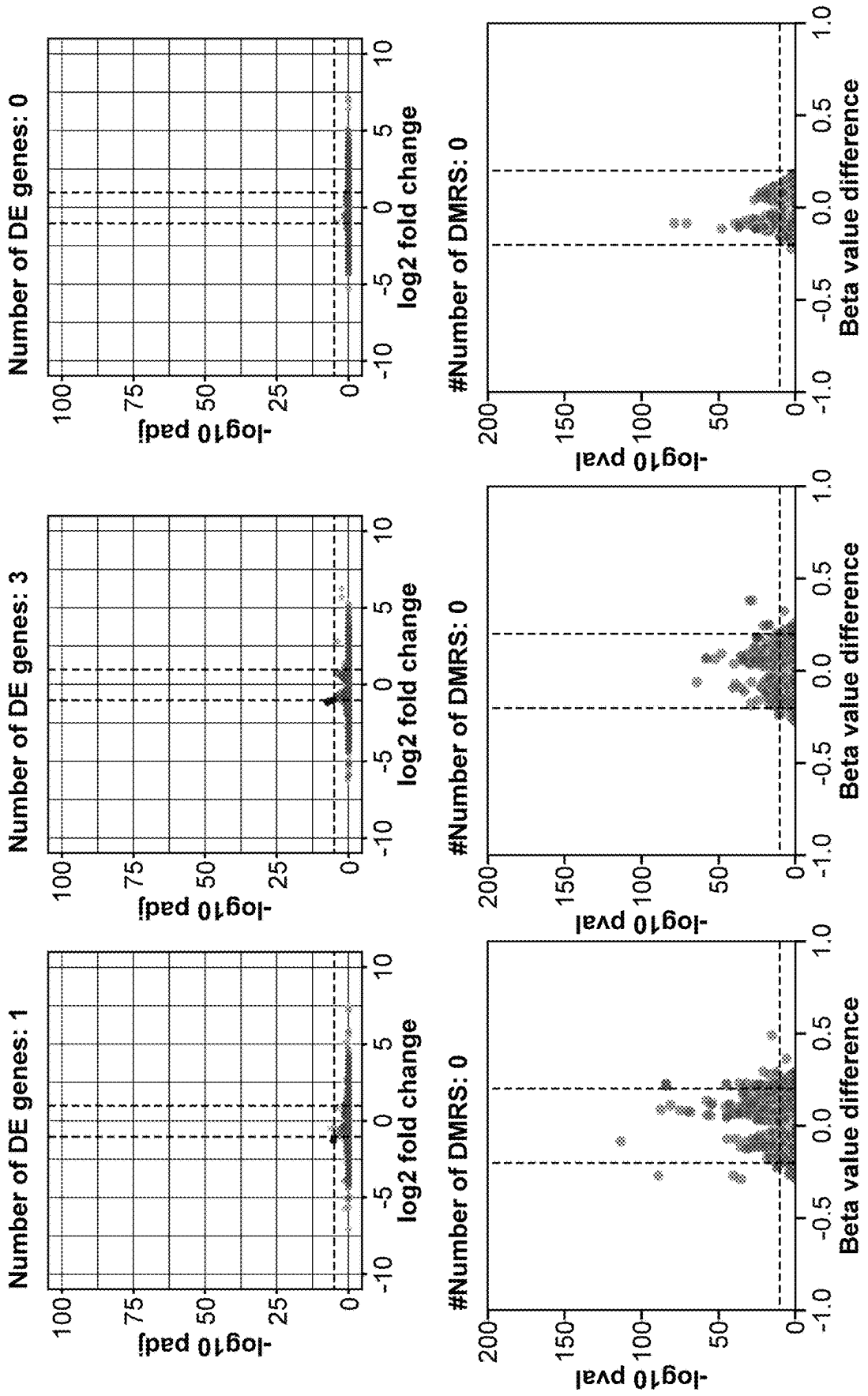

Number of DE genes: 1
Number of DE genes: 3
Number of DE genes: 0
-log10 padj
log2 fold change
#Number of DMRS: 0
-log10 pval
Beta value difference

FIGURE 40

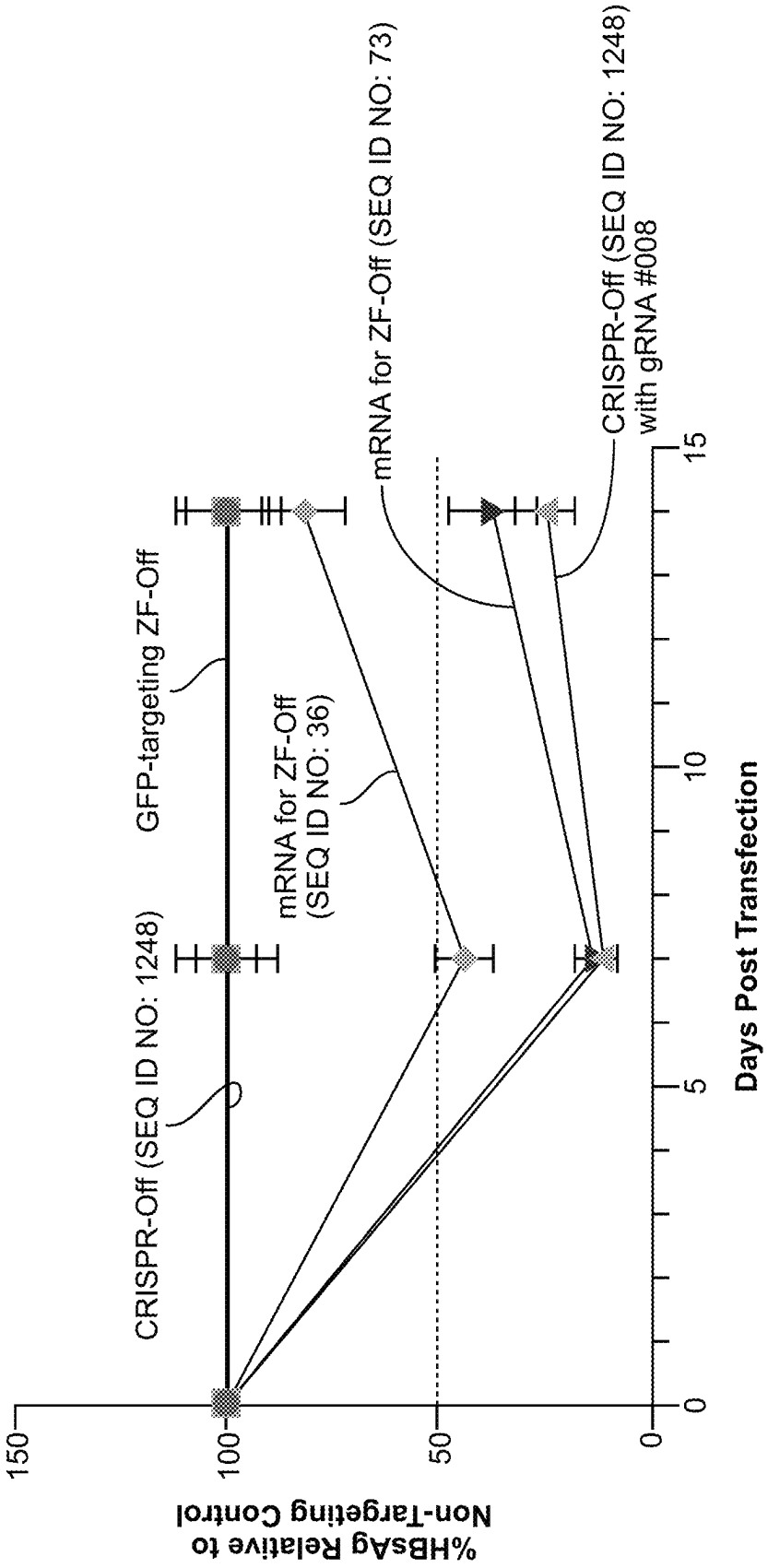
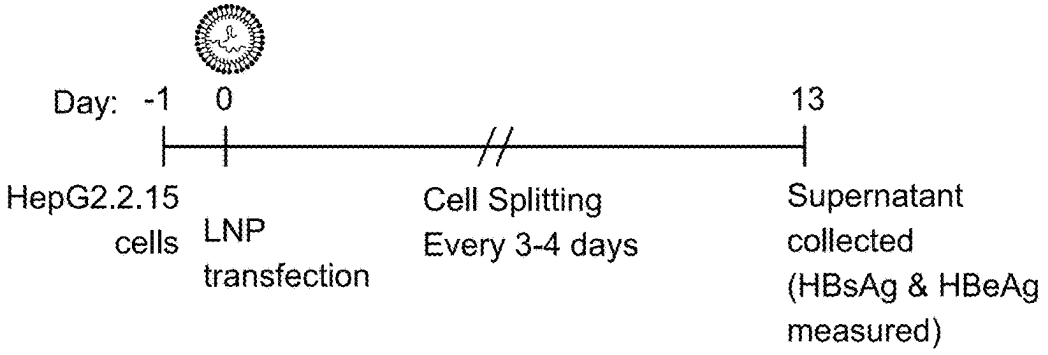

CRISPR-Off (SEQ ID NO: 1248)
GFP-targeting ZF-Off
mRNA for ZF-Off (SEQ ID NO: 36)
mRNA for ZF-Off (SEQ ID NO: 73)
CRISPR-Off (SEQ ID NO: 1248) with gRNA #008
%HBsAg Relative to Non-Targeting Control
150
100
50
0
0
5
10
15
Days Post Transfection

FIGURE 41


Day: -1
0
13
HepG2.2.15 cells
LNP transfection
Cell Splitting Every 3-4 days
Supernatant collected (HBsAg & HBeAg measured)

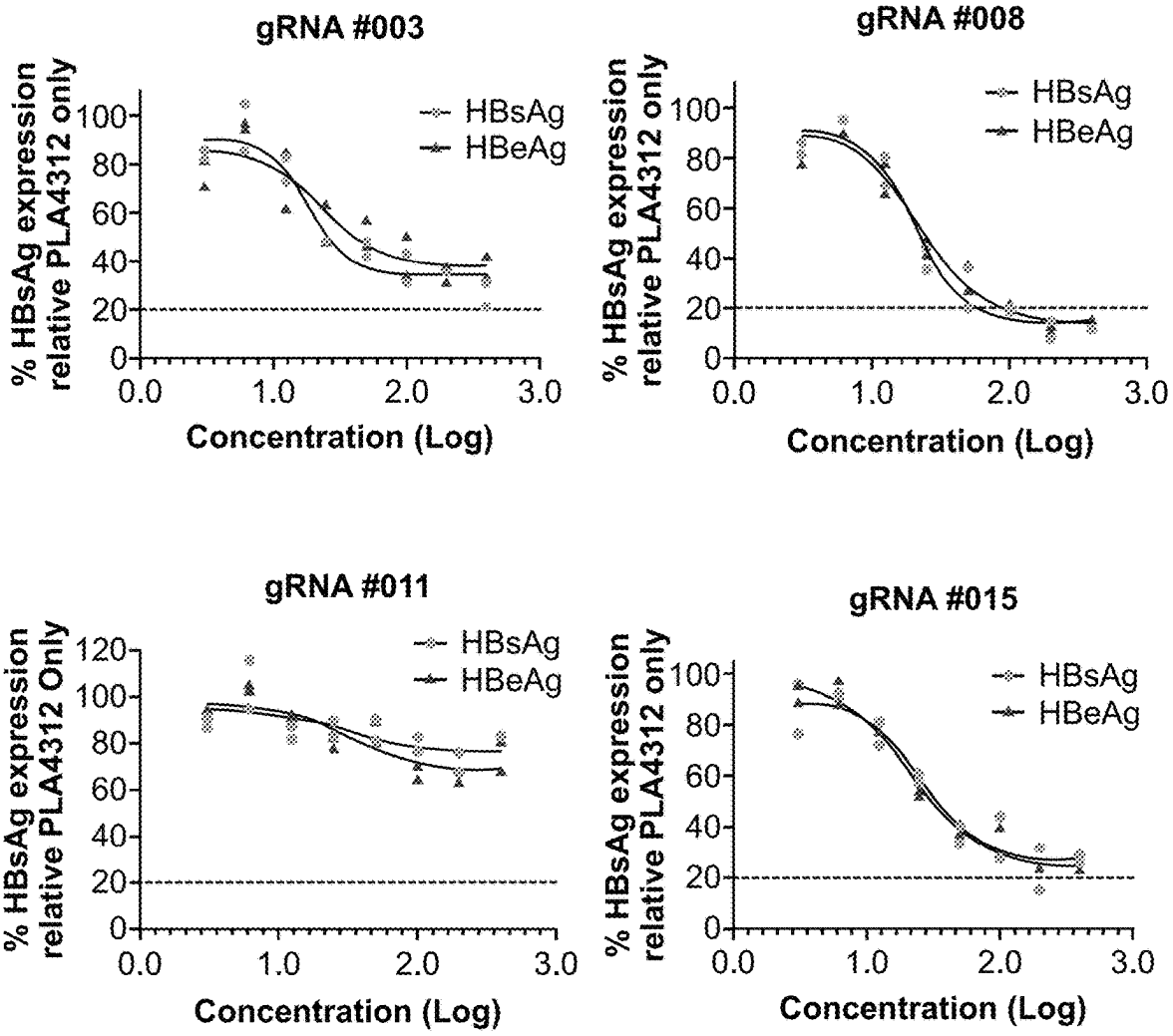
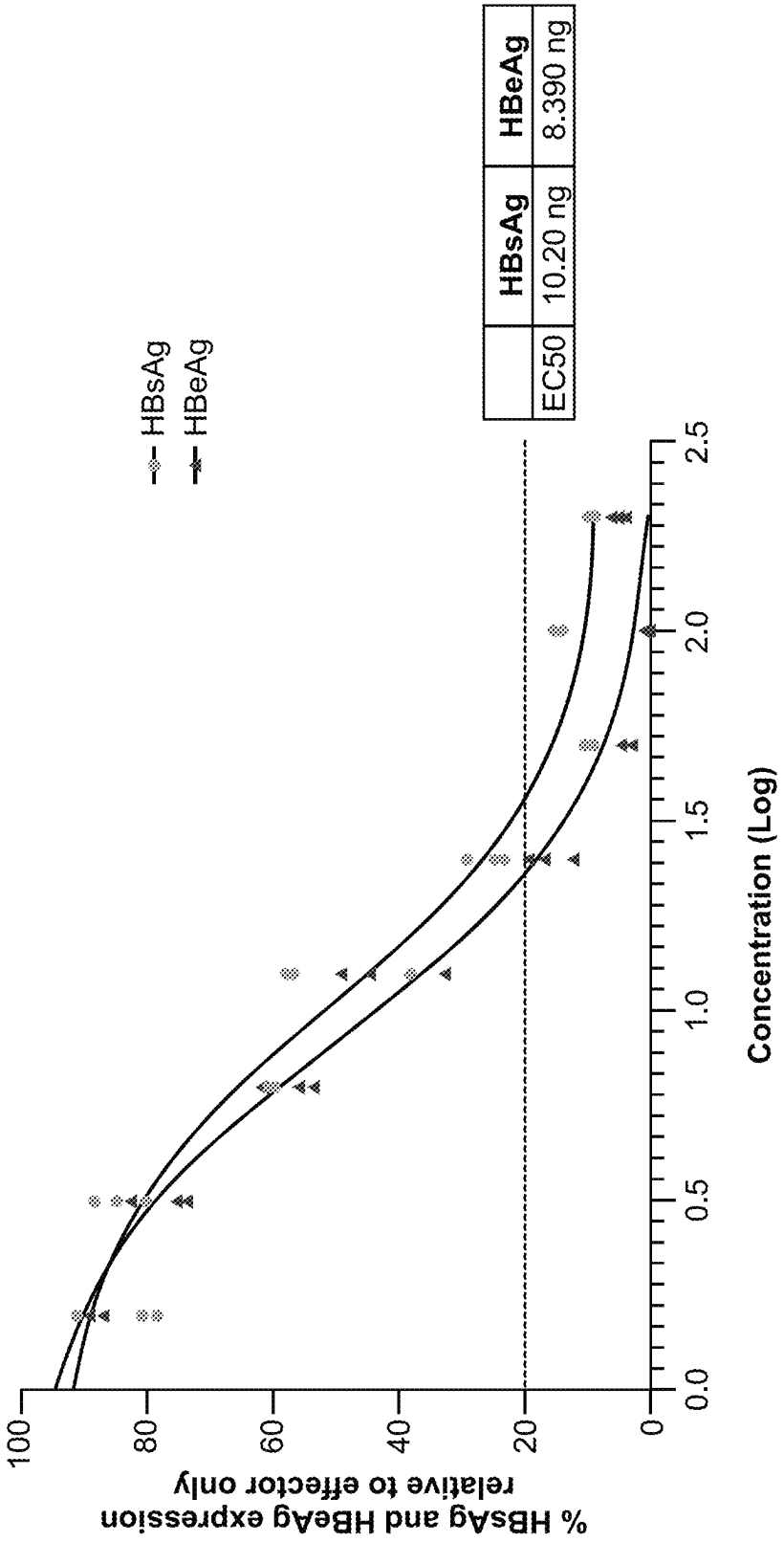

gRNA #003
gRNA #008
gRNA #011
gRNA #015
% HBsAg expression relative PLA4312 only
% HBsAg expression relative PLA4312 Only
HBsAg
HBeAg
Concentration (Log)
0.0
1.0
2.0
3.0
0
20
40
60
80
100
120

FIGURE 42



	HBsAg	HBeAg
EC50	10.20 ng	8.390 ng

FIGURE 43

COMPOSITIONS AND METHODS FOR EPIGENETIC REGULATION OF HBV GENE EXPRESSION

CROSS-REFERENCE

This application is a continuation of International Application No. PCT/US2024/029529, filed on May 15, 2024, which claims the benefit of U.S. Provisional Application No. 63/502,325, filed May 15, 2023, U.S. Provisional Application No. 63/516,096, filed Jul. 27, 2023, and U.S. Provisional Application No. 63/581,236, filed Sep. 7, 2023, each of which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in XML file format and is hereby incorporated by reference in its entirety. Said XML copy, created on Jul. 11, 2024, is named 59073-720.602_SL.xml and is 1,435,558 bytes in size.

BACKGROUND OF THE INVENTION

Despite available treatments, chronic hepatitis B (CHB) remains a high unmet medical need, with more than 250 million carriers of hepatitis B virus (HBV) worldwide and approximately 800,000 annual deaths due to HBV-related liver disease. Current approved CHB therapies elicit a functional cure rate (defined as durable HBsAg loss and undetectable serum HBV after completing a course of treatment) of less than 20%. Accordingly, there is a need for improved clinical modalities targeting HBV.

SUMMARY OF THE INVENTION

Some aspects of the present disclosure provide systems, compositions, strategies, and methods for the epigenetic modification of HBV, including HBV in host cells and organisms.

Some aspects of this disclosure provide methods of modifying an epigenetic state of a hepatitis B virus (HBV) gene or genome, comprising contacting the HBV gene or genome with an epigenetic editing system, wherein the epigenetic editing system comprises a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof, optionally, wherein the first DNA binding domain binds a first target region of the HBV gene or genome, and wherein the contacting results in a reduction of: number of HBV viral episomes, replication of the HBV gene or genome, and/or expression of a protein product encoded by the HBV gene or genome, wherein said reduction is at least about 20% compared to contacting the HBV gene or genome with a suitable control or without contacting the HBV gene or genome with the epigenetic editing system, and/or wherein said reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least 20%, at least 60%, at least 70%, at least 80%, at least 90% (i.e., at least a 1-log reduction), at least 95%, at least 99% (i.e., at least a 2-log reduction), or at least 99.9% (i.e., at least a 3-log reduction), compared to the number, replication, and/or expression in the subject before the contacting.

Some aspects of this disclosure provide methods of treating an HBV infection in a subject comprising administering

an epigenetic editing system to the subject, wherein the epigenetic editing system comprises a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof, optionally, wherein the first DNA binding domain binds a first target region of a HBV gene or genome, and wherein the administering results in a reduction of: number of HBV viral episomes, replication of the HBV gene or genome, and/or expression of a protein product encoded by the HBV gene or genome, wherein said reduction is at least about 20% compared to administering a suitable control or without administering the epigenetic editing system, and/or wherein said reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least 20%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, compared to the number, replication, and/or expression in the subject before administering.

Some aspects of this disclosure provide methods of modulating expression of an HBV gene or genome comprising contacting the HBV gene or genome with an epigenetic editing system, wherein the epigenetic editing system comprises a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof, wherein the first DNA binding domain binds a first target region of the HBV gene or genome, and wherein the contacting results in a reduction of expression of a gene product encoded by the HBV gene or genome, optionally, wherein the gene product is a nucleic acid or a protein, wherein said reduction is at least about 20% compared to contacting the HBV genome with a suitable control or without contacting the HBV gene or genome with the epigenetic editing system, and/or wherein said reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least 20%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, compared to the number, replication, and/or expression in the subject before the contacting.

Some aspects of this disclosure provide methods of inhibiting viral replication in a cell infected with an HBV comprising contacting the cell with an epigenetic editing system, wherein the epigenetic editing system comprises a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof, optionally, wherein the first DNA binding domain binds a first target region of a HBV gene or genome, and wherein the epigenetic editing system targets a target region of the HBV gene or genome, and wherein the contacting results in a reduction of number of HBV viral episomes or replication of the HBV gene or genome, wherein said reduction is at least about 20% compared to administering a suitable control or without contacting the HBV gene or genome with the epigenetic editing system, and/or wherein said reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least 20%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, compared to the number, replication, and/or expression in the subject before the contacting.

Some aspects of this disclosure provide methods comprising administering an epigenetic editing system to a subject in need thereof, wherein the epigenetic editing system comprises a first DNA binding domain, a first DNMT

domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof, wherein the first DNA binding domain binds a first target region of a HBV gene or genome, and wherein the contacting results in a reduction of: number of HBV viral episomes, replication of the HBV gene or genome, or expression of a protein product encoded by the HBV gene or genome, wherein said reduction is at least about 20% compared to administering a suitable control, and/or wherein said reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least about 20% compared to the number, replication, and/or expression in the subject before administering.

Some aspects of this disclosure provide methods of inhibiting viral replication in a subject infected with an HBV comprising administering an epigenetic editing system to the subject, wherein the epigenetic editing system comprises a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof, wherein the epigenetic editing system targets a target region of the HBV gene or genome, and wherein the administering results in a reduction of number of HBV viral episomes, replication of the HBV gene or genome, or expression of a protein product encoded by an HBV gene or genome, wherein the reduction is at least about 20% compared to administering a suitable control or without administering the epigenetic editing system. In some embodiments, the reduction is at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9% compared to administering a suitable control or compared to the respective number or level in the subject before the administering. In some embodiments, the reduction is maintained for at least 6 days, for at least 19 days, for at least 27 days, for at least 42 days, or for at least 168 days.

In some embodiments, the contacting further results in a reduction of a protein product. In some embodiments, the protein product comprises an HBV antigen, for example an HBe antigen (HBeAg). In some embodiments, the protein product comprises an HBs antigen (HBsAg).

In some embodiments, the HBV genome is a covalently closed circular DNA (cccDNA) or an HBV integrated DNA. In some embodiments, the HBV genome comprises HBV genotype A, HBV genotype B, HBV genotype C, HBV genotype D, HBV genotype E, HBV genotype F, HBV genotype G or HBV genotype H. In some embodiments, the HBV genome comprises a sequence with at least 80% identity to an HBV genome sequence provided herein. In some embodiments, the first target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182 of an HBV genome provided herein. In some embodiments, the first target region of the HBV genome is located in a CpG island. In some embodiments, the first target region of the HBV genome is located in a promotor. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a preCore mRNA, a preS mRNA, a S mRNA, and a X mRNA. In some embodiments, the first DNA binding domain comprises a CRISPR-Cas protein. In some embodiments, the epigenetic editing system further comprises a first guide RNA (gRNA) that comprises a region complementary to a strand of the first target region. In some embodiments, the gRNA comprises a sequence selected from a gRNA provided herein, e.g., in Table 12 or 13. In some embodiments, the first DNA binding domain comprises a zinc-finger protein. In some embodiments, the zinc-finger protein comprises a zinc-finger motif with a sequence selected from any zinc finger or zinc finger motif provided herein, e.g., in Table 1. In some embodiments, the zinc-finger protein comprises a sequence of any of the zinc finger epigenetic repressors provided herein. In some embodiments, the transcriptional repressor domain comprises ZIM3 In some embodiments, the first DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the first DNMT domain comprises a sequence of a DNMT domain provided herein. In some embodiments, the epigenetic editing system further comprises a second DNMT domain or a nucleic acid encoding thereof. In some embodiments, the second DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the second DNMT domain comprises a sequence of a DNMT domain provided herein. In some embodiments, the epigenetic editing system comprises a fusion protein or a nucleic acid encoding thereof, and wherein the fusion protein comprises the first DNA binding domain, the first DNMT domain, the repressor domain and the second DNMT domain. In some embodiments, the fusion protein further comprises a nuclear localization sequence (NLS). In some embodiments, the fusion protein comprises a sequence of a fusion protein provided herein. In some embodiments, the epigenetic editing system further comprises a second DNA binding domain or a nucleic acid encoding thereof, wherein the second DNA binding domain binds a second target region of the HBV genome. In some embodiments, the second target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182. In some embodiments, the second target region of the HBV genome is located in a CpG island. In some embodiments, the second target region of the HBV genome is located in a promotor. In some embodiments, the second target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a preCore mRNA, a preS mRNA, a S mRNA, and a X mRNA. In some embodiments, the second DNA binding domain comprises a CRISPR-Cas protein. In some embodiments, the epigenetic editing system further comprises a second gRNA that comprises a region complementary to a strand of the second target region. In some embodiments, the gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., a sequence provided in Table 12 or 13. In some embodiments, the second DNA binding domain comprises a zinc-finger protein. In some embodiments, the zinc-finger protein comprises a zinc-finger motif with a sequence selected from a zinc finger motif sequence provided herein, e.g., a zinc finger motif provided in Table 1. In some embodiments, the zinc-finger protein comprises a sequence of a zinc finger motif provided in Table 1. In some embodiments, the epigenetic editing system comprises a first fusion protein or a first nucleic acid encoding thereof and a second fusion protein or a second nucleic acid encoding thereof, wherein the first fusion protein comprises the first DNA binding domain and the first DNMT domain, and wherein the second fusion protein comprises the second DNA binding domain and the transcriptional repressor domain. In some embodiments, the first fusion protein comprises a sequence of a fusion protein provided herein. In some embodiments, the second fusion protein comprises a sequence of a fusion protein provided herein. In some embodiments, the epigenetic editing system further comprises a third DNA binding domain or a nucleic acid encoding thereof, wherein the third DNA binding domain binds to a third target region of the HBV genome. In some

embodiments, the third target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182. In some embodiments, the third target region of the HBV genome is located in a CpG island. In some embodiments, the third target region of the HBV genome is located in a promotor. In some embodiments, the third target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a preCore mRNA, a preS mRNA, a S mRNA, and a X mRNA. In some embodiments, the third DNA binding domain comprises a CRISPR-Cas protein. In some embodiments, the epigenetic editing system further comprises a third gRNA that comprises a region complementary to a strand of the third target region. In some embodiments, the third gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., of a gRNA sequence provided in Table 12 or 13. In some embodiments, the third DNA binding domain comprises a zinc-finger protein. In some embodiments, the zinc-finger protein comprises a zinc-finger motif with a sequence selected from a zinc finger motif provided herein. In some embodiments, the zinc-finger protein comprises a sequence of a zinc finger motif provided in Table 1. In some embodiments, the epigenetic editing system further comprises a second DNMT domain or a nucleic acid encoding thereof. In some embodiments, the second DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the epigenetic editing system comprises a third fusion protein or a nucleic acid encoding thereof, wherein the third fusion protein comprises the third DNA binding domain and the second DNMT domain. In some embodiments, the third fusion protein comprises a sequence of a fusion protein provided herein. In some embodiments, the epigenetic editing system comprises a nucleic acid sequence provided in Table 18. In some embodiments, the reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least about 20% compared to the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome measured or observed before contacting the HBV genome with the epigenetic editing system, or before administering the epigenetic editing system to the subject. In some embodiments, the reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least about 25%, at least about 50%, at least about 75%, at least about 80%, at least about 90%, at least about 95%, at least about 99%, at least about 99.5%, at least about 99.8%, at least about 99.9%, at least about 99.95%, at least about 99.99%, or more than 99.99%, compared to the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome measured or observed before contacting the HBV genome with the epigenetic editing system, or before administering the epigenetic editing system to the subject.

Some aspects of this disclosure provide epigenetic editing systems comprising: a fusion protein or a nucleic acid encoding the fusion protein, wherein the fusion protein comprises: (a) a DNA-binding domain that binds a target region of a HBV gene or genome, (b) a first DNA methyltransferase (DNMT) domain, and (c) a transcriptional repressor domain. In some embodiments, the epigenetic editing system is capable of reducing a number of the HBV viral episome, replication of the HBV, or expression of a gene product encoded by the HBV gene or genome, wherein said reduction is at least about 20% compared to contacting the HBV gene or genome with a suitable control. In some embodiments, the HBV genome is a covalently closed circular DNA (cccDNA) or an HBV integrated DNA. In some embodiments, the HBV genome comprises HBV genotype A, HBV genotype B, HBV genotype C, HBV genotype D, HBV genotype E, HBV genotype F, HBV genotype G or HBV genotype H. In some embodiments, the HBV genome comprises a sequence with at least 80% identity to an HBV genome sequence provided herein. In some embodiments, the target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182 of an HBV genome sequence provided herein. In some embodiments, the target region of the HBV genome is located in a CpG island. In some embodiments, the target region of the HBV genome is located in a promotor. In some embodiments, the target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a preCore mRNA, a preS mRNA, a S mRNA, and a X mRNA. In some embodiments, the DNA binding domain comprises a CRISPR-Cas protein. In some embodiments, the epigenetic editing system further comprises a gRNA that comprises a region complementary to a strand of the target region. In some embodiments, the gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., in Table 12 or 13. In some embodiments, the DNA binding domain comprises a zinc-finger protein. In some embodiments, the zinc-finger protein comprises a zinc-finger motif with a sequence selected from a zinc finger motif provided herein. In some embodiments, the zinc-finger protein comprises a sequence of a zinc finger motif provided in Table 1. In some embodiments, the transcriptional repressor domain comprises a sequence of a transcriptional repressor provided herein. In some embodiments, the first DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the DNMT domain comprises a sequence of a DNMT domain provided herein. In some embodiments, the fusion protein further comprises a second DNMT domain. In some embodiments, the second DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the fusion protein further comprises a nuclear localization sequence (NLS). In some embodiments, the fusion protein comprises a sequence of a fusion protein provided herein.

Some aspects of the present disclosure provide epigenetic editing systems comprising: a first fusion protein or a nucleic acid encoding the first fusion protein, wherein the first fusion protein comprises a first DNA binding domain and a first DNMT domain, wherein the first DNA binding domain binds a first target region of a HBV genome, and a second fusion protein or a nucleic acid encoding the second fusion protein, wherein the second fusion protein comprises a second DNA binding domain and a transcriptional repressor domain, wherein the second DNA binding domain binds a second target region of the HBV genome. In some embodiments, the epigenetic editing system is capable of reducing a number of the HBV viral episome, replication of the HBV, or expression of a gene product encoded by the HBV genome, wherein said reduction is at least about 20% compared to contacting the HBV genome with a suitable control. In some embodiments, the HBV genome is a covalently closed circular DNA (cccDNA) or an HBV integrated DNA. In some embodiments, the HBV genome comprises HBV genotype A, HBV genotype B, HBV genotype C, HBV genotype D, HBV genotype E, HBV genotype F, HBV genotype G or HBV genotype H In some embodi-

ments, the HBV genome comprises a sequence with at least 80% identity to an HBV genome provided herein. In some embodiments, the epigenetic editing system further comprises a third fusion protein or a nucleic acid encoding the third fusion protein, wherein the third fusion protein comprises a third DNA binding domain and a second DNMT domain, wherein the third DNA binding domain binds a third target region of the HBV genome. In some embodiments, the first target region, the second target region or the third target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182 of an HBV genome provided herein. In some embodiments, the first target region, the second target region or the third target region of the HBV genome is located in a CpG island In some embodiments, the first target region, the second target region or the third target region of the HBV genome is located in a promotor In some embodiments, the first target region, the second target region or the third target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a preCore mRNA, a preS mRNA, a S mRNA, and a X mRNA In some embodiments, the first DNA binding domain, the second DNA binding domain or the third DNA binding domain comprises a CRISPR-Cas protein. In some embodiments, the epigenetic editing system further comprises a first gRNA that comprises a region complementary to a strand of the first target region, a second gRNA that comprises a region complementary to a strand of the second target region or a third RNA that comprises a region complementary to a strand of the third target region. In some embodiments, the first gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., provided in Table 12 or 13, the second gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., provided in Table 12 or 13, and/or the third gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., provided in Table 12 or 13. In some embodiments, the first DNA binding domain, the second DNA binding domain or the third DNA binding domain comprises a zinc-finger protein In some embodiments, the zinc-finger protein comprises a zinc-finger motif with a sequence selected from a zinc finger motif provided herein In some embodiments, the zinc-finger protein comprises a sequence of a zinc finger motif provided in Table 1. In some embodiments, the transcriptional repressor domain comprises ZIM3. In some embodiments, the first DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the first DNMT domain comprises a sequence of a DNMT provided herein. In some embodiments, the second DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the second DNMT domain comprises a sequence of a DNMT domain provided herein. In some embodiments, the first fusion protein comprises a sequence of a fusion protein provided herein. In some embodiments, the second fusion protein comprises a sequence of a fusion protein provided herein. In some embodiments, the third fusion protein comprises a sequence of a fusion protein provided herein. In some embodiments, the epigenetic editing system comprises a nucleic acid sequence provided in Table 18. In some embodiments, the reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least about 20% compared to the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome measured or observed before contacting the HBV genome with the epigenetic editing system, or before administering the epigenetic editing system to the subject. In some embodiments, the reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least about 25%, at least about 50%, at least about 75%, at least about 80%, at least about 90%, at least about 95%, at least about 99%, at least about 99.5%, at least about 99.8%, at least about 99.9%, at least about 99.95%, at least about 99.99%, or more than 99.99%, compared to the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome measured or observed before contacting the HBV genome with the epigenetic editing system, or before administering the epigenetic editing system to the subject.

Some aspects of the present disclosure provide a method of treating an HDV infection in a subject comprising administering an epigenetic editing system to the subject, wherein the epigenetic editing system comprises a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof, wherein the first DNA binding domain binds a first target region of a HBV gene or genome, and wherein the contacting results in a reduction of: number of HDV viral episomes, replication of the HDV gene or genome, or expression of a protein product encoded by the HDV gene or genome, wherein said reduction is at least about 20% compared to administering a suitable control. Some aspects of the present disclosure provide a method of inhibiting viral replication in a cell infected with an HDV comprising administering an epigenetic editing system, wherein the epigenetic editing system comprises a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof, wherein the first DNA binding domain binds a first target region of a HBV gene or genome, and wherein the epigenetic editing system targets a target region of the HBV gene or genome, and wherein the contacting results in a reduction of number of HDV viral episomes or replication of the HDV gene or genome, wherein said reduction is at least about 20% compared to administering a suitable control. In some embodiments, the first DNA binding domain comprises a CRISPR-Cas protein. In some embodiments, the epigenetic editing system further comprises a first guide RNA (gRNA) that comprises a region complementary to a strand of the first target region. In some embodiments, the gRNA comprises a sequence selected from a gRNA provided herein, e.g., in Table 12 and/or 13. In some embodiments, the first DNA binding domain comprises a zinc-finger protein. In some embodiments, the zinc-finger protein comprises a zinc-finger motif with a sequence selected from any zinc finger or zinc finger motif provided herein, e.g., in Table 1 or Table 18. In some embodiments, the zinc-finger protein comprises a sequence of any of the zinc finger epigenetic repressors provided herein. In some embodiments, the transcriptional repressor domain comprises ZIM3. In some embodiments, the first DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the first DNMT domain comprises a sequence of a DNMT domain provided herein. In some embodiments, the epigenetic editing system further comprises a second DNMT domain or a nucleic acid encoding thereof. In some embodiments, the second DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the second DNMT domain comprises a sequence of a DNMT domain provided herein. In some embodiments, the epigenetic edit-

ing system comprises a fusion protein or a nucleic acid encoding thereof, and wherein the fusion protein comprises the first DNA binding domain, the first DNMT domain, the repressor domain and the second DNMT domain. In some embodiments, the fusion protein further comprises a nuclear localization sequence (NLS). In some embodiments, the fusion protein comprises a sequence of a fusion protein provided herein. In some embodiments, the first DNA binding domain binds a target region of an HBV gene or genome encoding or controlling expression of an S-antigen. In some embodiments, the epigenetic editing system comprises a nucleic acid sequence provided in Table 18. In some embodiments, the reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least about 20% compared to the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome measured or observed before contacting the HBV genome with the epigenetic editing system, or before administering the epigenetic editing system to the subject. In some embodiments, the reduction of the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome is at least about 25%, at least about 50%, at least about 75%, at least about 80%, at least about 90%, at least about 95%, at least about 99%, at least about 99.5%, at least about 99.8%, at least about 99.9%, at least about 99.95%, at least about 99.99%, or more than 99.99%, compared to the number of HBV viral episomes, of replication of the HBV gene or genome, or of expression of a protein product encoded by the HBV gene or genome measured or observed before contacting the HBV genome with the epigenetic editing system, or before administering the epigenetic editing system to the subject.

Some aspects of this disclosure provide methods comprising administering an epigenetic editing system to a subject characterized by the presence of detectable levels of HBV DNA, HBsAg, and/or HBeAg in the plasma of the subject, for example, a subject having a chronic HBV infection. In some such embodiments, the epigenetic editing system comprises a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding the same, wherein the first DNA binding domain binds a first target region of an HBV gene or genome, and the administering results in a reduction of the level of HBV DNA, the level of HBsAg, and/or the level of HBsAg in the plasma of the subject, and the reduction of the level of HBV DNA, of the level of HBsAg, and/or of the level of HBsAg in the plasma of the subject, is at least 90% (a 1-log reduction) compared to the respective level observed or observable in the plasma of the subject prior to the administering, and the 1-log reduction is maintained for at least 14 days after the administering. In some embodiments, the reduction of the level of HBV DNA in the plasma of the subject is at least 90% (a 1-log reduction). In some embodiments, the reduction of the level of HBV DNA in the plasma of the subject is at least 99% (a 2-log reduction). In some embodiments, the reduction of the level of HBsAg in the plasma of the subject is at least 90% (a 1-log reduction). In some embodiments, the reduction of the level of HBsAg in the plasma of the subject is at least 99% (a 2-log reduction). In some embodiments, the reduction of the level of HBeAg in the plasma of the subject is at least 90% (a 1-log reduction). In some embodiments, the reduction of the level of HBeAg in the plasma of the subject is at least 99% (a 2-log reduction). In some embodiments, the reduction is maintained for at least 21 days. In some embodiments, the reduction is maintained for at least 28 days. In some embodiments, the reduction is maintained for at least 35 days. In some embodiments, the reduction is maintained for at least 42 days. In some embodiments, the reduction is maintained for at least 56 days. In some embodiments, the reduction is maintained for at least 70 days. In some embodiments, the reduction is maintained for at least 84 days. In some embodiments, the reduction is maintained for at least 112 days. In some embodiments, the reduction is maintained for at least 140 days. In some embodiments, the reduction is maintained for at least 168 days. In some embodiments, the reduction is maintained for at least 6 months. In some embodiments, the reduction is maintained for at least 9 months. In some embodiments, the reduction is maintained for at least 12 months. In some embodiments, the reduction is maintained for at least 24 months. In some embodiments, the HBV genome comprises HBV genotype A. In some embodiments, the HBV genome comprises HBV genotype B. In some embodiments, the HBV genome comprises HBV genotype C. In some embodiments, the HBV genome comprises, HBV genotype D. In some embodiments, the HBV genome comprises HBV genotype E. In some embodiments, the HBV genome comprises HBV genotype F. In some embodiments, the HBV genome comprises HBV genotype G. In some embodiments, the HBV genome comprises HBV genotype H. In some embodiments, the HBV genome comprises a sequence with at least 80%, at least 90%, at least 95%, at least 99%, or greater than 99% sequence identity to an HBV genome sequence provided herein. In some embodiments, the first target region is located in a region of the HBV genome within nucleotides 0-303 of an HBV genome provided herein. In some embodiments, the first target region is located within nucleotides 0-303 of SEQ ID NO: 1082. In some embodiments, the first target region is located within nucleotides 0-303 of SEQ ID NO: 1083. In some embodiments, the first target region is located in a region of the HBV genome within nucleotides 1000-2448 of an HBV genome provided herein. In some embodiments, the first target region is located within nucleotides 1000-2448 of SEQ ID NO: 1082. In some embodiments, the first target region is located within nucleotides 1000-2448 of SEQ ID NO: 1083. In some embodiments, the first target region is located in a region of the HBV genome within nucleotides 2802-3182 of an HBV genome provided herein. In some embodiments, the first target region is located within nucleotides 2802-3182 of SEQ ID NO: 1082. In some embodiments, the first target region is located within nucleotides 2802-3182 of SEQ ID NO: 1083. In some embodiments, the first target region of the HBV genome is located in an HBV CpG island (CGI). In some embodiments, the CGI is an HBV canonical CGI. In some embodiments, the CGI is canonical CGI-I. In some embodiments, CGI is canonical CGI-I of HBV genotype D. In some embodiments, CGI-I spans nucleotides 186-288 of SEQ ID NO: 1082In some embodiments, CGI-I spans nucleotides 186-288 of SEQ ID NO: 10831n some embodiments, the CGI is canonical CGI-II. In some embodiments, the CGI is canonical CGI-II HBV genotype D. In some embodiments, the CGI is CGI II spans nucleotides 1,217-1,670 of SEQ ID NO: 1082. In some embodiments, the CGI is CGI II spans nucleotides 1,217-1,670 of SEQ ID NO: 1083. In some embodiments, the CGI is canonical CGI-III. In some embodiments, the CGI is canonical CGI-III HBV genotype D. In some embodiments, the CGI is CGI-III spans nucleotides 2,282-2,448 of SEQ ID NO: 1082. In some embodiments, the CGI

is CGI-III spans nucleotides 2,282-2,448 of SEQ ID NO: 1083. In some embodiments, the first target region of the HBV genome is located in a promotor. In some embodiments, the first target region of the HBV genome is located in the sp1 promoter. In some embodiments, the first target region of the HBV genome is located in sp2 promoter. In some embodiments, the first target region of the HBV genome is located in cp promoter. In some embodiments, the first target region of the HBV genome is located in xp promoter. In some embodiments, the first target region of the HBV genome is located in an enhancer region. In some embodiments, the first target region of the HBV genome is located in Enh I. In some embodiments, the first target region of the HBV genome is located in Enh II. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes a transcript. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes a pgRNA transcript. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes a preCore RNA transcript. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes a preS RNA transcript. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes an S RNA transcript. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes an HBx RNA transcript. In some embodiments, the first target region of the HBV genome is within 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) of an HBV transcription start site (TSS). In some embodiments, the TSS is a pg RNA TSS. In some embodiments, the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the pg RNA TSS. In some embodiments, the pg RNA TSS is located at nucleotide 1820 of SEQ ID NO: 1082 or at nucleotide 1820 of SEQ ID NO: 1083. In some embodiments, the first target region is within 600 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 600 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the first target region is within 500 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 500 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the first target region is within 400 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 400 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the first target region is within 300 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 300 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the first target region is within 200 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 200 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the first target region is within 100 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 100 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the TSS is a preC RNA TSS. In some embodiments, the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the preC RNA TSS. In some embodiments, the preC RNA TSS is located at nucleotide 1791 of SEQ ID NO: 1082 or at nucleotide 1791 of SEQ ID NO: 1083. In some embodiments, the first target region is within 600 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 600 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the first target region is within 500 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 500 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the first target region is within 400 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 400 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the first target region is within 300 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 300 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the first target region is within 200 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 200 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the first target region is within 100 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 100 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the TSS is a preS2 RNA TSS. In some embodiments, the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the preS2 RNA TSS. In some embodiments, the preS2 RNA TSS is located at nucleotide 3159 of SEQ ID NO: 1082 or at nucleotide 3159 of SEQ ID NO: 1083. In some embodiments, the first target region is within 600 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 600 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the first target region is within 500 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 500 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the first target region is within 400 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 400 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the first target region is within 300 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 300 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the first target region is within 200 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 200 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the first target region is within 100 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 100 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the TSS is an HBx RNA TSSs. In some embodiments, the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the HBx RNA TSS. In some embodiments, the HBx RNA TSS is located at a nucleotide within the sequence of nucleotides 1243-1338 of SEQ ID NO: 1082 or nucleotides 1243-1338 of SEQ ID NO: 1083. In some embodiments, the first target region is within 600 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 600 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 500 base pairs of nucleotide 1243 in SEQ ID NO:

1082. In some embodiments, the first target region is within 500 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 400 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 400 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 300 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 300 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 200 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 200 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 100 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 100 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 600 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, the first target region is within 500 base pairs of nucleotide 1338 in SEQ ID NO: 1082. In some embodiments, the first target region is within 500 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, first target region is within 400 base pairs of nucleotide 1338 in SEQ ID NO: 1082. In some embodiments, the first target region is within 400 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, the first target region is within 300 base pairs of nucleotide 1338 in SEQ ID NO: 1082. In some embodiments, the first target region is within 300 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, the first target region is within 200 base pairs of nucleotide 1338 in SEQ ID NO: 1082. In some embodiments, the first target region is within 200 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, the first target region is within 100 base pairs of nucleotide 1338 in SEQ ID NO: 1082. In some embodiments, the first target region is within 100 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, the reduction is a reduction in the number of HBV viral episomes. In some embodiments, the reduction is a reduction in the number of cccDNA genomes. In some embodiments, the reduction is a reduction in total HBV DNA. In some embodiments, the reduction is a reduction in the replication of the HBV genome. In some embodiments, the reduction is a reduction in a level of expression of a protein product encoded by the HBV genome. In some embodiments, the reduction is a reduction in a level of HBsAg. In some embodiments, the reduction is a reduction in a level of HBeAg. In some embodiments, the reduction is a reduction of total HBV DNA of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and the reduction is maintained for at least 14 days after the contacting or the administering. In some embodiments, the reduction is a reduction of HBeAg of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and the reduction is maintained for at least 14 days after the contacting or the administering. In some embodiments, the reduction is a reduction of HBsAg of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and the reduction is maintained at or below that level for at least 14 days after the contacting or the administering. In some embodiments, the reduction is a reduction of at least 90%. In some embodiments, the reduction is a reduction of at least 95%. In some embodiments, the reduction is a reduction of at least 99%. In some embodiments, the reduction is a reduction of at least 99.9%. In some embodiments, the reduction is maintained for at least 14 days after the contacting or the administering. In some embodiments, the reduction is maintained for at least 21 days. In some embodiments, the reduction is maintained for at least 28 days. In some embodiments, the reduction is maintained for at least 35 days. In some embodiments, the reduction is maintained for at least 42 days. In some embodiments, the reduction is maintained for at least 56 days. In some embodiments, the reduction is maintained for at least 70 days. In some embodiments, the reduction is maintained for at least 84 days. In some embodiments, the reduction is maintained for at least 112 days. In some embodiments, the reduction is maintained for at least 140 days. In some embodiments, the reduction is maintained for at least 168 days. In some embodiments, the reduction is maintained for at least 6 months. In some embodiments, the reduction is maintained for at least 7 months. In some embodiments, the reduction is maintained for at least 8 months. In some embodiments, the reduction is maintained for at least 9 months. In some embodiments, the reduction is maintained for at least 12 months. In some embodiments, the reduction is maintained for at least 18 months. In some embodiments, the reduction is maintained for at least 24 months. In some embodiments, the epigenetic editing system is administered as a monotherapy. Accordingly, in some embodiments, the method does not comprise administering a nucleoside or nucleotide analog (NUC) to the subject. In some embodiments, the method further comprises administering a NUC to the subject. In some embodiments, the first DNA binding domain comprises a CRISPR-Cas protein. In some embodiments, the epigenetic editing system further comprises a first guide RNA (gRNA) that comprises a region complementary to a strand of the first target region. In some embodiments, the gRNA comprises a sequence selected from a gRNA provided herein, and preferably the gRNA comprises a sequence provided in Table 12 or 13. In some embodiments, the first DNA binding domain comprises a zinc-finger protein. In some embodiments, the zinc-finger protein comprises a zinc-finger motif with a sequence selected from any zinc finger or zinc finger motif provided herein, e.g., in Table 1 or Table 18. In some embodiments, the zinc-finger protein comprises a sequence of any of the zinc finger epigenetic repressors provided herein. In some embodiments, the transcriptional repressor domain comprises ZIM3. In some embodiments, the first DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the first DNMT domain comprises a sequence of a DNMT domain provided herein. In some embodiments, the epigenetic editing system comprises the fusion protein provided in SEQ ID NO: 1248 or the fusion protein provided in SEQ ID NO: 1252 and at least one guide RNA provided as gRNA #003, gRNA #007, gRNA #008, gRNA #009, gRNA #011, or gRNA #015 herein. Some aspects of this disclosure provide epigenetic editing systems for use in the methods described herein. In some embodiments, the epigenetic editing system comprises a fusion protein or a nucleic acid encoding the fusion protein, and the fusion protein comprises: (a) a DNA-binding domain that binds a target region of a HBV gene or genome, (b) a first DNA methyltransferase (DNMT) domain, and (c) a transcriptional repressor domain. In some embodiments, the fusion protein comprises a sequence of a fusion protein provided herein. In some embodiments, the DNA-binding domain is a CRISPR-Cas DNA binding domain, and the epigenetic editing system comprises at least gRNA provided herein. In some embodiments, the epigenetic editing system comprises the fusion protein provided in SEQ ID NO: 1248 or the fusion protein

provided in SEQ ID NO: 1252 and at least one guide RNA provided as gRNA #003, gRNA #007, gRNA #008, gRNA #009, gRNA #011, or gRNA #015 herein.

Other features, objectives, and advantages of the invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating embodiments and embodiments of the invention, is given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a diagram illustrating an exemplary structure of a circular HBV genome. HBV genes and CpG islands are indicated. Exemplary target sites for CRISPR-based epigenetic repressors (red arrows) as well as for zinc-finger-based epigenetic repressors (green arrows) are identified.

FIG. **2** is a heat map showing conservation of guide RNA target domains across different HBV genotypes.

FIG. **3** is a bar graph illustrating the geographical distribution of different HBV genotypes.

FIG. **4**A is a diagram describing the experimental timeline for testing different CRISPR-based epigenetic repressors in HepAD38 cells, which express HPV in a doxycycline-inducible manner. FIG. **4**B is a diagram showing the repression of HBV by various CRISPR-based epigenetic repressors (#1.1-3.2). Controls: UT: untransfected control; GFP: transfection control without repressor; HBV-KO: CRISPR nuclease mediated knockout; sgRNA scramble: CRISPR-based repressor with sgRNA not targeting HBV; B2M: CRISPR-based repressor with sgRNA targeting B2M.

FIG. **5**A is a diagram describing the experimental timeline for testing different CRISPR-based epigenetic repressors in a HepG2-NTCP infection model (see, e.g., Methods Mol Biol. 2017; 1540:1-14). FIG. **5**B is a diagram showing the expression of HBe antigen (via ELISA) at different times after treatment of HBV-infected Hep2G-NTCT cells with different doses of CRISPR-based epigenetic repressors (ETRs), or with different doses of Cas9 nuclease targeting HBV (Cas9), plotted normalized to the expression value of HBe antigen measured for a negative control (empty).

FIG. **6** is a diagram describing the experimental timeline for a guide RNA screen testing different CRISPR-based epigenetic repressor systems in a HepG2-NTCP infection model with ELISA readout for HBe and HBs antigens at day 6.

FIG. **7** is a diagram showing QC results from different LNP batches used in the guide screen.

FIG. **8** is a bar graph showing the expression of HBe and HBs for an exemplary CRISPR-based epigenetic repressor (#3.2), calculated as the percentage of the expression of the respective antigen measured for a non-targeting control.

FIG. **9** is a diagram showing HBe expression values measured in the guide RNA screen for different guides (calculated as a percentage of the expression of HBe measured for a non-targeting control). Each guide/repressor combination is represented by a dot. A 50% repression cutoff is shown as a horizontal line. The position of the respective guide RNA within the HBV genome (shown at the bottom of the graph) is mapped on the X-axis. The position and the measured modulation of HBe expression for exemplary guide RNA #3.2 is indicated by red lines.

FIG. **10** is a diagram showing HBs expression values measured in the guide RNA screen for different guides (calculated as a percentage of the expression of HBs measured for a non-targeting control). Each guide/repressor combination is represented by a dot. A 50% repression cutoff is shown as a horizontal line. The position of the respective guide RNA within the HBV genome (shown at the bottom of the graph) is mapped on the X-axis. The position and the measured modulation of HBs expression for exemplary guide RNA #3.2 is indicated by red lines.

FIG. **11** is a diagram showing a correlation between HBs and HBe expression for the guides tested. The graph on the right shows HBe and HBs repression efficiencies for 25 exemplary guides.

FIG. **12**A is a diagram describing the experimental timeline for a guide RNA assay testing CRISPR-off single construct epigenetic editor in combination with individual exemplary gRNAs in a HepG2-NTCP infection model with ELISA readout for HBe and HBs antigens at day 6; and FIG. **12**B is a graph summarizing the percentage reduction in HBV antigens at day 6 relative to non-targeting control.

FIG. **13**A is a diagram describing the experimental timeline for a guide RNA assay testing CRISPR-off single construct epigenetic editor in combination with individual exemplary gRNAs in a PLC/PRF/5 cell model with ELISA readout for HBs antigen at day 4; and FIG. **13**B is a graph summarizing the percentage reduction in HBs antigen at day 4 relative to non-targeting control.

FIG. **14**A is a diagram describing the experimental timeline for a guide RNA assay testing CRISPR-off single construct epigenetic editor in combination with individual exemplary gRNAs in a PXB cell model with ELISA readout for HBe and HBs antigens at day 6; and FIG. **14**B is a graph summarizing the percentage reduction in HBV antigens at day 6 relative to non-targeting control. FIG. **14**C is a diagram describing the experimental timeline for a guide RNA assay testing CRISPR-off single construct epigenetic editor in combination with individual exemplary gRNAs in a PXB cell model with ELISA readout for HBe and HBs antigens at day 12. FIG. **14**D is a graph summarizing the percentage reduction in HBV antigens at day 12 relative to non-targeting control. Bars represent mean±SEM; N=5. EE1=PLA002 and gRNA #007, EE2=PLA002 and gRNA #008, EE3=PLA002 and gRNA #009, EE4=PLA002 and gRNA #015, and EE5=PLA002 and gRNA #011.

FIG. **15** is a diagram describing the design for in vivo experiments testing CRISPR-off single construct epigenetic editor in combination with individual exemplary gRNAs in AAV-HBV mouse HBV genotype D persistent infection model, and transgenic HBV genotype A mouse persistent infection model, respectively.

FIG. **16** shows time course graphs summarizing the level of serum HBV DNA, HBs and HBe antigens in transgenic mouse HBV model before and after single administration of an epigenetic editor (CRISPR-off with gRNA or ETR with gRNA), Cas9 with gRNA, or control vehicle at day 0.

FIG. **17** shows time course graphs summarizing the level of serum HBV DNA, HBs and HBe antigens in AAV-HBV mouse model before and after single administration of an epigenetic editor (CRISPR-off with gRNA or ETR with gRNA), Cas9 with gRNA, or control vehicle at day 0.

FIG. **18**A shows time course graphs summarizing the level of serum HBV DNA, HBs and HBe antigens in transgenic mouse HBV model, and a schematic of the timeline for the experiment. All mice received a single administration of an epigenetic editor (CRISPR-off with gRNA or ETR with gRNA), Cas9 with gRNA, or control vehicle at day 0, and some mice received a designated redosing at day 35. FIG. **18**B shows results for the single-administration (no redosing) groups and controls to 168 days

duration for HBV DNA and HBsAg. The lefthand panels shows the group data at each timepoint, whereas the right-hand panels show the readouts for individual animals at two timepoints. EE=epigenetic editor (CRISPR-off with gRNA #011).

FIG. **19** shows time course graphs summarizing the level of serum HBV DNA, HBs and HBe antigens in AAV-HBV mouse model, and a schematic of the timeline for the experiment. All mice received a single administration of an epigenetic editor (CRISPR-off with gRNA or ETR with gRNA), Cas9 with gRNA, or control vehicle at day 0, and some mice received a designated redosing at day 35.

FIG. **20**A is a diagram describing the experimental timeline for a zinc finger assay testing ZF-off single construct epigenetic editor that contains individual exemplary zinc finger motif in a HepG2-NTCP infection model with ELISA readout for HBe and HBs antigens at day 6; and FIG. **20**B is a graph summarizing the percentage reduction in HBV antigens at day 6 relative to non-targeting control. "N" denotes non-targeting control, "P" denotes the positive control, and the individual numbers on the x-axis denote exemplary constructs tested in the experiment, for instance, "1" represents "mRNA0001" construct, and "20" represents "mRNA0020" construct.

FIG. **21**A is a graph summarizing the results of top ten ZF-off constructs from FIG. **20**B. FIG. **21**B is a diagram showing HBsAg (top) and HBeAg (middle) expression values measured in the ZF-off screen (calculated as a percentage of the expression of HBsAg or HBeAg—top and middle, respectively—measured for a non-targeting control). Each ZF-off construct is represented by a dot. 50% and 60% repression cutoffs are shown as horizontal lines. The position of the respective guide RNA within the HBV genome (bottom) is mapped on the X-axis.

FIG. **22** is an experimental timeline for testing dose response (top) and two graphs showing dose response of % HbsAg (bottom left) and % HbeAg (bottom right) in HepG2-NTCP cells upon administration of ZF fusion proteins. The mRNA corresponding to the ZF motif for each fusion protein is indicated.

FIGS. **23**A-**23**C show an experimental timeline for testing durable silencing of HBsAg (FIG. **23**A), a graph showing the durability of HBsAg silencing by ZF fusion proteins (FIG. **23**B), and a graph showing the durability of HBsAg silencing by CRISPR-off fusion proteins with guide RNAs (FIG. **23**C) in an integrated cell line. The mRNA corresponding to the ZF motif for each fusion protein is indicated. Error bars represent mean +/− SEM; in FIG. **23**C, N=3, EE1=PLA002 and gRNA #007, EE2=PLA002 and gRNA #008, EE3=PLA002 and gRNA #009, EE4=PLA002 and gRNA #015, and EE5=PLA002 and gRNA #011).

FIG. **24** is an experimental timeline for testing HBsAg silencing in a PLC/PRF/5 in vitro model (top) and a graph showing % HBsAg relative to control on Day 14 after administration of ZF fusion proteins. The mRNA corresponding to the ZF motif for each fusion protein is indicated. Information about the % match to target for each construct is also indicated.

FIG. **25**A is a volcano plot showing differentially expressed (DE) genes for an exemplary ZF specificity assay. DE genes are shown with dots. FIG. **25**B is a volcano plot showing DE for CRISPR-off and gRNA epigenetic editors. Points represent genes with their change in expression (x-axis) and statistical significance of that change (y-axis). EE1=PLA002 and gRNA #007, EE2=PLA002 and gRNA #008, EE3=PLA002 and gRNA #009, EE4=PLA002 and gRNA #015, and EE5=PLA002 and gRNA #011. Also shown are results for low specificity and host target gene controls. FIGS. **25**C-**25**D are scatter plots showing methylation levels between treatment (y-axis) and control (x-axis) for 935,000 CpG sites in the human genome. Lines represent thresholds for changes in methylation considered significant (absolute [methylation difference]>=0.2). DMRs are noted on each figure. Results for a host target (PCSK9, next-to-final panel) as well as a low specificity control (final panel) are also shown. FIG. **25**C shows the results versus effector only; FIG. **25**D shows the results versus no treatment. EE1=PLA002 and gRNA #007, EE2=PLA002 and gRNA #008, EE3=PLA002 and gRNA #009, EE4=PLA002 and gRNA #015, EE5=PLA002 and gRNA #011, EE6=PLA002 and gRNA #003, and EE7=PLA002 and gRNA #016.

FIG. **26** is a schematic of an in vivo experiment testing ZF-off constructs.

FIG. **27** shows graphs showing log fold change, relative to baseline, for HBV DNA (left), HBsAg (middle), and HBeAg (right) in plasma of mice treated with the plasmids indicated in the experiment shown in FIG. **26**.

FIG. **28** is an experimental schematic for an in vivo study of multiplexing ZF fusion protein effectors.

FIG. **29** is a schematic for a dose response experiment using CRISPR-Off in an AAV-HBV in vivo model.

FIG. **30** is a line graph of plasma HBsAg levels for a dose response experiment using CRISPR-Off in an AAV-HBV in vivo model.

FIG. **31** is a schematic for a dose response experiment using CRISPR-Off in a Tg-HBV in vivo model.

FIG. **32** shows line graphs of plasma HBV DNA, HBsAg, and HBeAg levels for a dose response experiment using CRISPR-Off in a Tg-HBV in vivo model.

FIG. **33** is a dot plot of HBsAg levels of individual mice at the 207 day time point of a dose response experiment using CRISPR-Off in a Tg-HBV in vivo model.

FIG. **34** shows line graphs of HBV-DNA and HBsAg in plasma in AAV mice treated with CRISPR-Off mRNA with various single guide RNAs. n=5 for each guide RNA treatment group; n=4 for vehicle-only control.

FIG. **35**A shows line graphs of HBV-DNA and HBsAg in plasma in AAV mice treated with a single dose of ZF-Off mRNA.

FIG. **35**B shows line graphs of HBV-DNA and HBsAg in plasma in AAV mice treated with multiple doses of ZF-Off mRNA.

FIG. **36** shows line graphs of HBV-DNA, HBsAg, and HBeAg in plasma in AAV mice treated with single versus multiple doses of 1 mg/kg CRISPR-Off mRNA with guide RNA.

FIG. **37** shows line graphs of HBV-DNA and HBsAg in plasma in AAV mice treated with a single bolus dose of 3 mg/kg versus three doses of 1 mg/kg CRISPR-Off mRNA with guide RNA.

FIG. **38** shows line graphs of HBsAg in plasma in response to treatment with two different CRISPR-Off effectors (left, SEQ ID NO: 1248; right, SEQ ID NO: 1252) delivered via mRNA in combination with the same guide RNA.

FIGS. **39**A-**39**G show methylation of the HBV genome upon treatment with CRISPR-Off with various single guide RNAs versus wild type Cas9, CRISPRi, and non-targeting controls. The box in FIG. **39**A represents the region 500 bp both upstream and downstream of the target site. The arrows indicate the position of the target sequence for the guide RNA used in the depicted experiment.

FIG. **40** shows volcano plots of RNA-Seq (top) and methylation (bottom) experiments at Day 14 after treatment

in HepG2.2.15 cells treated with ZF-Off (left, SEQ ID NO: 36; center, SEQ ID NO: 73) and CRISPR-Off (right, SEQ ID NO: 1248) constructs (delivered as mRNA) targeting HBV. DE, differentially expressed. DMR: differentially methylated region.

FIG. **41** shows HBsAg levels over 14 days for the cells treated for the RNA-Seq and methylation plots in FIG. **40**.

FIG. **42** shows a schematic (top) and dose curves (bottom) for CRISPR-Off dose curve experiments in HepG2.2.15 cells using various single guide RNAs and measuring HBsAg and HBeAg.

FIG. **43** shows dose curves for a CRISPR-Off variant, delivered with guide RNA, in HepG2.2.15 cells measuring HBsAg and HBeAg.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides epigenetic editors, and strategies and methods of using such epigenetic editors, for regulating expression of HBV. By altering expression of HBV, and in particular, by repressing expression of HBV, e.g., of a gene comprised in the HBV genome or a gene product encoded by the HBV genome, the compositions and methods described herein are useful to suppress viral function in infected cells, e.g., in the context of treating an HBV infection in a human subject, or in the context of treating CHB.

The structure and biology of HBV as well as HBV-associated diseases have been reported (see, for example, Yuen, M F., Chen, D S., Dusheiko, G. et al. Hepatitis B virus infection. Nat Rev Dis Primers 4, 18035 (2018), incorporated herein by reference in its entirety).

Exemplary HBV sequences can be found at various NCBI database entries, e.g., representative sequences can be found under accession numbers NC_00397 and U95551, which are incorporated herein by reference in their entirety, and the sequences of which are provided elsewhere herein.

A number of treatment options for HBV has been reported, but there remains a need for effective treatment of HBV infections. Genetic editing approaches targeting HBV genomes for cutting of genomic DNA are associated with a risk of off-target cutting and genomic translocations. The present epigenetic editors and related methods of use have several advantages compared to other genome engineering methods, including increased efficiency, decreased risk of translocation, and durable silencing of HBV.

The present disclosure also provides methods for treating Hepatitis D virus (HDV). HDV is the smallest pathogen known to infect humans. HDV infection is only found in patients infected with HBV, as HDV relies on HBV functions for most of its functions, including viral packaging, infectivity, transmission, and inhibition of host immunity. About 5% of patients with HBV infection also have an HDV infection. HDV uses HBV S-antigen (HBsAg) as a capsid protein, and HDV infection is therefore dependent on HBV S-antigen production. Decreasing HBV S-antigen expression also reduces HDV infectivity. The structure and biology of HDV has been reported (see, for example, Asselah and Rizzetto, Hepatitis D Virus Infection, The New England Journal of Medicine (389; 1; Jul. 6, 2023), incorporated herein by reference in its entirety). In some embodiments of the present disclosure, HDV infection is addressed through methods targeting an HBV gene or genome that reduce the level of HBsAg.

In some embodiments, an epigenetic editor as described herein may comprise one or more fusion proteins, wherein each fusion protein comprises a DNA-binding domain linked to one or more effector domains for epigenetic modification. In certain embodiments, where the DNA-binding domain is a polynucleotide guided DNA-binding domain, the epigenetic editor may further comprise one or more guide polynucleotides. DNA-binding domains, effector domains, and guide polynucleotides of an epigenetic editor as described herein may be selected, e.g., from those described below, in any functional combination.

The epigenetic editors described herein may be expressed in a host cell transiently, or may be integrated in a genome of the host cell; such cells and their progeny are also contemplated by the present disclosure. Both transiently expressed and integrated epigenetic editors or components thereof can effect stable epigenetic modifications. For example, after introducing to a host cell an epigenetic editor described herein, the target gene in the host cell may be stably or permanently repressed or silenced. For example, in some embodiments provided herein, a transiently expressed epigenetic editor comprising a DNMT3A domain, a DNMT3L domain, and a KRAB domain effects stable epigenetic modifications. For example, in some embodiments provided herein, a constitutively expressed epigenetic editor comprising DNMT3A and a DNMT3L domain effects stable epigenetic modifications. In some embodiments, expression of the target gene is reduced or silenced for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 1 year, at least 2 years, or for the entire lifetime of the cell or the subject carrying the cell, as compared to the level of expression in the absence of the epigenetic editor. The epigenetic modification may be inherited by the progeny of the host cells into which the epigenetic editor was introduced. In some embodiments, the host cell is a liver cell characterized by the presence of an HBV genome in the cell.

The present epigenetic editors may be introduced to a patient in need thereof (e.g., a human patient), e.g., into the patient's hepatocytes, biliary epithelial cells (cholangiocytes), stellate cells, Kupffer cells, and liver sinusoidal endothelial cells.

I. DNA-Binding Domains

An epigenetic editor described herein may comprise one or more DNA-binding domains that direct the effector domain(s) of the epigenetic editor to target sequences within an HBV genome. A DNA-binding domain as described herein may be, e.g., a polynucleotide guided DNA-binding domain, a zinc finger protein (ZFP) domain, a transcription activator like effector (TALE) domain, a meganuclease DNA-binding domain, and the like. Examples of DNA-binding domains can be found in U.S. Pat. No. 11,162,114, which is incorporated by reference herein in its entirety.

In some embodiments, a DNA-binding domain described herein is encoded by its native coding sequence. In other embodiments, the DNA-binding domain is encoded by a nucleotide sequence that has been codon-optimized for optimal expression in human cells.

A. Polynucleotide Guided DNA-Binding Domains

In some embodiments, a DNA-binding domain herein may be a protein domain directed by a guide nucleic acid sequence (e.g., a guide RNA sequence) to a target site in an HBV genome. In certain embodiments, the protein domain may be derived from a CRISPR-associated nuclease, such as a Class I or II CRISPR-associated nuclease. In some

embodiments, the protein domain may be derived from a Cas nuclease such as a Type II, Type IIA, Type IIB, Type IIC, Type V, or Type VI Cas nuclease. In certain embodiments, the protein domain may be derived from a Class II Cas nuclease selected from Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9, Cas10, Cas14a, Cas14b, Cas14c, CasX, CasY, CasPhi, C2c4, C2c8, C2c9, C2c10, Csy1, Csy2, Csy3, Cse1, Cse2, Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx1S, Csf1, Csf2, CsO, Csf4, and homologues and modified versions thereof. "Derived from" is used to mean that the protein domain comprises the full polypeptide sequence of the parent protein, or comprises a variant thereof (e.g., with amino acid residue deletions, insertions, and/or substitutions). The variant retains the desired function of the parent protein (e.g., the ability to form a complex with the guide nucleic acid sequence and the target DNA).

In some embodiments, the CRISPR-associated protein domain may be a Cas9 domain described herein. Cas9 may, for example, refer to a polypeptide with at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity and/or sequence similarity to a wildtype Cas9 polypeptide described herein. In some embodiments, said wildtype polypeptide is Cas9 from *Streptococcus pyogenes* (NCBI Ref. No. NC_002737.2 (SEQ ID NO: 1)) and/or UniProt Ref. No. Q99ZW2 (SEQ ID NO: 2). In some embodiments, said wildtype polypeptide is Cas9 from *Staphylococcus aureus* (SEQ ID NO: 3). In some embodiments, the CRISPR-associated protein domain is a Cpf1 domain or protein, or a polypeptide with at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity and/or sequence similarity to a wildtype Cpf1 polypeptide described herein (e.g., Cpf1 from *Franscisella novicida* (UniProt Ref. No. U2UMQ6 or SEQ ID NO: 4). In certain embodiments, the CRISPR-associated protein domain may be a modified form of the wildtype protein comprising one or more amino acid residue changes such as a deletion, an insertion, or a substitution; a fusion or chimera; or any combination thereof.

Cas9 sequences and structures of variant Cas9 orthologs have been described for various organisms. Exemplary organisms from which a Cas9 domain herein can be derived include, but are not limited to, *Streptococcus pyogenes, Streptococcus thermophilus, Streptococcus* sp., *Staphylococcus aureus, Listeria innocua, Lactobacillus gasseri, Francisella novicida, Wolinella succinogenes, Sutterella wadsworthensis, Gamma proteobacterium, Neisseria meningitidis, Campylobacter jejuni, Pasteurella multocida, Fibrobacter succinogene, Rhodospirillum rubrum, Nocardiopsis dassonvillei, Streptomyces pristinaespiralis, Streptomyces viridochromogenes, Streptomyces viridochromogenes, Streptosporangium roseum, Alicyclobacillus acidocaldarius, Bacillus pseudomycoides, Bacillus selenitireducens, Exiguobacterium sibiricum, Lactobacillus delbrueckii, Lactobacillus salivarius, Lactobacillus buchneri, Treponema denticola, Microscilla marina, Burkholderiales bacterium, Polar omonas naphthalenivorans, Polar omonas* sp., *Crocosphaera watsonii, Cyanothece* sp., *Microcystis aeruginosa, Synechococcus* sp., *Acetohalobium arabaticum, Ammonifex degensii, Caldicelulosiruptor becscii, Candidatus Desulforudis, Clostridium botulinum, Clostridium difficile, Finegoldia magna, Natranaerobius thermophilus, Pelotomaculum thermopropionium, Acidithiobacillus caldus, Acidithiobacillus ferrooxidans, Allochromatium vinosum, Marinobacter* sp., *Nitrosococcus halophilus, Nitrosococcus watsoni, Pseudoalteromonas haloplanktis, Ktedonobacter racemifer, Methanohalobium evestigatum, Anabaena variabilis, Nodularia spumigena, Nostoc* sp., *Arthrospira maxima, Arthrospira platensis, Arthrospira* sp., *Lyngbya* sp., *Microcoleus chthonoplastes, Oscillator* ia sp., *Petrotoga mobilis, Thermosipho africanus, Streptococcus pasteurianus, Neisseria cinerea, Campylobacter lari, Parvibaculum lavamentivorans, Coryne bacterium diphtheria*, and *Acaryochloris marina*. Cas9 sequences also include those from the organisms and loci disclosed in Chylinski et al., RNA Biol. (2013) 10(5):726-37.

In some embodiments, the Cas9 domain is from *Streptococcus pyogenes*. In some embodiments, the Cas9 domain is from *Staphylococcus aureus*.

Other Cas domains are also contemplated for use in the epigenetic editors herein. These include, for example, those from CasX (Cas12E) (e.g., SEQ ID NO: 5), CasY (Cas12d) (e.g., SEQ ID NO: 6), Casφ (CasPhi) (e.g., SEQ ID NO: 7), Cas12f1 (Cas14a) (e.g., SEQ ID NO: 8), Cas12f2 (Cas14b) (e.g., SEQ ID NO: 9), Cas12f3 (Cas14c) (e.g., SEQ ID NO: 10), and C2c8 (e.g., SEQ ID NO: 11).

For epigenetic editing, the nuclease-derived protein domain (e.g., a Cas9 or Cpf1 domain) may have reduced or no nuclease activity through mutations such that the protein domain does not cleave DNA or has reduced DNA-cleaving activity while retaining the ability to complex with the guide nucleic acid sequence (e.g., guide RNA) and the target DNA. For example, the nuclease activity may be reduced by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% compared to the wildtype domain. In some embodiments, a CRISPR-associated protein domain described herein is catalytically inactive ("dead"). Examples of such domains include, for example, dCas9 ("dead" Cas9), dCpf1, ddCpf1, dCasPhi, ddCas12a, dLbCpf1, and dFnCpf1. A dCas9 protein domain, for example, may comprise one, two, or more mutations as compared to wildtype Cas9 that abrogate its nuclease activity. The DNA cleavage domain of Cas9 is known to include two subdomains: the HNH nuclease subdomain and the RuvC1 subdomain. The HNH subdomain cleaves the strand complementary to the gRNA, whereas the RuvC1 subdomain cleaves the non-complementary strand. Mutations within these subdomains can silence the nuclease activity of Cas9. For example, the mutations D10A (in RuvC1) and H840A (in HNH) completely inactivate the nuclease activity of SpCas9. SaCas9, similarly, may be inactivated by the mutations D10A and N580A. In some embodiments, the dCas9 comprises at least one mutation in the HNH subdomain and/or the RuvC1 subdomain that reduces or abrogates nuclease activity. In some embodiments, the dCas9 only comprises a RuvC1 subdomain, or only comprises an HNH subdomain. It is to be understood that any mutation that inactivates the RuvC1 and/or the HNH domain may be included in a dCas9 herein, e.g., insertion, deletion, or single or multiple amino acid substitution in the RuvC1 domain and/or the HNH domain.

In some embodiments, a dCas9 protein herein comprises a mutation at position(s) corresponding to position D10 (e.g., D10A), H840 (e.g., H840A), or both, of a wildtype SpCas9 sequence as numbered in the sequence provided at UniProt Accession No. Q99ZW2 (SEQ ID NO: 2). In particular embodiments, the dCas9 comprises the amino acid sequence of dSpCas9 (D10A and H840A) (SEQ ID NO: 12).

In some embodiments, a dCas9 protein as described herein comprises a mutation at position(s) corresponding to position D10 (e.g., D10A), N580 (e.g., N580A), or both, of

a wildtype SaCas9 sequence (e.g., SEQ ID NO: 9). In particular embodiments, the dCas9 comprises the amino acid sequence of dSaCas9 (D10A and N580A) (SEQ ID NO: 13).

Additional suitable mutations that inactivate Cas9 will be apparent to those of skill in the art based on this disclosure and knowledge in the field and are within the scope of this disclosure. Such mutations may include, but are not limited to, D839A, N863A, and/or K603R in SpCas9. The present disclosure contemplates any mutations that reduce or abrogate the nuclease activity of any Cas9 described herein (e.g., mutations corresponding to any of the Cas9 mutations described herein).

A dCpf1 protein domain may comprise one, two, or more mutations as compared to wildtype Cpf1 that reduce or abrogate its nuclease activity. The Cpf1 protein has a RuvC-like endonuclease domain that is similar to the RuvC domain of Cas9, but does not have an HNH endonuclease domain, and the N-terminal of Cpf1 does not have the alpha-helical recognition lobe of Cas9. In some embodiments, the dCpf1 comprises one or more mutations corresponding to position D917A, E1006A, or D1255A as numbered in the sequence of the *Francisella novicida* Cpf1 protein (FnCpf1; SEQ ID NO: 4). In certain embodiments, the dCpf1 protein comprises mutations corresponding to D917A, E1006A, D1255A, D917A/E1006A, D917A/D1255A, E1006A/D1255A, or D917A/E1006A/D1255A, or corresponding mutation(s) in any of the Cpf1 amino acid sequences described herein. In some embodiments, the dCpf1 comprises a D917A mutation. In particular embodiments, the dCpf1 comprises the amino acid sequence of dFnCpf1 (SEQ ID NO: 14).

Further nuclease inactive CRISPR-associated protein domains contemplated herein include those from, for example, dNmeCas9 (e.g., SEQ ID NO: 15), dCjCas9 (e.g., SEQ ID NO: 16), dSt1Cas9 (e.g., SEQ ID NO: 17), dSt3Cas9 (e.g., SEQ ID NO: 18), dLbCpf1 (e.g., SEQ ID NO: 19), dAsCpf1 (e.g., SEQ ID NO: 20), denAsCpf1 (e.g., SEQ ID NO: 21), dHFAsCpf1 (e.g., SEQ ID NO: 22), dRVRAsCpf1 (e.g., SEQ ID NO: 23), dRRAsCpf1 (e.g., SEQ ID NO: 24), dCasX (e.g., SEQ ID NO: 25), and dCasPhi (e.g., SEQ ID NO: 26).

In some embodiments, a Cas9 domain described herein may be a high fidelity Cas9 domain, e.g., comprising one or more mutations that decrease electrostatic interactions between the Cas9 domain and the sugar-phosphate backbone of DNA to confer increased target binding specificity. In certain embodiments, the high fidelity Cas9 domain may be nuclease inactive as described herein.

A CRISPR-associated protein domain described herein may recognize a protospacer adjacent motif (PAM) sequence in a target gene. A "PAM" sequence is typically a 2 to 6 bp DNA sequence immediately following the sequence targeted by the CRISPR-associated protein domain. The PAM sequence is required for CRISPR protein binding and cleavage but is not part of the target sequence. The CRISPR-associated protein domain may either recognize a naturally occurring or canonical PAM sequence or may have altered PAM specificity. CRISPR-associated protein domains that bind to non-canonical PAM sequences have been described in the art. For example, Cas9 domains that bind non-canonical PAM sequences have been described in Kleinstiver et al., Nature (2015) 523(7561): 481-5 and Kleinstiver et al., *Nat Biotechnol*. (2015) 33:1293-8. Such Cas9 domains may include, for example, those from "VRER (SEQ ID NO: 1261)" SpCas9, "EQR" SpCas9, "VQR" SpCas9, "SpG Cas9," "SpRYCas9," and "KKH" SaCas9. Nuclease inactive versions of these Cas9 domains are also contemplated, such as nuclease inactive VRER (SEQ ID NO: 1261) SpCas9 (e.g., SEQ ID NO: 27), nuclease inactive EQR SpCas9 (e.g., SEQ ID NO: 28), nuclease inactive VQR SpCas9 (e.g., SEQ ID NO: 29), nuclease inactive SpG Cas9 (e.g., SEQ ID NO: 30), nuclease inactive SpRY Cas9 (e.g., SEQ ID NO: 31), and nuclease inactive KKH SaCas9 (e.g., SEQ ID NO: 32). Another example is the Cas9 of *Francisella novicida* engineered to recognize 5'-YG-3' (where "Y" is a pyrimidine).

Additional suitable CRISPR-associated proteins, orthologs, and variants, including nuclease inactive variants and sequences, will be apparent to those of skill in the art based on this disclosure.

Guide RNAs that can be used in conjunction with the CRISPR-associated protein domains herein are further described in Section II below.

B. Zinc Finger Protein Domains

In some embodiments, the DNA-binding domain of an epigenetic editor described herein comprises a zinc finger protein (ZFP) domain (or "ZF domain" as used herein). ZFPs are proteins having at least one zinc finger, and bind to DNA in a sequence-specific manner. A "zinc finger" (ZF) or "zinc finger motif" (ZF motif) refers to a polypeptide domain comprising a beta-beta-alpha ($\beta\beta\alpha$)-protein fold stabilized by a zinc ion. A ZF binds from two to four base pairs of nucleotides, typically three or four base pairs (contiguous or noncontiguous). Each ZF typically comprises approximately 30 amino acids. ZFP domains may contain multiple ZFs that make tandem contacts with their target nucleic acid sequence. A tandem array of ZFs may be engineered to generate artificial ZFPs that bind desired nucleic acid targets. ZFPs may be rationally designed by using databases comprising triplet (or quadruplet) nucleotide sequences and individual ZF amino acid sequences, in which each triplet or quadruplet nucleotide sequence is associated with one or more amino acid sequences of ZFs that bind the particular triplet or quadruplet sequence. See, e.g., U.S. Pat. Nos. 6,453,242, 6,534,261, and 8,772,453.

ZFPs are widespread in eukaryotic cells, and may belong to, e.g., C2H2 class, CCHC class, PHD class, or RING class. An exemplary motif characterizing one class of these proteins (C2H2 class) is -Cys-$(X)_{2-4}$-Cys-$(X)_{12}$-His-$(X)_{3-5}$-His- (SEQ ID NO:1091), where X is any independently chosen amino acid. In some embodiments, a ZFP domain herein may comprise a ZF array comprising sequential C2H2-ZFs each contacting three or more sequential nucleotides. Additional architectures, e.g. as described in Paschon et al., Nat. Commun. 10, 1133 (2019), are also possible.

A ZFP domain of an epigenetic editor described herein may include 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more ZFs. The ZFP domain may include an array of two-finger or three-finger units, e.g., 3, 4, 5, 6, 7, 8, 9 or 10 or more units, wherein each unit binds a subsite in the target sequence. In some embodiments, a ZFP domain comprising at least three ZFs recognizes a target DNA sequence of 9 or 10 nucleotides. In some embodiments, a ZFP domain comprising at least four ZFs recognizes a target DNA sequence of 12 to 14 nucleotides. In some embodiments, a ZFP domain comprising at least six ZFs recognizes a target DNA sequence of 18 to 21 nucleotides.

In some embodiments, ZFs in a ZFP domain described herein are connected via peptide linkers. The peptide linkers may be, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more amino acids in length. In some embodiments, a linker comprises 5 or more amino acids. In

some embodiments, a linker comprises 7-17 amino acids. The linker may be flexible or rigid.

In some embodiments a zinc finger array may have the sequence:

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SRPGERPFQCRICMRNFSXXXXXXXHXXTHTGEKPFQCRICMRNF

SXXXXXXXHXXTH[linker]FQCRICMRNFSXXXXXXXHXXTHT

GEKPFQCRICMRNFSXXXXXXXHXXTH[linker]PFQCRICMRN

FSXXXXXXXHXXTHTGEKPFQCRICMRNFSXXXXXXXHXXTHLRG

S
(SEQ ID NOs: 1084 and 1258-1259, respectively,
in order of appearance),
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or a sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto, where "XXXXXXX" represents the amino acids of the ZF recognition helix, which confers DNA-binding specificity upon the zinc finger; each X may be independently chosen. In the above sequence, "XX" in italics may be TR, LR or LK, and "[linker]" represents a linker sequence. In some embodiments, the linker sequence is TGSQKP (SEQ ID NO: 1085); this linker may be used when sub-sites targeted by the ZFs are adjacent. In some embodiments, the linker sequence is TGGGGSQKP (SEQ ID NO: 1086); this linker may be used when there is a base between the sub-sites targeted by the zinc fingers. The two indicated linkers may be the same or different.

ZFP domains herein may contain arrays of two or more adjacent ZFs that are directly adjacent to one another (e.g., separated by a short (canonical) linker sequence), or are separated by longer, flexible or structured polypeptide sequences. In some embodiments, directly adjacent fingers bind to contiguous nucleic acid sequences, i.e., to adjacent trinucleotides/triplets. In some embodiments, adjacent fingers cross-bind between each other's respective target triplets, which may help to strengthen or enhance the recognition of the target sequence, and leads to the binding of overlapping sequences. In some embodiments, distant ZFs within the ZFP domain may recognize (or bind to) non-contiguous nucleotide sequences.

The amino acid sequences of the ZF DNA-recognition helices of exemplary ZFP domains herein, and their HBV target sequences, are shown below in Table 1. Table 1. Zinc finger transcriptional repressors for silencing HBV. ZF sequences of exemplary ZFP domains are presented. SEQ ID Nos for target sequences and ZF can be found in Table 18 sequence listing.

TABLE 18

sequence listing.

ZFP	SEQ ID	Target Sequence	Start	End	Strd	F1	F2	F3	F4	F5	F6
ZFP894	33	GATGAGGCAT AGCAGCAG (SEQ ID NO: 102)	415	432	-	KKEN LLQ (SEQ ID NO: 125)	RQDN LNS (SEQ ID NO: 156)	RSHN LKL (SEQ ID NO: 189)	QSTT LKR (SEQ ID NO: 222)	RNTN LTR (SEQ ID NO: 257)	IKHN LAR (SEQ ID NO: 297)
ZFP895	34	GATGAGGCAT AGCAGCAG (SEQ ID NO: 102)	415	432	-	KKEN LLQ (SEQ ID NO: 125)	RKDY LIS (SEQ ID NO: 157)	RSHN LKI (SEQ ID NO: 189)	QSTT LKR (SEQ ID NO: 222)	RQDN LGR (SEQ ID NO: 258)	VVNN LNR (SEQ ID NO: 298)
ZFP896	35	GATGAGGCAT AGCAGCAG (SEQ ID NO: 102)	415	432	-	KKEN LLO (SEQ ID NO: 125)	RKDY LIS (SEQ ID NO: 157)	RSHN LRL (SEQ ID NO: 190)	QSTT LKR (SEQ ID NO: 222)	RQDN LGR (SEQ ID NO: 258)	VVNN LNR (SEQ ID NO: 298)
ZFP899	36	GATGATTAGG CAGAGGTG (SEQ ID NO: 103)	1828	1845	-	RRHI LDR (SEQ ID NO: 126)	RQDN LGR (SEQ ID NO: 158)	QSTT LKR (SEQ ID NO: 191)	RRDG LAG (SEQ ID NO: 223)	VHHN LVR (SEQ ID NO: 259)	ISHN LAR (SEQ ID NO: 299)
ZFP900	37	GATGATTAGG CAGAGGTG (SEQ ID NO: 103)	1828	1845	-	RREV LEN (SEQ ID NO: 127)	RRDN LNR (SEQ ID NO: 159)	QSTT LKR (SEQ ID NO: 191)	RRDG LAG (SEQ ID NO: 223)	VHHN LVR (SEQ ID NO: 259)	ISHN LAR (SEQ ID NO: 299)
ZFP901	38	GATGATTAGG CAGAGGTG (SEQ ID NO : 103	1828	1845	-	RRAV LDR (SEQ ID NO: 128)	RQDN LGR (SEQ ID NO: 158)	QSTT LKR (SEQ ID NO: 191)	RRDG LAG (SEQ ID NO: 223)	VHHN LVR (SEQ ID NO: 259)	ISHN LAR (SEQ ID NO: 299)

TABLE 18-continued

sequence listing.

ZFP	SEQ ID	Target Sequence	Start	End	Strd	F1	F2	F3	F4	F5	F6
ZFP902	39	GGATTCAGCG CCGACGGG (SEQ ID NO: 104)	1433	1450	-	RQEH LVR (SEQ ID NO: 129)	EGGN LMR (SEQ ID NO: 160)	SDRR DLD (SEQ ID NO: 192)	SFQS YLE (SEQ ID NO: 224)	RPNH LAI (SEQ ID NO: 260)	QSPH LKR (SEQ ID NO: 300)
ZFP903	40	GGATTCAGCG CCGACGGG (SEQ ID NO: 104)	1433	1450	-	RREH LVR (SEQ ID NO: 130)	DPSN LOR (SEQ ID NO: 161)	SDRR DLD (SEQ ID NO: 192)	SFQS YLE (SEQ ID NO: 224)	RPNH LAI (SEQ ID NO: 260)	QSPH LKR (SEQ ID NO: 300)
ZFP904	41	GGATTCAGCG CCGACGGG (SEQ ID NO: 104)	1433	1450	-	RREH LVR (SEQ ID NO: 130)	DMGN LGR (SEQ ID NO: 162)	SDRR DLD (SEQ ID NO: 192)	SFQS YLE (SEQ ID NO: 224)	RPNH LAI (SEQ ID NO: 260)	QSPH LKR (SEQ ID NO: 300)
ZFP907	42	GGCAGTAGTC GGAACAGGG (SEQ ID NO: 105)	90	108	-	KKDH LHR (SEQ ID NO: 131)	QKEI LTR (SEQ ID NO: 163)	QSAH LKR (SEQ ID NO: 193)	ETGS LRR (SEQ ID NO: 225)	QSHS LKS (SEQ ID NO: 261)	ESGH LKR (SEQ ID NO: 301)
ZFP908	43	GGCAGTAGTC GGAACAGGG (SEQ ID NO: 105)	90	108	-	KKDH LHR (SEQ ID NO: 131)	QKEI LTR (SEQ ID NO: 163)	QSAH LKR (SEQ ID NO: 193)	DRTP LNR (SEQ ID NO: 226)	QSHS LKS (SEQ ID NO: 261)	ESGH LKR (SEQ ID NO: 301)
ZFP909	44	GGCAGTAGTC GGAACAGGG	90	108	-	KTDH LAR (SEQ ID NO: 132)	QKEI LTR (SEQ ID NO: 163)	QSAH LKR (SEQ ID NO: 193)	ETGS LRR (SEQ ID NO: 225)	QKHH LVT (SEQ ID NO: 262)	ENSK LRR (SEQ ID NO: 302)
ZFP912	45	GTAAACTGAG CCAGGAGAA (SEQ ID NO: 106)	664	682	-	QAGN LVR (SEQ ID NO: 133)	QNSH LRR (SEQ ID NO: 164)	DLST LRR (SEQ ID NO: 194)	QNEH LKV (SEQ ID NO: 227)	GGTA LRM (SEQ ID NO: 263)	QRSS LVR (SEQ ID NO: 303)
ZFP913	46	GTAAACTGAG CCAGGAGAA (SEQ ID NO: 106)	664	682	-	QRGN LQR (SEQ ID NO: 134)	QTTH LSR (SEQ ID NO: 165)	DGST LRR (SEQ ID NO: 195)	QKTH LAV (SEQ ID NO: 228)	GGTA LRM (SEQ ID NO: 263)	QRSS LVR (SEQ ID NO: 303)
ZFP914	47	GTAAACTGAG CCAGGAGAA (SEQ ID NO: 106)	664	682	-	QRGN LQR (SEQ ID NO: 134)	QTTH LSR (SEQ ID NO: 165)	DLST LRR (SEQ ID NO: 194)	QNEH LKV (SEQ ID NO: 227)	GGSA LSM (SEQ ID NO: 264)	QRSS LVR (SEQ ID NO: 303)
ZFP930	48	ACGGTGGTCT CCATGCGAC (SEQ ID NO: 107)	1605	1623	-	DRGN LTR (SEQ ID NO: 135)	QARS LRA (SEQ ID NO: 166)	EKAS LIK (SEQ ID NO: 196)	DHSS LKR (SEQ ID NO: 229)	RRFI LSR (SEQ ID NO: 265)	RNDS LKC (SEQ ID NO: 304)
ZFP931	49	ACGGTGGTCT CCATGCGAC (SEQ ID NO: 107)	1605	1623	-	DRGN LTR (SEQ ID	QARS LRA (SEQ ID	DKSS LRK (SEQ ID	DHSS LKR (SEQ ID	RNFI LQR (SEQ ID	RNDT LII (SEQ ID

TABLE 18-continued

sequence listing.

ZFP	SEQ ID	Target Sequence	Start	End	Strd	F1	F2	F3	F4	F5	F6
						NO: 135)	NO: 166)	NO: 197)	NO: 229)	NO: 266)	NO: 305)
ZFP932	50	ACGGTGGTCT CCATGCGAC (SEQ ID NO: 107)	1605	1623	-	DRGN LTR (SEQ ID NO: 135)	QARS LRA (SEQ ID NO: 166)	CNGS LKK (SEQ ID NO: 198)	DHSS LKR (SEQ ID NO: 229)	RNFI LQR (SEQ ID NO: 266)	RNDT LII (SEQ ID NO: 305)
ZFP933	51	GCTGGATGTG TCTGCGGCG (SEQ ID NO: 108)	372	393	+	RTDT LAR (SEQ ID NO: 136)	RTDS LPR (SEQ ID NO: 167)	DHSS LKR (SEQ ID NO: 199)	QPHG LAH (SEQ ID NO: 230)	QSAH LKR (SEQ ID NO: 267)	VGNS LSR (SEQ ID NO: 306)
ZFP934	52	GCTGGATGTG TCTGCGGCG (SEQ ID NO: 108)	372	393	+	RTDT LAR (SEQ ID NO: 136)	RTDS LPR (SEQ ID NO: 167)	DHSS LKR (SEQ ID NO: 199)	QPHG LRH (SEQ ID NO: 231)	QSAH LKR (SEQ ID NO: 267)	VGNS LSR (SEQ ID NO: 306)
ZFP935	53	GCTGGATGTG TCTGCGGCG (SEQ ID NO: 108)	372	393	+	RTDT LAR (SEQ ID NO: 136)	RLDM LAR (SEQ ID NO: 168)	DHSS LKR (SEQ ID NO: 199)	QPHG LST (SEQ ID NO: 232)	QQAH LVR (SEQ ID NO: 268)	VHES LKR (SEQ ID NO: 307)
ZFP938	54	GTCTGCGAGG CGAGGGAG (SEQ ID NO: 109)	2381	2398	-	RADN LGR (SEQ ID NO: 137)	RNTH LSY (SEQ ID NO: 169)	RGDG LRR (SEQ ID NO: 200)	RRDN LNR (SEQ ID NO: 233)	RARN LTL (SEQ ID NO: 269)	DPSS LKR (SEQ ID NO: 308)
ZFP939	55	GTCTGCGAGG CGAGGGAG (SEQ ID NO: 109)	2381	2398	-	RADN LGR (SEQ ID NO: 137)	RNTH LSY (SEQ ID NO: 169)	RKLG LLR (SEQ ID NO: 201)	RQDN LGR (SEQ ID NO: 234)	RARN LTL (SEQ ID NO: 269)	DPSS LKR (SEQ ID NO: 308)
ZFP940	56	GTCTGCGAGG CGAGGGAG (SEQ ID NO: 109)	2381	2398	-	RADN LGR (SEQ ID NO: 137)	RNTH LSY (SEQ ID NO: 169)	RKLG LLR (SEQ ID NO: 201)	RODN LGR (SEQ ID NO: 234)	RRRN LQL (SEQ ID NO: 270)	DHSS LKR (SEQ ID NO: 309)
ZFP943	57	GTTGCCGGGC AACGGGGTA (SEQ ID NO: 110)	1146	1164	-	QQSS LLR (SEQ ID NO: 138)	RREH LVR (SEQ ID NO: 170)	GLTA LRT (SEQ ID NO: 202)	ERAK LIR (SEQ ID NO: 235)	AKRD LDR (SEQ ID NO: 271)	VNSS LTR (SEQ ID NO: 310)
ZFP944	58	GTTGCCGGGC AACGGGGTA (SEQ ID NO: 110)	1146	1164	-	QQSS LLR (SEQ ID NO: 138)	RREH LVR (SEQ ID NO: 170)	GLTA LRT (SEQ ID NO: 202)	ERAK LIR (SEQ ID NO: 235)	LRKD LVR (SEQ ID NO: 272)	VRHS LTR (SEQ ID NO: 311)
ZFP945	59	GTTGCCGGGC AACGGGGTA (SEQ ID NO: 110)	1146	1164	-	QASA LSR (SEQ ID NO: 139)	RREH LVR (SEQ ID NO: 170)	GLTA LRT (SEQ ID NO: 202)	ERAK LIR (SEQ ID NO: 235)	AKRD LDR (SEQ ID NO: 271)	VNSS LTR (SEQ ID NO: 310)
ZFP951	60	CGAGAAAGTG AAAGCCTGC	1085	1103	-	RGRN LEM	DSSV LRR	QNAN LKR	QKHH LAV	QRSN LAR	QKVH LEA

TABLE 18-continued

sequence listing.

ZFP	SEQ ID	Target Sequence	Start	End	Strd	F1	F2	F3	F4	F5	F6
		(SEQ ID NO: 111)				(SEQ ID NO: 140)	(SEQ ID NO: 171)	(SEQ ID NO: 203)	(SEç ID NO: 236)	(SEQ ID NO: 273)	(SEQ ID NO: 312)
ZFP952	61	CGAGAAAGTG AAAGCCTGC (SEQ ID NO: 111)	1085	1103	-	RRRN LDV (SEQ ID NO: 141)	DSSV LRR (SEQ ID NO: 171)	QNAN LKR (SEQ ID NO: 203)	QKHH LAV (SEQ ID NO: 236)	QRSN LAR (SEQ ID NO: 273)	QKVH LEA (SEQ ID NO: 312)
ZFP953	62	CGAGAAAGTG AAAGCCTGC (SEQ ID NO: 111)	1085	1103	-	RGRN LAI (SEQ ID NO: 142)	DSSV LRR (SEQ ID NO: 171)	LKSN LHR (SEQ ID NO: 204)	LKQH LVV (SEQ ID NO: 237)	LKTN LAR (SEQ ID NO: 274)	QKCH LKA (SEQ ID NO: 313)
ZFP956	63	GAGGCTTGAA CAGTAGGAC (SEQ ID NO: 112)	1856	1874	-	DGSN LRR (SEQ ID NO: 143)	RIDN LDG (SEQ ID NO: 172)	QRRY LVE (SEQ ID NO: 205)	QQTN LAR (SEQ ID NO: 238)	QRSD LTR (SEQ ID NO: 275)	RGDN LNR (SEQ ID NO: 314)
ZFP957	64	GAGGCTTGAA CAGTAGGAC (SEQ ID NO: 112)	1856	1874	-	DPSN LOR (SEQ ID NO: 144)	RRDN LPK (SEQ ID NO: 173)	TTFN LRV (SEQ ID NO: 206)	QTQN LTR (SEQ ID NO: 239)	HKET LNR (SEQ ID NO: 276)	REDN LGR (SEQ ID NO: 315)
ZFP958	65	GAGGCTTGAA CAGTAGGAC (SEQ ID NO: 112)	1856	1874	-	DPSN LOR (SEQ ID NO: 144)	RRDN LPK (SEQ ID NO: 173)	QRRY LVE (SEQ ID NO: 205)	QQTN LAR (SEQ ID NO: 238)	QRSD LTR (SEQ ID NO: 275)	RGDN LNR (SEQ ID NO: 314)
ZFP961	66	GAGGTTGGGG ACTGCGAA (SEQ ID NO: 113)	312	329	-	QQTN LTR (SEQ ID NO: 145)	ANRT LVH (SEQ ID NO: 174)	EEAN LRR (SEQ ID NO: 207)	RGEH LTR (SEQ ID NO: 240)	TNSS LTR (SEQ ID NO: 277)	RIDN LIR (SEQ ID NO: 316)
ZFP962	67	GAGGTTGGGG ACTGCGAA (SEQ ID NO: 113)	312	329	-	QQTN LTR (SEQ ID NO: 145)	ANRT LVH (SEQ ID NO: 174)	EEAN LRR (SEQ ID NO: 207)	RREH LVR (SEQ ID NO: 241)	MTSS LRR (SEQ ID NO: 278)	RQDN LGR (SEQ ID NO: 317)
ZFP963	68	GAGGTTGGGG ACTGCGAA (SEQ ID NO: 113)	312	329	-	QQTN LTR (SEQ ID NO: 145)	ANRT LVH (SEQ ID NO: 174)	EEAN LRR (SEQ ID NO: 207)	RGEH LTR (SEQ ID NO: 240)	MTSS LRR (SEQ ID NO: 278)	RQDN LGR (SEQ ID NO: 317)
ZFP964	69	GATGATGTGG TATTGGGG (SEQ ID NO: 114)	742	762	+	RATH LTR (SEQ ID NO: 146)	RADV LKG (SEQ ID NO: 175)	QRSS LVR (SEQ ID NO: 208)	RKDA LHV (SEQ ID NO: 242)	VHHN LVR (SEQ ID NO: 259)	ISHN LAR (SEQ ID NO: 299)
ZFP965	70	GATGATGTGG TATTGGGG (SEQ ID NO: 114)	742	762	+	RATH LTR (SEQ ID NO: 146)	RADV LKG (SEQ ID NO: 175)	QSSS LVR (SEQ ID NO: 209)	RKER LAT (SEQ ID NO: 243)	VRHN LTR (SEQ ID NO: 279)	ISHN LAR (SEQ ID NO: 299)

TABLE 18-continued

sequence listing.

ZFP	SEQ ID	Target Sequence	Start	End	Strd	F1	F2	F3	F4	F5	F6
ZFP966	71	GATGATGTGG TATTGGGG (SEQ ID NO: 114)	742	762	+	KKDH LHR (SEQ ID NO: 131)	RKES LTV (SEQ ID NO: 176)	QSSS LVR (SEQ ID NO: 209)	RKER LAT (SEQ ID NO: 243)	VHHN LVR (SEQ ID NO: 259)	ISHN LAR (SEQ ID NO: 299)
ZFP969	72	GATGATGTGG TATTGGGGG (SEQ ID NO: 115)	742	763	+	RVDH LHR (SEQ ID NO: 147)	RREH LSG (SEQ ID NO: 177)	QSSS LVR (SEQ ID NO: 209)	RKER LAT (SEQ ID NO: 243)	VAHN LTR (SEQ ID NO: 280)	ISHN LAR (SEQ ID NO: 299)
ZFP970	73	GATGATGTGG TATTGGGGG (SEQ ID NO: 115)	742	763	+	RKHH LGR (SEQ ID NO: 148)	RREH LTI (SEQ ID NO: 178)	QSSS LVR (SEQ ID NO: 209)	RKER LAT (SEQ ID NO: 243)	VAHN LTR (SEQ ID NO: 280)	ISHN LAR (SEQ ID NO: 299)
ZFP971	74	GATGATGTGG TATTGGGGG (SEQ ID NO: 115)	742	763	+	RVDH LHR (SEQ ID NO: 147)	RSDH LSL (SEQ ID NO: 179)	QSSS LVR (SEQ ID NO: 209)	RKER LAT (SEQ ID NO: 243)	VAHN LTR (SEQ ID NO: 280)	ISHN LAR (SEQ ID NO: 299)
ZFP984	75	GCAGTAGTCG GAACAGGG (SEQ ID NO: 116)	90	107	–	KTDH LAR (SEQ ID NO: 132)	QKEI LTR (SEQ ID NO: 163)	QSAH LKR (SEQ ID NO: 193)	ETGS LRR (SEQ ID NO: 225)	QSSS LVR (SEQ ID NO: 281)	QTNT LGR (SEQ ID NO: 318)
ZFP985	76	GCAGTAGTCG GAACAGGG (SEQ ID NO: 116)	90	107	–	KKDH LHR (SEQ ID NO: 131)	QKEI LTR (SEQ ID NO: 163)	QSAH LKR (SEQ ID NO: 193)	ETGS LRR (SEQ ID NO: 225)	QSSS LVR (SEç ID NO: 281)	QGGT LRR (SEQ ID NO: 319)
ZFP986	77	GCAGTAGTCG GAACAGGG (SEQ ID NO: 116)	90	107	–	KKDH LHR (SEQ ID NO: 131)	QKEI LTR (SEQ ID NO: 163)	QSAH LKR (SEQ ID NO: 193)	DPTS LNR (SEQ ID NO: 244)	QSSS LVR (SEQ ID NO: 281)	QTNT LGR (SEQ ID NO: 318)
ZFP989	78	GCATAGCAGC AGGATGAA (SEQ ID NO: 117)	409	426	–	QQTN LTR (SEQ ID NO: 145)	VGGN LAR (SEQ ID NO: 180)	KRYN LYQ (SEQ ID NO: 210)	RQDN LNT (SEQ ID NO: 245)	RSHN LKL (SEQ ID NO: 283)	QSTT LKR (SEQ ID NO: 320)
ZFP990	79	GCATAGCAGC AGGATGAA (SEQ ID NO: 117)	409	426	–	QQTN LTR (SEQ ID NO: 145)	VGGN LSR (SEQ ID NO: 181)	KRYN LYQ (SEQ ID NO: 210)	RQDN LNT (SEQ ID NO: 245)	RSHN LRL (SEQ ID NO: 283)	QSTT LKR (SEQ ID NO: 320)
ZFP991	80	GCATAGCAGC AGGATGAA (SEQ ID NO: 117)	409	426	–	QQTN LTR (SEQ ID NO: 145)	VGGN LSR (SEQ ID NO: 181)	KKEN LLQ (SEQ ID NO: 211)	RRDN LKS (SEQ ID NO: 246)	RSHN LKI (SEQ ID NO: 282)	QSTT LKR (SEQ ID NO: 320)
ZFP994	81	GGCGTTCACG GTGGTCTCC (SEQ ID	1612	1630	–	DKSS LRK (SEQ	DHSS LKR (SEQ	RNFI LOR (SEQ	RNDT LII (SEQ	TSTL LKR (SEQ	LKEH LTR (SEQ

TABLE 18-continued

sequence listing.

ZFP	SEQ ID	Target Sequence	Start	End	Strd	F1	F2	F3	F4	F5	F6
		NO: 118)				ID NO: 149)	ID NO: 182)	ID NO: 212)	ID NO: 247)	ID NO: 284)	ID NO: 321)
ZFP995	82	GGCGTTCACG GTGGTCTCC (SEQ ID NO: 118)	1612	1630	-	CNGS LKK (SEQ ID NO: 150)	DHSS LKR (SEQ ID NO: 182)	RNFI LAR (SEQ ID NO: 213)	RQDI LVV (SEQ ID NO: 248)	HKSS LTR (SEQ ID NO: 285)	ESGH LKR (SEQ ID NO: 301)
ZFP996	83	GGCGTTCACG GTGGTCTCC (SEQ ID NO: 118)	1612	1630	-	CNGS LKK (SEQ ID NO: 150)	DHSS LKR (SEQ ID NO: 182)	RNFI LAR (SEQ ID NO: 213)	RQDI LVV (SEQ ID NO: 248)	TSTL LKR (SEQ ID NO: 284)	LKEH LTR (SEQ ID NO: 321)
ZFP999	84	GTTGGTGAGT GATTGGAG (SEQ ID NO: 119)	327	344	-	TNNN LAR (SEQ ID NO: 151)	RTDS LTL (SEQ ID NO: 183)	QREH LTT (SEQ ID NO: 214)	RRDN LNR (SEQ ID NO: 233)	RRQK LTI (SEQ ID NO: 286)	HKSS LTR (SEQ ID NO: 322)
ZFP1000	85	GTTGGTGAGT GATTGGAG (SEQ ID NO: 119)	327	344	-	TNNN LAR (SEQ ID NO: 151)	RTDS LTL (SEQ ID NO: 183)	QREH LTT (SEQ ID NO: 214)	RGDN LKR (SEQ ID NO: 249)	RRQK LTI (SEQ ID NO: 286)	HKSS LTR (SEQ ID NO: 322)
ZFP1001	86	GTTGGTGAGT GATTGGAG (SEQ ID NO: 119)	327	344	-	TNNN LAR (SEQ ID NO: 151)	RTDS LTL (SEQ ID NO: 183)	QREH LNG (SEQ ID NO: 215)	RGDN LAR (SEQ ID NO: 250)	RRQK LTI (SEQ ID NO: 286)	HKSS LTR (SEQ ID NO: 322)
ZFP1005	87	GGAGGTTGGG GACTGCGAA (SEQ ID NO: 120)	312	330	-	QQTN LTR (SEQ ID NO: 145)	ANRT LVH (SEQ ID NO: 174)	DPAN LRR (SEQ ID NO: 216)	RQEH LVR (SEQ ID NO: 251)	MKHH LGR (SEQ ID NO: 287)	QNSH LRR (SEQ ID NO: 323)
ZFP1006	88	GGAGGTTGGG GACTGCGAA (SEQ ID NO: 120)	312	330	-	QQTN LTR (SEQ ID NO: 145)	ANRT LVH (SEQ ID NO: 174)	EEAN LRR (SEQ ID NO: 207)	RREH LVR (SEQ ID NO: 241)	MKHH LGR (SEQ ID NO: 287)	QNSH LRR (SEQ ID NO: 323)
ZFP1007	89	GGAGGTTGGG GACTGCGAA (SEQ ID NO: 120)	312	330	-	QQTN LTR (SEQ ID NO: 145)	ANRT LVH (SEQ ID NO: 174)	DPAN LRR (SEQ ID NO: 216)	RQEH LVR (SEQ ID NO: 251)	LKQH LVR (SEQ ID NO: 288)	QGGH LAR (SEQ ID NO: 324)
ZFP1008	90	GGATGATGTG GTATTGGGG (SEQ ID NO: 121)	741	762	+	RNTH LAR (SEQ ID NO: 152)	RADV LKG (SEQ ID NO: 175)	QRSS LVR (SEQ ID NO: 208)	RKDA LHV (SEQ ID NO: 242)	QNEH LKV (SEQ ID NO: 289)	QNSH LRR (SEQ ID NO: 323)
ZFP1009	91	GGATGATGTG GTATTGGGG (SEQ ID NO: 121)	741	762	+	RNTH LAR (SEQ ID NO: 152)	RADV LKG (SEQ ID NO: 175)	QSSS LVR (SEQ ID NO: 209)	RKER LAT (SEQ ID NO: 243)	QKTH LAV (SEQ ID NO: 290)	QGGH LKR (SEQ ID NO: 325)

TABLE 18-continued

sequence listing.

ZFP	SEQ ID	Target Sequence	Start	End	Strd	F1	F2	F3	F4	F5	F6
ZFP1010	92	GGATGATGTG GTATTGGGG (SEQ ID NO: 121)	741	762	+	RNTH LAR (SEQ ID NO: 152)	RADV LKG (SEQ ID NO: 175)	QSSS LVR (SEQ ID NO: 209)	RKER LAT (SEQ ID NO: 243)	QKTH LAV (SEQ ID NO: 290)	QNSH LRR (SEQ ID NO: 323)
ZFP1013	93	GGATGTGTCT GCGGCGTT (SEQ ID NO: 122)	375	395	+	HKSS LTR (SEQ ID NO: 153)	ESGH LKR (SEQ ID NO: 184)	RRRN LTL (SEQ ID NO: 217)	DRSS LKR (SEQ ID NO: 252)	QPHS LAV (SEQ ID NO: 291)	QKPH LSR (SEQ ID NO: 326)
ZFP1014	94	GGATGTGTCT GCGGCGTT (SEQ ID NO: 122)	375	395	+	HKSS LTR (SEQ ID NO: 153)	EGGH LKR (SEQ ID NO: 185)	RRRN LQL (SEQ ID NO: 218)	DHSS LKR (SEQ ID NO: 229)	RRQH LQY (SEQ ID NO: 292)	QSAH LKR (SEQ ID NO: 327)
ZFP1015	95	GGATGTGTCT GCGGCGTT (SEQ ID NO: 122)	375	395	+	HKSS LTR (SEQ ID NO: 153)	EGGH LKR (SEQ ID NO: 185)	RRRN LTL (SEQ ID NO: 217)	DRSS LKR (SEQ ID NO: 252)	RRQH LQY (SEQ ID NO: 292)	QSAH LKR (SEQ ID NO: 327)
ZFP1018	96	GGGGGTTGCG TCAGCAAAC (SEQ ID NO: 123)	1184	1202	−	GHTA LRN (SEQ ID NO: 154)	QSGT LHR (SEQ ID NO: 186)	DHSS LKR (SEQ ID NO: 199)	AMRS LMG (SEQ ID NO: 253)	RRSR LVR (SEQ ID NO: 293)	RGEH LTR (SEQ ID NO: 328)
ZFP1019	97	GGGGGTTGCG TCAGCAAAC (SEQ ID NO: 123)	1184	1202	−	GHTA LRN (SEQ ID NO: 154)	QSTT LKR (SEQ ID NO: 187)	DHSS LKR (SEQ ID NO: 199)	QQRS LVG (SEQ ID NO: 254)	EAHH LSR (SEQ ID NO: 294)	RTEH LAR (SEQ ID NO: 329)
ZFP1020	98	GGGGGTTGCG TCAGCAAAC (SEQ ID NO: 123)	1184	1202	−	GHTA LRN (SEQ ID NO: 154)	QSTT LKR (SEQ ID NO: 187)	DHSS LKR (SEQ ID NO: 199)	AMRS LMG (SEQ ID NO: 253)	RQSR LQR (SEQ ID NO: 295)	RREH LVR (SEQ ID NO: 330)
ZFP1023	99	GTTGTTAGAC GACGAGGCA (SEQ ID NO: 124)	2342	2363	+	QGET LKR (SEQ ID NO: 155)	RADN LRR (SEQ ID NO: 188)	DKAN LTR (SEQ ID NO: 219)	DOGN LIR (SEQ ID NO: 255)	HRHV LIN (SEQ ID NO: 296)	TNSS LTR (SEQ ID NO: 331)
ZFP1024	100	GTTGTTAGAC GACGAGGCA (SEQ ID NO: 124)	2342	2363	+	QGET LKR (SEQ ID NO: 155)	RADN LRR (SEQ ID NO: 188)	DSSN LRR (SEQ ID NO: 220)	DQGN LIR (SEQ ID NO: 255)	HKSS LTR (SEQ ID NO: 285)	IRTS LKR (SEQ ID NO: 332)
ZFP1025	101	GTTGTTAGAC GACGAGGCA (SEQ ID NO: 124)	2342	2363	+	QGET LKR (SEQ ID NO: 155)	RADN LRR (SEQ ID NO: 188)	EQGN LLR (SEQ ID NO: 221)	DGGN LGR (SEQ ID NO: 256)	HRHV LIN (SEQ ID NO: 296)	TNSS LTR (SEQ ID NO: 331)

In some embodiments, the ZFP domain of the present epigenetic editor binds to a target sequence provided herein. In further embodiments, the ZFP domain comprises, in order, the F1-F6 amino acid sequences of any one of the zinc finger proteins as shown in Table 1 and Table 18. The F1-F6 amino acid sequences may be placed within the ZF framework sequence of SEQ ID NOs: 1084 and 1258-1259, or within any other ZF framework known in the art.

C. TALEs

In some embodiments, the DNA-binding domain of an epigenetic editor described herein comprises a transcription activator-like effector (TALE) domain. The DNA-binding domain of a TALE comprises a highly conserved sequence of about 33-34 amino acids, with a repeat variable di-residue (RVD) at positions 12 and 13 that is central to the recognition of specific nucleotides. TALEs can be engineered to bind practically any desired DNA sequence. Methods for programming TALEs are known in the art. For example, such methods are described in Carroll et al., *Genet Soc Amer*. (2011) 188(4):773-82; Miller et al., *Nat Biotechnol*. (2007) 25(7):778-85; Christian et al., *Genetics* (2008) 186 (2):757-61; Li et al., *Nucl Acids Res*. (2010) 39(1):359-72; and Moscou et al., *Science* (2009) 326(5959):1501.

D. Other DNA-Binding Domains

Other DNA-binding domains are contemplated for the epigenetic editors described herein. In some embodiments, the DNA-binding domain comprises an argonaute protein domain, e.g., from *Natronobacterium gregoryi* (NgAgo). NgAgo is a ssDNA-guided endonuclease that is guided to its target site by 5' phosphorylated ssDNA (gDNA), where it produces double-strand breaks. In contrast to Cas9, the NgAgo-gDNA system does not require a protospacer-adjacent motif (PAM). Thus, using a nuclease inactive NgAgo (dNgAgo) can greatly expand the bases that may be targeted. The characterization and use of NgAgo have been described, e.g., in Gao et al., *Nat Biotechnol*. (2016) 34(7):768-73; Swarts et al., *Nature* (2014) 507(7491):258-61; and Swarts et al., *Nucl Acids Res*. (2015) 43(10):5120-9.

In some embodiments, the DNA-binding domain comprises an inactivated nuclease, for example, an inactivated meganuclease. Additional non-limiting examples of DNA-binding domains include tetracycline-controlled repressor (tetR) DNA-binding domains, leucine zippers, helix-loop-helix (HLH) domains, helix-turn-helix domains, β-sheet motifs, steroid receptor motifs, bZIP domains homeodomains, and AT-hooks.

II. Guide Polynucleotides

Epigenetic editors described herein that comprise a polynucleotide guided DNA-binding domain may also include a guide polynucleotide that is capable of forming a complex with the DNA-binding domain. The guide polynucleotide may comprise RNA, DNA, or a mixture of both. For example, where the polynucleotide guided DNA-binding domain is a CRISPR-associated protein domain, the guide polynucleotide may be a guide RNA (gRNA). A "guide RNA" or "gRNA" refers to a nucleic acid that is able to hybridize to a target sequence and direct binding of the CRISPR-Cas complex to the target sequence. Methods of using guide polynucleotide sequences with programmable DNA-binding proteins (e.g., CRISPR-associated protein domains) for site-specific DNA targeting (e.g., to modify a genome) are known in the art.

A guide polynucleotide sequence (e.g., a gRNA sequence) may comprises two parts: 1) a nucleotide sequence comprising a "targeting sequence" that is complementary to a target nucleic acid sequence ("target sequence"), e.g., to a nucleic acid sequence comprised in a genomic target site; and 2) a nucleotide sequence that binds a polynucleotide guided DNA-binding domain (e.g., a CRISPR-Cas protein domain). The nucleotide sequence in 1) may comprise a targeting sequence that is 100% complementary to a genomic nucleic acid sequence, e.g., a nucleic acid sequence comprised in a genomic target site, and thus may hybridize to the target nucleic acid sequence. The nucleotide sequence in 1) may be referred to as, e.g., a crispr RNA, or crRNA. The nucleotide sequence in 2) may be referred to as a scaffold sequence of a guide nucleic acid, e.g., a tracrRNA, or an activating region of a guide nucleic acid, and may comprise a stem-loop structure. Parts 1) and 2) as described above may be fused to form one single guide (e.g., a single guide RNA, or sgRNA), or may be on two separate nucleic acid molecules. In some embodiments, a guide polynucleotide comprises parts 1) and 2) connected by a linker. In some embodiments, a guide polynucleotide comprises parts 1) and 2) connected by a non-nucleic acid linker, for example, a peptide linker or a chemical linker.

Part 2 (the scaffold sequence) of a guide polynucleotide as described herein may be, for example, as described in Jinek et al., *Science* (2012) 337:816-21; U.S. Patent Publication 2016/0208288; or U.S. Patent Publication 2016/0200779. Variants of part 2) are also contemplated by the present disclosure. For example, the tetraloop and stem loop of a gRNA scaffold (tracrRNA) sequence may be modified to include RNA aptamers, which can be bound by specific protein domains. In some embodiments, such modified gRNAs can be used to facilitate the recruitment of repressive or activating domains fused to the protein-interacting RNA aptamers.

A gRNA as provided herein typically comprises a targeting domain and a binding domain. The targeting domain (also termed "targeting sequence") may comprise a nucleic acid sequence that binds to a target site, e.g., to a genomic nucleic acid molecule within a cell. The target site may be a double-stranded DNA sequence comprising a PAM sequence as well as the target sequence, which is located on the same strand as, and directly adjacent to, the PAM sequence. The targeting domain of the gRNA may comprise an RNA sequence that corresponds to the target sequence, i.e., it resembles the sequence of the target domain, sometimes with one or more mismatches, but typically comprising an RNA sequence instead of a DNA sequence. The targeting domain of the gRNA thus may base pair (in full or partial complementarity) with the sequence of the double-stranded target site that is complementary to the target sequence, and thus with the strand complementary to the strand that comprises the PAM sequence. It will be understood that the targeting domain of the gRNA typically does not include a sequence that resembles the PAM sequence. It will further be understood that the location of the PAM may be 5' or 3' of the target sequence, depending on the nuclease employed. For example, the PAM is typically 3' of the target sequence for Cas9 nucleases, and 5' of the target sequence for Cas12a nucleases. For an illustration of the location of the PAM and the mechanism of gRNA binding to a target site, see, e.g., FIG. **1** of Vanegas et al., *Fungal Biol Biotechnol*. (2019) 6:6, which is incorporated by reference herein. For additional illustration and description of the mechanism of gRNA targeting of an RNA-guided nuclease to a target site, see Fu et al., *Nat Biotechnol* (2014) 32(3): 279-84 and Stemnberg et al., *Nature* (2014) 507(7490):62-7, each incorporated herein by reference.

In some embodiments, the targeting domain sequence comprises between 17 and 30 nucleotides and corresponds fully to the target sequence (i.e., without any mismatch nucleotides). In some embodiments, however, the targeting domain sequence may comprise one or more, but typically not more than 4, mismatches, e.g., 1, 2, 3, or 4 mismatches. As the targeting domain is part of gRNA, which is an RNA molecule, it will typically comprise ribonucleotides, while the DNA targeting domain will comprise deoxyribonucleotides.

An exemplary illustration of a Cas9 target site, comprising a 22 nucleotide target domain, and an NGG PAM sequence, as well as of a gRNA comprising a targeting domain that fully corresponds to the target sequence (and thus base pairs with full complementarity with the DNA strand complementary to the strand comprising the target sequence and PAM) is provided below:

```
[                 target domain (DNA)          ][ PAM  ]
5'-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-G-G-3' (DNA)
3'-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-C-C-5' (DNA)
   | | | | | | | | | | | | | | | | | | | | | |
5'-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-[ gRNA scaffold]-3' (RNA)
[            targeting domain ( RNA)           ][  binding domain  ]
```

An exemplary illustration of a Cas12a target site, comprising a 22 nucleotide target domain, and a TTN PAM sequence, as well as of a gRNA comprising a targeting domain that fully corresponds to the target sequence (and thus base pairs with full complementarity with the DNA strand complementary to the strand comprising the target sequence and PAM) is provided below:

```
          [  PAM  ][            target domain ( DNA)            ]
          5'-T-T-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-3' (DNA)
          3'-A-A-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-5' (DNA)
                    | | | | | | | | | | | | | | | | | | | | | | | | |
5'-[gRNA scaffold]-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-3' (RNA)
[ binding domain  ][              targeting domain ( RNA)          ]
```

While not wishing to be bound by theory, at least in some embodiments, it is believed that the length and complementarity of the targeting domain with the target sequence contributes to specificity of the interaction of the gRNA/Cas9 molecule complex with a target nucleic acid. In some embodiments, the targeting domain of a gRNA provided herein is 5 to 50 nucleotides in length. In some embodiments, the targeting domain is 15 to 25 nucleotides in length. In some embodiments, the targeting domain is 18 to 22 nucleotides in length. In some embodiments, the targeting domain is 19-21 nucleotides in length. In some embodiments, the targeting domain is 15 nucleotides in length. In some embodiments, the targeting domain is 16 nucleotides in length. In some embodiments, the targeting domain is 17 nucleotides in length. In some embodiments, the targeting domain is 18 nucleotides in length. In some embodiments, the targeting domain is 19 nucleotides in length. In some embodiments, the targeting domain is 20 nucleotides in length. In some embodiments, the targeting domain is 21 nucleotides in length. In some embodiments, the targeting domain is 22 nucleotides in length. In some embodiments, the targeting domain is 23 nucleotides in length. In some embodiments, the targeting domain is 24 nucleotides in length. In some embodiments, the targeting domain is 25 nucleotides in length. In certain embodiments, the targeting domain fully corresponds, without mismatch, to a target sequence provided herein, or a part thereof. In some embodiments, the targeting domain of a gRNA provided herein comprises 1 mismatch relative to a target sequence provided herein. In some embodiments, the targeting domain comprises 2 mismatches relative to the target sequence. In some embodiments, the target domain comprises 3 mismatches relative to the target sequence.

Methods for designing, selecting, and validating gRNAs are described herein and known in the art. Software tools can be used to optimize the gRNAs corresponding to a target DNA sequence, e.g., to minimize total off-target activity across the genome. For example, DNA sequence searching algorithms can be used to identify a target sequence in crRNAs of a gRNA for use with Cas9. Exemplary gRNA design tools include the ones described in Bae et al., *Bioinformatics* (2014) 30:1473-5.

Guide polynucleotides (e.g., gRNAs) described herein may be of various lengths. In some embodiments, the length of the spacer or targeting sequence depends on the CRISPR-associated protein component of the epigenetic editor system used. For example, Cas proteins from different bacterial species have varying optimal targeting sequence lengths. Accordingly, the spacer sequence may comprise, e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or more than 50 nucleotides in length. In some embodiments, the spacer comprises 10-24, 11-20, 11-16, 18-24, 19-21, or 20 nucleotides in length. In some embodiments, a guide polynucleotide (e.g., gRNA) is from 15-100 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length and comprises a spacer sequence of at least 10 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) contiguous nucleotides complementary to the target sequence. In some embodiments, a guide polynucleotide described herein may be truncated, e.g., by 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, 50 or more nucleotides.

In certain embodiments, the 3' end of the HBV target sequence is immediately adjacent to a PAM sequence (e.g., a canonical PAM sequence such as NGG for SpCas9). The degree of complementarity between the targeting sequence of the guide polynucleotide (e.g., the spacer sequence of a gRNA) and the target sequence may be at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%. In particular embodiments, the targeting and the target sequence may be 100% complementary. In other embodiments, the targeting sequence and the target sequence may contain, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mismatches.

A guide polynucleotide (e.g., gRNA) may be modified with, for example, chemical alterations and synthetic modifications. A modified gRNA, for instance, can include an alteration or replacement of one or both of the non-linking phosphate oxygens and/or of one or more of the linking phosphate oxygens in the phosphodiester backbone linkage, an alteration of the ribose sugar (e.g., of the 2' hydroxyl on the ribose sugar), an alteration of the phosphate moiety, modification or replacement of a naturally occurring nucleobase, modification or replacement of the ribose-phosphate backbone, modification of the 3' end and/or 5' end of the oligonucleotide, replacement of a terminal phosphate group or conjugation of a moiety, cap, or linker, or any combination thereof.

In some embodiments, one or more ribose groups of the gRNA may be modified. Examples of chemical modifications to the ribose group include, but are not limited to, 2'-O-methyl (2'-OMe), 2'-fluoro (2'-F), 2'-deoxy, 2'-O-(2-methoxyethyl) (2'-MOE), 2'-NH2,2'-O-allyl, 2'-O-ethylamine, 2'-O-cyanoethyl, 2'-O-acetalester, or a bicyclic nucleotide such as locked nucleic acid (LNA), 2'-(5-constrained ethyl (S-cEt)), constrained MOE, or 2'-0,4'-C-aminomethylene bridged nucleic acid (2',4'-BNANC). 2'-O-methyl modification and/or 2'-fluoro modification may increase binding affinity and/or nuclease stability of the gRNA oligonucleotides.

In some embodiments, one or more phosphate groups of the gRNA may be chemically modified. Examples of chemical modifications to a phosphate group include, but are not limited to, a phosphorothioate (PS), phosphonoacetate (PACE), thiophosphonoacetate (thioPACE), amide, triazole, phosphonate, and phosphotriester modification. In some embodiments, a guide polynucleotide described herein may comprise one, two, three, or more PS linkages at or near the 5' end and/or the 3' end; the PS linkages may be contiguous or noncontiguous.

In some embodiments, the gRNA herein comprises a mixture of ribonucleotides and deoxyribonucleotides and/or one or more PS linkages.

In some embodiments, one or more nucleobases of the gRNA may be chemically modified. Examples of chemically modified nucleobases include, but are not limited to, 2-thiouridine, 4-thiouridine, N6-methyladenosine, pseudouridine, 2,6-diaminopurine, inosine, thymidine, 5-methylcytosine, 5-substituted pyrimidine, isoguanine, isocytosine, and nucleobases with halogenated aromatic groups. Chemical modifications can be made in the spacer region, the tracr RNA region, the stem loop, or any combination thereof.

Table 2 below lists exemplary target sequences for epigenetic modification of HBV, as well as the coordinates of the start and end positions of the targeted site on the HBV genome.

TABLE 2

Targeting Domain Sequences of Exemplary gRNAs Targeting HBV. The following target sites were identified as suitable for targeting with an epigenetic repressor:

SEQ IDs	Target domain sequence	Start	End	Strand
333	CCTGCTGGTGGCTCCAGTTC	57	77	+
334	CTGAACTGGAGCCACCAGCA	59	79	-
335	CCTGAACTGGAGCCACCAGC	60	80	-

TABLE 2-continued

Targeting Domain Sequences of Exemplary gRNAs Targeting HBV. The following target sites were identified as suitable for targeting with an epigenetic repressor:

SEQ IDs	Target domain sequence	Start	End	Strand
336	CCTCGAGAAGATTGACGATA	115	135	-
337	TCGTCAATCTTCTCGAGGAT	117	137	+
338	CGTCAATCTTCTCGAGGATT	118	138	+
339	GTCAATCTTCTCGAGGATTG	119	139	+
340	AACATGGAGAACATCACATC	153	173	+
341	AACATCACATCAGGATTCCT	162	182	+
342	CTAGACTCTGCGGTATTGTG	233	253	-
343	TACCGCAGAGTCTAGACTCG	238	258	+
344	CGCAGAGTCTAGACTCGTGG	241	261	+
345	CACCACGAGTCTAGACTCTG	243	263	-
346	TGGACTTCTCTCAATTTTCT	261	281	+
347	GGACTTCTCTCAATTTTCTA	262	282	+
348	GACTTCTCTCAATTTTCTAG	263	283	+
349	ACTTCTCTCAATTTTCTAGG	264	284	+
350	CGAATTTTGGCCAAGACACA	295	315	-
351	AGGTTGGGGACTGCGAATTT	309	328	-
352	GGCATAGCAGCAGGATGAAG	408	427	-
353	AGAAGATGAGGCATAGCAGC	417	436	-
354	GCTATGCCTCATCTTCTTGT	420	439	+
355	GAAGAACCAACAAGAAGATG	429	448	-
356	CATCTTCTTGTTGGTTCTTC	429	448	+
357	CCCGTTTGTCCTCTAATTCC	469	488	+
358	CCTGGAATTAGAGGACAAAC	472	491	-
359	TCCTGGAATTAGAGGACAAA	473	492	-
360	TACTAGTGCCATTTGTTCAG	680	699	+
361	CCATTTGTTCAGTGGTTCGT	688	707	+
362	CATTTGTTCAGTGGTTCGTA	689	708	+
363	CCTACGAACCACTGAACAAA	691	710	-
364	TTTCAGTTATATGGATGATG	731	750	+
365	CAAAAGAAAATTGGTAACAG	799	818	-
366	TACCAATTTTCTTTTGTCTT	803	822	+
367	ACCAATTTTCTTTTGTCTTT	804	823	+
368	ACCCAAAGACAAAAGAAAAT	808	827	-
369	TGACATACTTTCCAATCAAT	975	994	-
370	CACTTTCTCGCCAACTTACA	1093	1113	+
371	CACAGAAAGGCCTTGTAAGT	1106	1126	-

TABLE 2-continued

Targeting Domain Sequences of Exemplary gRNAs Targeting HBV. The following target sites were identified as suitable for targeting with an epigenetic repressor:

SEQ IDs	Target domain sequence	Start	End	Strand
372	TGAACCTTTACCCCGTTGCC	1137	1157	+
373	GGGCAACGGGGTAAAGGTTC	1138	1158	–
374	TTTACCCCGTTGCCCGGCAA	1143	1163	+
375	GTTGCCGGGCAACGGGGTAA	1144	1164	–
376	CCCGTTGCCCGGCAACGGCC	1148	1168	+
377	CTGGCCGTTGCCGGGCAACG	1150	1170	–
378	CCTGGCCGTTGCCGGGCAAC	1151	1171	–
379	ACCTGGCCGTTGCCGGGCAA	1152	1172	–
380	GCACAGACCTGGCCGTTGCC	1158	1178	–
381	GGCACAGACCTGGCCGTTGC	1159	1179	–
382	GCAAACACTTGGCACAGACC	1169	1189	–
383	GGGTTGCGTCAGCAAACACT	1180	1200	–
384	TTTGCTGACGCAACCCCCAC	1184	1204	+
385	CTGACGCAACCCCCACTGGC	1188	1208	+
386	TGACGCAACCCCCACTGGCT	1189	1209	+
387	GACGCAACCCCCACTGGCTG	1190	1210	+
388	AACCCCCACTGGCTGGGGCT	1195	1215	+
389	TCCTCTGCCGATCCATACTG	1255	1275	+
390	TCCGCAGTATGGATCGGCAG	1259	1279	–
391	AGGAGTTCCGCAGTATGGAT	1265	1285	–
392	CGGCTAGGAGTTCCGCAGTA	1270	1290	–
393	TGCGAGCAAAACAAGCGGCT	1285	1305	–
394	CCGCTTGTTTTGCTCGCAGC	1287	1307	+
395	CCTGCTGCGAGCAAAACAAG	1290	1310	–
396	TGTTTTGCTCGCAGCAGGTC	1292	1312	+
397	GCAGCACAGCCTAGCAGCCA	1376	1396	–
398	TGCTAGGCTGTGCTGCCAAC	1380	1400	+
399	GCTGCCAACTGGATCCTGCG	1391	1411	+
400	CTGCCAACTGGATCCTGCGC	1392	1412	+
401	CGTCCCGCGCAGGATCCAGT	1398	1418	–
402	AAACAAAGGACGTCCCGCGC	1408	1428	–
403	GTCCTTTGTTTACGTCCCGT	1417	1437	+
404	CGCCGACGGGACGTAAACAA	1422	1442	–
405	TGCCGTTCCGACCGACCACG	1504	1523	+
406	AGGTGCGCCCCGTGGTCGGT	1513	1533	–
407	AGAGAGGTGCGCCCCGTGGT	1517	1537	–

TABLE 2-continued

Targeting Domain Sequences of Exemplary gRNAs Targeting HBV. The following target sites were identified as suitable for targeting with an epigenetic repressor:

SEQ IDs	Target domain sequence	Start	End	Strand
408	GTAAAGAGAGGTGCGCCCCG	1521	1541	–
409	GGGGCGCACCTCTCTTTACG	1522	1542	+
410	CGGGGAGTCCGCGTAAAGAG	1533	1553	–
411	CAGATGAGAAGGCACAGACG	1551	1571	–
412	GTCTGTGCCTTCTCATCTGC	1552	1572	+
413	GGCAGATGAGAAGGCACAGA	1553	1573	–
414	GCAGATGAGAAGGCACAGAC	1553	1572	–
415	ACACGGTCCGGCAGATGAGA	1562	1582	–
416	GAAGCGAAGTGCACACGGTC	1574	1594	–
417	GAGGTGAAGCGAAGTGCACA	1579	1599	–
418	CTTCACCTCTGCACGTCGCA	1590	1610	+
419	GGTCTCCATGCGACGTGCAG	1598	1618	–
420	TGCCCAAGGTCTTACATAAG	1640	1660	+
421	GTCCTCTTATGTAAGACCTT	1645	1665	–
422	AGTCCTCTTATGTAAGACCT	1646	1666	–
423	GTCTTACATAAGAGGACTCT	1648	1668	+
424	AATGTCAACGACCGACCTTG	1680	1700	+
425	TTTGAAGTATGCCTCAAGGT	1694	1714	–
426	AGTCTTTGAAGTATGCCTCA	1698	1718	–
427	AAGACTGTTTGTTTAAAGAC	1712	1732	+
428	AGACTGTTTGTTTAAAGACT	1713	1733	+
429	CTGTTTGTTTAAAGACTGGG	1716	1736	+
430	GTTTAAAGACTGGGAGGAGT	1722	1742	+
431	TCTTTGTACTAGGAGGCTGT	1766	1786	+
432	AGGAGGCTGTAGGCATAAAT	1776	1796	+
433	GTGAAAAAGTTGCATGGTGC	1810	1830	–
434	GCAGAGGTGAAAAAGTTGCA	1816	1836	–
435	AACAAGAGATGATTAGGCAG	1832	1852	–
436	GACATGAACAAGAGATGATT	1838	1858	–
437	AGCTTGGAGGCTTGAACAGT	1860	1880	–
438	CAAGCCTCCAAGCTGTGCCT	1866	1886	+
439	AAGCCTCCAAGCTGTGCCTT	1867	1887	+
440	CCTCCAAGCTGTGCCTTGGG	1871	1890	+
441	CCACCCAAGGCACAGCTTGG	1873	1893	–
442	AGCTGTGCCTTGGGTGGCTT	1876	1896	+
443	AAGCCACCCAAGGCACAGCT	1876	1896	–

TABLE 2-continued

Targeting Domain Sequences of Exemplary gRNAs Targeting HBV. The following target sites were identified as suitable for targeting with an epigenetic repressor:

SEQ IDs	Target domain sequence	Start	End	Strand
444	GCTGTGCCTTGGGTGGCTTT	1877	1897	+
445	CTGTGCCTTGGGTGGCTTTG	1878	1898	+
446	TAGCTCCAAATTCTTTATAA	1916	1936	-
447	GTAGCTCCAAATTCTTTATA	1917	1937	-
448	TAAAGAATTTGGAGCTACTG	1919	1939	+
449	ATGACTCTAGCTACCTGGGT	2097	2117	+
450	CACATTTCTTGTCTCACTTT	2211	2231	+
451	TAGTTTCCGGAAGTGTTGAT	2321	2341	-
452	CGTCTAACAACAGTAGTTTC	2334	2354	-
453	ACTACTGTTGTTAGACGACG	2337	2357	+
454	CTGTTGTTAGACGACGAGGC	2341	2361	+
455	CGAGGGAGTTCTTCTTCTAG	2368	2388	-
456	GCGAGGGAGTTCTTCTTCTA	2369	2389	-
457	GGCGAGGGAGTTCTTCTTCT	2370	2390	-
458	CTCCCTCGCCTCGCAGACGA	2380	2400	+
459	GACCTTCGTCTGCGAGGCGA	2385	2405	-
460	AGACCTTCGTCTGCGAGGCG	2386	2406	-
461	GATTGAGACCTTCGTCTGCG	2391	2411	-
462	GATTGAGATCTTCTGCGACG	2415	2435	-
463	GTCGCAGAAGATCTCAATCT	2416	2436	+
464	TCGCAGAAGATCTCAATCTC	2417	2437	+
465	ATATGGTGACCCACAAAATG	2807	2827	-
466	TTTGTGGGTCACCATATTCT	2810	2830	+
467	TTGTGGGTCACCATATTCTT	2811	2831	+
468	GCTGGATCCAACTGGTGGTC	2894	2914	-
469	CACCCCAAAAGGCCTCCGTG	3026	3046	-
470	CCTTTTGGGGTGGAGCCCTC	3034	3054	+
471	CCTGAGGGCTCCACCCCAAA	3037	3057	-
472	GGGGTGGAGCCCTCAGGCTC	3040	3060	+
473	GGGTGGAGCCCTCAGGCTCA	3041	3061	+
474	CGATTGGTGGAGGCAGGAGG	3092	3112	-
475	CTCATCCTCAGGCCATGCAG	3159	3179	+
102	GATGAGGCATAGCAGCAG	415	432	-
103	GATGATTAGGCAGAGGTG	1828	1845	-
104	GGATTCAGCGCCGACGGG	1433	1450	-
105	GGCAGTAGTCGGAACAGGG	90	108	-

TABLE 2-continued

Targeting Domain Sequences of Exemplary gRNAs Targeting HBV. The following target sites were identified as suitable for targeting with an epigenetic repressor:

SEQ IDs	Target domain sequence	Start	End	Strand
106	GTAAACTGAGCCAGGAGAA	664	682	-
107	ACGGTGGTCTCCATGCGAC	1605	1623	-
108	GCTGGATGTGTCTGCGGCG	372	393	+
109	GTCTGCGAGGCGAGGGAG	2381	2398	-
110	GTTGCCGGGCAACGGGGTA	1146	1164	-
111	CGAGAAAGTGAAAGCCTGC	1085	1103	-
112	GAGGCTTGAACAGTAGGAC	1856	1874	-
113	GAGGTTGGGGACTGCGAA	312	329	-
114	GATGATGTGGTATTGGGG	742	762	+
115	GATGATGTGGTATTGGGGG	742	763	+
116	GCAGTAGTCGGAACAGGG	90	107	-
117	GCATAGCAGCAGGATGAA	409	426	-
118	GGCGTTCACGGTGGTCTCC	1612	1630	-
119	GTTGGTGAGTGATTGGAG	327	344	-
120	GGAGGTTGGGGACTGCGAA	312	330	-
121	GGATGATGTGGTATTGGGG	741	762	+
122	GGATGTGTCTGCGGCGTT	375	395	+
123	GGGGGTTGCGTCAGCAAAC	1184	1202	-
124	GTTGTTAGACGACGAGGCA	2342	2363	+

Target domains identified above that are adjacent to a PAM sequence, e.g., an *S. pyogenes* Cas9 PAM sequence, can be targeted by a CRISPR-based epigenetic repressor, e.g., an epigenetic repressor comprising a dCas9 DNA-binding domain. For example, target sites 1-143 are suitable for dCas9-based epigenetic repressor targeting.

A suitable gRNA for targeting any of the target domain sequences would, in some embodiments, comprise a target domain sequence that is the RNA-equivalent sequence of the provided DNA sequence of the targeting domain sequence (i.e., an RNA nucleotide of that sequence instead of the provided DNA nucleotide, with uracil instead of thymine), and a suitable tracr RNA sequence.

Any tracr sequence known in the art is contemplated for a gRNA described herein. In some embodiments, a gRNA described herein has a tracr sequence shown in Table 3 below, or a tracr sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to the tracr sequence shown below (SEQ: SEQ ID NO).

TABLE 3

Exemplary TRACR Sequences	
SEQ	Sequence (5' to 3')
1087	GUUUAAGAGCUAUGCUGGAAACAGCAUAGCAAGUUUAAAUAAG GCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC UUUUUUU
1088	GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGU UAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU
1089	GUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAUAAG GCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC UUUUUU
1090	GUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAUAAG GCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC UUUUUUU

In some embodiments, the gRNA herein is provided to the cell directly (e.g., through an RNP complex together with the CRISPR-associated protein domain). In some embodiments, the gRNA is provided to the cell through an expression vector (e.g., a plasmid vector or a viral vector) introduced into the cell, where the cell then expresses the gRNA from the expression vector. Methods of introducing gRNAs and expression vectors into cells are well known in the art.

III. Effector Domains

Epigenetic editors described herein include one or more effector protein domains (also "epigenetic effector domains," or "effector domains," as used herein) that effect epigenetic modification of a target gene. An epigenetic editor with one or more effector domains may modulate expression of a target gene without altering its nucleobase sequence. In some embodiments, an effector domain described herein may provide repression or silencing of expression of HBV or an HBV gene, e.g., by repressing transcription or by modifying or remodeling HBV chromatin. Such effector domains are also referred to herein as "repression domains," "repressor domains," "epigenetic repressor domains," or "epigenetic repression domains." Non-limiting examples of chemical modifications that may be mediated by effector domains include methylation, demethylation, acetylation, deacetylation, phosphorylation, SUMOylation and/or ubiquitination of DNA or histone residues.

In some embodiments, an effector domain of an epigenetic editor described herein may make histone tail modifications, e.g., by adding or removing active marks on histone tails.

In some embodiments, an effector domain of an epigenetic editor described herein may comprise or recruit a transcription-related protein, e.g., a transcription repressor. The transcription-related protein may be endogenous or exogenous.

In some embodiments, an effector domain of an epigenetic editor described herein may, for example, comprise a protein that directly or indirectly blocks access of a transcription factor to the gene of interest harboring the target sequence.

An effector domain may be a full-length protein or a fragment thereof that retains the epigenetic effector function (a "functional domain"). Functional domains that are capable of modulating (e.g., repressing) gene expression can be derived from a larger protein. For example, functional domains that can reduce target gene expression may be identified based on sequences of repressor proteins. Amino acid sequences of gene expression-modulating proteins may be obtained from available genome browsers, such as the UCSD genome browser or Ensembl genome browser. Protein annotation databases such as UniProt or Pfam can be used to identify functional domains within the full protein sequence. As a starting point, the largest sequence, encompassing all regions identified by different databases, may be tested for gene expression modulation activity. Various truncations then may be tested to identify the minimal functional unit.

Variants of effector domains described herein are also contemplated by the present disclosure. A variant may, for example, refer to a polypeptide with at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity and/or sequence similarity to a wildtype effector domain described herein. In particular embodiments, the variant retains at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the epigenetic effector function of the wildtype effector domain.

In some embodiments, an epigenetic editor described herein may comprise 1 effector domain, 2 effector domains, 3 effector domains, 4 effector domains, 5 effector domains, 6 effector domains, 7 effector domains, 8 effector domains, 9 effector domains, 10 effector domains, or more. In certain embodiments, the epigenetic editor comprises one or more fusion proteins (e.g., one, two, or three fusion proteins), each with one or more effector domains (e.g., one, two, or three effector domains) linked to a DNA-binding domain. In some embodiments, the effector domains may induce a combination of epigenetic modifications, e.g., transcription repression and DNA methylation, DNA methylation and histone deacetylation, DNA methylation and histone demethylation, DNA methylation and histone methylation, DNA methylation and histone phosphorylation, DNA methylation and histone ubiquitylation, DNA methylation, and histone SUMOylation.

In certain embodiments, an effector domain described herein (e.g., DNMT3A and/or DNMT3L) is encoded by a nucleotide sequence as found in the native genome (e.g., human or murine) for that effector domain. In other embodiments, an effector domain described herein is encoded by a nucleotide sequence that has been codon-optimized for optimal expression in human cells.

Effector domains described herein may include, for example, transcriptional repressors, DNA methyltransferases, and/or histone modifiers, as further detailed below.

A. Transcriptional Repressors

In some embodiments, an epigenetic effector domain described herein mediates repression of a target gene's expression (e.g., transcription). The effector domain may comprise, e.g., a Krüppel-associated box (KRAB) repression domain, a Repressor Element Silencing Transcription Factor (REST) repression domain, a KRAB-associated protein 1 (KAP1) domain, a MAD domain, a FKHR (forkhead in rhabdosarcoma gene) repressor domain, an EGR-1 (early growth response gene product-1) repressor domain, an ets2 repressor factor repressor domain (ERD), a MAD smSIN3 interaction domain (SID), a WRPW motif (SEQ ID NO: 1257) of the hairy-related basic helix-loop-helix (bHLH) repressor proteins, an HP1 alpha chromo-shadow repression domain, an HP1 beta repression domain, or any combination thereof. The effector domain may recruit one or more protein domains that repress expression of the target gene, e.g., through a scaffold protein. In some embodiments, the effector domain may recruit or interact with a scaffold protein

domain that recruits a PRMT protein, a HDAC protein, a SETDB1 protein, or a NuRD protein domain.

In some embodiments, the effector domain comprises a functional domain derived from a zinc finger repressor protein, such as a KRAB domain. KRAB domains are found in approximately 400 human ZFP-based transcription factors. Descriptions of KRAB domains may be found, for example, in Ecco et al., *Development* (2017) 144(15):2719-29 and Lambert et al., *Cell* (2018) 172:650-65.

In certain embodiments, the effector domain comprises a repression domain (e.g., KRAB) derived from KOX1/ZNF10, KOX8/ZNF708, ZNF43, ZNF184, ZNF91, HPF4, HTF10, or HTF34. In some embodiments, the effector domain comprises a repression domain (e.g., KRAB) derived from ZIM3, ZNF436, ZNF257, ZNF675, ZNF490, ZNF320, ZNF331, ZNF816, ZNF680, ZNF41, ZNF189, ZNF528, ZNF543, ZNF554, ZNF140, ZNF610, ZNF264, ZNF350, ZNF8, ZNF582, ZNF30, ZNF324, ZNF98, ZNF669, ZNF677, ZNF596, ZNF214, ZNF37, ZNF34, ZNF250, ZNF547, ZNF273, ZNF354, ZFP82, ZNF224, ZNF33, ZNF45, ZNF175, ZNF595, ZNF184, ZNF419, ZFP28-1, ZFP28-2, ZNF18, ZNF213, ZNF394, ZFP1, ZFP14, ZNF416, ZNF557, ZNF566, ZNF729, ZIM2, ZNF254, ZNF764, ZNF785, or any combination thereof. For example, the repression domain may be a KRAB domain derived from KOX1, ZIM3, ZFP28, or ZN627. In particular embodiments, the repression domain is a ZIM3 KRAB domain. In further embodiments, the effector domain is derived from a human protein, e.g., a human ZIM3, a human KOX1, a human ZFP28, or a human ZN627.

Exemplary effector domains that may reduce or silence target gene expression are provided in Table 4 below (SEQ: SEQ ID NO, see Table 18 for sequences of exemplary effector domains). Further examples of repressors and transcriptional repressor domains can be found, e.g., in PCT Patent Publication WO 2021/226077 and Tycko et al., *Cell* (2020) 183(7):2020-35, each of which is incorporated herein by reference in its entirety.

TABLE 4

Exemplary Effector Domains Suitable for Silencing Gene Expression

Protein	SEQ
ZIM3	495
ZNF436	496
ZNF257	497
ZNF675	498
ZNF490	499
ZNF320	500
ZNF331	501
ZNF816	502
ZNF680	503
ZNF41	504
ZNF189	505
ZNF528	506
ZNF543	507
ZNF554	508
ZNF140	509
ZNF610	510
ZNF264	511
ZNF350	512
ZNF8	513
ZNF582	514
ZNF30	515
ZNF324	516
ZNF98	517
ZNF669	518
ZNF677	519

TABLE 4-continued

Exemplary Effector Domains Suitable for Silencing Gene Expression

Protein	SEQ
ZNF596	520
ZNF214	521
ZNF37A	522
ZNF34	523
ZNF250	524
ZNF547	525
ZNF273	526
ZNF354A	527
ZFP82	528
ZNF224	529
ZNF33A	530
ZNF45	531
ZNF175	532
ZNF595	533
ZNF184	534
ZNF419	535
ZFP28-1	536
ZFP28-2	537
ZNF18	538
ZNF213	539
ZNF394	540
ZFP1	541
ZFP14	542
ZNF416	543
ZNF557	544
ZNF566	545
ZNF729	546
ZIM2	547
ZNF254	548
ZNF764	549
ZNF785	550
ZNF10 (KOX1)	551
CBX5 (chromoshadow domain)	552
RYBP (YAF2_RYBP component of PRC1)	553
YAF2 (YAF2_RYBP component of PRC1)	554
MGA (component of PRC1.6)	555
CBX1 (chromoshadow)	556
SCMHI (SAM_1/SPM)	557
MPP8 (Chromodomain)	558
SUMO3 (Rad60-SLD)	559
HERC2 (Cyt-b5)	560
BIN1 (SH3_9)	561
PCGF2 (RING finger protein domain)	562
TOX (HMG box)	563
FOXA1 (HNF3A C-terminal domain)	564
FOXA2 (HNF3B C-terminal domain)	565
IRF2BP1 (IRF-2BP1_2 N-terminal domain)	566
IRF2BP2 (IRF-2BP1_2 N-terminal domain)	567
IRF2BPL IRF-2BP1_2 N-terminal domain	568
HOXA13 (homeodomain)	569
HOXB13 (homeodomain)	570
HOXC13 (homeodomain)	571
HOXA11 (homeodomain)	572
HOXC11 (homeodomain)	573
HOXC10 (homeodomain)	574
HOXA10 (homeodomain)	575
HOXB9 (homeodomain)	576
HOXA9 (homeodomain)	577
ZFP28_HUMAN	578
ZN334_HUMAN	579
ZN568_HUMAN	580
ZN37A_HUMAN	581
ZN181_HUMAN	582
ZN510_HUMAN	583
ZN862_HUMAN	584
ZN140_HUMAN	585

TABLE 4-continued

Exemplary Effector Domains Suitable for Silencing Gene Expression	
Protein	SEQ
ZN208_HUMAN	586
ZN248_HUMAN	587
ZN571_HUMAN	588
ZN699_HUMAN	589
ZN726_HUMAN	590
ZIK1_HUMAN	591
ZNF2_HUMAN	592
Z705F_HUMAN	593
ZNF14_HUMAN	594
ZN471_HUMAN	595
ZN624_HUMAN	596
ZNF84_HUMAN	597
ZNF7_HUMAN	598
ZN891_HUMAN	599
ZN337_HUMAN	600
Z705G_HUMAN	601
ZN529_HUMAN	602
ZN729_HUMAN	603
ZN419_HUMAN	604
Z705A_HUMAN	605
ZNF45_HUMAN	606
ZN302_HUMAN	607
ZN486_HUMAN	608
ZN621_HUMAN	609
ZN688_HUMAN	610
ZN33A_HUMAN	611
ZN554_HUMAN	612
ZN878_HUMAN	613
ZN772_HUMAN	614
ZN224_HUMAN	615
ZN184_HUMAN	616
ZN544_HUMAN	617
ZNF57_HUMAN	618
ZN283_HUMAN	619
ZN549_HUMAN	620
ZN211_HUMAN	621
ZN615_HUMAN	622
ZN253_HUMAN	623
ZN226_HUMAN	624
ZN730_HUMAN	625
Z585A_HUMAN	626
ZN732_HUMAN	627
ZN681_HUMAN	628
ZN667_HUMAN	629
ZN649_HUMAN	630
ZN470_HUMAN	631
ZN484_HUMAN	632
ZN431_HUMAN	633
ZN382_HUMAN	634
ZN254_HUMAN	635
ZN124_HUMAN	636
ZN607_HUMAN	637
ZN317_HUMAN	638
ZN620_HUMAN	639
ZN141_HUMAN	640
ZN584_HUMAN	641
ZN540_HUMAN	642
ZN75D_HUMAN	643
ZN555_HUMAN	644
ZN658_HUMAN	645
ZN684_HUMAN	646
RBAK_HUMAN	647
ZN829_HUMAN	648
ZN582_HUMAN	649
ZN112_HUMAN	650
ZN716_HUMAN	651
HKR1_HUMAN	652
ZN350_HUMAN	653
ZN480_HUMAN	654
ZN416_HUMAN	655
ZNF92_HUMAN	656
ZN100_HUMAN	657
ZN736_HUMAN	658
ZNF74_HUMAN	659

TABLE 4-continued

Exemplary Effector Domains Suitable for Silencing Gene Expression	
Protein	SEQ
CBX1_HUMAN	660
ZN443_HUMAN	661
ZN195_HUMAN	662
ZN530_HUMAN	663
ZN782_HUMAN	664
ZN791_HUMAN	665
ZN331_HUMAN	666
Z354C_HUMAN	667
ZN157_HUMAN	
ZN727_HUMAN	669
ZN550_HUMAN	670
ZN793_HUMAN	671
ZN235_HUMAN	672
ZNF8_HUMAN	673
ZN724_HUMAN	674
ZN573_HUMAN	675
ZN577_HUMAN	676
ZN789_HUMAN	677
ZN718_HUMAN	678
ZN300_HUMAN	679
ZN383_HUMAN	680
ZN429_HUMAN	681
ZN677_HUMAN	682
ZN850_HUMAN	683
ZN454_HUMAN	684
ZN257_HUMAN	685
ZN264_HUMAN	686
ZFP82_HUMAN	687
ZFP14_HUMAN	688
ZN485_HUMAN	689
ZN737_HUMAN	690
ZNF44_HUMAN	691
ZN596_HUMAN	692
ZN565_HUMAN	693
ZN543_HUMAN	694
ZFP69_HUMAN	695
SUMO1_HUMAN	696
ZNF12_HUMAN	697
ZN169_HUMAN	698
ZN433_HUMAN	699
SUMO3_HUMAN	700
ZNF98_HUMAN	701
ZN175_HUMAN	702
ZN347_HUMAN	703
ZNF25_HUMAN	704
ZN519_HUMAN	705
Z585B_HUMAN	706
ZIM3_HUMAN	707
ZN517_HUMAN	708
ZN846_HUMAN	709
ZN230_HUMAN	710
ZNF66_HUMAN	711
ZFP1_HUMAN	712
ZN713_HUMAN	713
ZN816_HUMAN	714
ZN426_HUMAN	715
ZN674_HUMAN	716
ZN627_HUMAN	717
ZNF20_HUMAN	718
Z587B_HUMAN	719
ZN316_HUMAN	720
ZN233_HUMAN	721
ZN611_HUMAN	722
ZN556_HUMAN	723
ZN234_HUMAN	724
ZN560_HUMAN	725
ZNF77_HUMAN	726
ZN682_HUMAN	727
ZN614_HUMAN	728
ZN785_HUMAN	729
ZN445_HUMAN	730
ZFP30_HUMAN	731
ZN225_HUMAN	732
ZN551_HUMAN	733

TABLE 4-continued

Exemplary Effector Domains Suitable for Silencing Gene Expression	
Protein	SEQ
ZN610_HUMAN	734
ZN528_HUMAN	735
ZN284_HUMAN	736
ZN418_HUMAN	737
MPP8_HUMAN	738
ZN490_HUMAN	739
ZN805_HUMAN	740
Z780B_HUMAN	741
ZN763_HUMAN	742
ZN285_HUMAN	743
ZNF85_HUMAN	744
ZN223_HUMAN	745
ZNF90_HUMAN	746
ZN557_HUMAN	747
ZN425_HUMAN	748
ZN229_HUMAN	749
ZN606_HUMAN	750
ZN155_HUMAN	751
ZN222_HUMAN	752
ZN442_HUMAN	753
ZNF91_HUMAN	754
ZN135_HUMAN	755
ZN778_HUMAN	756
RYBP_HUMAN	757
ZN534_HUMAN	758
ZN586_HUMAN	759
ZN567_HUMAN	760
ZN440_HUMAN	761
ZN583_HUMAN	762
ZN441_HUMAN	763
ZNF43_HUMAN	764
CBX5_HUMAN	765
ZN589_HUMAN	766
ZNF10_HUMAN	767
ZN563_HUMAN	768
ZN561_HUMAN	769
ZN136_HUMAN	770
ZN630_HUMAN	771
ZN527_HUMAN	772
ZN333_HUMAN	773
Z324B_HUMAN	774
ZN786_HUMAN	775
ZN709_HUMAN	776
ZN792_HUMAN	777
ZN599_HUMAN	778
ZN613_HUMAN	779
ZF69B_HUMAN	780
ZN799_HUMAN	781
ZN569_HUMAN	782
ZN564_HUMAN	783
ZN546_HUMAN	784
ZFP92_HUMAN	785
YAF2_HUMAN	786
ZN723_HUMAN	787
ZNF34_HUMAN	788
ZN439_HUMAN	789
ZFP57_HUMAN	790
ZNF19_HUMAN	791
ZN404_HUMAN	792
ZN274_HUMAN	793
CBX3_HUMAN	794
ZNF30_HUMAN	795
ZN250_HUMAN	796
ZN570_HUMAN	797
ZN675_HUMAN	798
ZN695_HUMAN	799
ZN548_HUMAN	800
ZN132_HUMAN	801
ZN738_HUMAN	802
ZN420_HUMAN	803
ZN626_HUMAN	804
ZN559_HUMAN	805
ZN460_HUMAN	806
ZN268_HUMAN	807

TABLE 4-continued

Exemplary Effector Domains Suitable for Silencing Gene Expression	
Protein	SEQ
ZN304_HUMAN	808
ZIM2_HUMAN	809
ZN605_HUMAN	810
ZN844_HUMAN	811
SUMO5_HUMAN	812
ZN101_HUMAN	813
ZN783_HUMAN	814
ZN417_HUMAN	815
ZN182_HUMAN	816
ZN823_HUMAN	817
ZN177_HUMAN	818
ZN197_HUMAN	819
ZN717_HUMAN	820
ZN669_HUMAN	821
ZN256_HUMAN	822
ZN251_HUMAN	823
CBX4_HUMAN	824
PCGF2_HUMAN	825
CDY2_HUMAN	826
CDYL2_HUMAN	827
HERC2_HUMAN	828
ZN562_HUMAN	829
ZN461_HUMAN	830
Z324A_HUMAN	831
ZN766_HUMAN	832
ID2_HUMAN	833
TOX_HUMAN	834
ZN274_HUMAN	835
SCMH1_HUMAN	836
ZN214_HUMAN	837
CBX7_HUMAN	838
ID1_HUMAN	839
CREM_HUMAN	840
SCX_HUMAN	841
ASCL1_HUMAN	842
ZN764_HUMAN	843
SCML2_HUMAN	844
TWSTI_HUMAN	845
CREB1_HUMAN	846
TERFI_HUMAN	847
ID3_HUMAN	848
CBX8_HUMAN	849
CBX4_HUMAN	850
GSX1_HUMAN	851
NKX22_HUMAN	852
ATF1_HUMAN	853
TWST2_HUMAN	854
ZNF17_HUMAN	855
TOX3_HUMAN	856
TOX4_HUMAN	857
ZMYM3_HUMAN	858
I2BP1_HUMAN	859
RHXF1_HUMAN	860
SSX2_HUMAN	861
I2BPL_HUMAN	862
ZN680_HUMAN	863
CBX1_HUMAN	864
TRI68_HUMAN	865
HXA13_HUMAN	866
PHC3_HUMAN	867
TCF24_HUMAN	868
CBX3_HUMAN	869
HXB13_HUMAN	870
HEY1_HUMAN	871
PHC2_HUMAN	872
ZNF81_HUMAN	873
FIGLA_HUMAN	874
SAM11_HUMAN	875
KMT2B_HUMAN	876
HEY2_HUMAN	877
JDP2_HUMAN	878
HXC13_HUMAN	879
ASCL4_HUMAN	880
HHEX_HUMAN	881

TABLE 4-continued

Exemplary Effector Domains Suitable for Silencing Gene Expression	
Protein	SEQ
HERC2_HUMAN	882
GSX2_HUMAN	883
BIN1_HUMAN	884
ETV7_HUMAN	885
ASCL3_HUMAN	886
PHC1_HUMAN	887
OTP_HUMAN	888
I2BP2_HUMAN	889
VGLL2_HUMAN	890
HXA11_HUMAN	891
PDLI4_HUMAN	892
ASCL2_HUMAN	893
CDX4_HUMAN	894
ZN860_HUMAN	895
LMBL4_HUMAN	896
PDIP3_HUMAN	897
NKX25_HUMAN	898
CEBPB_HUMAN	899
ISL1_HUMAN	900
CDX2_HUMAN	901
PROP1_HUMAN	902
SIN3B_HUMAN	903
SMBTI_HUMAN	904
HXC11_HUMAN	905
HXC10_HUMAN	906
PRS6A_HUMAN	907
VSX1_HUMAN	908
NKX23_HUMAN	909
MTG16_HUMAN	910
HMX3_HUMAN	911
HMX1_HUMAN	912
KIF22_HUMAN	913
CSTF2_HUMAN	914
CEBPE_HUMAN	915
DLX2_HUMAN	916
ZMYM3_HUMAN	917
PPARG_HUMAN	918
PRICI_HUMAN	919
UNC4_HUMAN	920
BARX2_HUMAN	921
ALX3_HUMAN	922
TCF15_HUMAN	923
TERA_HUMAN	924
VSX2_HUMAN	925
HXD12_HUMAN	926
CDX1_HUMAN	927
TCF23_HUMAN	928
ALX1_HUMAN	929
HXA10_HUMAN	930
RX_HUMAN	931
CXXC5_HUMAN	932
SCML1_HUMAN	933
NFIL3_HUMAN	934
DLX6_HUMAN	935
MTG8_HUMAN	936
CBX8_HUMAN	937
CEBPD_HUMAN	938
SEC13_HUMAN	939
FIP1_HUMAN	940
ALX4_HUMAN	941
LHX3_HUMAN	942
PRIC2_HUMAN	943
MAGI3_HUMAN	944
NELLI_HUMAN	945
PRRX1_HUMAN	946
MTG8R_HUMAN	947
RAX2_HUMAN	948
DLX3_HUMAN	949
DLX1_HUMAN	950
NKX26_HUMAN	951
NABI_HUMAN	952
SAMD7_HUMAN	953
PITX3_HUMAN	954
WDR5_HUMAN	955

TABLE 4-continued

Exemplary Effector Domains Suitable for Silencing Gene Expression	
Protein	SEQ
MEOX2_HUMAN	956
NAB2_HUMAN	957
DHX8_HUMAN	958
FOXA2_HUMAN	959
CBX6_HUMAN	960
EMX2_HUMAN	961
CPSF6_HUMAN	962
HXC12_HUMAN	963
KDM4B_HUMAN	964
LMBL3_HUMAN	965
PHX2A_HUMAN	966
EMX1_HUMAN	967
NC2B_HUMAN	968
DLX4_HUMAN	969
SRY_HUMAN	970
ZN777_HUMAN	971
NELLI_HUMAN	972
ZN398_HUMAN	973
GATA3_HUMAN	974
BSH_HUMAN	975
SF3B4_HUMAN	976
TEADI_HUMAN	977
TEAD3_HUMAN	978
RGAP1_HUMAN	979
PHF1_HUMAN	980
FOXA1_HUMAN	981
GATA2_HUMAN	982
FOX03_HUMAN	983
ZN212_HUMAN	984
IRX4_HUMAN	985
ZBED6_HUMAN	986
LHX4_HUMAN	987
SIN3A_HUMAN	988
RBBP7_HUMAN	989
NKX61_HUMAN	990
TRI68_HUMAN	991
R51A1_HUMAN	992
MB3L1_HUMAN	993
DLX5_HUMAN	994
NOTCI_HUMAN	995
TERF2_HUMAN	996
ZN282_HUMAN	997
RGS12_HUMAN	998
ZN840_HUMAN	999
SPI2B_HUMAN	1000
PAX7_HUMAN	1001
NKX62_HUMAN	1002
ASXL2_HUMAN	1003
FOX01_HUMAN	1004
GATA3_HUMAN	1005
GATAI_HUMAN	1006
ZMYM5_HUMAN	1007
ZN783_HUMAN	1008
SPI2B_HUMAN	1009
LRP1_HUMAN	1010
MIXLI_HUMAN	1011
SGT1_HUMAN	1012
LMCDI_HUMAN	1013
CEBPA_HUMAN	1014
GATA2_HUMAN	1015
SOX14_HUMAN	1016
WTIP_HUMAN	1017
PRP19_HUMAN	1018
CBX6_HUMAN	1019
NKX11_HUMAN	1020
RBBP4_HUMAN	1021
DMRT2_HUMAN	1022
SMCA2_HUMAN	1023
ZNF10_HUMAN	1024
EED_HUMAN	1025
RCORI_HUMAN	1026

A functional analog of any one of the above-listed proteins, i.e., a molecule having the same or substantially the same biological function (e.g., retaining 70% or more, 80% or more, 90% or more, 95% or more, or 98% or more) of the protein's transcription factor function) is encompassed by the present disclosure. For example, the functional analog may be an isoform or a variant of the above-listed protein, e.g., containing a portion of the above protein with or without additional amino acid residues and/or containing mutations relative to the above protein. In some embodiments, the functional analog has a sequence identity that is at least 75, 80, 85, 90, 95, 98, or 99% to one of the sequences listed in Table 4. Homologs, orthologs, and mutants of the above-listed proteins are also contemplated.

In certain embodiments, an epigenetic editor described herein comprises a KRAB domain derived from KOX1, ZIM3, ZFP28, or ZN627, and/or an effector domain derived from KAP1, MECP2, HP1a, HP1b, CBX8, CDYL2, TOX, TOX3, TOX4, EED, EZH2, RBBP4, RCOR1, or SCML2, optionally wherein the parental protein is a human protein. In particular embodiments, an epigenetic editor described herein comprises a domain derived from KOX1, ZIM3, ZFP28, and/or ZN627, optionally wherein the parental protein is a human protein. In certain embodiments, the epigenetic editor may comprise a KRAB domain derived from KOX1 (ZNF10), e.g., a human KOX1. In certain embodiments, the epigenetic editor may comprise a KRAB domain derived from ZIM3 (ZNF657 or ZNF264), e.g., a human ZIM3. In certain embodiments, the epigenetic editor may comprise a KRAB domain derived from ZFP28, e.g., a human ZFP28. In certain embodiments, the epigenetic editor may comprise a KRAB domain derived from ZN627, e.g., a human ZN627. In certain embodiments, an epigenetic editor described herein may comprise a CDYL2, e.g., a human CDYL2, and/or a TOX domain (e.g., a human TOX domain) in combination with a KOX1 KRAB domain (e.g., a human KOX1 KRAB domain).

In certain embodiments, an epigenetic effector described herein comprises a repression domain derived from ZNF10 (SEQ ID NO: 1024). For example, the repression domain may comprise the sequence of SEQ ID NO: 1024, or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1024.

B. DNA Methyltransferases

In some embodiments, an effector domain of an epigenetic editor described herein alters target gene expression through DNA modification, such as methylation. Highly methylated areas of DNA tend to be less transcriptionally active than less methylated areas. DNA methylation occurs primarily at CpG sites (shorthand for "C-phosphate-G-" or "cytosine-phosphate-guanine" sites). Many mammalian genes have promoter regions near or including CpG islands (nucleic acid regions with a high frequency of CpG dinucleotides).

An effector domain described herein may be, e.g., a DNA methyltransferase (DNMT) or a catalytic domain thereof, or may be capable of recruiting a DNA methyltransferase. DNMTs encompass enzymes that catalyze the transfer of a methyl group to a DNA nucleotide, such as canonical cytosine-5 DNMTs that catalyze the addition of methyl groups to genomic DNA (e.g., DNMT1, DNMT3A, DNMT3B, and DNMT3C). This term also encompasses non-canonical family members that do not catalyze methylation themselves but that recruit (including activate) catalytically active DNMTs; a non-limiting example of such a DNMT is DNMT3L. See, e.g., Lyko, *Nat Review* (2018) 19:81-92. Unless otherwise indicated, a DNMT domain may refer to a polypeptide domain derived from a catalytically active DNMT (e.g., DNMT1, DNMT3A, and DNMT3B) or from a catalytically inactive DNMT (e.g., DNMT3L). A DNMT may repress expression of the target gene through the recruitment of repressive regulatory proteins. In some embodiments, the methylation is at a CG (or CpG) dinucleotide sequence. In some embodiments, the methylation is at a CHG or CHH sequence, where H is any one of A, T, or C. In some embodiments, DNMTs in the epigenetic editors may include, e.g., DNMT1, DNMT3A, DNMT3B, and/or DNMT3C. In some embodiments, the DNMT is a mammalian (e.g., human or murine) DNMT. In particular embodiments, the DNMT is DNMT3A (e.g., human DNMT3A). In certain embodiments, an epigenetic editor described herein comprises a DNMT3A domain comprising SEQ ID NO: 1028, or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1028. In certain embodiments, an epigenetic editor described herein comprises a DNMT3A domain comprising SEQ ID NO: 1029, or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1029. In some embodiments, the DNMT3A domain may have, e.g., a mutation at position H739 (such as H739A or H739E), R771 (such as R771L) and/or R836 (such as R836A or R836Q), or any combination thereof (numbering according to SEQ ID NO: 1028).

In some embodiments, an effector domain described herein may be a DNMT-like domain. As used herein a "DNMT-like domain" is a regulatory factor of DNA methyltransferase that may activate or recruit other DNMT domains, but does not itself possess methylation activity. In some embodiments, the DNMT-like domain is a mammalian (e.g., human or mouse) DNMT-like domain. In certain embodiments, the DNMT-like domain is DNMT3L, which may be, for example, human DNMT3L or mouse DNMT3L. In certain embodiments, an epigenetic editor described herein comprises a DNMT3L domain comprising SEQ ID NO: 1032, or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1032. In certain embodiments, an epigenetic editor herein comprises a DNMT3L domain comprising SEQ ID NO: 1033, or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1033. In certain embodiments, an epigenetic editor described herein comprises a DNMT3L domain comprising SEQ ID NO: 1034, or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1034. In certain embodiments, an epigenetic editor described herein comprises a DNMT3L domain comprising SEQ ID NO: 1035, or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1035. In some embodiments, the DNMT3L domain may have, e.g., a mutation corresponding to that at position D226 (such as D226V), Q268 (such as Q268K), or both (numbering according to SEQ ID NO: 1032).

In certain embodiments, an epigenetic editor herein may comprise comprising both DNMT and DNMT-like effector domains. For example, the epigenetic editor may comprise a DNMT3A-3L domain, wherein DNMT3A and DNMT3L may be covalently linked. In other embodiments, an epigenetic editor described herein may comprise an effector domain that comprises only a DNMT3A domain (e.g., human DNMT3A), or only a DNMT-like domain (e.g., DNMT3L, which may be human or mouse DNMT3L).

Table 5 below provides exemplary methyltransferases from which an effector domain of an epigenetic editor described herein may be derived. See Table 18 for sequences of these exemplary methyltransferases.

TABLE 5

Exemplary DNA Methyltransferase Sequences

Protein Name	Species	Target	Protein Sequence
DNMT1	Human	5mC	SEQ ID NO: 1027
DNMT3A	Human	5mC	SEQ ID NO: 1028
DNMT3A (catalytic domain)	Human	5mC	SEQ ID NO: 1029
DNMT3B	Human	5mC	SEQ ID NO: 1030
DNMT3C	Mouse	5mC	SEQ ID NO: 1031
DNMT3L	Human	5mC	SEQ ID NO: 1032
DNMT3L (catalytic domain)	Human	5mC	SEQ ID NO: 1033
DNMT3L	Mouse	5mC	SEQ ID NO: 1034
DNMT3L (catalytic domain)	Mouse	5mC	SEQ ID NO: 1035
TRDMT1 (DNMT2)	Human	tRNA 5mC	SEQ ID NO: 1036
M.MpeI	*Mycoplasma penetrans*	5mC	SEQ ID NO: 1037
M.SssI	*Spiroplasma monobiae*	5mC	SEQ ID NO: 1038
M.HpaII	*Haemophilus parainfluenzae*	5mC (CCGG)	SEQ ID NO: 1039
M.AluI	*Arthrobacter luteus*	5mC (AGCT)	SEQ ID NO: 1040
M.HaeIII	*Haemophilus aegyptius*	5mC (GGCC)	SEQ ID NO: 1041
M.HhaI	*Haemophilus haemolyticus*	5mC (GCGC)	SEQ ID NO: 1042
M.MspI	*Moraxella*	5mC (CCGG)	SEQ ID NO: 1043
Masc1	*Ascobolus*	5mC	SEQ ID NO: 1044
MET1	*Arabidopsis*	5mC	SEQ ID NO: 1045
Masc2	*Ascobolus*	5mC	SEQ ID NO: 1046
Dim-2	*Neurospora*	5mC	SEQ ID NO: 1047
dDnmt2	*Drosophila*	5mC	SEQ ID NO: 1048
Pmt1	*S. pombe*	5mC	SEQ ID NO: 1049
DRM1	*Arabidopsis*	5mC	SEQ ID NO: 1050
DRM2	*Arabidopsis*	5mC	SEQ ID NO: 1051
CMT1	*Arabidopsis*	5mC	SEQ ID NO: 1052
CMT2	*Arabidopsis*	5mC	SEQ ID NO: 1053
CMT3	*Arabidopsis*	5mC	SEQ ID NO: 1054

TABLE 5-continued

Exemplary DNA Methyltransferase Sequences

Protein Name	Species	Target	Protein Sequence
Rid	*Neurospora*	5mC	SEQ ID NO: 1055
hsdM gene	bacteria (*E. coli*, strain 12)	m6A	SEQ ID NO: 1056
hsdS gene	bacteria (*E. coli*, strain 12)	m6A	SEQ ID NO: 1057
M.TaqI	Bacteria (*Thermus aquaticus*)	m6A	SEQ ID NO: 1058
M.EcoDam	*E. coli*	m6A	SEQ ID NO: 1059
M.CcrMI	*Caulobacter crescentus*	m6A	SEQ ID NO: 1060
CamA	*Clostridioides difficile*	m6A	SEQ ID NO: 1061

A functional analog of any one of the above-listed proteins, i.e., a molecule having the same or substantially the same biological function (e.g., retaining 70% or more, 80% or more, 90% or more, 95% or more, or 98% or more) of the protein's DNA methylation function or recruiting function) is encompassed by the present disclosure. For example, the functional analog may be an isoform or a variant of the above-listed protein, e.g., containing a portion of the above protein with or without additional amino acid residues and/or containing mutations relative to the above protein. In some embodiments, the functional analog has a sequence identity that is at least 75, 80, 85, 90, 95, 98, or 99% to one of the sequences listed in Table 5. In some embodiments, the effector domain herein comprises only the functional domain (or functional analog thereof), e.g., the catalytical domain or recruiting domain, of the above-listed proteins.

As used herein, a DNMT domain (e.g., a DNMT3A domain or a DNMT3L domain) refers to a protein domain that is identical to the parental protein (e.g., a human or murine DNMT3A or DNMT3L) or a functional analog thereof (e.g., having a functional fragment, such as a catalytic fragment or recruiting fragment, of the parental protein; and/or having mutations that improve the activity of the DNMT protein).

An epigenetic editor herein may effect methylation at, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 or more CpG dinucleotide sequences in the target gene or chromosome. The CpG dinucleotide sequences may be located within or near the target gene in CpG islands, or may be located in a region that is not a CpG island. A CpG island generally refers to a nucleic acid sequence or chromosome region that comprises a high frequency of CpG dinucleotides. For example, a CpG island may comprise at least 50% GC content. The CpG island may have a high observed-to-expected CpG ratio, for example, an observed-to-expected CpG ratio of at least 60%. As used herein, an observed-to-expected CpG ratio is determined by Number of CpG*(sequence length)/(Number of C*Number of G). In some embodiments, the CpG island has an observed-to-expected CpG ratio of at least 60%, 70%, 80%, 90% or more. A CpG island may be a sequence or

region of, e.g., at least 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, or 800 nucleotides. In some embodiments, only 1, or less than 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, or 50 CpG dinucleotides are methylated by the epigenetic editor.

In some embodiments, an epigenetic editor herein effects methylation at a hypomethylated nucleic acid sequence, i.e., a sequence that may lack methyl groups on the 5-methyl cytosine nucleotides (e.g., in CpG) as compared to a standard control. Hypomethylation may occur, for example, in aging cells or in cancer (e.g., early stages of neoplasia) relative to a younger cell or non-cancer cell, respectively.

In some embodiments, an epigenetic editor described herein induces methylation at a hypermethylated nucleic acid sequence.

In some embodiments, methylation may be introduced by the epigenetic editor at a site other than a CpG dinucleotide. For example, the target gene sequence may be methylated at the C nucleotide of CpA, CpT, or CpC sequences. In some embodiments, an epigenetic editor comprises a DNMT3A domain and effects methylation at CpG, CpA, CpT, CpC sequences, or any combination thereof. In some embodiments, an epigenetic editor comprises a DNMT3A domain that lacks a regulatory subdomain and only maintains a catalytic domain. In some embodiments, the epigenetic editor comprising a DNMT3A catalytic domain effects methylation exclusively at CpG sequences. In some embodiments, an epigenetic editor comprising a DNMT3A domain that comprises a mutation, e.g. a R836A or R836Q mutation (numbering according to SEQ ID NO: 1028), has higher methylation activity at CpA, CpC, and/or CpT sequences as compared to an epigenetic editor comprising a wildtype DNMT3A domain.

C. Histone Modifiers

In some embodiments, an effector domain of an epigenetic editor herein mediates histone modification. Histone modifications play a structural and biochemical role in gene transcription, such as by formation or disruption of the nucleosome structure that binds to the histone and prevents gene transcription. Histone modifications may include, for example, acetylation, deacetylation, methylation, phosphorylation, ubiquitination, SUMOylation and the like, e.g., at their N-terminal ends ("histone tails"). These modifications maintain or specifically convert chromatin structure, thereby controlling responses such as gene expression, DNA replication, DNA repair, and the like, which occur on chromosomal DNA. Post-translational modification of histones is an epigenetic regulatory mechanism and is considered essential for the genetic regulation of eukaryotic cells. Recent studies have revealed that chromatin remodeling factors such as SWI/SNF, RSC, NURF, NRD, and the like, which facilitate transcription factor access to DNA by modifying the nucleosome structure; histone acetyltransferases (HATs) that regulate the acetylation state of histones; and histone deacetylases (HDACs), act as important regulators.

In particular, the unstructured N-termini of histones may be modified by acetylation, deacetylation, methylation, ubiquitylation, phosphorylation, SUMOylation, ribosylation, citrullination O-GlcNAcylation, crotonylation, or any combination thereof. For example, histone acetyltransferases (HATs) utilize acetyl-CoA as a cofactor and catalyze the transfer of an acetyl group to the epsilon amino group of the lysine side chains. This neutralizes the lysine's positive charge and weakens the interactions between histones and DNA, thus opening the chromosomes for transcription factors to bind and initiate transcription. Acetylation of K14 and K9 lysines of histone H3 by histone acetyltransferase enzymes may be linked to transcriptional competence in humans. Lysine acetylation may directly or indirectly create binding sites for chromatin-modifying enzymes that regulate transcriptional activation. On the other hand, histone methylation of lysine 9 of histone H3 may be associated with heterochromatin, or transcriptionally silent chromatin.

In certain embodiments, an effector domain of an epigenetic editor described herein comprises a histone methyltransferase domain. The effector domain may comprise, for example, a DOT1L domain, a SET domain, a SUV39H1 domain, a G9a/EHMT2 protein domain, an EZH1 domain, an EZH2 domain, a SETDB1 domain, or any combination thereof. In particular embodiments, the effector domain comprises a histone-lysine-N-methyltransferase SETDB1 domain.

In some embodiments, the effector domain comprises a histone deacetylase protein domain. In certain embodiments, the effector domain comprises a HDAC family protein domain, for example, a HDAC1, HDAC3, HDAC5, HDAC7, or HDAC9 protein domain. In particular embodiments, the effector domain comprises a nucleosome remodeling and deacetylase complex (NURD), which removes acetyl groups from histones.

D. Other Effector Domains

In some embodiments, the effector domain comprises a tripartite motif containing protein (TRIM28, TIF1-beta, or KAP1). In certain embodiments, the effector domain comprises one or more KAP1 proteins. A KAP1 protein in an epigenetic editor herein may form a complex with one or more other effector domains of the epigenetic editor or one or more proteins involved in modulation of gene expression in a cellular environment. For example, KAP1 may be recruited by a KRAB domain of a transcriptional repressor. A KAP1 protein domain may interact with or recruit one or more protein complexes that reduces or silences gene expression. In some embodiments, KAP1 interacts with or recruits a histone deacetylase protein, a histone-lysine methyltransferase protein, a chromatin remodeling protein, and/or a heterochromatin protein. For example, a KAP1 protein domain may interact with or recruit a heterochromatin protein 1 (HP1) protein, a SETDB1 protein, an HDAC protein, and/or a NuRD protein complex component. In some embodiments, a KAP1 protein domain interacts with or recruits a ZFP90 protein (e.g., isoform 2 of ZFP90), and/or a FOXP3 protein. An exemplary KAP1 amino acid sequence is shown in SEQ ID NO: 1062.

In some embodiments, the effector domain comprises a protein domain that interacts with or is recruited by one or more DNA epigenetic marks. For example, the effector domain may comprise a methyl CpG binding protein 2 (MECP2) protein that interacts with methylated DNA nucleotides in the target gene (which may or may not be at a CpG island of the target gene). An MECP2 protein domain in an epigenetic editor described herein may induce condensed chromatin structure, thereby reducing or silencing expression of the target gene. In some embodiments, an MECP2 protein domain in an epigenetic editor described herein may interact with a histone deacetylase (e.g. HDAC), thereby repressing or silencing expression of the target gene. In some embodiments, an MECP2 protein domain in an epigenetic editor described herein may block access of a transcription factor or transcriptional activator to the target sequence, thereby repressing or silencing expression of the target gene. An exemplary MECP2 amino acid sequence is shown in SEQ ID NO: 1063.

Also contemplated as effector domains for the epigenetic editors described herein are, e.g., a chromoshadow domain,

a ubiquitin-2 like Rad60 SUMO-like (Rad60-SLD/SUMO) domain, a chromatin organization modifier domain (Chromo) domain, a Yaf2/RYBP C-terminal binding motif domain (YAF2_RYBP), a CBX family C-terminal motif domain (CBX7_C), a zinc finger C3HC4 type (RING finger) domain (ZF-C3HC4_2), a cytochrome b5 domain (Cyt-b5), a helix-loop-helix domain (HLH), a helix-hairpin-helix motif domain (e.g., HHH_3), a high mobility group box domain (HMG-box), a basic leucine zipper domain (e.g., bZIP_1 or bZIP_2), a Myb_DNA-binding domain, a homeodomain, a MYM-type Zinc finger with FCS sequence domain (ZF-FCS), an interferon regulatory factor 2-binding protein zinc finger domain (IRF-2BP1_2), an SSX repression domain (SSXRD), a B-box-type zinc finger domain (ZF-B_box), a CXXC zinc finger domain (ZF-CXXC), a regulator of chromosome condensation 1 domain (RCC1), an SRC homology 3 domain (SH3_9), a sterile alpha motif domain (SAM_1), a sterile alpha motif domain (SAM 2), a sterile alpha motif/Pointed domain (SAM_PNT), a Vestigial/Tondu family domain (Vg_Tdu), a LIM domain, an RNA recognition motif domain (RRM_1), a paired amphipathic helix domain (PAH), a proteasomal ATPase OB C-terminal domain (Prot_ATP_ID_OB), a nervy homology 2 domain (NHR2), a hinge domain of cleavage stimulation factor subunit 2 (CSTF2_hinge), a PPAR gamma N-terminal region domain (PPARgamma_N), a CDC48 N-terminal domain (CDC48_2), a WD40 repeat domain (WD40), a Fip1 motif domain (Fip1), a PDZ domain (PDZ_6), a Von Willebrand factor type C domain (VWC), a NAB conserved region 1 domain (NCD1), an S1 RNA-binding domain (S1), an HNF3C-terminal domain (HNF_C), a Tudor domain (Tudor_2), a histone-like transcription factor (CBF/NF-Y) and archaeal histone domain (CBFD_NFYB_HMF), a zinc finger protein domain (DUF3669), an EGF-like domain (cEGF), a GATA zinc finger domain (GATA), a TEA/ATTS domain (TEA), a phorbol esters/diacylglycerol binding domain (C1-1), polycomb-like MTF2 factor 2 domain (Mtf2_C), a transactivation domain of FOXO protein family (FOXO-TAD), a homeobox KN domain (Homeobox_KN), a BED zinc finger domain (ZF-BED), a zinc finger of C3HC4-type RING domain (ZF-C3HC4_4), a RAD51 interacting motif domain (RAD51_interact), a p55-binding region of a methyl-CpG-binding domain protein MBD (MBDa), a Notch domain, a Raf-like Ras-binding domain (RBD), a Spin/Ssty family domain (Spin-Ssty), a PHD finger domain (PHD_3), a Low-density lipoprotein receptor domain class A (Ldl_recept_a), a CS domain, a DM DNA-binding domain, and a QLQ domain.

In some embodiments, the effector domain is a protein domain comprising a YAF2_RYBP domain or homeodomain or any combination thereof. In certain embodiments, the homeodomain of the YAF2_RYBP domain is a PRD domain, an NKL domain, a HOXL domain, or a LIM domain. In particular embodiments, the YAF2_RYBP domain may comprise a 32 amino acid Yaf2/RYBP C-terminal binding motif domain (32 aa RYBP).

In some embodiments, the effector domain comprises a protein domain selected from a group consisting of SUMO3 domain, Chromo domain from M phase phosphoprotein 8 (MPP8), chromoshadow domain from Chromobox 1 (CBX1), and SAM_1/SPM domain from Scm Polycomb Group Protein Homolog 1 (SCMH1).

In some embodiments, the effector domain comprises an HNF3 C-terminal domain (HNF_C). The HNF_C domain may be from FOXA1 or FOXA2. In certain embodiments, the HNF_C domain comprises an EH1 (engrailed homology 1) motif.

In some embodiments, the effector domain may comprise an interferon regulatory factor 2-binding protein zinc finger domain (IRF-2BP1_2), a Cyt-b5 domain from DNA repair factor HERC2 E3 ligase, a variant SH3 domain (SH3_9) from Bridging Integrator 1 (BIN1), an HMG-box domain from transcription factor TOX or ZF-C3HC4-2 RING finger domain from the polycomb component PCGF2, a Chromodomain-helicase-DNA binding protein 3 (CHD3) domain, or a ZNF783 domain.

IV. Epigenetic Editors

Provided herein are epigenetic editors, also referred to herein as epigenetic editing systems, that direct epigenetic modification(s) to a target sequence in a gene of interest, e.g., using one or more DNA-binding domains as described herein and one or more effector domains (e.g., epigenetic repression domains) as described herein, in any combination. The DNA-binding domain (in concert with a guide polynucleotide such as one described herein, where the DNA-binding domain is a polynucleotide guided DNA-binding domain) directs the effector domain to epigenetically modify the target sequence, resulting in gene repression or silencing that may be durable and inheritable across cell generations. In some aspects, the epigenetic editors described herein can repress or silence genes reversibly or irreversibly in cells.

In particular embodiments, an epigenetic editor described herein comprises one or more fusion proteins, each comprising (1) DNA-binding domain(s) and (2) effector domain(s). The effector domains may be on one or more fusion proteins comprised by the epigenetic editor. For example, a single fusion protein may comprise all of the effector domains with a DNA-binding domain. Alternatively, the effector domains or subsets thereof may be on separate fusion proteins, each with a DNA-binding domain (which may be the same or different). A fusion protein described herein may further comprise one or more linkers (e.g., peptide linkers), detectable tags, nuclear localization signals (NLSs), or any combination thereof. As used herein, a "fusion protein" refers to a chimeric protein in which two or more coding sequences (e.g., for DNA-binding domain(s) and/or effector domain(s)) are covalently or non-covalently joined, directly or indirectly.

In some embodiments, an epigenetic editor described herein comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, or more effector (e.g., repression) domains, which may be identical or different. In certain embodiments, two or more of said effector domains function synergistically. Combinations of effector domains may comprise DNA methylation domains, histone deacetylation domains, histone methylation domains, and/or scaffold domains that recruit any of the above. For example, an epigenetic editor described herein may comprise one or more transcriptional repressor domains (e.g., a KRAB domain such as KOX1, ZIM3, ZFP28, or ZN627 KRAB) in combination with one or more DNA methylation domains (e.g., a DNMT domain) and/or recruiter domain (e.g., a DNMT3L domain). Such an epigenetic editor may comprise, for instance, a KRAB domain, a DNMT3A domain, and a DNMT3L domain. An epigenetic editor can comprise a DNMT3A domain and a DNMT3L domain and preferably further comprise a KRAB domain. In some embodiments, the epigenetic editor further comprises an additional effector domain (e.g., a KAP1, MECP2, HP1b, CBX8, CDYL2, TOX, TOX3, TOX4, EED, RBBP4, RCOR1, or SCML2 domain). In some embodiments, the additional effector domain is a CDYL2, TOX, TOX3, TOX4, or HP1a domain.

For example, an epigenetic editor described herein may comprise a CDYL2 and/or a TOX domain in combination with a KRAB domain (e.g., a KOX1 KRAB domain).

A. Linkers

A fusion protein as described herein may comprise one or more linkers that connect components of the epigenetic editor. A linker may be a peptide or non-peptide linker.

In some embodiments, one or more linkers utilized in an epigenetic editor provided herein is a peptide linker, i.e., a linker comprising a peptide moiety. A peptide linker can be any length applicable to the epigenetic editor fusion proteins described herein. In some embodiments, the linker can comprise a peptide between 1 and 200 (e.g., between 1 and 80) amino acids. In some embodiments, the linker comprises from 1 to 5, 1 to 10, 1 to 20, 1 to 30, 1 to 40, 1 to 50, 1 to 60, 1 to 80, 1 to 100, 1 to 150, 1 to 200, 5 to 10, 5 to 20, 5 to 30, 5 to 40, 5 to 60, 5 to 80, 5 to 100, 5 to 150, 5 to 200, 10 to 20, 10 to 30, 10 to 40, 10 to 50, 10 to 60, 10 to 80, 10 to 100, 10 to 150, 10 to 200, 20 to 30, 20 to 40, 20 to 50, 20 to 60, 20 to 80, 20 to 100, 20 to 150, 20 to 200, 30 to 40, 30 to 50, 30 to 60, 30 to 80, 30 to 100, 30 to 150, 30 to 200, 40 to 50, 40 to 60, 40 to 80, 40 to 100, 40 to 150, 40 to 200, 50 to 60 50 to 80, 50 to 100, 50 to 150, 50 to 200, 60 to 80, 60 to 100, 60 to 150, 60 to 200, 80 to 100, 80 to 150, 80 to 200, 100 to 150, 100 to 200, or 150 to 200 amino acids in length. Longer or shorter linkers are also contemplated. In some embodiments, the peptide linker is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 25, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids in length. For example, the peptide linker may be 4, 5, 16, 20, 24, 27, 32, 40, 64, 92, or 104 amino acids in length. The peptide linker may be a flexible or rigid linker. In particular embodiments, the peptide linker comprises the amino acid sequence of any one of SEQ ID NOs: 1064-1068 or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical thereto.

In certain embodiments, the peptide linker is an XTEN linker. Such a linker may comprise part of the XTEN sequence (Schellenberger et al., *Nat Biotechnol* (2009) 27(1):1186-90), an unstructured hydrophilic polypeptide consisting only of residues G, S, P, T, E, and A. The term "XTEN" as used herein refers to a recombinant peptide or polypeptide lacking hydrophobic amino acid residues. XTEN linkers typically are unstructured and comprise a limited set of natural amino acids. Fusion of XTEN to proteins alters its hydrodynamic properties and reduces the rate of clearance and degradation of the fusion protein. These XTEN fusion proteins are produced using recombinant technology, without the need for chemical modifications, and degraded by natural pathways. The XTEN linker may be, for example, 5, 10, 16, 20, 26, or 80 amino acids in length. In some embodiments, the XTEN linker is 16 amino acids in length. In some embodiments, the XTEN linker is 80 amino acids in length. In certain embodiments, the XTEN linker may be XTEN10, XTEN16, XTEN20, or XTEN80. In certain embodiments, the XTEN linker may comprise the amino acid sequence of any one of SEQ ID NOs: 1069-1073 and 1092 or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, the XTEN linker may be XTEN10, XTEN16, XTEN20, or XTEN80.

In some embodiments, one or more linkers utilized in an epigenetic editor provided herein is a non-peptide linker. For example, the linker may be a carbon bond, a disulfide bond, or carbon-heteroatom bond. In certain embodiments, the linker is a carbon-nitrogen bond of an amide linkage. In certain embodiments, the linker is a cyclic or acyclic, substituted or unsubstituted, or branched or unbranched aliphatic or heteroaliphatic linker.

In some embodiments, one or more linkers utilized in an epigenetic editor provided herein is polymeric (e.g., polyethylene, polyethylene glycol, polyamide, polyester, etc.). The linker may comprise, for example, a monomer, dimer, or polymer of aminoalkanoic acid; an aminoalkanoic acid (e.g., glycine, ethanoic acid, alanine, beta-alanine, 3-aminopropanoic acid, 4-aminobutanoic acid, 5-pentanoic acid, etc.); a monomer, dimer, or polymer of aminohexanoic acid (Ahx); or a polyethylene glycol moiety (PEG); or an aryl or heteroaryl moiety. In certain embodiments, the linker may be based on a carbocyclic moiety (e.g., cyclopentane or cyclohexane) or a phenyl ring. The linker may include functionalized moieties to facilitate attachment of a nucleophile (e.g., thiol, amino) from the peptide to the linker. Any electrophile may be used as part of the linker. Exemplary electrophiles include, but are not limited to, activated esters, activated amides, alkyl halides, aryl halides, acyl halides, and isothiocyanates.

Various linker lengths and flexibilities can be employed between any two components of an epigenetic editor (e.g., between an effector domain (e.g., a repressor domain) and a DNA-binding domain (e.g., a Cas9 domain), between a first effector domain and a second effector domain, etc.). The linkers may range from very flexible linkers, such as glycine/serine-rich linkers, to more rigid linkers, in order to achieve the optimal length for effector domain activity for the specific application. In some embodiments, the more flexible linkers are glycine/serine-rich linkers (GS-rich linkers), where more than 45% (e.g., more than 48, 50, 55, 60, 70, 80, or 90%) of the residues are glycine or serine residues. Non-limiting examples of the GS-rich linkers are (GGGGS)n (SEQ ID NO: 485), (G)n (SEQ ID NO: 1260), and W linker. In some embodiments, the more rigid linkers are in the form of the form (EAAAK)n (SEQ ID NO: 487), (SGGS)n (SEQ ID NO: 488), and (XP)n (SEQ ID NO: 489). In the aforementioned formulae of flexible and rigid linkers, n may be any integer between 1 and 30. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, the linker comprises a (GGS)n motif, wherein n is 1, 3, or 7 (SEQ ID NO: 490). In some embodiments, the linker comprises a (GGGGS)n motif, wherein n is 4 (SEQ ID NO: 491).

In some embodiments, a linker in an epigenetic editor described herein comprises a nuclear localization signal, for example, with the amino acid sequence of any one of SEQ ID NOs: 1074-1079. In some embodiments, a linker in an epigenetic editor described herein comprises an expression tag, e.g., a detectable tag such as a green fluorescence protein.

B. Nuclear Localization Signals

A fusion protein described herein may comprise one or more nuclear localization signals, and in certain embodiments, may comprise two or more nuclear localization signals. For example, the fusion protein may comprise 1, 2, 3, 4, or 5 nuclear localization signals. As used herein, a "nuclear localization signal" (NLS) is an amino acid sequence that directs proteins to the nucleus. In certain embodiments, the NLS may be an SV40 NLS. The fusion protein may comprise an NLS at its N-terminus, C-terminus, or both, and/or an NLS may be embedded in the middle of the fusion protein (e.g., at the N- or C-terminus of a DNA-binding domain or an effector domain). In certain embodiments, an NLS comprises the amino acid sequence of any one of SEQ ID NOs: 1074-1079, or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%,

96%, 97%, 98%, or 99% identical to the selected sequence. Additional NLSs are known in the art.

C. Tags

Epigenetic editors provided herein may comprise one or more additional sequences ("tags") for tracking, detection, and localization of the editors. In some embodiments, the epigenetic editor comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more detectable tags. Each of the detectable tags may be the same or different.

For example, an epigenetic editor fusion protein may comprise cytoplasmic localization sequences, export sequences, such as nuclear export sequences, or other localization sequences, as well as sequence tags that are useful for solubilization, purification, or detection of the fusion proteins. Suitable protein tags provided herein include, but are not limited to, biotin carboxylase carrier protein (BCCP) tags, myc-tags, calmodulin-tags, FLAG-tags, hemagglutinin (HA)-tags, poly-histidine tags (also referred to as histidine tags or His-tags), maltose binding protein (MBP)-tags, nus-tags, glutathione-S-transferase (GST)-tags, green fluorescent protein (GFP)-tags, thioredoxin-tags, S-tags, Softags (e.g., Softag 1 or Softag 3), strep-tags, biotin ligase tags, FlAsH tags, V5 tags, and SBP-tags. Additional suitable sequences will be apparent to those of skill in the art. Sequences disclosed herein that are presented with tag sequences included are also contemplated without the presented tag sequences; similarly, sequences disclosed herein without tag sequences are also contemplated to include the addition of suitable tag sequences apparent to those of skill in the art.

D. Fusion Protein Configurations

A fusion protein of an epigenetic editor described herein may have its components structured in different configurations. For example, the DNA-binding domain may be at the C-terminus, the N-terminus, or in between two or more epigenetic effector domains or additional domains. In some embodiments, the DNA-binding domain is at the C-terminus of the epigenetic editor. In some embodiments, the DNA-binding domain is at the N-terminus of the epigenetic editor. In some embodiments, the DNA-binding domain is linked to one or more nuclear localization signals. In some embodiments, the DNA-binding domain is flanked by an epigenetic effector domain and/or an additional domain on both sides. In some embodiments, where "DBD" indicates DNA-binding domain and "ED" indicates effector domain, the epigenetic editor comprises the configuration of:

N']-[ED1]-[DBD]-[ED2]-[C'
N']-[ED1]-[DBD]-[ED2]-[ED3]-[C'
N']-[ED1]-[ED2]-[DBD]-[ED3]-[C' or
N']-[ED1]-[ED2]-DBD]-[ED3]-[ED4]-[C'.

In some embodiments, an epigenetic editor comprises a DNA-binding domain (DBD), a DNA methyltransferase (DNMT) domain, and a transcriptional repressor ("repressor") domain that represses or silences expression of a target gene. The DBD, DNMT, and transcriptional repressor domains may be any as described herein, in any combination. For example, an epigenetic editor can comprise a DBD, a DNMT3A domain, and a DNMT3L domain. An epigenetic editor can comprise a DBD, a DNMT3A domain, a DNMT3L domain, and preferably further comprise a KRAB domain. In some embodiments, the epigenetic editor comprises a fusion protein with the configuration of

N']-[DNA methyltransferase domain]-[DBD]-[repressor domain]-[C'
N']-[repressor domain]-[DBD]-[DNA methyltransferase domain]-[C'
N']-[DNA methyltransferase domain]-[repressor domain]-[DBD]-[C' or
N']-[repressor domain]-[DNA methyltransferase domain]-[DBD]-[C'.

In some embodiments, a connecting structure "]-[" in any one of the epigenetic editor structures is a linker, e.g., a peptide linker; a detectable tag; a peptide bond; a nuclear localization signal; and/or a promoter or regulatory sequence. In an epigenetic editor structure, the multiple connecting structures "]-[" may be the same or may each be a different linker, tag, NLS, or peptide bond. In particular embodiments, the DNA methyltransferase domain comprises DNMT3A, DNMT3L, or both. In particular embodiments, the DBD is a catalytically inactive polynucleotide guided DNA-binding domain (e.g., a dCas9) or a ZFP domain. In particular embodiments, the repressor domain is a KRAB domain.

In some embodiments, the epigenetic editor comprises a configuration selected from

N']-[DNMT3A-DNMT3L]-[DBD]-[KRAB]-[C'
N']-[KRAB]-[DBD]-[DNMT3A-DNMT3L]-[C'
N']-[KRAB]-[DBD]-[DNMT3A]-[C'
N']-[DNMT3A]-[DBD]-[KRAB]-[C'
N']-[KRAB]-[DBD]-[DNMT3A]-[DNMT3L]-[C'
N']-[DNMT3A]-[DNMT3L]-[DBD]-[KRAB]-[C'
N']-[DNMT3A]-[DBD]-[C'
N']-[DBD]-[DNMT3A]-[C'
N']-[DNMT3L]-[DBD]-[C'
N']-[DBD]-[DNMT3L]-[C'

wherein [DNMT3A-DNMT3L] indicates that the DNMT3A and DNMT3L domains are directly fused via a peptide bond, and wherein the connecting structure]-[is any one of the linkers as described herein, a detectable tag, an affinity domain, a peptide bond, a nuclear localization signal, a promoter, and/or a regulatory sequence. The DBD, KRAB, DNMT3A, and DNMT3L domains may be any as described herein, in any combination. In particular embodiments, the DBD is a CRISPR-associated protein domain (e.g., dCas9) or a ZFP domain; the KRAB domain is derived from KOX1, ZIM3, ZFP28, or ZN627; the DNMT3A domain is a human DNMT3A domain; and the DNMT3L domain is a human or mouse DNMT3L domain; any combination of these components is also contemplated by the present disclosure.

In some embodiments, the epigenetic editor comprises a configuration selected from

N']-[DNMT3A]-[DBD]-[SETDB1]-[C'
N']-[DNMT3A]-[DNMT3L]-[DBD]-[SETDB1]-[C'
N']-[DNMT3A-DNMT3L]-[DBD]-[SETDB1]-[C'
N']-[SETDB1]-[DBD]-[DNMT3A]-[DNMT3L]-[C'
N']-[SETDB1]-[DBD]-[DNMT3A]-[C'

wherein [DNMT3A-DNMT3L] indicates that the DNMT3A and DNMT3L domains are directly fused via a peptide bond, and wherein the connecting structure]-[is any one of the linkers as described herein, a detectable tag, an affinity domain, a peptide bond, a nuclear localization signal, a promoter, and/or a regulatory sequence. The DBD, SETDB1, DNMT3A, and DNMT3L domains may be any as described herein, in any combination. In particular embodiments, the DBD is a CRISPR-associated protein domain (e.g., dCas9) or a ZFP domain; the SETDB1 domain is derived from human SETDB1, ZIM3, ZFP28, or ZN627; the DNMT3A domain is a human DNMT3A domain; and the DNMT3L domain is a human or mouse DNMT3L domain; any combination of these components is also contemplated by the present disclosure.

Particular constructs contemplated herein include:

DNMT3A-DNMT3L-XTEN80-NLS-dCas9-NLS-XTEN16-KOX1 KRAB (Configuration 1), and

DNMT3A-DNMT3L-XTEN80-NLS-ZFP domain-NLS-XTEN16-KOX1 KRAB (Configuration 2).

In particular embodiments, the DNMT3L and DNMT3A are both derived from human parental proteins. In particular embodiments, the DNMT3L and DNMT3A are derived from human and mouse parental proteins, respectively. In particular embodiments, the DNMT3L and DNMT3A are derived from mouse and human parental proteins, respectively. In particular embodiments, the DNMT3L and DNMT3A are both derived from mouse parental proteins. In some embodiments, the dCas9 is dSpCas9. In some embodiments, the KOX1 is human KOX1.

In particular embodiments, a fusion construct described herein may have Configuration 1 and comprise SEQ ID NO: 1080, or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical thereto. In SEQ ID NO: 1080 below, the XTEN linkers are underlined, the NLS sequences are bolded, the DNMT3A sequence is italicized, the DNMT3L sequence is underlined and italicized, the dCas9 domain is bolded and italicized, and the KOX1 KRAB domain is underlined and bolded:

(SEQ ID NO: 1080)

MNHDQEFDPPKVYPPVPAEKRKPIRVLSLEDGIATGLLVLKDLGIQVDRY

IASEVCEDSITVGMVRHQGKIMYVGDVRSVTQKHIQEWGPFDLVIGGSPC

NDLSIVNPARKGLYEGTGRLFFEFYRLLHDARPKEGDDRPFFWLFENVVA

MGVSDKRDISRFLESNPVMIDAKEVSAAHRARYFWGNLPGMNRPLASTVN

DKLELQECLEHGRIAKESKVRTITTRSNSIKQGKDQHFPVFMNEKEDILW

CTEMERVFGFPVHYTDVSNMSRLARQRLLGRSWSVPVIRHLFAPLKEYFA

CVSSGNSNANSRGPSFSSGLVPLSLRGSHMGPMEIYKTVSAWKRQPVRVL

SLERNIDKVLKSLGFLESGSGSGGGTLKYVEDVTNVVRRDVEKWGPEDLV

YGSTQPLGSSCDRCPGWYMEQFHRILQYALPRQESQRPFFWIFMDNLLLT

EDDQETTTRFLQTEAVTLQDVRGRDYQNAMRVWSNIPGLKSKHAPLTPKE

EEYLQAQVRSRSKLDAPKVDLLVKNCLLPLREYFKYFSQNSLPLGGPSSG

APPPSGGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPT

STEEGTSTEPSEGSAPGTSTE**PSEPKKKRKVY*MDKKYSIGLAIGTNSVGW***

AVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTA

RRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPI

FGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKERGHF

LIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSK

SRRLENLIAQLPGEKKNGLEGNLIALSLGLTPNEKSNEDLAEDAKLQLSK

DTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLS

ASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGAS

QEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGE

LHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRK

SEETITPWNFEEVVDKGASAQSFIERMTNEDKNLPNEKVLPKHSLLYEYF

TVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLEKTNRKVTVKQLKEDY

FKKIECFDSVEISGVEDRENASLGTYHDLLKIIKDKDELDNEENEDILED

-continued

IVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYTGWGRLSRKLIN

GIRDKQSGKTILDELKSDGEANRNEMQLIHDDSLTFKEDIQKAQVSGQGD

SLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQ

TTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQN

GRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSD

NVPSEEVVKKMKNYWRQLLNAKLITQRKEDNLTKAERGGLSELDKAGFIK

RQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERK

DFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDV

RKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGE

TGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDK

LIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITI

MERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAG

ELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDE

IIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNL

GAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGD

PKKKRKVSGSETPGTSESATPESTG**RTLVTFKDVFVDFTREEWKLLDTAQ**

QIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEP

In particular embodiments, a fusion construct described herein may have Configuration 2 and comprise SEQ ID NO: 1081, or a sequence at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical thereto. In SEQ ID NO: 1081 below, the XTEN linkers are underlined, the NLS sequences are bolded and underlined, the DNMT3A sequence is italicized, the DNMT3L sequence is underlined and italicized, the ZFP domain is bolded, and the KOX1 KRAB domain is underlined and bolded. Variable amino acids represented by Xs are the amino acids of the DNA-recognition helix of the zinc finger and XX in italics may be either TR, LR or LK.

MNHDQEFDPPKVYPPVPAEKRKPIRVLSLEDGIATGLLVLKDLGIQVDRY

IASEVCEDSITVGMVRHQGKIMYVGDVRSVTQKHIQEWGPEDLVIGGSPC

NDLSIVNPARKGLYEGTGRLFFEFYRLLHDARPKEGDDRPFFWLFENVVA

MGVSDKRDISRFLESNPVMIDAKEVSAAHRARYFWGNLPGMNRPLASTVN

DKLELQECLEHGRIAKFSKVRTITTRSNSIKQGKDQHFPVFMNEKEDILW

CTEMERVEGFPVHYTDVSNMSRLARQRLLGRSWSVPVIRHLFAPLKEYFA

CVSSGNSNANSRGPSESSGLVPLSLRGSHMGPMEIYKTVSAWKRQPVRVL

SLERNIDKVLKSLGFLESGSGSGGGTLKYVEDVTNVVRRDVEKWGPEDLV

YGSTQPLGSSCDRCPGWYMFQFHRILQYALPRQESQRPFFWIEMDNLLLT

EDDQETTTRELQTEAVTLQDVRGRDYQNAMRVWSNIPGLKSKHAPLTPKE

EEYLQAQVRSRSKLDAPKVDLLVKNCLLPLREYFKYFSQNSLPLGGPSSG

APPPSGGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPT

STEEGTSTEPSEGSAPGTSTEPSE**PKKKRKVYSRPGERPFQCRICMRNFS**

XXXXXXXHXXTHTGEKPFQCRICMRNFSXXXXXXXHXXTH[linker]PF

QCRICMRNFSXXXXXXXHXXTHTGEKPFQCRICMRNFSXXXXXXXHXXTH

-continued

[linker]PFQCRICMRNFSXXXXXXXHXXTHTGEKPFQCRICMRNFSXX

XXXXXHXXTHLRGSPKKKRKVSGSETPGTSESATPESTGRTLVTFKDVFV

DFTREEWKLLDTAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEE

P (SEQ ID NOs: 1081, 1262 and 1263, respectively,

in order of appearance)

In certain embodiments, the six "XXXXXXX" regions in SEQ ID NO: 1081, 1262 or 1263 comprise, in order, the F1-F6 amino acid sequences shown in Table 1. [linker] represents a linker sequence. In some embodiments, one or both linker sequences may be TGSQKP (SEQ ID NO: 1085). In some embodiments, one or both linker sequences may be TGGGGSQKP (SEQ ID NO: 1086). In some embodiments, one linker sequence may have the amino acid sequence of SEQ ID NO: 1085 and the other linker sequence may have the amino acid sequence of SEQ ID NO: 1086.

Multiple epigenetic editors may be used to effect activation or repression of a target gene or multiple target genes. For example, an epigenetic editor fusion protein comprising a DNA-binding domain (e.g., a dCas9 domain) and an effector domain may be co-delivered with two or more guide polynucleotides (e.g., gRNAs), each targeting a different target DNA sequence. The target sites for two of the DNA-binding domains may be the same or in the vicinity of each other, or separated by, for example, about 100 base pairs, about 200 base pairs, about 300 base pairs, about 400 base pairs, about 500 base pairs, or about 600 or more base pairs. In addition, when targeting double-strand DNA, such as an endogenous gene locus, the guide polynucleotides may target the same or different strands (one or more to the positive strand and/or one or more to the negative strand).

V. Target Sequences

An epigenetic editor herein may be directed to an HBV target sequence to effect epigenetic modification of HBV or an HBV gene. As used herein, a "target sequence," a "target site," or a "target region" is a nucleic acid sequence present in a genome or gene of interest, e.g., in an HBV genome or an HBV gene; in some instances, the target sequence may be outside but in the vicinity of the gene of interest wherein methylation or binding by a repressor of the target sequence represses expression of the gene. In some embodiments, the target sequence may be a hypomethylated or hypermethylated nucleic acid sequence.

The structure and biology of HBV as well as HBV-associated diseases have been reported (see, for example, Yuen, MF., Chen, DS., Dusheiko, G. et al. Hepatitis B virus infection. Nat Rev Dis Primers 4, 18035 (2018); R. Koshy and W. H. Caselman (Eds.), Hepatitis B Virus: Molecular Mechanism in Disease and Novel Strategies for Antiviral Therapy, Imperial College Press, London (1998), ISBN 1783262737; the entire contents of each of which are incorporated herein by reference). HBV genotypes and sub-types, as well as their genomic, transcript, and protein sequences have been described and are known to the skilled artisan. Some exemplary HBV sequences, e.g., those under accession numbers NC_00397 and U95551 are provided elsewhere herein, and the entire content of each such database entry is incorporated herein by reference.

Without wishing to be bound by any particular theory, it has been reported that HBV persists as a covalently closed circular DNA (cccDNA) of approximately 3.2 kb, as well as in an integrated form. The HBV genome has been extensively characterized. The HBV genome has been shown to comprise four genes (the S gene, the P gene, the C gene, and the X gene), regulated by four promoter elements (sp1, sp2, cp and xp) and two enhancer elements (Enh I and Enh II) that control the expression of four defined (and overlapping) protein-encoding open reading frames (S, C, X, and P). See FIG. **1**. The HBV genome has been described to express six major viral RNA transcripts encoding the viral proteins: (1) the preCore (preC) RNA, which encodes the C protein (also referred to as Core protein, HBe Antigen, or HBeAg); (2), the pre-genomic (pg)RNA, which encodes the two viral proteins C (core) and P (polymerase), and also serves as the template for the synthesis of viral DNA, which is mediated by the reverse transcriptase activity of the viral P protein once pg RNA and the P protein are encapsidated into the nucleocapsids formed by the C protein; (3) the large surface protein (preS1) RNA, which encodes the Large S Antigen (also referred to as L-HBsAg); (4) the middle surface protein (preS2) RNA, which encodes the Middle S Antigen (also referred to as M-HBsAg); (5) the small surface protein (S) RNA, which encodes the Small S Antigen (also referred to as S-HBsAg); and (6) the X protein (HBx) RNA, which encodes the X protein. Transcription start sites (TSSs) as well as the termination site of the HBV transcripts have been mapped in various HBV genotypes and sub-types. Notably, HBV transcripts have been described to terminate at a single termination/polyadenylation signal located downstream of the Hbx CDS and comprising a canonical ATAAA motif. It has further been reported that HBV DNA may be methylated by infected cells and such methylation has been postulated to correlate with inhibition of viral gene expression. However, naturally occurring cell-mediated methylation of viral DNA is typically insufficient to silence viral expression to a level that would result in control of HBV infection. DNA methylation typically occurs at CpG dinucleotides. Several CpG-rich genomic regions, also referred to as CpG islands or CGIs, have been identified in the HBV genome. CGIs are typically identified in HBV genomic sequences as sequences of a specific minimal length (e.g., at least 100 bp) that comprise a minimum percentage of G and C nucleotides (e.g., at least 50% or at least 60% GC content) and a ratio of observed vs. expected CpG dinucleotides of at least 0.6. CGIs satisfying these criteria have been identified in all HBV genotypes, and it has been demonstrated that HBV genomes typically contain three CpG islands (CGI-I, CHI-II, and CGI-III, respectively), which are also sometimes referred to as 'conventional' HBV CpG islands. Some HBV genotypes or sub-types have been reported to comprise additional, 'non-conventional' CGIs. FIG. **1** is a diagram illustrating an exemplary structure of a circular HBV genome (the underlying sequence of which is provided herein as SEQ ID NO: 1082), identifying the coding regions of HBV genes and CpG islands CGI-I-III. See, for example, M. J. Kosovsky, et al., The regulation of hepatitis B virus gene expression: an overview of the cis- and trans-acting components in R. Koshy and W. H. Caselman (Eds.), Hepatitis B Virus: Molecular Mechanism in Disease and Novel Strategies for Antiviral Therapy, Imperial College Press, London (1998), ISBN 1783262737; Miller et al Compact organization of the hepatitis B virus genome. Hepatology. 1989 February; 9(2):322-7; Stadelmayer et al., Full-length 5'RACE identifies all major HBV transcripts in HBV-infected hepatocytes and patient serum. J Hepatol. 2020 July; 73(1):40-51; Meier-Stephenson et al., Comprehensive Analysis of Hepatitis B Virus Promoter Region Mutations. Viruses. 2018 Nov. 1; 10(11):603; Vivekanandan

et al., Hepatitis B viral DNA is methylated in liver tissues. J Viral Hepat. 2008, 15(2):103-7; Chen et al., Detection of hepatitis B virus DNA in hepatocellular carcinoma: methylation of integrated viral DNA. J Virol Methods. 1988, 19(3-4):257-63; Zhang et al., Comparative Analysis of CpG Islands among HBV Genotypes. PLOS ONE 2013, 8(2): e56711; Jain et al., Comprehensive DNA methylation analysis of hepatitis B virus genome in infected liver tissues. Sci Rep 5, 10478 (2015); Low et al., Hepatitis B virus DNA methylation and its potential role in chronic hepatitis B. Expert Reviews in Molecular Medicine. 2023; 25:ell; Hou et al., CpG islands of hepatitis B virus genome isolated from Chinese patients. Gene (2015) 561:261-267; Mouzannar et al., The Post-Transcriptional Regulatory Element of Hepatitis B Virus: From Discovery to Therapy. Viruses. 2024 Mar. 29; 16(4):528; Peng et al., Nonproductive Hepatitis B Virus Covalently Closed Circular DNA Generates HBx-Related Transcripts from the HBx/Enhancer I Region and Acquires Reactivation by Superinfection in Single Cells. J Virol. 2023 Jan. 31; 97(1):e0171722; Altinel et al., Single-Nucleotide Resolution Mapping of Hepatitis B Virus Promoters in Infected Human Livers and Hepatocellular Carcinoma. J Virol. 2016 Nov. 14; 90(23):10811-10822; the entire contents of each of which, and, where applicable, including any supplemental information, are incorporated herein by reference.

The target sequence (also referred to herein as target site or target region) of an epigenetic editor provided herein may be any suitable HBV sequence.

The target sequence may be in any part of a target gene. In some embodiments, the target sequence is part of or near a noncoding sequence of the gene. In some embodiments, the target sequence is part of an exon of the gene. In some embodiments, the target sequence is part of or near a transcriptional regulatory sequence of the gene, such as a promoter or an enhancer. In some embodiments, the target sequence is adjacent to, overlaps with, or encompasses a CpG island, e.g., a CpG island identified within the HBV genome. In some embodiments, the target sequence is outside of a CpG island. In certain embodiments, the target sequence is within about 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) flanking an HBV TSS. In certain embodiments, the target sequence is within 500 bp flanking the HBV TSS. In certain embodiments, the target sequence is within 1000 bp flanking the HBV TSS.

Some exemplary embodiments in which the target sequence is part of a target gene are provided herein and additional embodiments will be apparent to the skilled artisan based on the present disclosure and the knowledge of the genomic structure of HBV in the art. For example, in some embodiments, the target sequence is part of the HBV S gene, the HBV P gene, the HBV C gene, or the HBV X gene. In some embodiments, the target sequence is part of the HBV S gene. In some embodiments, the target sequence is part of the HBV P gene. In some embodiments, the target sequence is part of the HBV C gene. In some embodiments, the target sequence is part of the HBV X gene. Some exemplary embodiments in which the target sequence is part of a noncoding sequence of a target gene are provided herein and additional embodiments will be apparent to the skilled artisan based on the present disclosure and the knowledge of the genomic structure of HBV in the art. For example, in some embodiments the target sequence is part of a noncoding sequence of the HBV S gene, of the HBV P gene, of the HBV C gene, or of the HBV X gene. For example, in some embodiments, the target sequence is part of a noncoding sequence of the HBV S gene. In some embodiments, the target sequence is part of a noncoding sequence of the HBV P gene. In some embodiments, the target sequence is part of a noncoding sequence of the HBV C gene. In some embodiments, the target sequence is part of a noncoding sequence of the HBV X gene. Noncoding sequences of the various HBV genes are known in the art and include, for example, the promoter and enhancer sequences of the HBV genome. Accordingly, in some embodiments, the target sequence is part of an HBV promoter sequence (e.g., of a promoter sequence within the HBV genome driving the transcription of one of the HBV transcripts described elsewhere herein, including, for example, of a sequence of the sp1, the sp2, the cp, and the xp promoter elements). In some embodiments, the target sequences is part of an HBV enhancer sequence (e.g., of the Enh I or of the Enh II sequence).

Some exemplary embodiments, in which the target sequence is adjacent to, overlaps with, or encompasses a CpG island, e.g., a CpG island identified within the HBV genome include embodiments in which the target sequence is adjacent to, overlaps with, or encompasses a conventional CGI of HBV, e.g., CGI I, CGI II, or CGI III. CGIs of HBV have been identified and described in numerous publications and are thus known to the skilled artisan. Bioinformatics tools for the identification of CGIs in any specific HBV sequence, e.g., in a sequence of a specific HBV genotype or sub-type, or in an HBV sequence isolated from a patient, are known in the art, including, for example, EMBOSS CpG plot (EMBL-EBI) and Methprimer (Li LC and Dahiya R. MethPrimer: designing primers for methylation PCRs. Bioinformatics. 2002 November; 18(11):1427-31). Conventional CGIs of HBV include CGI I, which overlaps the S and the P gene ORFs; CGI-II, which overlaps the P gene and X gene ORFs; and CGI III, which overlaps the C gene and P gene ORFs (see FIG. **1**). In some embodiments, an HBV CGI is identified as a sequence within the HBV genome that is (1) at least 100 nucleotides long; (2) is characterized by a GC content of at least 50%; and (3) is characterized by an observed-to-expected CpG dinucleotide ratio of at least 0.6. According to these criteria, in the exemplary HBV genome referenced in FIG. **1**, i.e., NC_003977 (provided herein as SEQ ID NO: 1082), CGI I spans nucleotides 186-288, CGI II spans nucleotides 1,217-1,670, and CGI III spans nucleotides 2,282-2,448 (see FIG. **1**). CGIs of HBV fulfilling these criteria, including conventional HBV CGIs I-III, of other HBV sequences, including other genotypes, sub-types, or specific HBV sequences, will be apparent to the skilled artisan. In some embodiments, the target sequence overlaps with HBV CGI I. In some embodiments, the target sequence overlaps with HBV CGI II. In some embodiments, the target sequence overlaps with CGI III.

Exemplary embodiments in which the target sequence is within about 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) flanking an HBV TSS (transcription start site) include embodiments, in which the target sequence is within the respective number of base pairs of the TSS of any of the six major viral RNA transcripts, i.e., the TSS of the preCore (pre-C) RNA, the TSS of the pre-genomic (pg)RNA, the TSS of the large surface protein (preS1) RNA, the TSS of the middle surface protein (preS2) RNA, the TSS of the small surface protein (S) RNA, and the TSS of the X protein (HBx) RNA. The positions of the transcription start sites of the various HBV transcripts have

been identified in various HBV genotypes and sub-types and are thus known to the skilled artisan. For example, for HBV of genotype D, as exemplified by NCBI database entries NC_003977 and U95551.1 (provided as SEQ ID NOs 1082 and 1083 herein), the TSS of the pg RNA transcript has been identified as nucleotide 1820, the TSS of the pre-C RNA as nucleotide 1791, and the TSS of the pre-S2 RNA as nucleotide 3159. The initiation of HBx RNA transcripts encoded by HBV genomes has been reported to not be limited to a single nucleotide, but to be spread over a short sequence. For example, TSSs for canonical HBx transcripts have been reported to initiate closely upstream of the first ATG in the sequence encoding the X protein, with HBx transcript TSS positions having been mapped to nucleotides 1243-1338 of HBV of genotype D, as exemplified by NCBI database entries NC_003977 and U95551.1 (provided as SEQ ID NOs 1082 and 1083 herein). TSSs for additional transcripts have also been identified and TSSs have been mapped to various HBV genotypes and sub-types.

In some embodiments in which the target sequence is within about 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) flanking an HBV TSS, the HBV TSS is an HBV pg RNA TSS. For example, in some embodiments provided herein, the target sequence of an epigenetic editor is within 100 bp flanking an HBV pg RNA TSS, e.g., within 100 bp of nucleotide 1820 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 200 bp flanking an HBV pg RNA TSS, e.g., within 200 bp of nucleotide 1820 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 300 bp flanking an HBV pg RNA TSS, e.g., within 300 bp of nucleotide 1820 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 400 bp flanking an HBV pg RNA TSS, e.g., within 400 bp of nucleotide 1820 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 500 bp flanking an HBV pg RNA TSS, e.g., within 500 bp of nucleotide 1820 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 600 bp flanking an HBV pg RNA TSS, e.g., within 600 bp of nucleotide 1820 of SEQ ID NO: 1082 or 1083.

In some embodiments in which the target sequence is within about 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) flanking an HBV TSS, the HBV TSS is an HBV preCore (preC) RNA TSS. For example, in some embodiments provided herein, the target sequence of an epigenetic editor is within 100 bp flanking an HBV preC RNA TSS, e.g., within 100 bp of nucleotide 1791 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 200 bp flanking an HBV preC RNA TSS, e.g., within 200 bp of nucleotide 1791 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 300 bp flanking an HBV preC RNA TSS, e.g., within 300 bp of nucleotide 17910f SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 400 bp flanking an HBV preC RNA TSS, e.g., within 400 bp of nucleotide 1791 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 500 bp flanking an HBV preC RNA TSS, e.g., within 500 bp of nucleotide 1791 of SEQ ID NO: 1082 or 1083.

In some embodiments in which the target sequence is within about 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) flanking an HBV TSS, the HBV TSS is an HBV preS2 RNA TSS. For example, in some embodiments provided herein, the target sequence of an epigenetic editor is within 100 bp flanking an HBV preS2 RNA TSS, e.g., within 100 bp of nucleotide 3159 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 200 bp flanking an HBV preS2 RNA TSS, e.g., within 200 bp of nucleotide 3159 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 300 bp flanking an HBV preS2 RNA TSS, e.g., within 300 bp of nucleotide 3159 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 400 bp flanking an HBV preS2 RNA TSS, e.g., within 400 bp of nucleotide 3159 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 500 bp flanking an HBV preS2 RNA TSS, e.g., within 500 bp of nucleotide 3159 of SEQ ID NO: 1082 or 1083.

In some embodiments in which the target sequence is within about 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) flanking an HBV TSS, the HBV TSS is an HBV HBx RNA TSS. For example, in some embodiments provided herein, the target sequence of an epigenetic editor is within 100 bp flanking an HBV HBx RNA TSS, e.g., within 100 bp of nucleotide 1243 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 200 bp flanking an HBV HBx RNA TSS, e.g., within 200 bp of nucleotide 1243 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 300 bp flanking an HBV HBx RNA TSS, e.g., within 300 bp of nucleotide 1243 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 400 bp flanking an HBV HBx RNA TSS, e.g., within 400 bp of nucleotide 1243 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 500 bp flanking an HBV HBx RNA TSS, e.g., within 500 bp of nucleotide 1243 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 600 bp flanking an HBV HBx RNA TSS, e.g., within 600 bp of nucleotide 1243 of SEQ ID NO: 1082 or 1083.

In some embodiments in which the target sequence is within about 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) flanking an HBV TSS, the HBV TSS is an HBV HBx RNA TSS. For example, in some embodiments provided herein, the target sequence of an epigenetic editor is within 100 bp flanking an HBV HBx RNA TSS, e.g., within 100 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 200 bp flanking an HBV HBx RNA TSS, e.g., within 200 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083. In some

embodiments provided herein, the target sequence of an epigenetic editor is within 300 bp flanking an HBV HBx RNA TSS, e.g., within 300 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 400 bp flanking an HBV HBx RNA TSS, e.g., within 400 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 500 bp flanking an HBV HBx RNA TSS, e.g., within 500 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 600 bp flanking an HBV HBx RNA TSS, e.g., within 600 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083.

In some embodiments in which the target sequence is within about 3000, 2900, 2800, 2700, 2600, 2500, 2400, 2300, 2200, 2100, 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) flanking an HBV TSS, the HBV TSS is an HBV HBx RNA TSS. For example, in some embodiments provided herein, the target sequence of an epigenetic editor is within 100 bp flanking an HBV HBx RNA TSS, e.g., within 100 bp of nucleotide 1243 and within 100 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 200 bp flanking an HBV HBx RNA TSS, e.g., within 200 bp of nucleotide 1243 and within 200 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 300 bp flanking an HBV HBx RNA TSS, e.g., within 300 bp of nucleotide 1243 and within 300 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 400 bp flanking an HBV HBx RNA TSS, e.g., within 400 bp of nucleotide 1243 and within 400 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 500 bp flanking an HBV HBx RNA TSS, e.g., within 500 bp of nucleotide 1243 and within 500 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083. In some embodiments provided herein, the target sequence of an epigenetic editor is within 600 bp flanking an HBV HBx RNA TSS, e.g., within 600 bp of nucleotide 1243 and within 600 bp of nucleotide 1338 of SEQ ID NO: 1082 or 1083.

In some embodiments, the target sequence may hybridize to a guide polynucleotide sequence (e.g., gRNA) complexed with a fusion protein comprising a polynucleotide guided DNA-binding domain (e.g., a CRISPR protein such as dCas9) and effector domain(s). The guide polynucleotide sequence may be designed to have complementarity to the target sequence, or identity to the opposing strand of the target sequence. In some embodiments, the guide polynucleotide comprises a spacer sequence that is about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a protospacer sequence in the target sequence. In particular embodiments, the guide polynucleotide comprises a spacer sequence that is 100% identical to a protospacer sequence in the target sequence.

In some embodiments, where the DNA-binding domain of an epigenetic editor described herein is a zinc finger array, the target sequence may be recognized by said zinc finger array.

In some embodiments, where the DNA-binding domain of an epigenetic editor described herein is a TALE, the target sequence may be recognized by said TALE.

A target sequence described herein may be specific to one genotype of HBV, to one copy of am HBV target gene, or may be specific to one allele of an HBV target gene. In some embodiments, however, the target sequence may be conserved across two or more HBV genotypes, across two or more copies of an HBV gene, and across alleles of an HBV gene. Accordingly, the epigenetic modification and modulation of expression thereof may be specific to one copy or one allele of the target gene, or, in other embodiments, may be universal to different HBV genotypes, or HBV gene copies or alleles.

In some embodiments, the target sequence is comprised in the following sequence:

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>NC_003977.2 Hepatitis B virus (strain ayw)
genome
                                        (SEQ ID No. 1082)
AATTCCACAACCTTCCACCAAACTCTGCAAGATCCCAGAGTGAGAGGCCT

GTATTTCCCTGCTGGTGGCTCCAGTTCAGGAACAGTAAACCCTGTTCTGA

CTACTGCCTCTCCCTTATCGTCAATCTTCTCGAGGATTGGGGACCCTGCG

CTGAACATGGAGAACATCACATCAGGATTCCTAGGACCCCTTCTCGTGTT

ACAGGCGGGGTTTTTCTTGTTGACAAGAATCCTCACAATACCGCAGAGTC

TAGACTCGTGGTGGACTTCTCTCAATTTTCTAGGGGGAACTACCGTGTGT

CTTGGCCAAAATTCGCAGTCCCCAACCTCCAATCACTCACCAACCTCTTG

TCCTCCAACTTGTCCTGGTTATCGCTGGATGTGTCTGCGGCGTTTTATCA

TCTTCCTCTTCATCCTGCTGCTATGCCTCATCTTCTTGTTGGTTCTTCTG

GACTATCAAGGTATGTTGCCCGTTTGTCCTCTAATTCCAGGATCCTCAAC

AACCAGCACGGGACCATGCCGGACCTGCATGACTACTGCTCAAGGAACCT

CTATGTATCCCTCCTGTTGCTGTACCAAACCTTCGGACGGAAATTGCACC

TGTATTCCCATCCCATCATCCTGGGCTTTCGGAAAATTCCTATGGGAGTG

GGCCTCAGCCCGTTTCTCCTGGCTCAGTTTACTAGTGCCATTTGTTCAGT

GGTTCGTAGGGCTTTCCCCCACTGTTTGGCTTTCAGTTATATGGATGATG

TGGTATTGGGGGCCAAGTCTGTACAGCATCTTGAGTCCCTTTTTACCGCT

GTTACCAATTTTCTTTTGTCTTTGGGTATACATTTAAACCCTAACAAAAC

AAAGAGATGGGGTTACTCTCTAAATTTTATGGGTTATGTCATTGGATGTT

ATGGGTCCTTGCCACAAGAACACATCATACAAAAAATCAAAGAATGTTTT

AGAAAACTTCCTATTAACAGGCCTATTGATTGGAAAGTATGTCAACGAAT

TGTGGGTCTTTTGGGTTTTGCTGCCCCTTTTACACAATGTGGTTATCCTG

CGTTGATGCCTTTGTATGCATGTATTCAATCTAAGCAGGCTTTCACTTTC

TCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCC

CGTTGCCCGGCAACGGCCAGGTCTGTGCCAAGTGTTTGCTGACGCAACCC

CCACTGGCTGGGGCTTGGTCATGGGCCATCAGCGCATGCGTGGAACCTTT

TCGGCTCCTCTGCCGATCCATACTGCGGAACTCCTAGCCGCTTGTTTTGC

TCGCAGCAGGTCTGGAGCAAACATTATCGGGACTGATAACTCTGTTGTCC

TATCCCGCAAATATACATCGTTTCCATGGCTGCTAGGCTGTGCTGCCAAC

TGGATCCTGCGCGGGACGTCCTTTGTTTACGTCCCGTCGGCGCTGAATCC

TGCGGACGACCCTTCTCGGGGTCGCTTGGGACTCTCTCGTCCCCTTCTCC

GTCTGCCGTTCCGACCGACCACGGGGCGCACCTCTCTTTACGCGGACTCC

CCGTCTGTGCCTTCTCATCTGCCGGACCGTGTGCACTTCGCTTCACCTCT
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GCACGTCGCATGGAGACCACCGTGAACGCCCACCAAATATTGCCCAAGGT

CTTACATAAGAGGACTCTTGGACTCTCAGCAATGTCAACGACCGACCTTG

AGGCATACTTCAAAGACTGTTTGTTTAAAGACTGGGAGGAGTTGGGGGAG

GAGATTAGGTTAAAGGTCTTTGTACTAGGAGGCTGTAGGCATAAATTGGT

CTGCGCACCAGCACCATGCAACTTTTTCACCTCTGCCTAATCATCTCTTG

TTCATGTCCTACTGTTCAAGCCTCCAAGCTGTGCCTTGGGTGGCTTTGGG

GCATGGACATCGACCCTTATAAAGAATTTGGAGCTACTGTGGAGTTACTC

TCGTTTTTGCCTTCTGACTTCTTTCCTTCAGTACGAGATCTTCTAGATAC

CGCCTCAGCTCTGTATCGGGAAGCCTTAGAGTCTCCTGAGCATTGTTCAC

CTCACCATACTGCACTCAGGCAAGCAATTCTTTGCTGGGGGGAACTAATG

ACTCTAGCTACCTGGGTGGGTGTTAATTTGGAAGATCCAGCGTCTAGAGA

CCTAGTAGTCAGTTATGTCAACACTAATATGGGCCTAAAGTTCAGGCAAC

TCTTGTGGTTTCACATTTCTTGTCTCACTTTTGGAAGAGAAACAGTTATA

GAGTATTTGGTGTCTTTCGGAGTGTGGATTCGCACTCCTCCAGCTTATAG

ACCACCAAATGCCCCTATCCTATCAACACTTCCGGAGACTACTGTTGTTA

GACGACGAGGCAGGTCCCCTAGAAGAAGAACTCCCTCGCCTCGCAGACGA

AGGTCTCAATCGCCGCGTCGCAGAAGATCTCAATCTCGGGAATCTCAATG

TTAGTATTCCTTGGACTCATAAGGTGGGGAACTTTACTGGGCTTTATTCT

TCTACTGTACCTGTCTTTAATCCTCATTGGAAAACACCATCTTTTCCTAA

TATACATTTACACCAAGACATTATCAAAAAATGTGAACAGTTTGTAGGCC

CACTCACAGTTAATGAGAAAAGAAGATTGCAATTGATTATGCCTGCCAGG

TTTTATCCAAAGGTTACCAAATATTTACCATTGGATAAGGGTATTAAACC

TTATTATCCAGAACATCTAGTTAATCATTACTTCCAAACTAGACACTATT

TACACACTCTATGGAAGGCGGGTATATTATATAAGAGAGAAACAACACAT

AGCGCCTCATTTTGTGGGTCACCATATTCTTGGGAACAAGATCTACAGCA

TGGGGCAGAATCTTTCCACCAGCAATCCTCTGGGATTCTTTCCCGACCAC

CAGTTGGATCCAGCCTTCAGAGCAAACACCGCAAATCCAGATTGGGACTT

CAATCCCAACAAGGACACCTGGCCAGACGCCAACAAGGTAGGAGCTGGAG

CATTCGGGCTGGGTTTCACCCCACCGCACGGAGGCCTTTTGGGGTGGAGC

CCTCAGGCTCAGGGCATACTACAAACTTTGCCAGCAAATCCGCCTCCTGC

CTCCACCAATCGCCAGTCAGGAAGGCAGCCTACCCCGCTGTCTCCACCTT

TGAGAAACACTCATCCTCAGGCCATGCAGTGG

FIG. **1** provides a diagram illustrating the structure of a circular HBV genome comprising SEQ ID NO: 1082. The coding regions of the HBV genes and CpG islands CGI-I-III are identified. Nucleotides 2309-1625 of SEQ ID NO: 1082 encode the P protein (NCBI reference number YP_009173866.1). Nucleotides 2850-837 of SEQ ID NO: 1082 encode the long surface protein (L-HBsAG or LHBS; NCBI reference number YP_009173869.1). Nucleotides 3174-837 of SEQ ID NO: 1082 encode the middle surface protein (M-HBsAg or MHBS; NCBI reference number YP_009173870.1). Nucleotides 157-837 of SEQ ID NO: 1082 encode the small surface protein (S-HBsAg or SHBs; NCBI reference number YP_009173871.1). Nucleotides 1816-2454 of SEQ ID NO: 1082 encode the C Protein (core protein, NCBI reference number AAB59971.1). Nucleotides 1376-1840 of SEQ ID NO: 1082 encode the X protein (HBx, NCBI reference number YP_009173867.1). CGI I spans nucleotides 186-288, CGI II spans nucleotides 1,217-1,670, and CGI III spans nucleotides 2,282-2,448. See, NCBI database entry NC 003977.2. TSSs of various transcripts have been mapped: pg RNA TSS: 1820; pre-C RNA TSS: 1791; pre-S2 RNA TSS: 3159; HBx RNA TSSs: 1243-1338. The ATAAA motif of the transcription termination/polyadenylation site is located at nucleotide 1919. See references cited elsewhere herein. See also, e.g., Abraham, T. M. and Loeb, D. D., The topology of hepatitis B virus pregenomic RNA promotes its replication, J. Virol. 81 (21), 11577-11584 (2007); Chen, A., Kao, Y. F. and Brown, C. M., Translation of the first upstream ORF in the hepatitis B virus pregenomic RNA modulates translation at the core and polymerase initiation codons, Nucleic Acids Res. 33 (4), 1169-1181 (2005); Borisova, G. P., Pumpen, P. P., Bychko, V. V., Pushko, P. M., Kalis, Y. V., Dishler, A. V., Gren, E. Y., Tsibinogin, V. V. and Kukain, R. A., Structure and expression of the gene of the core antigen of human hepatitis B virus (HBV) in *Escherichia coli* cells, Dokl. Biochem. 279, 386-390 (1985); Galibert, F., Mandart, E., Fitoussi, F., Tiollais, P. and Chamay, P., Nucleotide sequence of the hepatitis B virus genome (subtype ayw) cloned in *E. coli*, Nature 281 (5733), 646-650 (1979), the entire contents of each of which are incorporated herein by reference.

In some embodiments, the target sequence is comprised in the following sequence:

>U95551.1 Hepatitis B virus subtype ayw, complete genome

(SEQ ID No. 1083)

AATTCCACAACCTTTCACCAAACTCTGCAAGATCCCAGAGTGAGAGGCCT

GTATTTCCCTGCTGGTGGCTCCAGTTCAGGAGCAGTAAACCCTGTTCCGA

CTACTGCCTCTCCCTTATCGTCAATCTTCTCGAGGATTGGGGACCCTGCG

CTGAACATGGAGAACATCACATCAGGATTCCTAGGACCCCTTCTCGTGTT

ACAGGCGGGGTTTTTCTTGTTGACAAGAATCCTCACAATACCGCAGAGTC

TAGACTCGTGGTGGACTTCTCTCAATTTTCTAGGGGGAACTACCGTGTGT

CTTGGCCAAAATTCGCAGTCCCCAACCTCCAATCACTCACCAACCTCCTG

TCCTCCAACTTGTCCTGGTTATCGCTGGATGTGTCTGCGGCGTTTTATCA

TCTTCCTCTTCATCCTGCTGCTATGCCTCATCTTCTTGTTGGTTCTTCTG

GACTATCAAGGTATGTTGCCCGTTTGTCCTCTAATTCCAGGATCCTCAAC

CACCAGCACGGGACCATGCCGAACCTGCATGACTACTGCTCAAGGAACCT

CTATGTATCCCTCCTGTTGCTGTACCAAACCTTCGGACGGAAATTGCACC

TGTATTCCCATCCCATCATCCTGGGCTTTCGGAAAATTCCTATGGGAGTG

GGCCTCAGCCCGTTTCTCCTGGCTCAGTTTACTAGTGCCATTTGTTCAGT

GGTTCGTAGGGCTTTCCCCCACTGTTTGGCTTTCAGTTATATGGATGATG

TGGTATTGGGGGCCAAGTCTGTACAGCATCTTGAGTCCCTTTTTACCGCT

GTTACCAATTTTCTTTTGTCTTTGGGTATACATTTAAACCCTAACAAAAC

AAAGAGATGGGGTTACTCTCTGAATTTTATGGGTTATGTCATTGGAAGTT

ATGGGTCCTTGCCACAAGAACACATCATACAAAAAATCAAAGAATGTTTT

AGAAAACTTCCTATTAACAGGCCTATTGATTGGAAAGTATGTCAACGAAT

-continued

TGTGGGTCTTTTGGGTTTTGCTGCCCCATTTACACAATGTGGTTATCCTG

CGTTAATGCCCTTGTATGCATGTATTCAATCTAAGCAGGCTTTCACTTTC

TCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCC

CGTTGCCCGGCAACGGCCAGGTCTGTGCCAAGTGTTTGCTGACGCAACCC

CCACTGGCTGGGGCTTGGTCATGGGCCATCAGCGCGTGCGTGGAACCTTT

TCGGCTCCTCTGCCGATCCATACTGCGGAACTCCTAGCCGCTTGTTTTGC

TCGCAGCAGGTCTGGAGCAAACATTATCGGGACTGATAACTCTGTTGTCC

TCTCCCGCAAATATACATCGTATCCATGGCTGCTAGGCTGTGCTGCCAAC

TGGATCCTGCGCGGGACGTCCTTTGTTTACGTCCCGTCGGCGCTGAATCC

TGCGGACGACCCTTCTCGGGGTCGCTTGGGACTCTCTCGTCCCCTTCTCC

GTCTGCCGTTCCGACCGACCACGGGGCGCACCTCTCTTTACGCGGACTCC

CCGTCTGTGCCTTCTCATCTGCCGGACCGTGTGCACTTCGCTTCACCTCT

GCACGTCGCATGGAGACCACCGTGAACGCCCACCGAATGTTGCCCAAGGT

CTTACATAAGAGGACTCTTGGACTCTCTGCAATGTCAACGACCGACCTTG

AGGCATACTTCAAAGACTGTTTGTTTAAAGACTGGGAGGAGTTGGGGGAG

GAGATTAGATTAAAGGTCTTTGTACTAGGAGGCTGTAGGCATAAATTGGT

CTGCGCACCAGCACCATGCAACTTTTTCACCTCTGCCTAATCATCTCTTG

TTCATGTCCTACTGTTCAAGCCTCCAAGCTGTGCCTTGGGTGGCTTTGGG

GCATGGACATCGACCCTTATAAAGAATTTGGAGCTACTGTGGAGTTACTC

TCGTTTTTGCCTTCTGACTTCTTTCCTTCAGTACGAGATCTTCTAGATAC

CGCCTCAGCTCTGTATCGGGAAGCCTTAGAGTCTCCTGAGCATTGTTCAC

CTCACCATACTGCACTCAGGCAAGCAATTCTTTGCTGGGGGGAACTAATG

ACTCTAGCTACCTGGGTGGGTGTTAATTTGGAAGATCCAGCATCTAGAGA

CCTAGTAGTCAGTTATGTCAACACTAATATGGGCCTAAAGTTCAGGCAAC

TCTTGTGGTTTCACATTTCTTGTCTCACTTTTGGAAGAGAAACCGTTATA

GAGTATTTGGTGTCTTTCGGAGTGTGGATTCGCACTCCTCCAGCTTATAG

ACCACCAAATGCCCCTATCCTATCAACACTTCCGGAAACTACTGTTGTTA

GACGACGAGGCAGGTCCCCTAGAAGAAGAACTCCCTCGCCTCGCAGACGA

AGGTCTCAATCGCCGCGTCGCAGAAGATCTCAATCTCGGGAACCTCAATG

TTAGTATTCCTTGGACTCATAAGGTGGGGAACTTTACTGGTCTTTATTCT

TCTACTGTACCTGTCTTTAATCCTCATTGGAAAACACCATCTTTTCCTAA

TATACATTTACACCAAGACATTATCAAAAAATGTGAACAGTTTGTAGGCC

CACTTACAGTTAATGAGAAAAGAAGATTGCAATTGATTATGCCTGCTAGG

TTTTATCCAAAGGTTACCAAATATTTACCATTGGATAAGGGTATTAAACC

TTATTATCCAGAACATCTAGTTAATCATTACTTCCAAACTAGACACTATT

TACACACTCTATGGAAGGCGGGTATATTATATAAGAGAGAAACAACACAT

AGCGCCTCATTTTGTGGGTCACCATATTCTTGGGAACAAGATCTACAGCA

TGGGGCAGAATCTTTCCACCAGCAATCCTCTGGGATTCTTTCCCGACCAC

CAGTTGGATCCAGCCTTCAGAGCAAACACAGCAAATCCAGATTGGGACTT

CAATCCCAACAAGGACACCTGGCCAGACGCCAACAAGGTAGGAGCTGGAG

CATTCGGGCTGGGTTTCACCCCACCGCACGGAGGCCTTTTGGGGTGGAGC

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CCTCAGGCTCAGGGCATACTACAAACTTTGCCAGCAAATCCGCCTCCTGC

CTCCACCAATCGCCAGACAGGAAGGCAGCCTACCCCGCTGTCTCCACCTT

TGAGAAACACTCATCCTCAGGCCATGCAGTGG.

Annotation of SEQ ID NO: 1083: P protein CDS: 2309-1625; L-HBsAG CDS: 2850-837; M-HBsAg CDS: 3174-837; S-HBsAg CDS: 157-837; C Protein CDS: 1816-2454; X protein CDS: 1376-1840; CGI: 186-288; CGI II: 1,217-1,670; CGI III: 2,282-2,448; pg RNA TSS: 1820; pre-C RNA TSS: 1791; pre-S2 RNA TSS: 3159; HBx RNA TSSs: 1243-1338; termination/polyA site: 1919. See references cited elsewhere herein.

VI. Epigenetic Modifications

An epigenetic editor described herein may perform sequence-specific epigenetic modification(s) (e.g., alteration of chemical modification(s)) of a target gene that harbors the target sequence. Such epigenetic modulation may be safer and more easily reversible than modulation due to gene editing, e.g., with generation of DNA double-strand breaks. In some embodiments, the epigenetic modulation may reduce or silence the target gene. In some embodiments, the modification is at a specific site of the target sequence. In some embodiments, the modification is at a specific allele of the target gene. Accordingly, the epigenetic modification may result in modulated (e.g., reduced) expression of one copy of a target gene harboring a specific allele, and not the other copy of the target gene. In some embodiments, the specific allele is associated with a disease, condition, or disorder.

In some embodiments, the epigenetic modification reduces or abolishes transcription of the target gene harboring the target sequence. In some embodiments, the epigenetic modification reduces or abolishes transcription of a copy of the target gene harboring a specific allele recognized by the epigenetic editor. In some embodiments, the epigenetic editor reduces the level of or eliminates expression of a protein encoded by the target gene. In some embodiments, the epigenetic editor reduces the level of or eliminates expression of a protein encoded by a copy of the target gene harboring a specific allele recognized by the epigenetic editor. The target HBV gene may be epigenetically modified in vitro, ex vivo, or in vivo.

The effector domain of an epigenetic editor described herein may alter (e.g., deposit or remove) a chemical modification at a nucleotide of the target gene or at a histone associated with the target gene. The chemical modification may be altered at a single nucleotide or a single histone, or may be altered at 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000 or more nucleotides.

In some embodiments, an effector domain of an epigenetic editor described herein may alter a CpG dinucleotide within the target gene. In some embodiments, all CpG dinucleotides within 2000, 1500, 1000, 500, or 200 bps flanking a target sequence (e.g., in an alteration site as described herein) are altered according to a modification type described herein, as compared to the original state of the gene or the gene in a comparable cell not contacted with the epigenetic editor. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300,

350, 400, 450, 500, 550, 600, 650, 700 or more of the CpG dinucleotides are altered as compared to the original state of the gene or the gene in a comparable cell not contacted with the epigenetic editor. In some embodiments, at least 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% of the CpG dinucleotides are altered as compared to the original state of the gene or the gene in a comparable cell not contacted with the epigenetic editor. In some embodiments, one single CpG dinucleotide is altered, as compared to the original state of the gene or the gene in a comparable cell not contacted with the epigenetic editor.

An effector domain of an epigenetic editor described herein may alter a histone modification state of a histone associated with or bound to the target gene. For example, an effector domain may deposit a modification on one or more lysine residues of histone tails of histones associated with the target gene. In some embodiments, the effector domain may result in deacetylation of one or more histone tails of histones associated with the target gene, thereby reducing or silencing expression of the target gene. In some embodiments, the histone modification state is a methylation state. For example, the effector domain may result in a H3K9, H3K27 or H4K20 methylation (e.g. one or more of a H3K9me2, H3K9me3, H3K27me2, H3K27me3, and H4K20me3 methylation) at one or more histone tails associated with the target gene, thereby reducing or silencing expression of the target gene.

In some embodiments, all histone tails of histones bound to DNA nucleotides within 2000, 1500, 1000, 500, or 200 bps flanking the target sequence are altered according to a modification type as described herein, as compared to the original state of the chromosome or the chromosome in a comparable cell not contacted with the epigenetic editor. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120 or more histone tails of the bound histones are altered as compared to the original state of the chromosome or the chromosome in a comparable cell not contacted with the epigenetic editor. In some embodiments, at least 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% of histone tails of the bound histones are altered as compared to the original state of the chromosome or the chromosome in a comparable cell not contacted with the epigenetic editor. For example, one single histone tail of the bound histones may be altered as compared to the original state of the chromosome or the chromosome in a comparable cell not contacted with the epigenetic editor. As another example, one single bound histone octamer may be altered as compared to the original state of the chromosome or the chromosome in a comparable cell not contacted with the epigenetic editor.

The chemical modification deposited at target gene DNA nucleotides or histone residues may be at or in close proximity to a target sequence in the target gene. In some embodiments, an effector domain of an epigenetic editor described herein alters a chemical modification state of a nucleotide or histone tail bound to a nucleotide 100-200, 200-300, 300-400, 400-55, 500-600, 600-700, or 700-800 nucleotides 5' or 3' to the target sequence in the target gene. In some embodiments, an effector domain alters a chemical modification state of a nucleotide or histone tail bound to a nucleotide within 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 nucleotides flanking the target sequence. As used herein, "flanking" refers to nucleotide positions 5' to the 5' end of and 3' to the 3' end of a particular sequence, e.g. a target sequence.

In some embodiments, an effector domain mediates or induces a chemical modification change of a nucleotide or a histone tail bound to a nucleotide distant from a target sequence. Such modification may be initiated near the target sequence, and may subsequently spread to one or more nucleotides in the target gene distant from the target sequence. For example, an effector domain may initiate alteration of a chemical modification state of one or more nucleotides or one or more histone residues bound to one or more nucleotides within 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500 nucleotides flanking the target sequence, and the chemical modification state alteration may spread to one or more nucleotides at least 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, or more nucleotides from the target sequence in the target gene, either upstream or downstream of the target sequence. In certain embodiments, the chemical modification may be initiated at less than 2, 3, 5, 10, 20, 30, 40, 50, or 100 nucleotides in the target gene and spread to at least 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, or more nucleotides in the target gene. In some embodiments, the chemical modification spreads to nucleotides in the entire target gene. Additional proteins or transcription factors, for example, transcription repressors, methyltransferases, or transcription regulation scaffold proteins, may be involved in the spreading of the chemical modification. Alternatively, the epigenetic editor alone may be involved.

In some embodiments, an epigenetic editor described herein reduces expression of a target gene by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 99%, or more, as measured by transcription of the target gene in a cell, a tissue, or a subject as compared to a control cell, control tissue, or a control subject (e.g., in the absence of the epigenetic editor). In some embodiments, the epigenetic editors described herein reduces expression of a copy of target gene by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 99%, at least about 99.9%, or more, as measured by transcription of the copy of the target gene in a cell, a tissue, or a subject as compared to a control cell, control tissue, or a control subject. For example, in some embodiments, an epigenetic editor described herein reduces expression of an HBV target gene in vitro or in vivo (e.g., as measured as the level of an HBV biomarker in a subject), by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, at least 99.9%, or more, as measured for example, by transcription of the target gene, or by assessing an HBV biomarker (e.g., plasma HBV DNA, plasma HBVsAg, or plasma HBVeAg) in a cell, a tissue, or a subject contacted or administered with the epigenetic editor as compared to a control cell, control tissue, or a control subject (e.g., in the absence of the epigenetic editor). In certain embodiments, the copy of the target gene harbors a specific sequence or allele recognized by the epigenetic editor. In particular embodiments, the epigenetically modified copy encodes a functional protein, and accordingly an epigenetic editor disclosed herein may reduce or abolish expression and/or function of the protein. For example, an

epigenetic editor described herein may reduce expression and/or function of a protein encoded by the target gene by at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 11-fold, at least 12-fold, at least 13-fold, at least 14-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, at least 50-fold, at least 60-fold, at least 70-fold, at least 80-fold, at least 90-fold, or at least 100 fold in a cell, a tissue, or a subject as compared to a control cell, control tissue, or a control subject.

Modulation of target gene expression can be assayed by determining any parameter that is indirectly or directly affected by the expression of the target gene. Such parameters include, e.g., changes in RNA or protein levels; changes in protein activity; changes in product levels; changes in downstream gene expression; changes in transcription or activity of reporter genes such as, for example, luciferase, CAT, beta-galactosidase, or GFP; changes in signal transduction; changes in phosphorylation and dephosphorylation; changes in receptor-ligand interactions; changes in concentrations of second messengers such as, for example, cGMP, cAMP, IP3, and $Ca2^{+}$; changes in cell growth; changes in neovascularization; and/or changes in any functional effect of gene expression. Measurements can be made in vitro, in vivo, and/or ex vivo, and can be made by conventional methods, e.g., measurement of RNA or protein levels, measurement of RNA stability, and/or identification of downstream or reporter gene expression. Readout can be by way of, for example, chemiluminescence, fluorescence, colorimetric reactions, antibody binding, inducible markers, ligand binding assays, changes in intracellular second messengers such as cGMP and inositol triphosphate (IP3), changes in intracellular calcium levels; cytokine release, and the like.

Methods for determining the expression level of a gene, for example the target of an epigenetic editor, may include, e.g., determining the transcript level of a gene by reverse transcription PCR, quantitative RT-PCR, droplet digital PCR (ddPCR), Northern blot, RNA sequencing, DNA sequencing (e.g., sequencing of complementary deoxyribonucleic acid (cDNA) obtained from RNA); next generation (Next-Gen) sequencing, nanopore sequencing, pyrosequencing, or Nanostring sequencing. Levels of protein expressed from a gene may be determined, e.g., by Western blotting, enzyme linked immuno-absorbance assays, mass-spectrometry, immunohistochemistry, or flow cytometry analysis. Gene expression product levels may be normalized to an internal standard such as total messenger ribonucleic acid (mRNA) or the expression level of a particular gene, e.g., a housekeeping gene.

In some embodiments, the effect of an epigenetic editor in modulating target gene expression may be examined using a reporter system. For example, an epigenetic editor may be designed to target a reporter gene encoding a reporter protein, such as a fluorescent protein. Expression of the reporter gene in such a model system may be monitored by, e.g., flow cytometry, fluorescence-activated cell sorting (FACS), or fluorescence microscopy. In some embodiments, a population of cells may be transfected with a vector that harbors a reporter gene. The vector may be constructed such that the reporter gene is expressed when the vector transfects a cell. Suitable reporter genes include genes encoding fluorescent proteins, for example green, yellow, cherry, cyan or orange fluorescent proteins. The population of cells carrying the reporter system may be transfected with DNA, mRNA, or vectors encoding the epigenetic editor targeting the reporter gene.

VII. Pharmaceutical Compositions

Another aspect of the present disclosure is a pharmaceutical composition comprising as an active ingredient (or as the sole active ingredient) one or more epigenetic editors described herein or component(s) (e.g., fusion proteins and/or guide polynucleotides) thereof, or nucleic acid molecule(s) encoding said epigenetic editors or component(s) thereof. For example, a pharmaceutical composition may comprise nucleic acid molecule(s) encoding the fusion protein(s) (and guide polynucleotides, where applicable) of an epigenetic editor described herein. In some embodiments, separate pharmaceutical compositions comprise the fusion protein(s) and the guide polynucleotide(s). In some embodiments, multiple pharmaceutical compositions, each comprising one epigenetic editor, are administered simultaneously. A pharmaceutical composition may also comprise cells that have undergone epigenetic modification(s) mediated or induced by an epigenetic editor provided herein.

Generally, the epigenetic editors described herein or component(s) thereof, or nucleic acid molecule(s) encoding said epigenetic editors or component(s) thereof, of the present disclosure are suitable to be administered as a formulation in association with one or more pharmaceutically acceptable excipient(s), e.g., as described below.

The term "excipient" is used herein to describe any ingredient other than the compound(s) of the present disclosure. The choice of excipient(s) will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. As used herein, "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Some examples of pharmaceutically acceptable excipients are water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Additional examples of pharmaceutically acceptable substances are wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives, or buffers, which enhance the shelf life or effectiveness of the antibody.

Formulations of a pharmaceutical composition suitable for parenteral administration typically comprise the active ingredient combined with a pharmaceutically acceptable carrier, such as sterile water or sterile isotonic saline. Such formulations may be prepared, packaged, or sold in a form suitable for bolus administration or for continuous administration. In some embodiments, the epigenetic editor or its component(s) are introduced to target cells in the form of nucleic acid molecule(s) encoding the epigenetic editor or its component(s); accordingly, the pharmaceutical compositions herein comprise the nucleic acid molecule(s). Such nucleic acid molecule(s) may be, for example, DNA, RNA or mRNA, and/or modified nucleic acid sequence(s) (e.g., with chemical modifications, a 5' cap, or one or more 3' modifications). In some embodiments, the nucleic acid molecule(s) may be delivered as naked DNA or RNA, for instance by means of transfection or electroporation, or can

be conjugated to molecules (e.g., N-acetylgalactosamine) promoting uptake by target cells. In some embodiments, the nucleic acid molecule(s) may be in nucleic acid expression vector(s), which may include expression control sequences such as promoters, enhancers, transcription signal sequences, transcription termination sequences, introns, polyadenylation signals, Kozak consensus sequences, internal ribosome entry sites (IRES), etc. Such expression control sequences are well known in the art. A vector may also comprise a sequence encoding a signal peptide (e.g., for nuclear localization, nucleolar localization, or mitochondrial localization), associated with (e.g., inserted into or fused to) a sequence coding for a protein.

Examples of vectors include, but are not limited to, plasmid vectors; viral vectors based on vaccinia virus, poliovirus, adenovirus, adeno-associated virus, SV40, herpes simplex virus, human immunodeficiency virus, retrovirus (e.g., Murine Leukemia Virus, or spleen necrosis virus, vectors derived from retroviruses such as Rous Sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, a lentivirus, human immunodeficiency virus, myeloproliferative sarcoma virus, and mammary tumor virus); and other recombinant vectors. In certain embodiments, the vector is a plasmid or a viral vector. Viral particles may also be used to deliver nucleic acid molecule(s) encoding epigenetic editors or component(s) thereof as described herein. For example, "empty" viral particles can be assembled to contain any suitable cargo. Viral vectors and viral particles may also be engineered to incorporate targeting ligands to alter target tissue specificity.

In certain embodiments, an epigenetic editor as described herein or component(s) thereof are encoded by nucleic acid sequence(s) present in one or more viral vectors, or a suitable capsid protein of any viral vector. Examples of viral vectors include adeno-associated viral vectors (e.g., derived from AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVrh8, AAV10, and/or variants thereof); retroviral vectors (e.g., Maloney murine leukemia virus, MML-V), adenoviral vectors (e.g., AD100), lentiviral vectors (e.g., HIV and FIV-based vectors), and herpesvirus vectors (e.g., HSV-2).

In some embodiments, delivery involves an adeno-associated virus (AAV) vector. AAV vector delivery may be particularly useful where the DNA-binding domain of an epigenetic editor fusion protein is a zinc finger array. Without wishing to be bound by any theory, the smaller size of zinc finger arrays compared to larger DNA-binding domains such as Cas protein domains may allow such a fusion protein to be conveniently packed in viral vectors such as an AAV vector.

Any AAV serotype, e.g., human AAV serotype, can be used for an AAV vector as described herein, including, but not limited to, AAV serotype 1 (AAV1), AAV serotype 2 (AAV2), AAV serotype 3 (AAV3), AAV serotype 4 (AAV4), AAV serotype 5 (AAV5), AAV serotype 6 (AAV6), AAV serotype 7 (AAV7), AAV serotype 8 (AAV8), AAV serotype 9 (AAV9), AAV serotype 10 (AAV10), and AAV serotype 11 (AAV11), as well as variants thereof. In some embodiments, an AAV variant has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity to a wildtype AAV. In certain embodiments, the AAV variant may be engineered such that its capsid proteins have reduced immunogenicity or enhanced transduction ability in humans. In some instances, one or more regions of at least two different AAV serotype viruses are shuffled and reassembled to generate a chimeric variant. For example, a chimeric AAV may comprise inverted terminal repeats (ITRs) that are of a heterologous serotype compared to the serotype of the capsid. The resulting chimeric AAV can have a different antigenic reactivity or recognition compared to its parental serotypes. In some embodiments, a chimeric variant of an AAV includes amino acid sequences from 2, 3, 4, 5, or more different AAV serotypes.

Non-viral systems are also contemplated for delivery as described herein. Non-viral systems include, but are not limited to, nucleic acid transfection methods including electroporation, sonoporation, calcium phosphate transfection, microinjection, DNA biolistics, lipid-mediated transfection, transfection through heat shock, compacted DNA-mediated transfection, lipofection, cationic agent-mediated transfection, and transfection with liposomes, immunoliposomes, or cationic facial amphiphiles (CFAs). In certain embodiments, one or more mRNAs encoding epigenetic editor fusion proteins as described herein may be co-electroporated with one or more guide polynucleotides (e.g., gRNAs) as described herein. One important category of non-viral nucleic acid vectors is nanoparticles, which can be organic (e.g., lipid) or inorganic (e.g., gold). For instance, organic (e.g. lipid and/or polymer) nanoparticles can be suitable for use as delivery vehicles in certain embodiments of this disclosure.

In some embodiments, delivery is accomplished using a lipid nanoparticle (LNP). LNP compositions are typically sized on the order of micrometers or smaller and may include a lipid bilayer. In some embodiments, a LNP refers to any particle that has a diameter of less than 1000 nm, 500 nm, 250 nm, 200 nm, 150 nm, 100 nm, 75 nm, 50 nm, or 25 nm. Nanoparticle compositions encompass lipid nanoparticles (LNPs), liposomes (e.g., lipid vesicles), and lipoplexes.

An LNP as described herein may be made from cationic, anionic, or neutral lipids. In some embodiments, an LNP may comprise neutral lipids, such as the fusogenic phospholipid 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) or the membrane component cholesterol, as helper lipids to enhance transfection activity and nanoparticle stability. In some embodiments, an LNP may comprise hydrophobic lipids, hydrophilic lipids, or both hydrophobic and hydrophilic lipids. Any lipid or combination of lipids that are known in the art can be used to produce an LNP. The lipids may be combined in any molar ratios to produce the LNP. In some embodiments, the LNP is a liver-targeting (e.g., preferentially or specifically targeting the liver) LNP.

LNP formulations and methods of LNP delivery that can be used will be apparent to those skilled in the art based on the present disclosure and the state of the art. Non-limiting exemplary compositions and methods can be found in Shah, R., Eldridge, D., Palombo, E., and Harding, I., Lipid Nanoparticles: Production, Characterization and Stability, Springer, 2015, ISBN-13 978-3319107103; Ziegler, S., Lipid Nanoparticles: Advances in Research and Applications, Nova Science Pub., Inc, ISBN-13 978-1536186536; Mitchell, M. J., Billingsley, M. M., Haley, R. M. et al. *Engineering precision nanoparticles for drug delivery*, Nat Rev Drug Discov 20, 101-124 (2021); Hou, X., Zaks, T., Langer, R. et al. *Lipid nanoparticles for mRNA delivery*. Nat Rev Mater 6, 1078-1094 (2021); *Lipid-Nanoparticle-Based Delivery of CRISPR/Cas9 Genome-Editing Components*, Pardis Kazemian, Si-Yue Yu, Sarah B. Thomson, Alexandra Birkenshaw, Blair R. Leavitt, and Colin J. D. Ross. Molecular Pharmaceutics 2022 19 (6), 1669-1686; Cullis P R, Hope M J. *Lipid Nanoparticle Systems for Enabling Gene Therapies*, Mol Ther. 2017 Jul. 5; 25(7):1467-1475; Hatit, M. Z. C.,

Lokugamage, M. P., Dobrowolski, C. N. et al. Species-*dependent in vivo mRNA delivery* and *cellular responses to nanoparticles*, Nat. Nanotechnol. 17, 310-318 (2022); Lam, K., Schreiner, P., Leung, A., Stainton, P., Reid, S., Yaworski, E., Lutwyche, P. and Heyes, J. (2023), *Optimizing Lipid Nanoparticles for Delivery in Primates*, Adv. Mater; Dilliard, S. A., Siegwart, D. J. *Passive, active and endogenous organ-targeted lipid and polymer nanoparticles for delivery of genetic drugs*, Nat Rev Mater (2023); Kasiewicz, L. N., et. al., *Lipid nanoparticles incorporating a GalNAc ligand enable in vivo liver ANGPTL3 editing in wild-type and somatic LDLR knockout non-human primates,* bioRxiv 2021.11.08.467731, doi: https://doi.org/10.1101/2021.11.08.467731; Tombácz, I., et. al., *Highly efficient CD4+ T cell targeting and genetic recombination using engineered CD4'+ cell-homing mRNA-LNPs*, Molecular Therapy, Volume 29, Issue 11, 2021, 3293-3304; Cheng, Q., Wei, T., Farbiak, L. et al. *Selective organ targeting (SORT) nanoparticles for tissue-specific mRNA delivery and CRISPR-Cas gene editing*, Nat. Nanotechnol. 15, 313-320 (2020); Zhang, Y., et. al., *Lipids and Lipid Derivatives for RNA Delivery*, Chemical Reviews 2021 121 (20); Lam, K., et. al, Unsaturated, *Trialkyl Ionizable Lipids are Versatile Lipid-Nanoparticle Components for Therapeutic and Vaccine Applications, Adv. Mater.* 2023, 35; Han, X., Zhang, H., Butowska, K. et al. *An ionizable lipid toolbox for RNA delivery*, Nat Commun 12, 7233 (2021); U.S. Pat. Nos. 9,364,435; 8,058,069; 8,822,668; 8,492,359; 11,141,378; 9,518,272; 9,404,127; 9,006,417; 7,901,708; 9,005,654; 9,878,042; 9,682,139; 8,642,076; 9,593,077; 9,415,109; 9,701,623; 10,369,226; 9,999,673; 9,301,923; 10,342,761; 10,137,201; International Patent Application PCT/US2014/070882; International Publication No. WO2015199952A1; International Publication No. WO2017075531A1; International Publication No. WO2018081480A1; International Publication No. WO2016081029A1; European Application No. EP3852911A2; each of which are incorporated herein by reference in their entirety. The ordinarily skilled artisan will be able to identify an appropriate LNP and method of delivery based on the present disclosure and the state of the art. The present disclosure is not limited in this respect.

Other methods of delivery to target cells will be known to those skilled in the art and can be used with the compositions of the present disclosure.

Any type of cell may be targeted for delivery of an epigenetic editor or component(s) thereof as described herein. For example, the cells may be eukaryotic or prokaryotic. In some embodiments, the cells are mammalian (e.g., human) cells. Human cells may include, for example, hepatocytes, biliary epithelial cells (cholangiocytes), stellate cells, Kupffer cells, and liver sinusoidal endothelial cells.

In some embodiments, an epigenetic editor described herein, or component(s) thereof, are delivered to a host cell for transient expression, e.g., via a transient expression vector. Transient expression of the epigenetic editor or its component(s) may result in prolonged or permanent epigenetic modification of the target gene. For example, the epigenetic modification may be stable for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks or more; or 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, after introduction of the epigenetic editor into the host cell. The epigenetic modification may be maintained after one or more mitotic and/or meiotic events of the host cell. In particular embodiments, the epigenetic modification is maintained across generations in offspring generated or derived from the host cell.

VIII. Therapeutic Uses of Epigenetic Editors

The present disclosure also provides methods for treating or preventing a condition in a subject, comprising administering to the subject an epigenetic editor or pharmaceutical composition as described herein. The epigenetic editor may effectuate an epigenetic modification of a target polynucleotide sequence in a target gene associated with a disease, condition, or disorder in the subject, thereby modulating expression of the target gene to treat or prevent the disease, condition, or disorder. In some embodiments, the epigenetic editor reduces the expression of the target gene to an extent sufficient to achieve a desired effect, e.g., a therapeutically relevant effect such as the prevention or treatment of the disease, condition, or disorder.

In some embodiments, a subject is administered a system for modulating (e.g., repressing) expression of HBV or of an HBV gene, wherein the system comprises (1) the fusion protein(s) and, where relevant, guide polynucleotide(s) of an epigenetic editor as described herein, or (2) nucleic acid molecules encoding said fusion protein(s) and, where relevant, guide polynucleotide(s).

"Treat," "treating" and "treatment" refer to a method of alleviating or abrogating a biological disorder and/or at least one of its attendant symptoms. As used herein, to "alleviate" a disease, disorder or condition means reducing the severity and/or occurrence frequency of the symptoms of the disease, disorder, or condition. Further, references herein to "treatment" include references to curative, palliative and prophylactic treatment. In some embodiments, as compared with an equivalent untreated control, alleviating a symptom may involve reduction of the symptom by at least 3%, 5%, 10%, 20%, 40%, 50%, 60%, 80%, 90%, 95%, 98%, 99%, 99.5%, 99.9%, or 100% as measured by any standard technique.

In some embodiments, the subject may be a mammal, e.g., a human. In some embodiments, the subject is selected from a non-human primate such as chimpanzee, cynomolgus monkey, or macaque, and other apes and monkey species.

Some aspects of this disclosure provide methods comprising administering an epigenetic editing system to a subject characterized by the presence of detectable levels of HBV DNA, HBsAg, and/or HBeAg in the plasma of the subject, for example, a subject having a chronic HBV infection. In some such embodiments, the epigenetic editing system comprises a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding the same, wherein the first DNA binding domain binds a first target region of an HBV gene or genome, and the administering results in a reduction of the level of HBV DNA, the level of HBsAg, and/or the level of HBsAg in the plasma of the subject, and the reduction of the level of HBV DNA, of the level of HBsAg, and/or of the level of HBsAg in the plasma of the subject, is at least 90% (a 1-log reduction) compared to the respective level observed or observable in the plasma of the subject prior to the administering, and the 1-log reduction is maintained for at least 14 days after the administering. In some embodiments, the reduction of the level of HBV DNA in the plasma of the subject is at least 90% (a 1-log reduction). In some embodiments, the reduction of the level of HBV DNA in the plasma of the subject is at least 99% (a 2-log reduction). In some embodiments, the reduction of the level of HBsAg in the plasma of the subject is at least 90% (a 1-log reduction). In some embodiments, the reduction of the level of HBsAg in the plasma of the subject is at least 99% (a 2-log reduction). In some embodiments, the reduction of the level of HBeAg in the plasma of the subject is at least 90% (a 1-log reduction). In some embodiments, the reduction of the level of HBeAg in the plasma of the subject is at least 99% (a 2-log reduction). In some embodiments, the reduction is maintained for at least 21 days. In some

embodiments, the reduction is maintained for at least 28 days. In some embodiments, the reduction is maintained for at least 35 days. In some embodiments, the reduction is maintained for at least 42 days. In some embodiments, the reduction is maintained for at least 56 days. In some embodiments, the reduction is maintained for at least 70 days. In some embodiments, the reduction is maintained for at least 84 days. In some embodiments, the reduction is maintained for at least 112 days. In some embodiments, the reduction is maintained for at least 140 days. In some embodiments, the reduction is maintained for at least 168 days. In some embodiments, the reduction is maintained for at least 6 months. In some embodiments, the reduction is maintained for at least 9 months. In some embodiments, the reduction is maintained for at least 12 months. In some embodiments, the reduction is maintained for at least 24 months. In some embodiments, the HBV genome comprises HBV genotype A. In some embodiments, the HBV genome comprises HBV genotype B. In some embodiments, the HBV genome comprises HBV genotype C. In some embodiments, the HBV genome comprises, HBV genotype D. In some embodiments, the HBV genome comprises HBV genotype E. In some embodiments, the HBV genome comprises HBV genotype F. In some embodiments, the HBV genome comprises HBV genotype G. In some embodiments, the HBV genome comprises HBV genotype H. In some embodiments, the HBV genome comprises a sequence with at least 80%, at least 90%, at least 95%, at least 99%, or greater than 99% sequence identity to an HBV genome sequence provided herein. In some embodiments, the first target region is located in a region of the HBV genome within nucleotides 0-303 of an HBV genome provided herein. In some embodiments, the first target region is located within nucleotides 0-303 of SEQ ID NO: 1082. In some embodiments, the first target region is located within nucleotides 0-303 of SEQ ID NO: 1083. In some embodiments, the first target region is located in a region of the HBV genome within nucleotides 1000-2448 of an HBV genome provided herein. In some embodiments, the first target region is located within nucleotides 1000-2448 of SEQ ID NO: 1082. In some embodiments, the first target region is located within nucleotides 1000-2448 of SEQ ID NO: 1083. In some embodiments, the first target region is located in a region of the HBV genome within nucleotides 2802-3182 of an HBV genome provided herein. In some embodiments, the first target region is located within nucleotides 2802-3182 of SEQ ID NO: 1082. In some embodiments, the first target region is located within nucleotides 2802-3182 of SEQ ID NO: 1083. In some embodiments, the first target region of the HBV genome is located in an HBV CpG island (CGI). In some embodiments, the CGI is an HBV canonical CGI. In some embodiments, the CGI is canonical CGI-I. In some embodiments, CGI is canonical CGI-I of HBV genotype D. In some embodiments, CGI-I spans nucleotides 186-288 of SEQ ID NO: 1082In some embodiments, CGI-I spans nucleotides 186-288 of SEQ ID NO: 10831n some embodiments, the CGI is canonical CGI-II. In some embodiments, the CGI is canonical CGI-II HBV genotype D. In some embodiments, the CGI is CGI II spans nucleotides 1,217-1,670 of SEQ ID NO: 1082. In some embodiments, the CGI is CGI II spans nucleotides 1,217-1,670 of SEQ ID NO: 1083. In some embodiments, the CGI is canonical CGI-III. In some embodiments, the CGI is canonical CGI-III HBV genotype D. In some embodiments, the CGI is CGI-III spans nucleotides 2,282-2,448 of SEQ ID NO: 1082. In some embodiments, the CGI is CGI-III spans nucleotides 2,282-2,448 of SEQ ID NO: 1083. In some embodiments, the first target region of the HBV genome is located in a promotor. In some embodiments, the first target region of the HBV genome is located in the sp1 promoter. In some embodiments, the first target region of the HBV genome is located in sp2 promoter. In some embodiments, the first target region of the HBV genome is located in cp promoter. In some embodiments, the first target region of the HBV genome is located in xp promoter. In some embodiments, the first target region of the HBV genome is located in an enhancer region. In some embodiments, the first target region of the HBV genome is located in Enh I. In some embodiments, the first target region of the HBV genome is located in Enh II. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes a transcript. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes a pgRNA transcript. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes a preCore RNA transcript. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes a preS RNA transcript. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes an S RNA transcript. In some embodiments, the first target region of the HBV genome is located in a section of the HBV genome that encodes an HBx RNA transcript. In some embodiments, the first target region of the HBV genome is within 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) of an HBV transcription start site (TSS). In some embodiments, the TSS is a pg RNA TSS. In some embodiments, the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the pg RNA TSS. In some embodiments, the pg RNA TSS is located at nucleotide 1820 of SEQ ID NO: 1082 or at nucleotide 1820 of SEQ ID NO: 1083. In some embodiments, the first target region is within 600 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 600 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the first target region is within 500 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 500 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the first target region is within 400 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 400 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the first target region is within 300 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 300 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the first target region is within 200 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 200 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the first target region is within 100 base pairs of nucleotide 1820 in SEQ ID NO: 1082. In some embodiments, the first target region is within 100 base pairs of nucleotide 1820 in SEQ ID NO: 1083. In some embodiments, the TSS is a preC RNA TSS. In some embodiments, the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the preC RNA TSS. In some embodiments, the preC RNA TSS is located at nucleotide 1791 of SEQ ID NO: 1082 or at nucleotide 1791 of SEQ ID NO: 1083. In some embodi-

ments, the first target region is within 600 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 600 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the first target region is within 500 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 500 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the first target region is within 400 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 400 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the first target region is within 300 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 300 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the first target region is within 200 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 200 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the first target region is within 100 base pairs of nucleotide 1791 in SEQ ID NO: 1082. In some embodiments, the first target region is within 100 base pairs of nucleotide 1791 in SEQ ID NO: 1083. In some embodiments, the TSS is a preS2 RNA TSS. In some embodiments, the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the preS2 RNA TSS. In some embodiments, the preS2 RNA TSS is located at nucleotide 3159 of SEQ ID NO: 1082 or at nucleotide 3159 of SEQ ID NO: 1083. In some embodiments, the first target region is within 600 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 600 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the first target region is within 500 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 500 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the first target region is within 400 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 400 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the first target region is within 300 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 300 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the first target region is within 200 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 200 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the first target region is within 100 base pairs of nucleotide 3159 in SEQ ID NO: 1082. In some embodiments, the first target region is within 100 base pairs of nucleotide 3159 in SEQ ID NO: 1083. In some embodiments, the TSS is an HBx RNA TSSs. In some embodiments, the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the HBx RNA TSS. In some embodiments, the HBx RNA TSS is located at a nucleotide within the sequence of nucleotides 1243-1338 of SEQ ID NO: 1082 or nucleotides 1243-1338 of SEQ ID NO: 1083. In some embodiments, the first target region is within 600 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 600 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 500 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 500 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 400 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 400 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 300 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 300 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 200 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 200 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 100 base pairs of nucleotide 1243 in SEQ ID NO: 1082. In some embodiments, the first target region is within 100 base pairs of nucleotide 1243 in SEQ ID NO: 1083. In some embodiments, the first target region is within 600 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, the first target region is within 500 base pairs of nucleotide 1338 in SEQ ID NO: 1082. In some embodiments, the first target region is within 500 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, first target region is within 400 base pairs of nucleotide 1338 in SEQ ID NO: 1082. In some embodiments, the first target region is within 400 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, the first target region is within 300 base pairs of nucleotide 1338 in SEQ ID NO: 1082. In some embodiments, the first target region is within 300 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, the first target region is within 200 base pairs of nucleotide 1338 in SEQ ID NO: 1082. In some embodiments, the first target region is within 200 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, the first target region is within 100 base pairs of nucleotide 1338 in SEQ ID NO: 1082. In some embodiments, the first target region is within 100 base pairs of nucleotide 1338 in SEQ ID NO: 1083. In some embodiments, the reduction is a reduction in the number of HBV viral episomes. In some embodiments, the reduction is a reduction in the number of cccDNA genomes. In some embodiments, the reduction is a reduction in total HBV DNA. In some embodiments, the reduction is a reduction in the replication of the HBV genome. In some embodiments, the reduction is a reduction in a level of expression of a protein product encoded by the HBV genome. In some embodiments, the reduction is a reduction in a level of HBsAg. In some embodiments, the reduction is a reduction in a level of HBeAg. In some embodiments, the reduction is a reduction of total HBV DNA of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and the reduction is maintained for at least 14 days after the contacting or the administering. In some embodiments, the reduction is a reduction of HBeAg of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and the reduction is maintained for at least 14 days after the contacting or the administering. In some embodiments, the reduction is a reduction of HBsAg of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and the reduction is maintained at or below that level for at least 14 days after the contacting or the administering. In some embodiments, the reduction is a reduction of at least 90%. In some embodiments, the reduction is a reduction of at least 95%. In some embodiments, the reduction is a reduction of at least 99%. In some embodiments, the reduction is a reduction of at least 99.9%. In some embodiments, the reduction is maintained for at least 14

days after the contacting or the administering. In some embodiments, the reduction is maintained for at least 21 days. In some embodiments, the reduction is maintained for at least 28 days. In some embodiments, the reduction is maintained for at least 35 days. In some embodiments, the reduction is maintained for at least 42 days. In some embodiments, the reduction is maintained for at least 56 days. In some embodiments, the reduction is maintained for at least 70 days. In some embodiments, the reduction is maintained for at least 84 days. In some embodiments, the reduction is maintained for at least 112 days. In some embodiments, the reduction is maintained for at least 140 days. In some embodiments, the reduction is maintained for at least 168 days. In some embodiments, the reduction is maintained for at least 6 months. In some embodiments, the reduction is maintained for at least 7 months. In some embodiments, the reduction is maintained for at least 8 months. In some embodiments, the reduction is maintained for at least 9 months. In some embodiments, the reduction is maintained for at least 12 months. In some embodiments, the reduction is maintained for at least 18 months. In some embodiments, the reduction is maintained for at least 24 months. In some embodiments, the epigenetic editing system is administered as a monotherapy. Accordingly, in some embodiments, the method does not comprise administering a nucleoside or nucleotide analog (NUC) to the subject. In some embodiments, the method further comprises administering a NUC to the subject. In some embodiments, the first DNA binding domain comprises a CRISPR-Cas protein. In some embodiments, the epigenetic editing system further comprises a first guide RNA (gRNA) that comprises a region complementary to a strand of the first target region. In some embodiments, the gRNA comprises a sequence selected from a gRNA provided herein, and preferably the gRNA comprises a sequence provided in Table 12 or 13. In some embodiments, the first DNA binding domain comprises a zinc-finger protein. In some embodiments, the zinc-finger protein comprises a zinc-finger motif with a sequence selected from any zinc finger or zinc finger motif provided herein, e.g., in Table 1 or Table 18. In some embodiments, the zinc-finger protein comprises a sequence of any of the zinc finger epigenetic repressors provided herein. In some embodiments, the transcriptional repressor domain comprises ZIM3. In some embodiments, the first DNMT domain is a DNMT3A domain or a DNMT3L domain. In some embodiments, the first DNMT domain comprises a sequence of a DNMT domain provided herein. In some embodiments, the epigenetic editing system comprises the fusion protein provided in SEQ ID NO: 1248 or the fusion protein provided in SEQ ID NO: 1252 and at least one guide RNA provided as gRNA #003, gRNA #007, gRNA #008, gRNA #009, gRNA #011, or gRNA #015 herein. Some aspects of this disclosure provide epigenetic editing systems for use in the methods described herein. In some embodiments, the epigenetic editing system comprises a fusion protein or a nucleic acid encoding the fusion protein, and the fusion protein comprises: (a) a DNA-binding domain that binds a target region of a HBV gene or genome, (b) a first DNA methyltransferase (DNMT) domain, and (c) a transcriptional repressor domain. In some embodiments, the fusion protein comprises a sequence of a fusion protein provided herein. In some embodiments, the DNA-binding domain is a CRISPR-Cas DNA binding domain, and the epigenetic editing system comprises at least gRNA provided herein. In some embodiments, the epigenetic editing system comprises the fusion protein provided in SEQ ID NO: 1248 or the fusion protein provided in SEQ ID NO: 1252 and at least one guide RNA provided as gRNA #003, gRNA #007, gRNA #008, gRNA #009, gRNA #011, or gRNA #015 herein.

In some embodiments, the subject is a mammalian subject having, or having been diagnosed with, a Hepatitis B virus (HBV) infection. In some embodiments, the subject is a mammalian subject having, or having been diagnosed with, a Hepatitis D virus infection.

In some embodiments, the subject is a mammalian subject, for example, a human subject, having, or having been diagnosed with, a Hepatitis B virus (HBV) infection. In some embodiments, the subject is a mammalian subject, for example, a human subject, having, or having been diagnosed with Hepatitis B In some embodiments, the subject is a mammalian subject, for example, a human subject, having, or having been diagnosed with, a Hepatitis D virus infection. In some embodiments, a patient to be treated with an epigenetic editor of the present disclosure has received prior treatment for the condition to be treated (e.g., an HBV and/or HDV infection, or Hepatitis B). In other embodiments, the patient has not received such prior treatment. In some embodiments, the patient has failed on (or is refractory to) a prior treatment for the condition (e.g., a prior HBV treatment).

In some embodiments, contacting the HBV gene or genome or a cell with an epigenetic editor as described herein results in a reduction of: number of HBV viral episomes, replication of the HBV gene or genome, or expression of a protein product encoded by the HBV gene or genome. In some embodiments, the reduction is at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% compared to contacting the HBV gene or genome or the cell with a suitable control or without contacting the HBV gene or genome or the cell with the epigenetic editor described herein. In some embodiments, the reduction is maintained for at least 6 days, 19 days, 27 days, 42 days, or 168 days. In some embodiments, the protein product comprises a HBe antigen or a HBs antigen.

In some embodiments, administering to the subject an epigenetic editor or pharmaceutical composition as described herein results in a reduction of: number of HBV viral episomes, replication of the HBV gene or genome, or expression of a protein product encoded by the HBV gene or genome. In some embodiments, the reduction is at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% compared to administering a suitable control or without administering the epigenetic editor or pharmaceutical composition described herein. In some embodiments, the reduction is maintained for at least 6 days, 19 days, 27 days, 42 days, or 168 days. In some embodiments, the protein product comprises a HBe antigen or a HBs antigen.

An epigenetic editor of the present disclosure may be administered in a therapeutically effective amount to a patient with a condition described herein. "Therapeutically effective amount," as used herein, refers to an amount of the therapeutic agent being administered that will relieve to some extent one or more of the symptoms of the disorder being treated, and/or result in clinical endpoint(s) desired by healthcare professionals. An effective amount for therapy may be measured by its ability to stabilize disease progression and/or ameliorate symptoms in a patient, and preferably to reverse disease progression. The ability of an epigenetic editor of the present disclosure to reduce or silence HBV expression may be evaluated by in vitro assays, e.g., as

described herein, as well as in suitable animal models that are predictive of the efficacy in humans. Suitable dosage regimens will be selected in order to provide an optimum therapeutic response in each particular situation, for example, administered as a single bolus or as a continuous infusion, and with possible adjustment of the dosage as indicated by the exigencies of each case.

An epigenetic editor of the present disclosure may be administered without additional therapeutic treatments, i.e., as a stand-alone therapy (monotherapy). Alternatively, treatment with an epigenetic editor of the present disclosure may include at least one additional therapeutic treatment (combination therapy). In some embodiments, the additional therapeutic agent is any known in the art to treat an HBV infection. The current standard therapy for HBV employs nucleoside/nucleotide analogs (NUCs) and interferon (IFN). NUCs are viral polymerase and reverse transcriptase inhibitors that can efficiently suppress HBV viral replication, resulting in rapid HBV DNA reduction. NUCs do not directly target HBV cccDNA transcription, but NUC treatment of human HBV patients has been reported to reduce plasma HBV biomarkers such as HBeAg and HBsAg tp some extent. Prolonged therapy with NUCs is frequently associated with the pathogen developing a resistance to the treatment, but some NUCs have been reported to be able to achieve long-term viral suppression and halt disease progression. IFN-based therapy has both direct antiviral and immunomodulatory effects, and has been reported to prevent the formation of replication-competent pregenomic RNA-containing HBV capsids, or otherwise accelerates their degradation, thereby inhibiting HBV replication. See, e.g., Su et al., Improving clinical outcomes of chronic hepatitis B virus infection. Expert Rev Gastroenterol Hepatol. 2015; 9:141-154; European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2012; 57:167-185; Wieland et al., Intrahepatic induction of alpha/beta interferon eliminates viral RNA-containing capsids in hepatitis B virus transgenic mice. J Virol. 2000; and Wieland et al., Interferon prevents formation of replication-competent hepatitis B virus RNA-containing nucleocapsids. Proc Natl Acad Sci USA. 2005; 102:9913-9917, the entire contents of each of which are incorporated herein by reference.

In some embodiments, an epigenetic editor of the present disclosure is administered to a subject in need thereof, e.g., a subject having an HBV infection, without additional therapeutic treatment, e.g., without the co-administration of NUCs or IFN, or any other therapeutic treatment aimed at HBV, i.e., as a stand-alone therapy (monotherapy). In some such embodiments, a durable reduction of an HBV biomarker (e.g., as measured as the plasma level of HBV DNA, HBsAg, or HBeAG) by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, at least 99.9%, or more, is achieved over a time period of at least 14 days, at least 21 days, at least 28 days, at least 35 days, at least 42 days, at least 56 days, at least 70 days, at least 84 days, at least 112 days, at least 140 days, at least 168 days, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, at least 24 months, or longer, after a single-dose administration of the epigenetic editor to the subject.

In some embodiments, an epigenetic editor of the present disclosure is administered to a subject in need thereof, e.g., a subject having an HBV infection, in combination with (i.e., in temporal proximity) at least one additional HBV therapeutics, e.g., with NUCs and/or IFN therapeutics, or with any other therapeutic treatment aimed at HBV, i.e., as a combination therapy (monotherapy). In some such embodiments, a durable reduction of an HBV biomarker (e.g., as measured as the plasma level of HBV DNA, HBsAg, or HBeAG) by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, at least 99.9%, or more, is achieved over a time period of at least 14 days, at least 21 days, at least 28 days, at least 35 days, at least 42 days, at least 56 days, at least 70 days, at least 84 days, at least 112 days, at least 140 days, at least 168 days, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, at least 24 months, or longer.

An epigenetic editor of the present disclosure may be administered without additional therapeutic treatments, i.e., as a stand-alone therapy (monotherapy). Alternatively, treatment with an epigenetic editor of the present disclosure may include at least one additional therapeutic treatment (combination therapy). In some embodiments, the additional therapeutic agent is any known in the art to HBV and/or HDV. In some embodiments, therapeutic agents include, but are not limited to, antivirals, such as entecavir, tenofovir, lamivudine, telvivudine, bictegravir, emtricitabine, or defovir, as well as immune modulators, such as pegylated interferon and interferon alpha.

The epigenetic editors or components thereof (or nucleic acid molecules encoding the epigenetic editors or components thereof) of the present disclosure may be administered by any method accepted in the art (e.g., parenterally, intravenously, intradermally, or intramuscularly).

The epigenetic editors or components thereof (or nucleic acid molecules encoding the epigenetic editors or components thereof) of the present disclosure may be administered to a subject once, twice, three times, or 4, 5, 6, 7, 8, 9, 10, or more times. In some embodiments, the one, two, three, or 4, 5, 6, 7, 8, 9, 10, or more administrations of epigenetic editors or components thereof (or nucleic acid molecules encoding the epigenetic editors or components thereof) are in temporal proximity, e.g., within 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 4 weeks, 1 month or two months of each other. In some embodiments, a subject is re-dosed with the epigenetic editors or components thereof (or nucleic acid molecules encoding the epigenetic editors or components thereof) of the present disclosure for at least one more time after an initial dose. In some cases, a subject is administered with a subsequent dose of the epigenetic editors or components thereof (or nucleic acid molecules encoding the epigenetic editors or components thereof) of the present disclosure, which target a different DNA region of the HBV genome than the DNA region of the HBV genome that is targeted by the epigenetic editors or components thereof that the subject receives at the initial dose. In some cases, a subject is administered with multiple doses (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) of the same epigenetic editors or components thereof (or nucleic acid molecules encoding the epigenetic editors or components thereof) of the present disclosure. In some cases, a subject is administered with a single dose of different epigenetic editors or components thereof (or nucleic acid molecules encoding the epigenetic editors or components thereof) of the present disclosure, at least two of which target different DNA regions of the HBV genome. In some cases, a subject is administered with multiple doses (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) of different epigenetic editors or components thereof (or nucleic acid molecules encoding the epigenetic

editors or components thereof) of the present disclosure, at least two of which target different DNA regions of the HBV genome. In some embodiments, redosing of the epigenetic editors or components thereof (or nucleic acid molecules encoding the epigenetic editors or components thereof) of the present disclosure has a better therapeutic efficacy than a single dose of the same, e.g., more potent suppression of HBV replication, or more profound reduction in HBV DNA and/or HBV antigens (e.g., HBsAg, HBeAg, and/or HBV core antigen (HBcAg)) present in the subject, e.g., in the circulation system and/or liver of the subject.

XII. Definitions

The term "nucleic acid" as used herein refers to any oligonucleotide or polynucleotide containing nucleotides (e.g., deoxyribonucleotides or ribonucleotides) in either single- or double-strand form, and includes DNA and RNA. "Nucleotides" contain a sugar deoxyribose (DNA) or ribose (RNA), a base, and a phosphate group, and are linked together through the phosphate groups. "Bases" include purines and pyrimidines, which include natural compounds such as adenine, thymine, guanine, cytosine, uracil, inosine, and natural analogs; as well as synthetic derivatives of purines and pyrimidines, which include, but are not limited to, modified versions which place new reactive groups such as amines, alcohols, thiols, carboxylates, alkylhalides, etc. Nucleic acids may contain known nucleotide analogs and/or modified backbone residues or linkages, which may be synthetic, naturally occurring, and non-naturally occurring. Such nucleotide analogs, modified residues, and modified linkages are well known in the art, and may provide a nucleic acid molecule with enhanced cellular uptake, reduced immunogenicity, and/or increased stability in the presence of nucleases.

As used herein, an "isolated" or "purified" nucleic acid molecule is a nucleic acid molecule that exists apart from its native environment. For example, an "isolated" or "purified" nucleic acid molecule (1) has been separated away from the nucleic acids of the genomic DNA or cellular RNA of its source of origin; and/or (2) does not occur in nature. In some embodiments, an "isolated" or "purified" nucleic acid molecule is a recombinant nucleic acid molecule.

It will be understood that in addition to the specific proteins and nucleic acid molecules mentioned herein, the present disclosure also contemplates the use of variants, derivatives, homologs, and fragments thereof. A variant of any given sequence may have the specific sequence of residues (whether amino acid or nucleic acid residues) modified in such a manner that the polypeptide or polynucleotide in question substantially retains at least one of its endogenous functions. A variant sequence can be obtained by addition, deletion, substitution, modification, replacement and/or variation of at least one residue present in the naturally-occurring sequence (in some embodiments, no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 residues). For specific proteins described herein (e.g., KRAB, dCas9, DNMT3A, and DNMT3L proteins described herein), the present disclosure also contemplates any of the protein's naturally occurring forms, or variants or homologs that retain at least one of its endogenous functions (e.g., at least 50%, 60%, 70%, 80%, 90%, 85%, 96%, 97%, 98%, or 99% of its function as compared to the specific protein described).

As used herein, a homologue of any polypeptide or nucleic acid sequence contemplated herein includes sequences having a certain homology with the wildtype amino acid and nucleic sequence. A homologous sequence may include a sequence, e.g. an amino acid sequence which may be at least 50%, 55%, 65%, 75%, 85%, 90%, 91%, 92%<93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the subject sequence. The term "percent identical" in the context of amino acid or nucleotide sequences refers to the percent of residues in two sequences that are the same when aligned for maximum correspondence. In some embodiments, the length of a reference sequence aligned for comparison purposes is at least 30%, (e.g., at least 40, 50, 60, 70, 80, or 90%, or 100%) of the reference sequence. Sequence identity may be measured using sequence analysis software (for example, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705, BLAST, BESTFIT, GAP, or PILEUP/PRETTYBOX programs). Such software matches identical or similar sequences by assigning degrees of homology to various substitutions, deletions, and/or other modifications. In an exemplary approach to determining the degree of identity, a BLAST program may be used, with a probability score between e-3 and e-100 indicating a closely related sequence.

The percent identity of two nucleotide or polypeptide sequences is determined by, e.g., BLAST® using default parameters (available at the U.S. National Library of Medicine's National Center for Biotechnology Information website). In some embodiments, the length of a reference sequence aligned for comparison purposes is at least 30%, (e.g., at least 40, 50, 60, 70, 80, or 90%) of the reference sequence.

It will be understood that the numbering of the specific positions or residues in polypeptide sequences depends on the particular protein and numbering scheme used. Numbering might be different, e.g., in precursors of a mature protein and the mature protein itself, and differences in sequences from species to species may affect numbering. One of skill in the art will be able to identify the respective residue in any homologous protein and in the respective encoding nucleic acid by methods well known in the art, e.g., by sequence alignment and determination of homologous residues.

The term "modulate" or "alter" refers to a change in the quantity, degree, or extent of a function. For example, an epigenetic editor as described herein may modulate the activity of a promoter sequence by binding to a motif within the promoter, thereby inducing, enhancing, or suppressing transcription of a gene operatively linked to the promoter sequence. As other examples, an epigenetic editor as described herein may block RNA polymerase from transcribing a gene, or may inhibit translation of an mRNA transcript. The terms "inhibit," "repress," "suppress," "silence" and the like, when used in reference to an epigenetic editor or a component thereof as described herein, refers to decreasing or preventing the activity (e.g., transcription) of a nucleic acid sequence (e.g., a target gene) or protein relative to the activity of the nucleic acid sequence or protein in the absence of the epigenetic editor or component thereof. The term may include partially or totally blocking activity, or preventing or delaying activity. The inhibited activity may be, e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% less than that of a control, or may be, e.g., at least 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, or 10-fold less than that of a control. For example, in some embodiments, the inhibited activity (e.g., the transcription or expression of an HBV target gene, or the level of an HBV biomarker) may be at least 70% less than that of a control. In some embodiments, the inhibited activity may be at least 80% less than

that of a control. In some embodiments, the inhibited activity may be at least 90% less than that of a control (1 log reduction). In some embodiments, the inhibited activity may be at least 91% less than that of a control. In some embodiments, the inhibited activity may be at least 92% less than that of a control. In some embodiments, the inhibited activity may be at least 93% less than that of a control. In some embodiments, the inhibited activity may be at least 94% less than that of a control. In some embodiments, the inhibited activity may be at least 95% less than that of a control. In some embodiments, the inhibited activity may be at least 96% less than that of a control. In some embodiments, the inhibited activity may be at least 97% less than that of a control. In some embodiments, the inhibited activity may be at least 98% less than that of a control. In some embodiments, the inhibited activity may be at least 99% less than that of a control (2 log reduction). In some embodiments, the inhibited activity may be at least 99.9% less than that of a control (3 log reduction).

The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, e.g., the limitations of the measurement system. For example, "about" can mean within one or more than one standard deviation, per the practice in the given value. Where particular values are described in the application and claims, unless otherwise stated, the term "about" should be assumed to mean an acceptable error range for the particular value.

Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50, as well as all intervening decimal values between the aforementioned integers such as, for example, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. With respect to sub-ranges, "nested sub-ranges" that extend from either end point of the range are specifically contemplated. For example, a nested sub-range of an exemplary range of 1 to 50 may comprise 1 to 10, 1 to 20, 1 to 30, and 1 to 40 in one direction, or 50 to 40, 50 to 30, 50 to 20, and 50 to 10 in the other direction.

Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. Exemplary methods and materials are described below, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure. In case of conflict, the present specification, including definitions, will control. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Throughout this specification and embodiments, the words "have" and "comprise," or variations such as "has," "having," "comprises," or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. The recitation of a listing of elements herein includes any of the elements singly or in any combination. The recitation of an embodiment herein includes that embodiment as a single embodiment, or in combination with any other embodiment(s) herein. All publications, patents, patent applications, and other references mentioned herein, including, where applicable, any supplementary information, are incorporated by reference in their entirety. To the extent that references incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material. Although a number of documents are cited herein, this citation does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

Listings of Exemplary Embodiments

In order that the present disclosure may be better understood, the following listings of exemplary embodiments is provided. This listing is for purposes of illustration of certain embodiments only. Additional embodiments will be apparent to the skilled artisan based on the present disclosure, and the listing below is not to be construed as limiting the scope of the present disclosure.

LISTING #1 of Exemplary Embodiments:

1. A method of modifying an epigenetic state of a hepatitis B virus (HBV) gene or genome, comprising contacting the HBV gene or genome with an epigenetic editing system,
   wherein the epigenetic editing system comprises
   a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding the same,
   wherein the first DNA binding domain binds a first target region of the HBV gene or genome, and
   wherein the contacting results in a reduction of
   number of HBV viral episomes,
   replication of the HBV gene or genome, and/or
   expression of a protein product encoded by the HBV gene or genome, wherein the reduction is at least about 50%, and preferably wherein the reduction is at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or greater than 99%, compared to contacting the HBV gene or genome with a suitable control.

2. A method of treating an HBV infection in a subject comprising administering an epigenetic editing system to the subject,
   wherein the epigenetic editing system comprises
   a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof,
   wherein the first DNA binding domain binds a first target region of a HBV gene or genome, and
   wherein the administering results in a reduction of
   number of HBV viral episomes,
   replication of the HBV gene or genome, and/or
   expression of a protein product encoded by the HBV gene or genome,
   wherein the reduction is at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or greater than 99%, compared to administering a suitable control.

3. A method of modulating expression of an HBV gene or genome comprising contacting the HBV gene or genome with an epigenetic editing system,
   wherein the epigenetic editing system comprises
   a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof,
   wherein the first DNA binding domain binds a first target region of the HBV gene or genome, and
   wherein the contacting results in a reduction of expression of a gene product encoded by the HBV gene or genome, optionally, wherein the gene product is a nucleic acid or a protein,

wherein the reduction is at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or greater than 99%, compared to contacting the HBV genome with a suitable control.

4. A method of inhibiting viral replication in a cell infected with an HBV comprising administering an epigenetic editing system,

wherein the epigenetic editing system comprises

a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or

one or more nucleic acid molecules encoding thereof,

wherein the first DNA binding domain binds a first target region of a HBV gene or genome, and wherein the epigenetic editing system targets a target region of the HBV gene or genome, and

wherein the administering results in a reduction of number of HBV viral episomes or replication of the HBV gene or genome,

wherein the reduction is at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or greater than 99%, compared to administering a suitable control.

5. The method of any one of embodiments 1-4, wherein the reduction is at least 70%.

6. The method of any one of embodiments 1-4, wherein the reduction is at least 80%.

7. The method of any one of embodiments 1-4, wherein the reduction is at least 90%.

8. The method of any one of embodiments 1-4, wherein the reduction is at least 95%.

9. The method of any one of embodiments 1-4, wherein the reduction is at least 99%,

10. The method of any one of embodiments 1-4, wherein the reduction is greater than 99%.

11. The method of any one of embodiments 1-10, wherein the HBV genome is a covalently closed circular DNA (cccDNA).

12. The method of any one of embodiments 1-10, wherein the HBV genome is an HBV integrated DNA.

13. The method of any one of embodiments 1-12, wherein the HBV genome comprises HBV genotype A.

14. The method of any one of embodiments 1-12, wherein the HBV genome comprises HBV genotype B.

15. The method of any one of embodiments 1-12, wherein the HBV genome comprises HBV genotype C.

16. The method of any one of embodiments 1-12, wherein the HBV genome comprises, HBV genotype D.

17. The method of any one of embodiments 1-12, wherein the HBV genome comprises HBV genotype E.

18. The method of any one of embodiments 1-12, wherein the HBV genome comprises HBV genotype F.

19. The method of any one of embodiments 1-12, wherein the HBV genome comprises HBV genotype G.

20. The method of any one of embodiments 1-12, wherein the HBV genome comprises HBV genotype H.

21. The method of any one of embodiments 1-12, wherein the HBV genome comprises a sequence with at least 80%, at least 90%, at least 95%, at least 99%, or greater than 99% sequence identity to an HBV genome sequence provided herein.

22. The method of any one of embodiments 1-21, wherein the first target region is located in a region of the HBV genome within nucleotides 0-303 of an HBV genome provided herein.

23. The method of any one of embodiments 1-21, wherein the first target region is located within nucleotides 0-303 of SEQ ID NO: 1082.

24. The method of any one of embodiments 1-21, wherein the first target region is located within nucleotides 0-303 of SEQ ID NO: 1083.

25. The method of any one of embodiments 1-21, wherein the first target region is located in a region of the HBV genome within nucleotides 1000-2448 of an HBV genome provided herein.

26. The method of any one of embodiments 1-21, wherein the first target region is located within nucleotides 1000-2448 of SEQ ID NO: 1082.

27. The method of any one of embodiments 1-21, wherein the first target region is located within nucleotides 1000-2448 of SEQ ID NO: 1083.

28. The method of any one of embodiments 1-21, wherein the first target region is located in a region of the HBV genome within nucleotides 2802-3182 of an HBV genome provided herein.

29. The method of any one of embodiments 1-21, wherein the first target region is located within nucleotides 2802-3182 of SEQ ID NO: 1082.

30. The method of any one of embodiments 1-21, wherein the first target region is located within nucleotides 2802-3182 of SEQ ID NO: 1083.

31. The method of any one of embodiments 1-21, wherein the first target region of the HBV genome is located in an HBV CpG island (CGI).

32. The method of embodiment 31, wherein the CGI is an HBV canonical CGI.

33. The method of embodiment 31, wherein the CGI is canonical CGI-I.

34. The method of embodiment 31, wherein the CGI is canonical CGI-I of HBV genotype D.

35. The method of embodiment 33, wherein CGI-I spans nucleotides 186-288 of SEQ ID NO: 1082.

36. The method of embodiment 33, wherein CGI-I spans nucleotides 186-288 of SEQ ID NO: 1083.

37. The method of embodiment 31, wherein the CGI is canonical CGI-II.

38. The method of embodiment 31, wherein the CGI is canonical CGI-II HBV genotype D.

39. The method of embodiment 38, wherein the CGI is CGI II spans nucleotides 1,217-1,670 of SEQ ID NO: 1082.

40. The method of embodiment 38, wherein the CGI is CGI II spans nucleotides 1,217-1,670 of SEQ ID NO: 1083.

41. The method of embodiment 31, wherein the CGI is canonical CGI-III.

42. The method of embodiment 31, wherein the CGI is canonical CGI-III HBV genotype D.

43. The method of embodiment 42, wherein the CGI is CGI-III spans nucleotides 2,282-2,448 of SEQ ID NO: 1082.

44. The method of embodiment 42, wherein the CGI is CGI-III spans nucleotides 2,282-2,448 of SEQ ID NO: 1083.

45. The method of any one of embodiments 1-21, wherein the first target region of the HBV genome is located in a promotor.

46. The method of embodiment 45, wherein the first target region of the HBV genome is located in the sp1 promoter.

47. The method of embodiment 45, wherein the first target region of the HBV genome is located in sp2 promoter.

48. The method of embodiment 45, wherein the first target region of the HBV genome is located in cp promoter.

49. The method of embodiment 45, wherein the first target region of the HBV genome is located in xp promoter.

50. The method of any one of embodiments 1-21, wherein the first target region of the HBV genome is located in an enhancer region.

51. The method of embodiment 50, wherein the first target region of the HBV genome is located in Enh I.

52. The method of embodiment 50, wherein the first target region of the HBV genome is located in Enh II.

53. The method of any one of embodiments 1-21, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes a transcript.

54. The method of embodiment 53, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes a pgRNA transcript.

55. The method of embodiment 53, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes a preCore RNA transcript.

56. The method of embodiment 53, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes a preS RNA transcript.

57. The method of embodiment 53, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes an S RNA transcript.

58. The method of embodiment 53, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes an HBx RNA transcript.

59. The method of any one of embodiments 1-21, wherein the first target region of the HBV genome is within 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) of an HBV transcription start site (TSS).

60. The method of embodiment 59, wherein the TSS is a pg RNA TSS.

61. The method of embodiment 60, wherein the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the pg RNA TSS.

62. The method of embodiment 60, wherein the pg RNA TSS is located at nucleotide 1820 of SEQ ID NO: 1082 or at nucleotide 1820 of SEQ ID NO: 1083.

63. The method of embodiment 60, wherein the first target region is within 600 base pairs of nucleotide 1820 in SEQ ID NO: 1082.

64. The method of embodiment 60, wherein the first target region is within 600 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

65. The method of embodiment 60, wherein the first target region is within 500 base pairs of nucleotide 1820 in SEQ ID NO: 1082.

66. The method of embodiment 60, wherein the first target region is within 500 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

67. The method of embodiment 60, wherein the first target region is within 400 base pairs of nucleotide 1820 in SEQ ID NO: 1082.

68. The method of embodiment 60, wherein the first target region is within 400 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

69. The method of embodiment 60, wherein the first target region is within 300 base pairs of nucleotide 1820 in SEQ ID NO: 1082.

70. The method of embodiment 60, wherein the first target region is within 300 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

71. The method of embodiment 60, wherein the first target region is within 200 base pairs of nucleotide 1820 in SEQ ID NO: 1082.

72. The method of embodiment 60, wherein the first target region is within 200 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

73. The method of embodiment 60, wherein the first target region is within 100 base pairs of nucleotide 1820 in SEQ ID NO: 1082 or wherein the first target region is within 100 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

74. The method of embodiment 59, wherein the TSS is a preC RNA TSS.

75. The method of embodiment 74, wherein the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the preC RNA TSS.

76. The method of embodiment 74, wherein the preC RNA TSS is located at nucleotide 1791 of SEQ ID NO: 1082 or at nucleotide 1791 of SEQ ID NO: 1083.

77. The method of embodiment 74, wherein the first target region is within 600 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

78. The method of embodiment 74, wherein the first target region is within 600 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

79. The method of embodiment 74, wherein the first target region is within 500 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

80. The method of embodiment 74, wherein the first target region is within 500 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

81. The method of embodiment 74, wherein the first target region is within 400 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

82. The method of embodiment 74, wherein the first target region is within 400 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

83. The method of embodiment 74, wherein the first target region is within 300 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

84. The method of embodiment 74, wherein the first target region is within 300 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

85. The method of embodiment 74, wherein the first target region is within 200 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

86. The method of embodiment 74, wherein the first target region is within 200 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

87. The method of embodiment 74, wherein the first target region is within 100 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

88. The method of embodiment 74, wherein the first target region is within 100 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

89. The method of embodiment 59, wherein the TSS is a preS2 RNA TSS.

90. The method of embodiment 89, wherein the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the preS2 RNA TSS.

91. The method of embodiment 89, wherein the preS2 RNA TSS is located at nucleotide 3159 of SEQ ID NO: 1082 or at nucleotide 3159 of SEQ ID NO: 1083.

92. The method of embodiment 89, wherein the first target region is within 600 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

93. The method of embodiment 89, wherein the first target region is within 600 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

94. The method of embodiment 89, wherein the first target region is within 500 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

95. The method of embodiment 89, wherein the first target region is within 500 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

96. The method of embodiment 89, wherein the first target region is within 400 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

97. The method of embodiment 89, wherein the first target region is within 400 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

98. The method of embodiment 89, wherein the first target region is within 300 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

99. The method of embodiment 89, wherein the first target region is within 300 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

100. The method of embodiment 89, wherein the first target region is within 200 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

101. The method of embodiment 89, wherein the first target region is within 200 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

102. The method of embodiment 89, wherein the first target region is within 100 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

103. The method of embodiment 89, wherein the first target region is within 100 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

104. The method of embodiment 89, wherein the TSS is an HBx RNA TSSs.

105. The method of embodiment 104, wherein the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the HBx RNA TSS.

106. The method of embodiment 105, wherein the HBx RNA TSS is located at a nucleotide within the sequence of nucleotides 1243-1338 of SEQ ID NO: 1082 or nucleotides 1243-1338 of SEQ ID NO: 1083.

107. The method of embodiment 105, wherein the first target region is within 600 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

108. The method of embodiment 105, wherein the first target region is within 600 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

109. The method of embodiment 105, wherein the first target region is within 500 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

110. The method of embodiment 105, wherein the first target region is within 500 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

111. The method of embodiment 105, wherein the first target region is within 400 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

112. The method of embodiment 105, wherein the first target region is within 400 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

113. The method of embodiment 105, wherein the first target region is within 300 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

114. The method of embodiment 105, wherein the first target region is within 300 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

115. The method of embodiment 105, wherein the first target region is within 200 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

116. The method of embodiment 105, wherein the first target region is within 200 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

117. The method of embodiment 105, wherein the first target region is within 100 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

118. The method of embodiment 105, wherein the first target region is within 100 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

119. The method of embodiment 105, wherein the first target region is within 600 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

120. The method of embodiment 105, wherein the first target region is within 500 base pairs of nucleotide 1338 in SEQ ID NO: 1082.

121. The method of embodiment 105, wherein the first target region is within 500 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

122. The method of embodiment 105, wherein the first target region is within 400 base pairs of nucleotide 1338 in SEQ ID NO: 1082.

123. The method of embodiment 105, wherein the first target region is within 400 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

124. The method of embodiment 105, wherein the first target region is within 300 base pairs of nucleotide 1338 in SEQ ID NO: 1082.

125. The method of embodiment 105, wherein the first target region is within 300 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

126. The method of embodiment 105, wherein the first target region is within 200 base pairs of nucleotide 1338 in SEQ ID NO: 1082.

127. The method of embodiment 105, wherein the first target region is within 200 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

128. The method of embodiment 105, wherein the first target region is within 100 base pairs of nucleotide 1338 in SEQ ID NO: 1082.

129. The method of embodiment 105, wherein the first target region is within 100 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

130. The method of any one of embodiments 1-129, wherein the reduction is a reduction in the number of HBV viral episomes.

131. The method of embodiment 130, wherein the reduction is a reduction in the number of cccDNA genomes.

132. The method of embodiment 130, wherein the reduction is a reduction in total HBV DNA.

133. The method of any one of embodiments 1-129, wherein the reduction is a reduction in the replication of the HBV genome.

134. The method of any one of embodiments 1-129, wherein the reduction is a reduction in a level of expression of a protein product encoded by the HBV genome.

135. The method of embodiment 130, wherein the reduction is a reduction in a level of HBsAg.

136. The method of embodiment 130, wherein the reduction is a reduction in a level of HBeAg.

137. The method of any one of embodiments 1-129, wherein the reduction is a reduction of total HBV DNA of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and wherein the reduction is maintained for at least 14 days after the contacting or the administering.

138. The method of any one of embodiments 1-129, wherein the reduction is a reduction of HBeAg of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and wherein the reduction is maintained for at least 14 days after the contacting or the administering.

139. The method of any one of embodiments 1-129, wherein the reduction is a reduction of HBsAg of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and wherein the reduction is maintained at or below that level for at least 14 days after the contacting or the administering.

140. The method of any one of embodiments 137-139, wherein the reduction is a reduction of at least 90%.

141. The method of any one of embodiments 137-139, wherein the reduction is a reduction of at least 95%.

142. The method of any one of embodiments 137-139, wherein the reduction is a reduction of at least 99%.

143. The method of any one of embodiments 137-139, wherein the reduction is a reduction of at least 99.9%.

144. The method of any one of embodiments 140-143, wherein the reduction is maintained for at least 14 days after the contacting or the administering.

145. The method of embodiment 144, wherein the reduction is maintained for at least 21 days.

146. The method of embodiment 144, wherein the reduction is maintained for at least 28 days.

147. The method of embodiment 144, wherein the reduction is maintained for at least 35 days.

148. The method of embodiment 144, wherein the reduction is maintained for at least 42 days.

149. The method of embodiment 144, wherein the reduction is maintained for at least 56 days.

150. The method of embodiment 144, wherein the reduction is maintained for at least 70 days.

151. The method of embodiment 144, wherein the reduction is maintained for at least 84 days.

152. The method of embodiment 144, wherein the reduction is maintained for at least 112 days.

153. The method of embodiment 144, wherein the reduction is maintained for at least 140 days.

154. The method of embodiment 144, wherein the reduction is maintained for at least 168 days.

155. The method of embodiment 144, wherein the reduction is maintained for at least 6 months.

156. The method of embodiment 144, wherein the reduction is maintained for at least 7 months.

157. The method of embodiment 144, wherein the reduction is maintained for at least 8 months.

158. The method of embodiment 144, wherein the reduction is maintained for at least 9 months.

159. The method of embodiment 144, wherein the reduction is maintained for at least 12 months.

160. The method of embodiment 144, wherein the reduction is maintained for at least 18 months.

161. The method of embodiment 144, wherein the reduction is maintained for at least 24 months.

162. The method of any one of embodiments 1-161, wherein the method does not comprise contacting the HBV gene or genome with a nucleoside or nucleotide analog (NUC) or wherein the method does not comprise administering a NUC to the subject.

163. The method of any one of embodiments 1-162, wherein the method further comprises contacting the HBV gene or genome with a nucleoside or nucleotide analog (NUC) or wherein the method further comprises administering a NUC to the subject.

164. The method of any one of embodiments 1-163, wherein the first DNA binding domain comprises a CRISPR-Cas protein.

165. The method of embodiment 164, wherein the epigenetic editing system further comprises a first guide RNA (gRNA) that comprises a region complementary to a strand of the first target region.

166. The method of embodiment 165, wherein the gRNA comprises a sequence selected from a gRNA provided herein, preferably wherein the gRNA comprises a sequence provided in Table 12 or 13.

167. The method of any one of embodiments 1-164, wherein the first DNA binding domain comprises a zinc-finger protein.

168. The method of embodiment 167, wherein the zinc-finger protein comprises a zinc-finger motif with a sequence selected from any zinc finger or zinc finger motif provided herein, e.g., in Table 1 or Table 18.

169. The method of embodiment 167 or 168, wherein the zinc-finger protein comprises a sequence of any of the zinc finger epigenetic repressors provided herein.

170. The method of any one of embodiments 1-169, wherein the transcriptional repressor domain comprises ZIM3.

171. The method of any one of embodiments 1-170, wherein the first DNMT domain is a DNMT3A domain or a DNMT3L domain.

172. The method of embodiment 171, wherein the first DNMT domain comprises a sequence of a DNMT domain provided herein.

173. The method of any one of embodiments 1-172, wherein the epigenetic editing system further comprises a second DNMT domain or a nucleic acid encoding thereof.

174. The method of embodiment 173, wherein the second DNMT domain is a DNMT3A domain or a DNMT3L domain.

175. The method of embodiment 173 or 174, wherein the second DNMT domain comprises a sequence of a DNMT domain provided herein.

176. The method of any one of embodiments 173-175, wherein the epigenetic editing system comprises a fusion protein or a nucleic acid encoding thereof, and wherein the fusion protein comprises the first DNA binding domain, the first DNMT domain, the repressor domain and the second DNMT domain.

177. The method of embodiment 176, wherein the fusion protein further comprises a nuclear localization sequence (NLS).

178. The method of embodiment 177, wherein the fusion protein comprises a sequence of a fusion protein provided herein.

179. The method of any one of embodiments 1-178, wherein the epigenetic editing system further comprises a second DNA binding domain or a nucleic acid encoding a second DNA binding domain, wherein the second DNA binding domain binds a second target region of the HBV genome.

180. The method of embodiment 179, wherein the second target region is a target region recited in any of embodiments 22-129.

181. The method of embodiment 179 or 180, wherein the second DNA binding domain comprises a CRISPR-Cas protein.

182. The method of any one of embodiments 1-180, wherein the epigenetic editing system comprises at least one CRISPR-Cas DNA binding domain and at least two different gRNAs.

183. The method of embodiment 182, wherein the epigenetic editing system comprises a first gRNA binding the

first HBV target region and a second gRNA binding a second HBV target region, wherein the first and second target regions are not identical.

184. The method of embodiment 183, wherein the first gRNA comprises a gRNA sequence provided herein, e.g., a sequence provided in Table 12 or 13, and wherein the second gRNA comprises a different gRNA sequence provided herein, e.g., a sequence provided in Table 12 or 13.

185. The method of embodiment 179, wherein the second DNA binding domain comprises a zinc-finger protein.

186. The method of embodiment 185, wherein the zinc-finger protein of the second DNA binding domain comprises a zinc-finger motif with a sequence selected from a zinc finger motif sequence provided herein, e.g., a zinc finger motif provided in Table 1.

187. The method of embodiment 185 or 186, wherein the zinc-finger protein of the second DNA binding domain comprises a sequence of a zinc finger motif provided in Table 1.

188. The method of any one of embodiments 179-187, wherein the epigenetic editing system comprises a first fusion protein or a first nucleic acid encoding thereof and a second fusion protein or a second nucleic acid encoding thereof,

wherein the first fusion protein comprises the first DNA binding domain and the first DNMT domain, and

wherein the second fusion protein comprises the second DNA binding domain and the transcriptional repressor domain.

189. The method of embodiment 188, wherein the first fusion protein comprises a sequence of a fusion protein provided herein.

190. The method of embodiment 188 or 189, wherein the second fusion protein comprises a sequence of a fusion protein provided herein.

191. The method of any one of embodiments 179-190, wherein the epigenetic editing system further comprises a third DNA binding domain or a nucleic acid encoding a third DNA binding domain, wherein the third DNA binding domain binds to a third target region of the HBV genome, optionally, wherein the third DNA binding domain comprises a comprises at least one CRISPR-Cas DNA binding domain, optionally wherein the epigenetic editing system comprises a third gRNA comprising a sequence complementary to a strand of a third HBV target region, optionally wherein the third gRNA comprises a gRNA sequence provided herein, optionally, a gRNA sequence provided in Table 12 or 13, optionally, wherein the third DNA binding domain is comprised in a fusion protein comprising a DNMT domain and a transcriptional repressor domain, optionally, wherein the fusion protein is a fusion protein provided herein.

192. A method, comprising administering an epigenetic editing system to a subject,

wherein the subject is characterized by the presence of detectable levels of HBV DNA, HBsAg, and/or HBeAg in the plasma of the subject,

wherein the epigenetic editing system comprises a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding the same, wherein the first DNA binding domain binds a first target region of an HBV gene or genome,

wherein the administering results in a reduction of the level of HBV DNA, the level of HBsAg, and/or the level of HBsAg in the plasma of the subject,

wherein the reduction of the level of HBV DNA, of the level of HBsAg, and/or of the level of HBsAg in the plasma of the subject, is at least 90% (a 1-log reduction) compared to the respective level observed or observable in the plasma of the subject prior to the administering, and

wherein the 1-log reduction is maintained for at least 14 days after the administering.

193. The method of embodiment 192, wherein the reduction of the level of HBV DNA in the plasma of the subject is at least 90% (a 1-log reduction).

194. The method of embodiment 192, wherein the reduction of the level of HBV DNA in the plasma of the subject is at least 99% (a 2-log reduction).

195. The method of embodiment 192, wherein the reduction of the level of HBsAg in the plasma of the subject is at least 90% (a 1-log reduction).

196. The method of embodiment 192, wherein the reduction of the level of HBsAg in the plasma of the subject is at least 99% (a 2-log reduction).

197. The method of embodiment 192, wherein the reduction of the level of HBeAg in the plasma of the subject is at least 90% (a 1-log reduction).

198. The method of embodiment 192, wherein the reduction of the level of HBeAg in the plasma of the subject is at least 99% (a 2-log reduction).

199. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 21 days.

200. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 28 days.

201. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 35 days.

202. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 42 days.

203. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 56 days.

204. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 70 days.

205. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 84 days.

206. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 112 days.

207. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 140 days.

208. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 168 days.

209. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 6 months.

210. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 9 months.

211. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 12 months.

212. The method of any one of embodiments 192-198, wherein the reduction is maintained for at least 24 months.

213. The method of any one of embodiments 192-212, wherein the HBV genome comprises HBV genotype A.

214. The method of any one of embodiments 192-212, wherein the HBV genome comprises HBV genotype B.

215. The method of any one of embodiments 192-212, wherein the HBV genome comprises HBV genotype C.

216. The method of any one of embodiments 192-212, wherein the HBV genome comprises, HBV genotype D.

217. The method of any one of embodiments 192-212, wherein the HBV genome comprises HBV genotype E.

218. The method of any one of embodiments 192-212, wherein the HBV genome comprises HBV genotype F.

219. The method of any one of embodiments 192-212, wherein the HBV genome comprises HBV genotype G.

220. The method of any one of embodiments 192-212, wherein the HBV genome comprises HBV genotype H.

221. The method of any one of embodiments 192-212, wherein the HBV genome comprises a sequence with at least 80%, at least 90%, at least 95%, at least 99%, or greater than 99% sequence identity to an HBV genome sequence provided herein.

222. The method of any one of embodiments 192-221, wherein the first target region is located in a region of the HBV genome within nucleotides 0-303 of an HBV genome provided herein.

223. The method of any one of embodiments 192-221, wherein the first target region is located within nucleotides 0-303 of SEQ ID NO: 1082.

224. The method of any one of embodiments 192-221, wherein the first target region is located within nucleotides 0-303 of SEQ ID NO: 1083.

225. The method of any one of embodiments 192-221, wherein the first target region is located in a region of the HBV genome within nucleotides 1000-2448 of an HBV genome provided herein.

226. The method of any one of embodiments 192-221, wherein the first target region is located within nucleotides 1000-2448 of SEQ ID NO: 1082.

227. The method of any one of embodiments 192-221, wherein the first target region is located within nucleotides 1000-2448 of SEQ ID NO: 1083.

228. The method of any one of embodiments 192-221, wherein the first target region is located in a region of the HBV genome within nucleotides 2802-3182 of an HBV genome provided herein.

229. The method of any one of embodiments 192-221, wherein the first target region is located within nucleotides 2802-3182 of SEQ ID NO: 1082.

230. The method of any one of embodiments 192-221, wherein the first target region is located within nucleotides 2802-3182 of SEQ ID NO: 1083.

231. The method of any one of embodiments 192-221, wherein the first target region of the HBV genome is located in an HBV CpG island (CGI).

232. The method of embodiment 231, wherein the CGI is an HBV canonical CGI.

233. The method of embodiment 231, wherein the CGI is canonical CGI-I.

234. The method of embodiment 231, wherein the CGI is canonical CGI-I of HBV genotype D.

235. The method of embodiment 233, wherein CGI-I spans nucleotides 186-288 of SEQ ID NO: 1082.

236. The method of embodiment 233, wherein CGI-I spans nucleotides 186-288 of SEQ ID NO: 1083.

237. The method of embodiment 231, wherein the CGI is canonical CGI-II.

238. The method of embodiment 231, wherein the CGI is canonical CGI-II HBV genotype D.

239. The method of embodiment 238, wherein the CGI is CGI II spans nucleotides 1,217-1,670 of SEQ ID NO: 1082.

240. The method of embodiment 238, wherein the CGI is CGI II spans nucleotides 1,217-1,670 of SEQ ID NO: 1083.

241. The method of embodiment 231, wherein the CGI is canonical CGI-III.

242. The method of embodiment 231, wherein the CGI is canonical CGI-III HBV genotype D.

243. The method of embodiment 242, wherein the CGI is CGI-III spans nucleotides 2,282-2,448 of SEQ ID NO: 1082.

244. The method of embodiment 242, wherein the CGI is CGI-III spans nucleotides 2,282-2,448 of SEQ ID NO: 1083.

245. The method of any one of embodiments 192-221, wherein the first target region of the HBV genome is located in a promotor.

246. The method of embodiment 245, wherein the first target region of the HBV genome is located in the sp1 promoter.

247. The method of embodiment 245, wherein the first target region of the HBV genome is located in sp2 promoter.

248. The method of embodiment 245, wherein the first target region of the HBV genome is located in cp promoter.

249. The method of embodiment 245, wherein the first target region of the HBV genome is located in xp promoter.

250. The method of any one of embodiments 192-221, wherein the first target region of the HBV genome is located in an enhancer region.

251. The method of embodiment 250, wherein the first target region of the HBV genome is located in Enh I.

252. The method of embodiment 250, wherein the first target region of the HBV genome is located in Enh II.

253. The method of any one of embodiments 192-221, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes a transcript.

254. The method of embodiment 253, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes a pgRNA transcript.

255. The method of embodiment 253, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes a preCore RNA transcript.

256. The method of embodiment 253, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes a preS RNA transcript.

257. The method of embodiment 253, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes an S RNA transcript.

258. The method of embodiment 253, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes an HBx RNA transcript.

259. The method of any one of embodiments 192-221, wherein the first target region of the HBV genome is within 1000, 900, 800, 700, 600, 500, 400, 300, 200, or 100 base pairs (bp) of an HBV transcription start site (TSS).

260. The method of embodiment 259, wherein the TSS is a pg RNA TSS.

261. The method of embodiment 260, wherein the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the pg RNA TSS.

262. The method of embodiment 260, wherein the pg RNA TSS is located at nucleotide 1820 of SEQ ID NO: 1082 or at nucleotide 1820 of SEQ ID NO: 1083.

263. The method of embodiment 260, wherein the first target region is within 600 base pairs of nucleotide 1820 in SEQ ID NO: 1082.

264. The method of embodiment 260, wherein the first target region is within 600 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

265. The method of embodiment 260, wherein the first target region is within 500 base pairs of nucleotide 1820 in SEQ ID NO: 1082.

266. The method of embodiment 260, wherein the first target region is within 500 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

267. The method of embodiment 260, wherein the first target region is within 400 base pairs of nucleotide 1820 in SEQ ID NO: 1082.

268. The method of embodiment 260, wherein the first target region is within 400 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

269. The method of embodiment 260, wherein the first target region is within 300 base pairs of nucleotide 1820 in SEQ ID NO: 1082.

270. The method of embodiment 260, wherein the first target region is within 300 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

271. The method of embodiment 260, wherein the first target region is within 200 base pairs of nucleotide 1820 in SEQ ID NO: 1082.

272. The method of embodiment 260, wherein the first target region is within 200 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

273. The method of embodiment 260, wherein the first target region is within 100 base pairs of nucleotide 1820 in SEQ ID NO: 1082 or wherein the first target region is within 100 base pairs of nucleotide 1820 in SEQ ID NO: 1083.

274. The method of embodiment 259, wherein the TSS is a preC RNA TSS.

275. The method of embodiment 274, wherein the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the preC RNA TSS.

276. The method of embodiment 274, wherein the preC RNA TSS is located at nucleotide 1791 of SEQ ID NO: 1082 or at nucleotide 1791 of SEQ ID NO: 1083.

277. The method of embodiment 274, wherein the first target region is within 600 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

278. The method of embodiment 274, wherein the first target region is within 600 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

279. The method of embodiment 274, wherein the first target region is within 500 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

280. The method of embodiment 274, wherein the first target region is within 500 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

281. The method of embodiment 274, wherein the first target region is within 400 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

282. The method of embodiment 274, wherein the first target region is within 400 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

283. The method of embodiment 274, wherein the first target region is within 300 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

284. The method of embodiment 274, wherein the first target region is within 300 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

285. The method of embodiment 274, wherein the first target region is within 200 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

286. The method of embodiment 274, wherein the first target region is within 200 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

287. The method of embodiment 274, wherein the first target region is within 100 base pairs of nucleotide 1791 in SEQ ID NO: 1082.

288. The method of embodiment 274, wherein the first target region is within 100 base pairs of nucleotide 1791 in SEQ ID NO: 1083.

289. The method of embodiment 259, wherein the TSS is a preS2 RNA TSS. 290. The method of embodiment 289, wherein the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the preS2 RNA TSS. 291. The method of embodiment 289, wherein the preS2 RNA TSS is located at nucleotide 3159 of SEQ ID NO: 1082 or at nucleotide 3159 of SEQ ID NO: 1083.

292. The method of embodiment 289, wherein the first target region is within 600 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

293. The method of embodiment 289, wherein the first target region is within 600 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

294. The method of embodiment 289, wherein the first target region is within 500 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

295. The method of embodiment 289, wherein the first target region is within 500 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

296. The method of embodiment 289, wherein the first target region is within 400 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

297. The method of embodiment 289, wherein the first target region is within 400 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

298. The method of embodiment 289, wherein the first target region is within 300 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

299. The method of embodiment 289, wherein the first target region is within 300 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

300. The method of embodiment 289, wherein the first target region is within 200 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

301. The method of embodiment 289, wherein the first target region is within 200 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

302. The method of embodiment 289, wherein the first target region is within 100 base pairs of nucleotide 3159 in SEQ ID NO: 1082.

303. The method of embodiment 289, wherein the first target region is within 100 base pairs of nucleotide 3159 in SEQ ID NO: 1083.

304. The method of embodiment 259, wherein the TSS is an HBx RNA TSSs.

305. The method of embodiment 304, wherein the first target region is within 600, within 500, within 400, within 300, within 200, or within 100 base pairs of the HBx RNA TSS.

306. The method of embodiment 304, wherein the HBx RNA TSS is located at a nucleotide within the sequence of nucleotides 1243-1338 of SEQ ID NO: 1082 or nucleotides 1243-1338 of SEQ ID NO: 1083.

307. The method of embodiment 304, wherein the first target region is within 600 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

308. The method of embodiment 304, wherein the first target region is within 600 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

309. The method of embodiment 304, wherein the first target region is within 500 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

310. The method of embodiment 304, wherein the first target region is within 500 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

311. The method of embodiment 304, wherein the first target region is within 400 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

312. The method of embodiment 304, wherein the first target region is within 400 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

313. The method of embodiment 304, wherein the first target region is within 300 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

314. The method of embodiment 304, wherein the first target region is within 300 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

315. The method of embodiment 304, wherein the first target region is within 200 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

316. The method of embodiment 304, wherein the first target region is within 200 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

317. The method of embodiment 304, wherein the first target region is within 100 base pairs of nucleotide 1243 in SEQ ID NO: 1082.

318. The method of embodiment 304, wherein the first target region is within 100 base pairs of nucleotide 1243 in SEQ ID NO: 1083.

319. The method of embodiment 304, wherein the first target region is within 600 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

320. The method of embodiment 304, wherein the first target region is within 500 base pairs of nucleotide 1338 in SEQ ID NO: 1082.

321. The method of embodiment 304, wherein the first target region is within 500 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

322. The method of embodiment 304, wherein the first target region is within 400 base pairs of nucleotide 1338 in SEQ ID NO: 1082.

323. The method of embodiment 304, wherein the first target region is within 400 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

324. The method of embodiment 304, wherein the first target region is within 300 base pairs of nucleotide 1338 in SEQ ID NO: 1082.

325. The method of embodiment 304, wherein the first target region is within 300 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

326. The method of embodiment 304, wherein the first target region is within 200 base pairs of nucleotide 1338 in SEQ ID NO: 1082.

327. The method of embodiment 304, wherein the first target region is within 200 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

328. The method of embodiment 304, wherein the first target region is within 100 base pairs of nucleotide 1338 in SEQ ID NO: 1082.

329. The method of embodiment 304, wherein the first target region is within 100 base pairs of nucleotide 1338 in SEQ ID NO: 1083.

330. The method of any one of embodiments 192-329, wherein the reduction is a reduction in the number of HBV viral episomes.

331. The method of embodiment 330, wherein the reduction is a reduction in the number of cccDNA genomes.

332. The method of embodiment 330, wherein the reduction is a reduction in total HBV DNA.

333. The method of any one of embodiments 192-329, wherein the reduction is a reduction in the replication of the HBV genome.

334. The method of any one of embodiments 192-329, wherein the reduction is a reduction in a level of expression of a protein product encoded by the HBV genome.

335. The method of embodiment 330, wherein the reduction is a reduction in a level of HBsAg.

336. The method of embodiment 330, wherein the reduction is a reduction in a level of HBeAg.

337. The method of any one of embodiments 192-329, wherein the reduction is a reduction of total HBV DNA of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and wherein the reduction is maintained for at least 14 days after the contacting or the administering.

338. The method of any one of embodiments 192-329, wherein the reduction is a reduction of HBeAg of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and wherein the reduction is maintained for at least 14 days after the contacting or the administering.

339. The method of any one of embodiments 192-329, wherein the reduction is a reduction of HBsAg of at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, or at least 99.9%, and wherein the reduction is maintained at or below that level for at least 14 days after the contacting or the administering.

340. The method of any one of embodiments 337-339, wherein the reduction is a reduction of at least 90%.

341. The method of any one of embodiments 337-339, wherein the reduction is a reduction of at least 95%.

342. The method of any one of embodiments 337-339, wherein the reduction is a reduction of at least 99%.

343. The method of any one of embodiments 337-339, wherein the reduction is a reduction of at least 99.9%.

344. The method of any one of embodiments 340-343, wherein the reduction is maintained for at least 14 days after the contacting or the administering.

345. The method of embodiment 344, wherein the reduction is maintained for at least 21 days.

346. The method of embodiment 344, wherein the reduction is maintained for at least 28 days.

347. The method of embodiment 344, wherein the reduction is maintained for at least 35 days.

348. The method of embodiment 344, wherein the reduction is maintained for at least 42 days.

349. The method of embodiment 344, wherein the reduction is maintained for at least 56 days.

350. The method of embodiment 344, wherein the reduction is maintained for at least 70 days.

351. The method of embodiment 344, wherein the reduction is maintained for at least 84 days.

352. The method of embodiment 344, wherein the reduction is maintained for at least 112 days.

353. The method of embodiment 344, wherein the reduction is maintained for at least 140 days.

354. The method of embodiment 344, wherein the reduction is maintained for at least 168 days.

355. The method of embodiment 344, wherein the reduction is maintained for at least 6 months.

356. The method of embodiment 344, wherein the reduction is maintained for at least 7 months.

357. The method of embodiment 344, wherein the reduction is maintained for at least 8 months.

358. The method of embodiment 344, wherein the reduction is maintained for at least 9 months.

359. The method of embodiment 344, wherein the reduction is maintained for at least 12 months.

360. The method of embodiment 344, wherein the reduction is maintained for at least 18 months.

361. The method of embodiment 344, wherein the reduction is maintained for at least 24 months.

362. The method of any one of embodiments 192-361, wherein the method does not comprise contacting the HBV gene or genome with a nucleoside or nucleotide analog (NUC) or wherein the method does not comprise administering a NUC to the subject.

363. The method of any one of embodiments 192-362, wherein the method further comprises contacting the HBV gene or genome with a nucleoside or nucleotide analog (NUC) or wherein the method further comprises administering a NUC to the subject.

364. The method of any one of embodiments 192-363, wherein the first DNA binding domain comprises a CRISPR-Cas protein.

365. The method of embodiment 364, wherein the epigenetic editing system further comprises a first guide RNA (gRNA) that comprises a region complementary to a strand of the first target region.

366. The method of embodiment 365, wherein the gRNA comprises a sequence selected from a gRNA provided herein, preferably wherein the gRNA comprises a sequence provided in Table 12 or 13.

367. The method of any one of embodiments 192-364, wherein the first DNA binding domain comprises a zinc-finger protein.

368. The method of embodiment 367, wherein the zinc-finger protein comprises a zinc-finger motif with a sequence selected from any zinc finger or zinc finger motif provided herein, e.g., in Table 1 or Table 18.

369. The method of embodiment 367 or 368, wherein the zinc-finger protein comprises a sequence of any of the zinc finger epigenetic repressors provided herein.

370. The method of any one of embodiments 192-369, wherein the transcriptional repressor domain comprises ZIM3.

371. The method of any one of embodiments 192-370, wherein the first DNMT domain is a DNMT3A domain or a DNMT3L domain.

372. The method of embodiment 371, wherein the first DNMT domain comprises a sequence of a DNMT domain provided herein.

373. The method of any one of embodiments 1-372, wherein the epigenetic editing system comprises the fusion protein provided in SEQ ID NO: 1248 or the fusion protein provided in SEQ ID NO: 1252 and at least one guide RNA, wherein the guide RNA is the guide RNA provided as gRNA #003, gRNA #007, gRNA #008, gRNA #009, gRNA #011, or gRNA #015 herein.

374. An epigenetic editing system for use in the method of any one of embodiments 1-373, comprising:

a fusion protein or a nucleic acid encoding the fusion protein,

wherein the fusion protein comprises:

(a) a DNA-binding domain that binds a target region of a HBV gene or genome,

(b) a first DNA methyltransferase (DNMT) domain, and

(c) a transcriptional repressor domain.

375. The epigenetic editing system of embodiment 374, wherein the fusion protein comprises a sequence of a fusion protein provided herein.

376. The epigenetic editing system of embodiment 374 or 375, wherein the DNA-binding domain is a CRISPR-Cas DNA binding domain, and wherein the epigenetic editing system comprises at least gRNA provided herein.

377. The epigenetic editing system of embodiment 374, wherein the epigenetic editing system comprises the fusion protein provided in SEQ ID NO: 1248 or the fusion protein provided in SEQ ID NO: 1252 and at least one guide RNA, wherein the guide RNA is the guide RNA provided as gRNA #003, gRNA #007, gRNA #008, gRNA #009, gRNA #011, or gRNA #015 herein.

378. An epigenetic editing system comprising:

1. a first fusion protein or a nucleic acid encoding the first fusion protein, wherein the first fusion protein comprises a first DNA binding domain and a first DNMT domain, wherein the first DNA binding domain binds a first target region of a HBV genome, and
2. a second fusion protein or a nucleic acid encoding the second fusion protein, wherein the second fusion protein comprises a second DNA binding domain and a transcriptional repressor domain, wherein the second DNA binding domain binds a second target region of the HBV genome.

379. The epigenetic system of embodiment 378, wherein the epigenetic editing system is capable of reducing a number of the HBV viral episome, replication of the HBV, or expression of a gene product encoded by the HBV genome, wherein said reduction is at least about 20% compared to contacting the HBV genome with a suitable control.

380. The epigenetic system of embodiment 378 or 379, wherein the HBV genome is a covalently closed circular DNA (cccDNA) or an HBV integrated DNA.

381. The epigenetic system of embodiments 378-380, wherein the HBV genome comprises HBV genotype A, HBV genotype B, HBV genotype C, HBV genotype D, HBV genotype E, HBV genotype F, HBV genotype G or HBV genotype H.

382. The epigenetic system of embodiments 378-381, wherein the HBV genome comprises a sequence with at least 80% identity to an HBV genome provided herein.

383. The epigenetic system of embodiments 378-381, further comprising a third fusion protein or a nucleic acid encoding the third fusion protein, wherein the third fusion protein comprises a third DNA binding domain and a second DNMT domain, wherein the third DNA binding domain binds a third target region of the HBV genome.

384. The epigenetic system of embodiment 383, wherein the first target region, the second target region or the third target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182 of an HBV genome provided herein.

385. The epigenetic system of embodiment 383, wherein the first target region, the second target region or the third target region of the HBV genome is located in a CpG island.

386. The epigenetic system of embodiment 383, wherein the first target region, the second target region or the third target region of the HBV genome is located in a promotor.

387. The epigenetic system of embodiment 383, wherein the first target region, the second target region or the third target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a precure mRNA, a preS mRNA, a S mRNA, and a X mRNA.

388. The epigenetic system of embodiment 383, wherein the first DNA binding domain, the second DNA binding domain or the third DNA binding domain comprises a CRISPR-Cas protein.

389. The epigenetic system of embodiment 388, wherein the epigenetic editing system further comprises a first gRNA that comprises a region complementary to a strand of the

first target region, a second gRNA that comprises a region complementary to a strand of the second target region or a third RNA that comprises a region complementary to a strand of the third target region.

390. The epigenetic system of embodiment 389, wherein the first gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., provided in Table 12 or 13, the second gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., provided in Table 12 or 13, and/or the third gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., provided in Table 12 or 13.

391. The epigenetic system of embodiment 383, wherein the first DNA binding domain, the second DNA binding domain or the third DNA binding domain comprises a zinc-finger protein.

392. The epigenetic system of embodiment 391, wherein the zinc-finger protein comprises a zinc-finger motif with a sequence selected from a zinc finger motif provided herein.

393. The epigenetic system of embodiment 391 or 392, wherein the zinc-finger protein comprises a sequence of a zinc finger motif provided in Table 1.

394. The epigenetic system of embodiments 378-393, wherein the transcriptional repressor domain comprises ZIM3.

395. The epigenetic system of embodiments 378-394, wherein the first DNMT domain is a DNMT3A domain or a DNMT3L domain.

396. The epigenetic system of embodiment 395, wherein the first DNMT domain comprises a sequence of a DNMT provided herein.

397. The epigenetic system of embodiment 383, wherein the second DNMT domain is a DNMT3A domain or a DNMT3L domain.

398. The epigenetic system of embodiment 397, wherein the second DNMT domain comprises a sequence of a DNMT domain provided herein.

399. The epigenetic system of embodiment 378-398, wherein the first fusion protein comprises a sequence of a fusion protein provided herein.

400. The epigenetic system of embodiments 378-399, wherein the second fusion protein comprises a sequence of a fusion protein provided herein.

401. The epigenetic system of embodiments 383-399, wherein the third fusion protein comprises a sequence of a fusion protein provided herein.

402. The method of any one of embodiments 1-401, wherein the epigenetic editing system comprises a nucleic acid sequence provided in Table 18.

LISTING #2 of Exemplary Embodiments:

1. A method of modifying an epigenetic state of a hepatitis B virus (HBV) gene or genome, comprising contacting the HBV gene or genome with an epigenetic editing system,
   wherein the epigenetic editing system comprises
   a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or
   one or more nucleic acid molecules encoding thereof, and
   wherein the contacting results in a reduction of:
   number of HBV viral episomes,
   replication of the HBV gene or genome, or
   expression of a protein product encoded by the HBV gene or genome,
   wherein the reduction is at least about 20% compared to contacting the HBV gene or genome with a suitable control or without contacting the HBV gene or genome with the epigenetic editing system.

2. A method of treating an HBV infection in a subject comprising administering an epigenetic editing system to the subject,
   wherein the epigenetic editing system comprises
   a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or
   one or more nucleic acid molecules encoding thereof, and
   wherein the administering results in a reduction of:
   number of HBV viral episomes,
   replication of the HBV gene or genome, or
   expression of a protein product encoded by an HBV gene or genome,
   wherein the reduction is at least about 20% compared to administering a suitable control or without administering the epigenetic editing system.

3. A method of modulating expression of an HBV gene or genome comprising contacting the HBV gene or genome with an epigenetic editing system,
   wherein the epigenetic editing system comprises
   a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or
   one or more nucleic acid molecules encoding thereof, and
   wherein the contacting results in a reduction of expression of a gene product encoded by the HBV gene or genome, optionally, wherein the gene product is a nucleic acid or a protein,
   wherein the reduction is at least about 20% compared to contacting the HBV gene or genome with a suitable control or without contacting the HBV gene or genome with the epigenetic editing system.

4. A method of inhibiting viral replication in a cell infected with an HBV comprising contacting the cell with an epigenetic editing system,
   wherein the epigenetic editing system comprises
   a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof,
   wherein the epigenetic editing system targets a target region of an HBV gene or genome, and
   wherein the contacting results in a reduction of number of HBV viral episomes or replication of the HBV gene or genome,
   wherein the reduction is at least about 20% compared to contacting the cell with a suitable control or without contacting the cell with the epigenetic editing system.

5. A method of inhibiting viral replication in a subject infected with an HBV comprising administering an epigenetic editing system to the subject,
   wherein the epigenetic editing system comprises
   a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof,
   wherein the epigenetic editing system targets a target region of the HBV gene or genome, and
   wherein the administering results in a reduction of
   number of HBV viral episomes,
   replication of the HBV gene or genome, or
   expression of a protein product encoded by an HBV gene or genome,
   wherein the reduction is at least about 20% compared to administering a suitable control or without administering the epigenetic editing system.

6. The method of embodiment 2 or 5, wherein the reduction is at least about 30%, about 40%, about 50%, about 60% or about 70% compared to administering the suitable control.

7. The method of any one of embodiments 1, and 3-4, wherein the reduction is at least about 30%, about 40%, about 50%, about 60% or about 70% compared to contacting with the suitable control.

8. The method of any one of embodiments 1-7, wherein the reduction is maintained for at least 6 days, 19 days, 27 days, 42 days, or 168 days.

9. The method of embodiment 4, wherein the contacting further results in a reduction of a protein product.

10. The method of embodiment 5, wherein the administering further results in a reduction of a protein product.

11. The method of any one of embodiments 1-2 and 9-10, wherein the protein product comprises a HBe antigen.

12. The method of any one of embodiments 1-2 and 9-10, wherein the protein produce comprises a HBs antigen.

13. The method of any one of embodiments 1-12, wherein the HBV genome is a covalently closed circular DNA (cccDNA) or an HBV integrated DNA.

14. The method of any one of embodiments 1-13, wherein the HBV genome comprises HBV genotype A, HBV genotype B, HBV genotype C, HBV genotype D, HBV genotype E, HBV genotype F, HBV genotype G or HBV genotype H.

15. The method of any one of embodiments 1-14, wherein the HBV genome comprises a sequence with at least 80% identity to an HBV genome sequence provided herein.

16. The method of embodiment 15, wherein the first target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182 of an HBV genome provided herein.

17. The method of any one of embodiments 1-15, wherein the first target region of the HBV genome is located in a CpG island.

18. The method of any one of embodiments 1-15, wherein the first target region of the HBV genome is located in a promotor.

19. The method of any one of embodiments 1-15, wherein the first target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a precure mRNA, a preS mRNA, a S mRNA, and a X mRNA.

20. The method of any one of embodiments 1-19, wherein the first DNA binding domain comprises a CRISPR-Cas protein.

21. The method of any one of embodiments 1-20, wherein the epigenetic editing system further comprises a first guide RNA (gRNA) that comprises a region complementary to a strand of the first target region.

22. The method of embodiment 21, wherein the gRNA comprises a sequence selected from a gRNA provided herein, e.g., in Table 12 and/or 13.

23. The method of any one of embodiments 1-19, wherein the first DNA binding domain comprises a zinc-finger protein.

24. The method of embodiment 23, wherein the zinc-finger protein comprises a zinc-finger motif with a sequence selected from any zinc finger or zinc finger motif provided herein, e.g., in Table 1 or Table 18.

25. The method of embodiment 23 or 24, wherein the zinc-finger protein comprises a sequence of any of the zinc finger epigenetic repressors provided herein.

26. The method of any one of embodiments 1-25, wherein the transcriptional repressor domain comprises ZIM3.

27. The method of any one of embodiments 1-26, wherein the first DNMT domain is a DNMT3A domain or a DNMT3L domain.

28. The method of embodiment 27, wherein the first DNMT domain comprises a sequence of a DNMT domain provided herein.

29. The method of any one of embodiments 1-28, wherein the epigenetic editing system further comprises a second DNMT domain or a nucleic acid encoding thereof.

30. The method of embodiments 29, wherein the second DNMT domain is a DNMT3A domain or a DNMT3L domain.

31. The method of embodiment 30, wherein the second DNMT domain comprises a sequence of a DNMT domain provided herein.

32. The method of any one of embodiments 29-31, wherein the epigenetic editing system comprises a fusion protein or a nucleic acid encoding thereof, and wherein the fusion protein comprises the first DNA binding domain, the first DNMT domain, the repressor domain and the second DNMT domain.

33. The method of embodiment 32, wherein the fusion protein further comprises a nuclear localization sequence (NLS).

34. The method of embodiment 33, wherein the fusion protein comprises a sequence of a fusion protein provided herein.

35. The method of any one of embodiments 1-34, wherein the epigenetic editing system further comprises a second DNA binding domain or a nucleic acid encoding thereof, wherein the second DNA binding domain binds a second target region of the HBV genome.

36. The method of embodiment 35, wherein the second target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182.

37. The method of embodiment 35, wherein the second target region of the HBV genome is located in a CpG island.

38. The method of embodiment 35, wherein the second target region of the HBV genome is located in a promotor.

39. The method of embodiment 35, wherein the second target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a precure mRNA, a preS mRNA, a S mRNA, and a X mRNA.

40. The method of any one of embodiments 35-39, wherein the second DNA binding domain comprises a CRISPR-Cas protein.

41. The method of embodiment 40, wherein the epigenetic editing system further comprises a second gRNA that comprises a region complementary to a strand of the second target region.

42. The method of embodiment 41, wherein the gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., a sequence provided in Table 12 and/or 13.

43. The method of any one of embodiments 35-39, wherein the second DNA binding domain comprises a zinc-finger protein.

44. The method of embodiment 43, wherein the zinc-finger protein comprises a zinc-finger motif with a sequence selected from a zinc finger motif sequence provided herein, e.g., a zinc finger motif provided in Table 1 and/or 18.

45. The method of embodiment 43 or 44, wherein the zinc-finger protein comprises a sequence of a zinc finger motif provided in Table 1 and/or 18.

46. The method of any one of embodiments 35-45, wherein the epigenetic editing system comprises a first

fusion protein or a first nucleic acid encoding thereof and a second fusion protein or a second nucleic acid encoding thereof,

wherein the first fusion protein comprises the first DNA binding domain and the first DNMT domain, and

wherein the second fusion protein comprises the second DNA binding domain and the transcriptional repressor domain.

47. The method of embodiment 46, wherein the first fusion protein comprises a sequence of a fusion protein provided herein.

48. The method of embodiment 46, wherein the second fusion protein comprises a sequence of a fusion protein provided herein.

49. The method of any one of embodiments 46-48, wherein the epigenetic editing system further comprises a third DNA binding domain or a nucleic acid encoding thereof, wherein the third DNA binding domain binds to a third target region of the HBV genome.

50. The method of embodiment 49, wherein the third target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182.

51. The method of embodiment 49, wherein the third target region of the HBV genome is located in a CpG island.

52. The method of embodiment 49, wherein the third target region of the HBV genome is located in a promotor.

53. The method of embodiment 49, wherein the third target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a precure mRNA, a preS mRNA, a S mRNA, and a X mRNA.

54. The method of any one of embodiments 49-53, wherein the third DNA binding domain comprises a CRISPR-Cas protein.

55. The method of embodiment 54, wherein the epigenetic editing system further comprises a third gRNA that comprises a region complementary to a strand of the third target region.

56. The method of embodiment 55, wherein the third gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., of a gRNA sequence provided in Table 12 and/or 13.

57. The method of any one of embodiments 49-53, wherein the third DNA binding domain comprises a zinc-finger protein.

58. The method of embodiment 57, wherein the zinc-finger protein comprises a zinc-finger motif with a sequence selected from a zinc finger motif provided herein.

59. The method of embodiment 57 or 58, wherein the zinc-finger protein comprises a sequence of a zinc finger motif provided in Table 1 and/or 18.

60. The method of any one of embodiments 49-59, wherein the epigenetic editing system further comprises a second DNMT domain or a nucleic acid encoding thereof.

61. The method of embodiment 60, wherein the second DNMT domain is a DNMT3A domain or a DNMT3L domain.

62. The method of embodiment 61, wherein the epigenetic editing system comprises a third fusion protein or a nucleic acid encoding thereof, wherein the third fusion protein comprises the third DNA binding domain and the second DNMT domain.

63. The method of embodiment 62, wherein the third fusion protein comprises a sequence of a fusion protein provided herein.

64. An epigenetic editing system comprising:

a fusion protein or a nucleic acid encoding the fusion protein,

wherein the fusion protein comprises:

(a) a DNA-binding domain that binds a target region of a HBV gene or genome,

(b) a first DNA methyltransferase (DNMT) domain, and

(c) a transcriptional repressor domain.

65. The epigenetic system of embodiment 64, wherein the epigenetic editing system is capable of reducing a number of the HBV viral episome, replication of the HBV, or expression of a gene product encoded by the HBV gene or genome, wherein said reduction is at least about 20% compared to contacting the HBV gene or genome with a suitable control.

66. The epigenetic system of embodiment 64 or 65, wherein the HBV genome is a covalently closed circular DNA (cccDNA) or an HBV integrated DNA.

67. The epigenetic system of any one of embodiments 64-66, wherein the HBV genome comprises HBV genotype A, HBV genotype B, HBV genotype C, HBV genotype D, HBV genotype E, HBV genotype F, HBV genotype G or HBV genotype H.

68. The epigenetic system of any one of embodiments 64-67, wherein the HBV genome comprises a sequence with at least 80% identity to an HBV genome sequence provided herein.

69. The epigenetic system of any one of embodiments 64-68, wherein the target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182 of an HBV genome sequence provided herein.

70. The epigenetic system of any one of embodiments 64-68, wherein the target region of the HBV genome is located in a CpG island.

71. The epigenetic system of any one of embodiments 63-68, wherein the target region of the HBV genome is located in a promotor.

72. The epigenetic system of any one of embodiments 63-68, wherein the target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a precure mRNA, a preS mRNA, a S mRNA, and a X mRNA.

73. The epigenetic system of embodiments 63-72, wherein the DNA binding domain comprises a CRISPR-Cas protein.

74. The epigenetic system of embodiment 73, wherein the epigenetic editing system further comprises a gRNA that comprises a region complementary to a strand of the target region.

75. The epigenetic system of embodiment 74, wherein the gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., in Table 12 and/or 13.

76. The epigenetic system of any one of embodiments 63-72, wherein the DNA binding domain comprises a zinc-finger protein.

77. The epigenetic system of embodiment 76, wherein the zinc-finger protein comprises a zinc-finger motif with a sequence selected from a zinc finger motif provided herein.

78. The epigenetic system of embodiment 76 or 77, wherein the zinc-finger protein comprises a sequence of a zinc finger motif provided in Table 1 and/or 18.

79. The epigenetic system of any one of embodiments 63-78, wherein the transcriptional repressor domain comprises a sequence of a transcriptional repressor provided herein.

80. The epigenetic system of any one of embodiments 63-79, wherein the first DNMT domain is a DNMT3A domain or a DNMT3L domain.

81. The epigenetic system of embodiment 80, wherein the DNMT domain comprises a sequence of a DNMT domain provided herein.

82. The epigenetic system of any one of embodiments 63-81, wherein the fusion protein further comprises a second DNMT domain.

83. The epigenetic system of embodiment 82, wherein the second DNMT domain is a DNMT3A domain or a DNMT3L domain.

84. The epigenetic system of any one of embodiments 63-83, wherein the fusion protein further comprises a nuclear localization sequence (NLS).

85. The epigenetic system of embodiment 84, wherein the fusion protein comprises a sequence of a fusion protein provided herein.

86. An epigenetic editing system comprising:

a first fusion protein or a nucleic acid encoding the first fusion protein, wherein the first fusion protein comprises a first DNA binding domain and a first DNMT domain, wherein the first DNA binding domain binds a first target region of a HBV genome, and

a second fusion protein or a nucleic acid encoding the second fusion protein, wherein the second fusion protein comprises a second DNA binding domain and a transcriptional repressor domain, wherein the second DNA binding domain binds a second target region of the HBV genome.

87. The epigenetic system of embodiment 86, wherein the epigenetic editing system is capable of reducing a number of the HBV viral episome, replication of the HBV, or expression of a gene product encoded by the HBV genome, wherein said reduction is at least about 20% compared to contacting the HBV genome with a suitable control.

88. The epigenetic system of embodiment 86 or 87, wherein the HBV genome is a covalently closed circular DNA (cccDNA) or an HBV integrated DNA.

89. The epigenetic system of any one of embodiments 86-88, wherein the HBV genome comprises HBV genotype A, HBV genotype B, HBV genotype C, HBV genotype D, HBV genotype E, HBV genotype F, HBV genotype G or HBV genotype H.

90. The epigenetic system of any one of embodiments 86-89, wherein the HBV genome comprises a sequence with at least 80% identity to an HBV genome provided herein.

91. The epigenetic system of any one of embodiments 86-89, further comprising a third fusion protein or a nucleic acid encoding the third fusion protein, wherein the third fusion protein comprises a third DNA binding domain and a second DNMT domain, wherein the third DNA binding domain binds a third target region of the HBV genome.

92. The epigenetic system of embodiment 91, wherein the first target region, the second target region or the third target region is located in a region of the HBV genome within nucleotide 0-303, 1000-2448 or 2802-3182 of an HBV genome provided herein.

93. The epigenetic system of embodiment 91, wherein the first target region, the second target region or the third target region of the HBV genome is located in a CpG island.

94. The epigenetic system of embodiment 91, wherein the first target region, the second target region or the third target region of the HBV genome is located in a promotor.

95. The epigenetic system of embodiment 91, wherein the first target region, the second target region or the third target region of the HBV genome is located in a section of the HBV genome that encodes a transcript selected from the group consisting of a pgRNA, a precure mRNA, a preS mRNA, a S mRNA, and a X mRNA.

96. The epigenetic system of embodiment 91, wherein the first DNA binding domain, the second DNA binding domain or the third DNA binding domain comprises a CRISPR-Cas protein.

97. The epigenetic system of embodiment 96, wherein the epigenetic editing system further comprises a first gRNA that comprises a region complementary to a strand of the first target region, a second gRNA that comprises a region complementary to a strand of the second target region or a third RNA that comprises a region complementary to a strand of the third target region.

98. The epigenetic system of embodiment 97, wherein the first gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., provided in Table 12 and/or 13, the second gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., provided in Table 12 and/or 13, and/or the third gRNA comprises a sequence selected from a gRNA sequence provided herein, e.g., provided in Table 12 and/or 13.

99. The epigenetic system of embodiment 91, wherein the first DNA binding domain, the second DNA binding domain or the third DNA binding domain comprises a zinc-finger protein.

100. The epigenetic system of embodiment 99, wherein the zinc-finger protein comprises a zinc-finger motif with a sequence selected from a zinc finger motif provided herein.

101. The epigenetic system of embodiment 99 or 100, wherein the zinc-finger protein comprises a sequence of a zinc finger motif provided in Table 1 and/or 18.

102. The epigenetic system of any one of embodiments 86-101, wherein the transcriptional repressor domain comprises ZIM3.

103. The epigenetic system of any one of embodiments 86-102, wherein the first DNMT domain is a DNMT3A domain or a DNMT3L domain.

104. The epigenetic system of embodiment 103, wherein the first DNMT domain comprises a sequence of a DNMT provided herein.

105. The epigenetic system of embodiment 91, wherein the second DNMT domain is a DNMT3A domain or a DNMT3L domain.

106. The epigenetic system of embodiment 105, wherein the second DNMT domain comprises a sequence of a DNMT domain provided herein.

107. The epigenetic system of any one of embodiment 86-106, wherein the first fusion protein comprises a sequence of a fusion protein provided herein.

108. The epigenetic system of any one of embodiments 86-107, wherein the second fusion protein comprises a sequence of a fusion protein provided herein.

109. The epigenetic system of any one of embodiments 91-107, wherein the third fusion protein comprises a sequence of a fusion protein provided herein.

110. The method of any one of embodiments 1-63, wherein the epigenetic editing system comprises a nucleic acid sequence provided in Table 18.

111. A method of treating an HDV infection in a subject comprising administering an epigenetic editing system to the subject,

wherein the epigenetic editing system comprises

a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof,

wherein the first DNA binding domain binds a first target region of a HBV gene or genome, and

wherein the contacting results in a reduction of:
number of HDV viral episomes,
replication of the HDV gene or genome, or
expression of a protein product encoded by the HDV gene or genome,
wherein said reduction is at least about 20% compared to administering a suitable control.

112. A method of inhibiting viral replication in a cell infected with an HDV comprising administering an epigenetic editing system,
wherein the epigenetic editing system comprises
a first DNA binding domain, a first DNMT domain, and a transcriptional repressor domain or one or more nucleic acid molecules encoding thereof,
wherein the first DNA binding domain binds a first target region of a HBV gene or genome, and wherein the epigenetic editing system targets a target region of the HBV gene or genome, and
wherein the contacting results in a reduction of number of HDV viral episomes or replication of the HDV gene or genome,
wherein said reduction is at least about 20% compared to administering a suitable control.

113. The method of embodiment 111 or 112, wherein the first DNA binding domain comprises a CRISPR-Cas protein.

114. The method of embodiment 113, wherein the epigenetic editing system further comprises a first guide RNA (gRNA) that comprises a region complementary to a strand of the first target region.

115. The method of embodiment 114, wherein the gRNA comprises a sequence selected from a gRNA provided herein, e.g., in Table 12 and/or 13.

116. The method of embodiment 111 or 112, wherein the first DNA binding domain comprises a zinc-finger protein.

117. The method of embodiment 116, wherein the zinc-finger protein comprises a zinc-finger motif with a sequence selected from any zinc finger or zinc finger motif provided herein, e.g., in Table 1 and/or 18.

118. The method of embodiment 116 or 117, wherein the zinc-finger protein comprises a sequence of any of the zinc finger epigenetic repressors provided herein.

119. The method of any one of embodiments 111-118, wherein the transcriptional repressor domain comprises ZIM3.

120. The method of any one of embodiments 111-119, wherein the first DNMT domain is a DNMT3A domain or a DNMT3L domain.

121. The method of embodiment 120, wherein the first DNMT domain comprises a sequence of a DNMT domain provided herein.

122. The method of any one of embodiments 111-121, wherein the epigenetic editing system further comprises a second DNMT domain or a nucleic acid encoding thereof.

123. The method of embodiment 122, wherein the second DNMT domain is a DNMT3A domain or a DNMT3L domain.

124. The method of embodiment 123, wherein the second DNMT domain comprises a sequence of a DNMT domain provided herein.

125. The method of any one of embodiments 122-123, wherein the epigenetic editing system comprises a fusion protein or a nucleic acid encoding thereof, and wherein the fusion protein comprises the first DNA binding domain, the first DNMT domain, the repressor domain and the second DNMT domain.

126. The method of embodiment 125, wherein the fusion protein further comprises a nuclear localization sequence (NLS).

127. The method of embodiment 126, wherein the fusion protein comprises a sequence of a fusion protein provided herein.

128. The method of any one of embodiments 111-127, wherein the first DNA binding domain binds a target region of an HBV gene or genome encoding or controlling expression of an S-antigen.

In order that the present disclosure may be better understood, the following examples are set forth. These examples are for purposes of illustration only and are not to be construed as limiting the scope of the present disclosure in any manner.

EXAMPLES

Example 1: Selection of Target HBV Sequences for Epigenetic Silencing

Target sequences were manually and computationally designed using the representative HBV genome sequences (SEQ ID Nos. 1082, 1083) as a reference:

While target site design focused on CpG islands identified within the HBV genome, target sites outside of HBV CpG islands were also considered.

Table 2 presents some representative target sites that were identified as suitable for targeting with an epigenetic repressor.

Target domains identified above that are adjacent to a PAM sequence, e.g., an *S. pyogenes* Cas9 PAM sequence, can be targeted by a CRISPR-based epigenetic repressor, e.g., an epigenetic repressor comprising a dCas9 DNA-binding domain. For example, target sites 1-143 are suitable for dCas9-based epigenetic repressor targeting. FIG. **1** provides an overview over the position of the target sites identified in the HBV genome.

Target sites were analyzed for conservation across HBV genotypes A-E (FIGS. 2 and 3). Some target sites were identified that were well conserved across two or more, or in some cases all, HBV genotypes. Targeting such conserved sites allows for silencing different genotypes with the same epigenetic repressor.

Example 2: Guide RNA Assays in HepAD38 HBV Cells

The HepAD38 cell line expresses the HBV genome under a doxycycline-inducible promoter (see, e.g., Ladner et al., Inducible expression of human hepatitis B virus (HBV) in stably transfected hepatoblastoma cells: a novel system for screening potential inhibitors of HBV replication. Antimicrob. Agents Chemother. 41:1715-1720(1997), incorporated herein by reference).

Results are shown in FIGS. **4**A and B.

Example 3: Guide RNA Assays in HepG2-NTCP Cells

HepG2 cells were engineered by lentiviral transduction to express the human NTCP receptor which is used by hepatitis B virus (HBV) to infect the cells.

HBV viral particles were produced using the HepAD38 cell line. HepAD38 is a subclone, derived from HepG2 cell line, that expresses HBV genome (genotype D subtype ayw)

under the transcriptional control of a tetracycline-responsive promoter in a TET-OFF system.

A triple combination of Engineered Transcriptional Repressors (ETRs) consisting of three plasmids expressing dCas9-KRAB, dCas9-DNMT3A and dCas9-DNMT3L was used in combination with one or more of the designed sgRNAs.

LNPs were formulated using GENVOY ILM Lipid Mix (Precision Nanosystem) and the formulator Nanoassemblr Spark (Precision Nanosystem). LNPs were formulated according to the manufacturer's recommendations with Nitrogen:Phosphate (NP) ratio equal to 6 and flow rate ratio (FRR) 2:1. The RNA payload was diluted to a final concentration of 350 ng/uL in the PNI formulation buffer. The ETRs, dCas9-KRAB, dCas9-DNMT3A, dCas9-DNMT3L and each of the 121 sgRNA were mixed at 1:1:1:4 ratio. The RNA mix, the Genvoy lipid mix (25 mM) and PBS were loaded each in the dedicated chambers of the Spark cartridge and formulated. The quality of the formulated LNPs was evaluated quantifying the packaged mRNA using Quant-it™ RiboGreen RNA Assay Kit (Thermo Fisher) and sizing the LNP by Dynamic Light Scattering (Zetasizer, Malvern Panalytic).

HepG2-NTCP cells were plated at 20,000 cells/well in collagen coated 96 well plates. After 24 h cells were infected with HBV at 5,000 multiplicity of genome equivalent (MGE) and 16 h after viral inoculum was removed, cells were washed with PBS, and fresh media was added. Three days post-infection, using LNPs, each sgRNA and the mRNAs encoding each of the components of the triple constructs of ETRs (dCas9-KRAB, dCas9-DNMT3A, dCas9-DNMT3L) were delivered. Three days after, LNP was removed, medium was replaced, and cells were maintained in complete medium for three days.

Viral antigens HBeAg and HBsAg were quantified 6 days after LNP removal using ELISA assays. Data were normalized to a non-targeting guide designed against the mouse PCSK9 and control 3.2 gRNA was used as positive control. Cells viability assay were performed and normalized to non-targeting control.

The Table below provides amino acid sequences of exemplary epigenetic editors used in the gRNA screen (the ETR constructs):

TABLE 6

amino acid sequences of exemplary epigenetic editors

SEQ ID NO	Description	Amino acid sequence
476	dCas9:G:KRAB	MYPYDVPDYASPKKKRKVEASDKKYSIGLAIGTNSVGWAVITDEYKVPSKKEK VLGNTDRHSIKKNLIGALLEDSGETAEATRLKRTARRRYTRRKNRICYLQEIF SNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLR KKLVDSTDKADLRLIYLALAHMIKERGHFLIEGDLNPDNSDVDKLFIQLVQTY NQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALS LGLTPNFKSNEDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLELAAKNLSD AILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIF FDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKORT FDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLAR GNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNEDKNLPNEKVLPK HSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRENASLGTYHDLLKIIKDKDELDNEENEDIL EDIVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYTGWGRLSRKLING IRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHE HIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQK NSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQEL DINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKN YWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQI LDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQFYKVREINNYHHAHDA YLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYS NIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVN IVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVV AKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLP KYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDN EQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQ AENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYET RIDLSQLGGDSPKKKRKVGVD**GSGGG**ALSPQHSAVTQGSIIKNKEGMDAKSLT AWSRTLVTFKDVFVDETREEWKLLDTAQQIVYRNVMLENYKNLVSLGYQLTKP DVILRLEKGEEPWLVEREIHQETHPDSETAFEIKSSV* YPYDVPDYA - HA-Tag (SEQ ID NO: 479) **GSGGG** - Linker (SEQ ID NO: 480)
477	dCas9:G:DNMT3A	MYPYDVPDYASPKKKRKVEASDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFK VLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIF SNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLR KKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTY NQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLEGNLIALS LGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSD AILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVROQLPEKYKEIF FDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKORT FDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLAR GNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNEDKNLPNEKVLPK HSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLEKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRENASLGTYHDLLKIIKDKDELDNEENEDIL EDIVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYTGWGRLSRKLING IRDKQSGKTILDELKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHE

TABLE 6-continued

amino acid sequences of exemplary epigenetic editors

SEQ ID NO	Description	Amino acid sequence
		HIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQK NSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLONGRDMYVDQEL DINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKN YWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQI LDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDA YLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYS NIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVN IVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGEDSPTVAYSVLVV AKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLP KYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDN EQKOLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQ AENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYET RIDLSQLGGDSPKKKRKVGVD**GSGGG**TYGLLRRREDWPSRLQMFFANNHDQEF DPPKVYPPVPAEKRKPIRVLSLEDGIATGLLVLKDLGIQVDRYIASEVCEDSI TVGMVRHQGKIMYVGDVRSVTQKHIQEWGPFDLVIGGSPCNDLSIVNPARKGL YEGTGRLFFEFYRLLHDARPKEGDDRPFFWLFENVVAMGVSDKRDISRFLESN PVMIDAKEVSAAHRARYFWGNLPGMNRPLASTVNDKLELQECLEHGRIAKESK VRTITTRSNSIKQGKDQHFPVFMNEKEDILWCTEMERVFGFPVHYTDVSNMSR LARQRLLGRSWSVPVIRHLFAPLKEYFACV* YPYDVPDYA - HA-Tag (SEQ ID NO: 479) **GSGGG** - Linker (SEQ ID NO: 480)
478	dCas9:G:hDNMT3L	MYPYDVPDYASPKKKRKVEASDKKYSIGLAIGTNSVGWAVITDEYKVPSKKEK VLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIF SNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLR KKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTY NQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLEGNLIALS LGLTPNFKSNEDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSD AILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIF FDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKORT FDNGSIPHQIHLGELHAILRRQEDFYPELKDNREKIEKILTFRIPYYVGPLAR GNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNEDKNLPNEKVLPK HSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLEKTNRKVTVKQ LKEDYFKKIECFDSVEISGVEDRENASLGTYHDLLKIIKDKDELDNEENEDIL EDIVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYTGWGRLSRKLING IRDKQSGKTILDELKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHE HIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQK NSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQEL DINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKN YWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQI LDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQFYKVREINNYHHAHDA YLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYS NIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVN IVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGEDSPTVAYSVLVV AKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLP KYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDN EQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQ AENIIHLFTLTNLGAPAAFKYEDTTIDRKRYTSTKEVLDATLIHQSITGLYET RIDLSQLGGDSPKKKRKVGVD**GSGGG**MAAIPALDPEAEPSMDVILVGSSELSS SVSPGTGRDLIAYEVKANQRNIEDICICCGSLQVHTQHPLFEGGICAPCKDKF LDALFLYDDDGYQSYCSICCSGETLLICGNPDCTRCYCFECVDSLVGPGTSGK VHAMSNWVCYLCLPSSRSGLLQRRRKWRSQLKAFYDRESENPLEMFETVPVWR RQPVRVLSLFEDIKKELTSLGFLESGSDPGQLKHVVDVTDTVRKDVEEWGPED LVYGATPPLGHTCDRPPSWYLFQFHRLLQYARPKPGSPRPFFWMFVDNLVLNK EDLDVASRFLEMEPVTIPDVHGGSLQNAVRVWSNIPAIRSRHWALVSEEELSL LAQNKQSSKLAAKWPTKLVKNCELPLREYFKYFSTELTSSL* YPYDVPDYA - HA-Tag (SEQ ID NO: 479) **GSGGG** - Linker (SEQ ID NO: 480)
479	HA-Tag	YPYDVPDYA
480	linker	GSGGG

The Table below provides amino acid sequences and polynucleotide sequences of exemplary epigenetic editors

TABLE 7

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
481	PLA001 amino acid sequence	MPKKKRKVPKKKRKVYNHDQEFDPPKVYPPVPAEKRKPIRVLSLEDGIATG LLVLKDLGIQVDRYIASEVCEDSITVGMVRHQGKIMYVGDVRSVTQKHIQE WGPFDLVIGGSPCNDLSIVNPARKGLYEGTGRLFFEFYRLLHDARPKEGDD RPFFWLFENVVAMGVSDKRDISRFLESNPVMIDAKEVSAAHRARYFWGNLP GMNRPLASTVNDKLELQECLEHGRIAKFSKVRTITTRSNSIKQGKDQHFPV FMNEKEDILWCTEMERVFGFPVHYTDVSNMSRLARQRLLGRSWSVPVIRHL FAPLKEYFACVSSGNSNANSRGPSESSGLVPLSLRGSHMAAIPALDPEAEP SMDVILVGSSELSSSVSPGTGRDLIAYEVKANQRNIEDICICCGSLQVHTQ HPLFEGGICAPCKDKFLDALFLYDDDGYQSYCSICCSGETLLICGNPDCTR CYCFECVDSLVGPGTSGKVHAMSNWVCYLCLPSSRSGLLQRRRKWRSQLKA FYDRESENPLEMFETVPVWRRQPVRVLSLFEDIKKELTSLGFLESGSDPGQ LKHVVDVTDTVRKDVEEWGPFDLVYGATPPLGHTCDRPPSWYLFQFHRLLQ YARPKPGSPRPFFWMFVDNLVLNKEDLDVASRFLEMEPVTIPDVHGGSLQN AVRVWSNIPAIRSRHWALVSEEELSLLAQNKQSSKLAAKWPTKLVKNCFLP LREYFKYFSTELTSSLGGPSSGAPPPSGGSPAGSPTSTEEGTSESATPESG PGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSELEDKKY SIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLEDSG ETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELV EEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLAL AHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAK AILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNEKSNEDLAE DAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTE ITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGY IDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTEDNGSIPHQ IHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAW MTRKSEETITPWNFEEVVDKGASAQSFIERMTNEDKNLPNEKVLPKHSLLY EYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLEKTNRKVTVKQLKE DYFKKIECFDSVEISGVEDRENASLGTYHDLLKIIKDKDELDNEENEDILE DIVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYTGWGRLSRKLIN GIRDKQSGKTILDELKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDS LHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTT QKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRD MYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPS EEVVKKMKNYWRQLLNAKLITQRKEDNLTKAERGGLSELDKAGFIKRQLVE TRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQFYK VREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKS EQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDK GRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWD PKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNP IDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALP SKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRV ILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYEDTTI DRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSPKKKRKVGVDGSS GSETPGTSESATPESTGDSVAFEDVAVNETLEEWALLDPSQKNLYRDVMRE TFRNLASVGKQWEDQNIEDPFKIPRRNISHIPERLCESKEGGQGEESADYK DDDDKAPKKKRKVPKKKRKV
482	PLA001 polynucleotide sequence	ATGCCAAAAAAGAAGAGAAAGGTACCGAAGAAAAAAAGAAAGGTATACAAT CACGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAG AAGAGGAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGC CTGCTGGTGCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCC GAGGTGTGCGAGGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAG ATCATGTATGTGGGCGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAG TGGGGCCCATTCGATCTGGTGATCGGCGGCAGCCCCTGTAATGACCTGTCC ATCGTGAACCCTGCAAGGAAGGGACTGTACGAGGGAACCGGCCGGCTGTTC TTTGAGTTTTATAGACTGCTGCACGACGCCAGGCCTAAGGAGGGCGACGAT AGACCATTCTTTTGGCTGTTCGAGAATGTGGTGGCTATGGGCGTGAGCGAT AAGAGGGACATCTCCAGGTTTCTGGAGTCTAACCCCGTGATGATCGATGCA AAGGAGGTGTCCGCCGCACACAGAGCCAGGTATTTCTGGGGCAATCTGCCA GGAATGAACAGGCCACTGGCAAGCACCGTGAATGACAAGCTGGAGCTGCAG GAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAAGGTGCGCACAATC ACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCACTTCCCCGTG TTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGAGAGAGTG TTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCTGGCA AGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCTG TTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAAT GCCAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTG AGGGGCTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCT AGCATGGACGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCT CCAGGAACCGGAAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGG AACATCGAGGACATCTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAG CACCCACTGTTCGAGGGAGGAATCTGCGCACCCTGTAAGGATAAGTTCCTG

TABLE 7-continued

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
		GACGCCCTGTTTCTGTACGACGATGACGGCTACCAGTCCTATTGCTCTATC
		TGCTGTTCCGGCGAGACCCTGCTGATCTGCGGCAATCCAGATTGTACAAGG
		TGCTATTGTTTTGAGTGCGTGGACTCTCTGGTGGGACCAGGCACCAGCGGA
		AAGGTGCACGCCATGTCCAACTGGGTGTGCTACCTGTGCCTGCCATCCTCT
		CGCAGCGGACTGCTGCAGCGGAGAAGGAAGTGGAGATCCCAGCTGAAGGCC
		TTCTATGATAGGGAGTCTGAGAACCCCCTGGAGATGTTTGAGACCGTGCCA
		GTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTTCGAGGATATCAAG
		AAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGACCCCGGACAG
		CTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGTGGAGGAG
		TGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACACACA
		TGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCAG
		TATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTG
		GATAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTG
		GAGATGGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAAT
		GCCGTGCGCGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCA
		CTGGTGAGCGAGGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGC
		AAGCTGGCCGCCAAGTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCA
		CTGCGGGAGTACTTCAAGTATTTTTCCACCGAGCTGACATCTAGCCTGGGA
		GGACCCTCCTCTGGCGCCCCACCACCTAGCGGCGGCTCCCCTGCCGGCTCT
		CCAACCAGCACAGAGGAGGGCACCAGCGAGTCCGCCACACCAGAGTCTGGA
		CCTGGCACCAGCACAGAGCCATCCGAGGGCTCTGCCCCAGGCTCTCCTGCA
		GGCAGCCCTACCTCCACCGAAGAGGGCACCAGCACAGAGCCTTCTGAGGGC
		AGCGCCCCAGGCACCTCTACAGAGCCAAGCGAGCTCGAGGACAAGAAGTAC
		AGCATCGGCCTGGCCATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACC
		GACGAGTACAAGGTGCCCAGCAAGAAATTCAAGGTGCTGGGCAACACCGAC
		CGGCACAGCATCAAGAAGAACCTGATCGGAGCCCTGCTGTTCGACAGCGGC
		GAAACAGCCGAGGCCACCCGGCTGAAGAGAACCGCCAGAAGAAGATACACC
		AGACGGAAGAACCGGATCTGCTATCTGCAAGAGATCTTCAGCAACGAGATG
		GCCAAGGTGGACGACAGCTTCTTCCACAGACTGGAAGAGTCCTTCCTGGTG
		GAAGAGGATAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGAC
		GAGGTGGCCTACCACGAGAAGTACCCCACCATCTACCACCTGAGAAAGAAA
		CTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGATCTATCTGGCCCTG
		GCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAAC
		CCCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCAGACCTAC
		AACCAGCTGTTCGAGGAAAACCCCATCAACGCCAGCGGCGTGGACGCCAAG
		GCCATCCTGTCTGCCAGACTGAGCAAGAGCAGACGGCTGGAAAATCTGATC
		GCCCAGCTGCCCGGCGAGAAGAAGAATGGCCTGTTCGGCAACCTGATTGCC
		CTGAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAG
		GATGCCAAACTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAAC
		CTGCTGGCCCAGATCGGCGACCAGTACGCCGACCTGTTTCTGGCCGCCAAG
		AACCTGTCCGACGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAG
		ATCACCAAGGCCCCCCTGAGCGCCTCTATGATCAAGAGATACGACGAGCAC
		CACCAGGACCTGACCCTGCTGAAAGCTCTCGTGCGGCAGCAGCTGCCTGAG
		AAGTACAAAGAGATTTTCTTCGACCAGAGCAAGAACGGCTACGCCGGCTAC
		ATTGACGGCGGAGCCAGCCAGGAAGAGTTCTACAAGTTCATCAAGCCCATC
		CTGGAAAAGATGGACGGCACCGAGGAACTGCTCGTGAAGCTGAACAGAGAG
		GACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAG
		ATCCACCTGGGAGAGCTGCACGCCATTCTGCGGCGGCAGGAAGATTTTTAC
		CCATTCCTGAAGGACAACCGGGAAAAGATCGAGAAGATCCTGACCTTCCGC
		ATCCCCTACTACGTGGGCCCTCTGGCCAGGGGAAACAGCAGATTCGCCTGG
		ATGACCAGAAAGAGCGAGGAAACCATCACCCCCTGGAACTTCGAGGAAGTG
		GTGGACAAGGGCGCTTCCGCCCAGAGCTTCATCGAGCGGATGACCAACTTC
		GATAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCTGTAC
		GAGTACTTCACCGTGTATAACGAGCTGACCAAAGTGAAATACGTGACCGAG
		GGAATGAGAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTG
		GACCTGCTGTTCAAGACCAACCGGAAAGTGACCGTGAAGCAGCTGAAAGAG
		GACTACTTCAAGAAAATCGAGTGCTTCGACTCCGTGGAAATCTCCGGCGTG
		GAAGATCGGTTCAACGCCTCCCTGGGCACATACCACGATCTGCTGAAAATT
		ATCAAGGACAAGGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAA
		GATATCGTGCTGACCCTGACACTGTTTGAGGACAGAGAGATGATCGAGGAA
		CGGCTGAAAACCTATGCCCACCTGTTCGACGACAAAGTGATGAAGCAGCTG
		AAGCGGCGGAGATACACCGGCTGGGGCAGGCTGAGCCGGAAGCTGATCAAC
		GGCATCCGGGACAAGCAGTCCGGCAAGACAATCCTGGATTTCCTGAAGTCC
		GACGGCTTCGCCAACAGAAACTTCATGCAGCTGATCCACGACGACAGCCTG
		ACCTTTAAAGAGGACATCCAGAAAGCCCAGGTGTCCGGCCAGGGCGATAGC
		CTGCACGAGCACATTGCCAATCTGGCCGGCAGCCCCGCCATTAAGAAGGGC
		ATCCTGCAGACAGTGAAGGTGGTGGACGAGCTCGTGAAAGTGATGGGCCGG
		CACAAGCCCGAGAACATCGTGATCGAAATGGCCAGAGAGAACCAGACCACC
		CAGAAGGGACAGAAGAACAGCCGCGAGAGAATGAAGCGGATCGAAGAGGGC
		ATCAAAGAGCTGGGCAGCCAGATCCTGAAAGAACACCCCGTGGAAAACACC
		CAGCTGCAGAACGAGAAGCTGTACCTGTACTACCTGCAGAATGGGCGGGAT
		ATGTACGTGGACCAGGAACTGGACATCAACCGGCTGTCCGACTACGATGTG
		GACGCCATCGTGCCTCAGAGCTTTCTGAAGGACGACTCCATCGACAACAAG
		GTGCTGACCAGAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCTCC
		GAAGAGGTCGTGAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAACGCC

TABLE 7-continued

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
		AAGCTGATTACCCAGAGAAAGTTCGACAATCTGACCAAGGCCGAGAGAGGC GGCCTGAGCGAACTGGATAAGGCCGGCTTCATCAAGAGACAGCTGGTGGAA ACCCGGCAGATCACAAAGCACGTGGCACAGATCCTGGACTCCCGGATGAAC ACTAAGTACGACGAGAATGACAAGCTGATCCGGGAAGTGAAAGTGATCACC CTGAAGTCCAAGCTGGTGTCCGATTTCCGGAAGGATTTCCAGTTTTACAAA GTGCGCGAGATCAACAACTACCACCACGCCCACGACGCCTACCTGAACGCC GTCGTGGGAACCGCCCTGATCAAAAAGTACCCTAAGCTGGAAAGCGAGTTC GTGTACGGCGACTACAAGGTGTACGACGTGCGGAAGATGATCGCCAAGAGC GAGCAGGAAATCGGCAAGGCTACCGCCAAGTACTTCTTCTACAGCAACATC ATGAACTTTTTCAAGACCGAGATTACCCTGGCCAACGGCGAGATCCGGAAG CGGCCTCTGATCGAGACAAACGGCGAAACCGGGGAGATCGTGTGGGATAAG GGCCGGGATTTTGCCACCGTGCGGAAAGTGCTGAGCATGCCCCAAGTGAAT ATCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCAGCAAAGAGTCTATC CTGCCCAAGAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTGGGAC CCTAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTATTCTGTGCTG GTGGTGGCCAAAGTGGAAAAGGGCAAGTCCAAGAAACTGAAGAGTGTGAAA GAGCTGCTGGGGATCACCATCATGGAAAGAAGCAGCTTCGAGAAGAATCCC ATCGACTTTCTGGAAGCCAAGGGCTACAAAGAAGTGAAAAAGGACCTGATC ATCAAGCTGCCTAAGTACTCCCTGTTCGAGCTGGAAAACGGCCGGAAGAGA ATGCTGGCCTCTGCCGGCGAACTGCAGAAGGGAAACGAACTGGCCCTGCCC TCCAAATATGTGAACTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAG GGCTCCCCCGAGGATAATGAGCAGAAACAGCTGTTTGTGGAACAGCACAAG CACTACCTGGACGAGATCATCGAGCAGATCAGCGAGTTCTCCAAGAGAGTG ATCCTGGCCGACGCTAATCTGGACAAAGTGCTGTCCGCCTACAACAAGCAC CGGGATAAGCCCATCAGAGAGCAGGCCGAGAATATCATCCACCTGTTTACC CTGACCAATCTGGGAGCCCCTGCCGCCTTCAAGTACTTTGACACCACCATC GACCGGAAGAGGTACACCAGCACCAAAGAGGTGCTGGACGCCACCCTGATC CACCAGAGCATCACCGGCCTGTACGAGACACGGATCGACCTGTCTCAGCTG GGAGGCGACAGCCCCAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGC GGCTCCGAGACCCCAGGCACATCTGAGAGCGCCACCCCTGAGTCCACCGGT GACTCCGTTGCTTTCGAGGACGTGGCCGTGAACTTCACACTTGAGGAATGG GCCTTGCTCGACCCAAGTCAGAAGAATCTGTACAGAGACGTGATGCGGGAG ACATTCAGGAATCTCGCCAGTGTCGGAAAGCAGTGGGAAGACCAGAACATC GAAGATCCTTTCAAGATACCACGGCGCAATATCTCCCACATTCCTGAGAGG CTGTGTGAATCTAAGGAAGGCGGACAAGGTGAGGAAAGCGCTGATTACAAA GATGATGACGATAAAGCCCCCAAGAAGAAAAGGAAGGTCCCAAAGAAAAAA AGAAAGGTGTGA
483	PLA002 Amino acid sequence	MPKKKRKVPKKKRKVYNHDQEFDPPKVYPPVPAEKRKPIRVLSLEDGIATG LLVLKDLGIQVDRYIASEVCEDSITVGMVRHQGKIMYVGDVRSVTQKHIQE WGPFDLVIGGSPCNDLSIVNPARKGLYEGTGRLFFEFYRLLHDARPKEGDD RPFFWLFENVVAMGVSDKRDISRFLESNPVMIDAKEVSAAHRARYFWGNLP GMNRPLASTVNDKLELQECLEHGRIAKFSKVRTITTRSNSIKQGKDQHFPV FMNEKEDILWCTEMERVFGFPVHYTDVSNMSRLARQRLLGRSWSVPVIRHL FAPLKEYFACVSSGNSNANSRGPSFSSGLVPLSLRGSHMAAIPALDPEAEP SMDVILVGSSELSSSVSPGTGRDLIAYEVKANQRNIEDICICCGSLQVHTQ HPLFEGGICAPCKDKFLDALFLYDDDGYQSYCSICCSGETLLICGNPDCTR CYCFECVDSLVGPGTSGKVHAMSNWVCYLCLPSSRSGLLQRRRKWRSQLKA FYDRESENPLEMFETVPVWRRQPVRVLSLFEDIKKELTSLGFLESGSDPGQ LKHVVDVTDTVRKDVEEWGPFDLVYGATPPLGHTCDRPPSWYLFQFHRLLQ YARPKPGSPRPFFWMFVDNLVLNKEDLDVASRFLEMEPVTIPDVHGGSLQN AVRVWSNIPAIRSRHWALVSEEELSLLAQNKQSSKLAAKWPTKLVKNCFLP LREYFKYFSTELTSSLGGPSSGAPPPSGGSPAGSPTSTEEGTSESATPESG PGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSELEDKKY SIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLEDSG ETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELV EEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLAL AHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAK AILSARLSKSRRLENLIAQLPGEKKNGLEGNLIALSLGLTPNEKSNEDLAE DAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTE ITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGY IDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTEDNGSIPHQ IHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAW MTRKSEETITPWNFEEVVDKGASAQSFIERMTNEDKNLPNEKVLPKHSLLY EYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLEKTNRKVTVKQLKE DYFKKIECFDSVEISGVEDRENASLGTYHDLLKIIKDKDELDNEENEDILE DIVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYTGWGRLSRKLIN GIRDKQSGKTILDELKSDGFANRNEMQLIHDDSLTFKEDIQKAQVSGQGDS LHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTT QKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRD MYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPS EEVVKKMKNYWRQLLNAKLITQRKEDNLTKAERGGLSELDKAGFIKRQLVE TRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQFYK VREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKS EQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDK

TABLE 7-continued

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
		GRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWD PKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNP IDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALP SKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRV ILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYEDTTI DRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSPKKKRKVGVDGSS GSETPGTSESATPESTGMNNSQGRVTFEDVTVNFTQGEWQRLNPEQRNLYR DVMLENYSNLVSVGQGETTKPDVILRLEQGKEPWLEEEEVLGSGRAEKNGD IGGQIWKPKDVKESLSADYKDDDDKAPKKKRKVPKKKRKV
484	PLA002 polynucleotide sequence	ATGCCAAAAAAGAAGAGAAAGGTACCGAAGAAAAAAAGAAAGGTATACAAT CACGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAG AAGAGGAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGC CTGCTGGTGCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCC GAGGTGTGCGAGGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAG ATCATGTATGTGGGCGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAG TGGGGCCCATTCGATCTGGTGATCGGCGGCAGCCCCTGTAATGACCTGTCC ATCGTGAACCCTGCAAGGAAGGGACTGTACGAGGGAACCGGCCGGCTGTTC TTTGAGTTTTATAGACTGCTGCACGACGCCAGGCCTAAGGAGGGCGACGAT AGACCATTCTTTTGGCTGTTCGAGAATGTGGTGGCTATGGGCGTGAGCGAT AAGAGGGACATCTCCAGGTTTCTGGAGTCTAACCCCGTGATGATCGATGCA AAGGAGGTGTCCGCCGCACACAGAGCCAGGTATTTCTGGGGCAATCTGCCA GGAATGAACAGGCCACTGGCAAGCACCGTGAATGACAAGCTGGAGCTGCAG GAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAAGGTGCGCACAATC ACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCACTTCCCCGTG TTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGAGAGAGTG TTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCTGGCA AGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCTG TTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAAT GCCAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTG AGGGGCTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCT AGCATGGACGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCT CCAGGAACCGGAAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGG AACATCGAGGACATCTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAG CACCCACTGTTCGAGGGAGGAATCTGCGCACCCTGTAAGGATAAGTTCCTG GACGCCCTGTTTCTGTACGACGATGACGGCTACCAGTCCTATTGCTCTATC TGCTGTTCCGGCGAGACCCTGCTGATCTGCGGCAATCCAGATTGTACAAGG TGCTATTGTTTTGAGTGCGTGGACTCTCTGGTGGGACCAGGCACCAGCGGA AAGGTGCACGCCATGTCCAACTGGGTGTGCTACCTGTGCCTGCCATCCTCT CGCAGCGGACTGCTGCAGCGGAGAAGGAAGTGGAGATCCCAGCTGAAGGCC TTCTATGATAGGGAGTCTGAGAACCCCCTGGAGATGTTTGAGACCGTGCCA GTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTTCGAGGATATCAAG AAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGACCCCGGACAG CTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGTGGAGGAG TGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACACACA TGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCAG TATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTG GATAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTG GAGATGGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAAT GCCGTGCGCGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCA CTGGTGAGCGAGGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGC AAGCTGGCCGCCAAGTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCA CTGCGGGAGTACTTCAAGTATTTTTCCACCGAGCTGACATCTAGCCTGGGA GGACCCTCCTCTGGCGCCCCACCACCTAGCGGCGGCTCCCCTGCCGGCTCT CCAACCAGCACAGAGGAGGGCACCAGCGAGTCCGCCACACCAGAGTCTGGA CCTGGCACCAGCACAGAGCCATCCGAGGGCTCTGCCCCAGGCTCTCCTGCA GGCAGCCCTACCTCCACCGAAGAGGGCACCAGCACAGAGCCTTCTGAGGGC AGCGCCCCAGGCACCTCTACAGAGCCAAGCGAGCTCGAGGACAAGAAGTAC AGCATCGGCCTGGCCATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACC GACGAGTACAAGGTGCCCAGCAAGAAATTCAAGGTGCTGGGCAACACCGAC CGGCACAGCATCAAGAAGAACCTGATCGGAGCCCTGCTGTTCGACAGCGGC GAAACAGCCGAGGCCACCCGGCTGAAGAGAACCGCCAGAAGAAGATACACC AGACGGAAGAACCGGATCTGCTATCTGCAAGAGATCTTCAGCAACGAGATG GCCAAGGTGGACGACAGCTTCTTCCACAGACTGGAAGAGTCCTTCCTGGTG GAAGAGGATAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGAC GAGGTGGCCTACCACGAGAAGTACCCCACCATCTACCACCTGAGAAAGAAA CTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGATCTATCTGGCCCTG GCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAAC CCCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCAGACCTAC AACCAGCTGTTCGAGGAAAACCCCATCAACGCCAGCGGCGTGGACGCCAAG GCCATCCTGTCTGCCAGACTGAGCAAGAGCAGACGGCTGGAAAATCTGATC GCCCAGCTGCCCGGCGAGAAGAAGAATGGCCTGTTCGGCAACCTGATTGCC CTGAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAG GATGCCAAACTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAAC CTGCTGGCCCAGATCGGCGACCAGTACGCCGACCTGTTTCTGGCCGCCAAG

TABLE 7-continued

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
		AACCTGTCCGACGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAG
		ATCACCAAGGCCCCCCTGAGCGCCTCTATGATCAAGAGATACGACGAGCAC
		CACCAGGACCTGACCCTGCTGAAAGCTCTCGTGCGGCAGCAGCTGCCTGAG
		AAGTACAAAGAGATTTTCTTCGACCAGAGCAAGAACGGCTACGCCGGCTAC
		ATTGACGGCGGAGCCAGCCAGGAAGAGTTCTACAAGTTCATCAAGCCCATC
		CTGGAAAAGATGGACGGCACCGAGGAACTGCTCGTGAAGCTGAACAGAGAG
		GACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAG
		ATCCACCTGGGAGAGCTGCACGCCATTCTGCGGCGGCAGGAAGATTTTTAC
		CCATTCCTGAAGGACAACCGGGAAAAGATCGAGAAGATCCTGACCTTCCGC
		ATCCCCTACTACGTGGGCCCTCTGGCCAGGGGAAACAGCAGATTCGCCTGG
		ATGACCAGAAAGAGCGAGGAAACCATCACCCCCTGGAACTTCGAGGAAGTG
		GTGGACAAGGGCGCTTCCGCCCAGAGCTTCATCGAGCGGATGACCAACTTC
		GATAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCTGTAC
		GAGTACTTCACCGTGTATAACGAGCTGACCAAAGTGAAATACGTGACCGAG
		GGAATGAGAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTG
		GACCTGCTGTTCAAGACCAACCGGAAAGTGACCGTGAAGCAGCTGAAAGAG
		GACTACTTCAAGAAAATCGAGTGCTTCGACTCCGTGGAAATCTCCGGCGTG
		GAAGATCGGTTCAACGCCTCCCTGGGCACATACCACGATCTGCTGAAAATT
		ATCAAGGACAAGGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAA
		GATATCGTGCTGACCCTGACACTGTTTGAGGACAGAGAGATGATCGAGGAA
		CGGCTGAAAACCTATGCCCACCTGTTCGACGACAAAGTGATGAAGCAGCTG
		AAGCGGCGGAGATACACCGGCTGGGGCAGGCTGAGCCGGAAGCTGATCAAC
		GGCATCCGGGACAAGCAGTCCGGCAAGACAATCCTGGATTTCCTGAAGTCC
		GACGGCTTCGCCAACAGAAACTTCATGCAGCTGATCCACGACGACAGCCTG
		ACCTTTAAAGAGGACATCCAGAAAGCCCAGGTGTCCGGCCAGGGCGATAGC
		CTGCACGAGCACATTGCCAATCTGGCCGGCAGCCCCGCCATTAAGAAGGGC
		ATCCTGCAGACAGTGAAGGTGGTGGACGAGCTCGTGAAAGTGATGGGCCGG
		CACAAGCCCGAGAACATCGTGATCGAAATGGCCAGAGAGAACCAGACCACC
		CAGAAGGGACAGAAGAACAGCCGCGAGAGAATGAAGCGGATCGAAGAGGGC
		ATCAAAGAGCTGGGCAGCCAGATCCTGAAAGAACACCCCGTGGAAAACACC
		CAGCTGCAGAACGAGAAGCTGTACCTGTACTACCTGCAGAATGGGCGGGAT
		ATGTACGTGGACCAGGAACTGGACATCAACCGGCTGTCCGACTACGATGTG
		GACGCCATCGTGCCTCAGAGCTTTCTGAAGGACGACTCCATCGACAACAAG
		GTGCTGACCAGAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCTCC
		GAAGAGGTCGTGAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAACGCC
		AAGCTGATTACCCAGAGAAAGTTCGACAATCTGACCAAGGCCGAGAGAGGC
		GGCCTGAGCGAACTGGATAAGGCCGGCTTCATCAAGAGACAGCTGGTGGAA
		ACCCGGCAGATCACAAAGCACGTGGCACAGATCCTGGACTCCCGGATGAAC
		ACTAAGTACGACGAGAATGACAAGCTGATCCGGGAAGTGAAAGTGATCACC
		CTGAAGTCCAAGCTGGTGTCCGATTTCCGGAAGGATTTCCAGTTTTACAAA
		GTGCGCGAGATCAACAACTACCACCACGCCCACGACGCCTACCTGAACGCC
		GTCGTGGGAACCGCCCTGATCAAAAAGTACCCTAAGCTGGAAAGCGAGTTC
		GTGTACGGCGACTACAAGGTGTACGACGTGCGGAAGATGATCGCCAAGAGC
		GAGCAGGAAATCGGCAAGGCTACCGCCAAGTACTTCTTCTACAGCAACATC
		ATGAACTTTTTCAAGACCGAGATTACCCTGGCCAACGGCGAGATCCGGAAG
		CGGCCTCTGATCGAGACAAACGGCGAAACCGGGGAGATCGTGTGGGATAAG
		GGCCGGGATTTTGCCACCGTGCGGAAAGTGCTGAGCATGCCCCAAGTGAAT
		ATCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCAGCAAAGAGTCTATC
		CTGCCCAAGAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTGGGAC
		CCTAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTATTCTGTGCTG
		GTGGTGGCCAAAGTGGAAAAGGGCAAGTCCAAGAAACTGAAGAGTGTGAAA
		GAGCTGCTGGGGATCACCATCATGGAAAGAAGCAGCTTCGAGAAGAATCCC
		ATCGACTTTCTGGAAGCCAAGGGCTACAAAGAAGTGAAAAAGGACCTGATC
		ATCAAGCTGCCTAAGTACTCCCTGTTCGAGCTGGAAAACGGCCGGAAGAGA
		ATGCTGGCCTCTGCCGGCGAACTGCAGAAGGGAAACGAACTGGCCCTGCCC
		TCCAAATATGTGAACTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAG
		GGCTCCCCCGAGGATAATGAGCAGAAACAGCTGTTTGTGGAACAGCACAAG
		CACTACCTGGACGAGATCATCGAGCAGATCAGCGAGTTCTCCAAGAGAGTG
		ATCCTGGCCGACGCTAATCTGGACAAAGTGCTGTCCGCCTACAACAAGCAC
		CGGGATAAGCCCATCAGAGAGCAGGCCGAGAATATCATCCACCTGTTTACC
		CTGACCAATCTGGGAGCCCCTGCCGCCTTCAAGTACTTTGACACCACCATC
		GACCGGAAGAGGTACACCAGCACCAAAGAGGTGCTGGACGCCACCCTGATC
		CACCAGAGCATCACCGGCCTGTACGAGACACGGATCGACCTGTCTCAGCTG
		GGAGGCGACAGCCCCAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGC
		GGCTCCGAGACCCCAGGCACATCTGAGAGCGCCACCCCTGAGTCCACCGGT
		ATGAACAATTCACAGGGGAGAGTGACATTCGAAGACGTGACCGTGAACTTC
		ACCCAGGGAGAATGGCAGCGCTTGAACCCAGAACAAAGGAACCTCTATCGG
		GACGTGATGCTGGAAAACTACTCAAATTTGGTGAGCGTTGGGCAGGGTGAG
		ACCACTAAGCCTGACGTGATCCTGAGATTGGAACAGGGCAAGGAGCCTTGG
		CTCGAGGAAGAGGAAGTCCTGGGCTCAGGGAGGGCCGAGAAAAACGGTGAT
		ATAGGAGGCCAGATATGGAAGCCTAAGGACGTCAAGGAGAGCCTGAGCGCT
		GATTACAAAGATGATGACGATAAAGCCCCCAAGAAGAAAAGGAAGGTCCCA
		AAGAAAAAAAGAAAGGTGTGA

TABLE 7-continued

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
492	PLA003 amino acid sequence	MPKKKRKVPKKKRKVYNHDQEFDPPKVYPPVPAEKRKPIRVLSLEDGIATG LLVLKDLGIQVDRYIASEVCEDSITVGMVRHQGKIMYVGDVRSVTQKHIQE WGPFDLVIGGSPCNDLSIVNPARKGLYEGTGRLFFEFYRLLHDARPKEGDD RPFFWLFENVVAMGVSDKRDISRFLESNPVMIDAKEVSAAHRARYFWGNLP GMNRPLASTVNDKLELQECLEHGRIAKFSKVRTITTRSNSIKQGKDQHFPV FMNEKEDILWCTEMERVFGFPVHYTDVSNMSRLARQRLLGRSWSVPVIRHL FAPLKEYFACVSSGNSNANSRGPSFSSGLVPLSLRGSHMAAIPALDPEAEP SMDVILVGSSELSSSVSPGTGRDLIAYEVKANQRNIEDICICCGSLQVHTQ HPLFEGGICAPCKDKFLDALFLYDDDGYQSYCSICCSGETLLICGNPDCTR CYCFECVDSLVGPGTSGKVHAMSNWVCYLCLPSSRSGLLQRRRKWRSQLKA FYDRESENPLEMFETVPVWRRQPVRVLSLFEDIKKELTSLGFLESGSDPGQ LKHVVDVTDTVRKDVEEWGPFDLVYGATPPLGHTCDRPPSWYLFQFHRLLQ YARPKPGSPRPFFWMFVDNLVLNKEDLDVASRFLEMEPVTIPDVHGGSLQN AVRVWSNIPAIRSRHWALVSEEELSLLAQNKQSSKLAAKWPTKLVKNCFLP LREYFKYFSTELTSSLGGPSSGAPPPSGGSPAGSPTSTEEGTSESATPESG PGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSELEDKKY SIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLEDSG ETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLV EEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLAL AHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAK AILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNEDLAE DAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTE ITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGY IDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTEDNGSIPHQ IHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAW MTRKSEETITPWNFEEVVDKGASAQSFIERMTNEDKNLPNEKVLPKHSLLY EYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKE DYFKKIECFDSVEISGVEDRENASLGTYHDLLKIIKDKDELDNEENEDILE DIVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYTGWGRLSRKLIN GIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDS LHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTT QKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRD MYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPS EEVVKKMKNYWRQLLNAKLITQRKEDNLTKAERGGLSELDKAGFIKRQLVE TRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQFYK VREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKS EQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDK GRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWD PKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNP IDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALP SKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRV ILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYEDTTI DRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSPKKKRKVGVDGSS GSETPGTSESATPESTGMNNSQGRVTFEDVTVNETQGEWQRLNPEQRNLYR DVMLENYSNLVSVGQGETTKPDVILRLEQGKEPWLEEEEVLGSGRAEKNGD IGGQIWKPKDVKESLSAPKKKRKVPKKKRKV
493	PLA003 full plasmid sequence	GGGCGCTCGAGCAGGTTCAGAAGGAGATCAAAAACCCCCAAGGATCAAACA TGCCAAAAAAGAAGAGAAAGGTACCGAAGAAAAAAAGAAAGGTATACAATC ACGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGA AGAGGAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCC TGCTGGTGCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCG AGGTGTGCGAGGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGA TCATGTATGTGGGCGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGT GGGGCCCATTCGATCTGGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCA TCGTGAACCCTGCAAGGAAGGGACTGTACGAGGGAACCGGCCGGCTGTTCT TTGAGTTTTATAGACTGCTGCACGACGCCAGGCCTAAGGAGGGCGACGATA GACCATTCTTTTGGCTGTTCGAGAATGTGGTGGCTATGGGCGTGAGCGATA AGAGGGACATCTCCAGGTTTCTGGAGTCTAACCCCGTGATGATCGATGCAA AGGAGGTGTCCGCCGCACACAGAGCCAGGTATTTCTGGGGCAATCTGCCAG GAATGAACAGGCCACTGGCAAGCACCGTGAATGACAAGCTGGAGCTGCAGG AGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAAGGTGCGCACAATCA CCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCACTTCCCCGTGT TCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGAGAGAGTGT TCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCTGGCAA GGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCTGT TCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATG CCAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGA GGGGCTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTA GCATGGACGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTC CAGGAACCGGAAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGA ACATCGAGGACATCTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGC ACCCACTGTTCGAGGGAGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGG ACGCCCTGTTTCTGTACGACGATGACGGCTACCAGTCCTATTGCTCTATCT

TABLE 7-continued

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
		GCTGTTCCGGCGAGACCCTGCTGATCTGCGGCAATCCAGATTGTACAAGGT
		GCTATTGTTTTGAGTGCGTGGACTCTCTGGTGGGACCAGGCACCAGCGGAA
		AGGTGCACGCCATGTCCAACTGGGTGTGCTACCTGTGCCTGCCATCCTCTC
		GCAGCGGACTGCTGCAGCGGAGAAGGAAGTGGAGATCCCAGCTGAAGGCCT
		TCTATGATAGGGAGTCTGAGAACCCCCTGGAGATGTTTGAGACCGTGCCAG
		TGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTTCGAGGATATCAAGA
		AGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGACCCCGGACAGC
		TGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGTGGAGGAGT
		GGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACACACAT
		GCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCAGT
		ATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGG
		ATAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGG
		AGATGGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATG
		CCGTGCGCGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCAC
		TGGTGAGCGAGGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCA
		AGCTGGCCGCCAAGTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCAC
		TGCGGGAGTACTTCAAGTATTTTTCCACCGAGCTGACATCTAGCCTGGGAG
		GACCCTCCTCTGGCGCCCCACCACCTAGCGGCGGCTCCCCTGCCGGCTCTC
		CAACCAGCACAGAGGAGGGCACCAGCGAGTCCGCCACACCAGAGTCTGGAC
		CTGGCACCAGCACAGAGCCATCCGAGGGCTCTGCCCCAGGCTCTCCTGCAG
		GCAGCCCTACCTCCACCGAAGAGGGCACCAGCACAGAGCCTTCTGAGGGCA
		GCGCCCCAGGCACCTCTACAGAGCCAAGCGAGCTCGAGGACAAGAAGTACA
		GCATCGGCCTGGCCATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACCG
		ACGAGTACAAGGTGCCCAGCAAGAAATTCAAGGTGCTGGGCAACACCGACC
		GGCACAGCATCAAGAAGAACCTGATCGGAGCCCTGCTGTTCGACAGCGGCG
		AAACAGCCGAGGCCACCCGGCTGAAGAGAACCGCCAGAAGAAGATACACCA
		GACGGAAGAACCGGATCTGCTATCTGCAAGAGATCTTCAGCAACGAGATGG
		CCAAGGTGGACGACAGCTTCTTCCACAGACTGGAAGAGTCCTTCCTGGTGG
		AAGAGGATAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACG
		AGGTGGCCTACCACGAGAAGTACCCCACCATCTACCACCTGAGAAAGAAAC
		TGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGATCTATCTGGCCCTGG
		CCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACC
		CCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCAGACCTACA
		ACCAGCTGTTCGAGGAAAACCCCATCAACGCCAGCGGCGTGGACGCCAAGG
		CCATCCTGTCTGCCAGACTGAGCAAGAGCAGACGGCTGGAAAATCTGATCG
		CCCAGCTGCCCGGCGAGAAGAAGAATGGCCTGTTCGGCAACCTGATTGCCC
		TGAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAGG
		ATGCCAAACTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAACC
		TGCTGGCCCAGATCGGCGACCAGTACGCCGACCTGTTTCTGGCCGCCAAGA
		ACCTGTCCGACGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAGA
		TCACCAAGGCCCCCCTGAGCGCCTCTATGATCAAGAGATACGACGAGCACC
		ACCAGGACCTGACCCTGCTGAAAGCTCTCGTGCGGCAGCAGCTGCCTGAGA
		AGTACAAAGAGATTTTCTTCGACCAGAGCAAGAACGGCTACGCCGGCTACA
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		TGGAAAAGATGGACGGCACCGAGGAACTGCTCGTGAAGCTGAACAGAGAGG
		ACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAGA
		TCCACCTGGGAGAGCTGCACGCCATTCTGCGGCGGCAGGAAGATTTTTACC
		CATTCCTGAAGGACAACCGGGAAAAGATCGAGAAGATCCTGACCTTCCGCA
		TCCCCTACTACGTGGGCCCTCTGGCCAGGGGAAACAGCAGATTCGCCTGGA
		TGACCAGAAAGAGCGAGGAAACCATCACCCCCTGGAACTTCGAGGAAGTGG
		TGGACAAGGGCGCTTCCGCCCAGAGCTTCATCGAGCGGATGACCAACTTCG
		ATAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCTGTACG
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		GAATGAGAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTGG
		ACCTGCTGTTCAAGACCAACCGGAAAGTGACCGTGAAGCAGCTGAAAGAGG
		ACTACTTCAAGAAAATCGAGTGCTTCGACTCCGTGGAAATCTCCGGCGTGG
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		TCAAGGACAAGGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAAG
		ATATCGTGCTGACCCTGACACTGTTTGAGGACAGAGAGATGATCGAGGAAC
		GGCTGAAAACCTATGCCCACCTGTTCGACGACAAAGTGATGAAGCAGCTGA
		AGCGGCGGAGATACACCGGCTGGGGCAGGCTGAGCCGGAAGCTGATCAACG
		GCATCCGGGACAAGCAGTCCGGCAAGACAATCCTGGATTTCCTGAAGTCCG
		ACGGCTTCGCCAACAGAAACTTCATGCAGCTGATCCACGACGACAGCCTGA
		CCTTTAAAGAGGACATCCAGAAAGCCCAGGTGTCCGGCCAGGGCGATAGCC
		TGCACGAGCACATTGCCAATCTGGCCGGCAGCCCCGCCATTAAGAAGGGCA
		TCCTGCAGACAGTGAAGGTGGTGGACGAGCTCGTGAAAGTGATGGGCCGGC
		ACAAGCCCGAGAACATCGTGATCGAAATGGCCAGAGAGAACCAGACCACCC
		AGAAGGGACAGAAGAACAGCCGCGAGAGAATGAAGCGGATCGAAGAGGGCA
		TCAAAGAGCTGGGCAGCCAGATCCTGAAAGAACACCCCGTGGAAAACACCC
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		TGTACGTGGACCAGGAACTGGACATCAACCGGCTGTCCGACTACGATGTGG
		ACGCCATCGTGCCTCAGAGCTTTCTGAAGGACGACTCCATCGACAACAAGG
		TGCTGACCAGAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCTCCG
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TABLE 7-continued

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
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		CCCGGCAGATCACAAAGCACGTGGCACAGATCCTGGACTCCCGGATGAACA
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		TGAAGTCCAAGCTGGTGTCCGATTTCCGGAAGGATTTCCAGTTTTACAAAG
		TGCGCGAGATCAACAACTACCACCACGCCCACGACGCCTACCTGAACGCCG
		TCGTGGGAACCGCCCTGATCAAAAAGTACCCTAAGCTGGAAAGCGAGTTCG
		TGTACGGCGACTACAAGGTGTACGACGTGCGGAAGATGATCGCCAAGAGCG
		AGCAGGAAATCGGCAAGGCTACCGCCAAGTACTTCTTCTACAGCAACATCA
		TGAACTTTTTCAAGACCGAGATTACCCTGGCCAACGGCGAGATCCGGAAGC
		GGCCTCTGATCGAGACAAACGGCGAAACCGGGGAGATCGTGTGGGATAAGG
		GCCGGGATTTTGCCACCGTGCGGAAAGTGCTGAGCATGCCCCAAGTGAATA
		TCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCAGCAAAGAGTCTATCC
		TGCCCAAGAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTGGGACC
		CTAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTATTCTGTGCTGG
		TGGTGGCCAAAGTGGAAAAGGGCAAGTCCAAGAAACTGAAGAGTGTGAAAG
		AGCTGCTGGGGATCACCATCATGGAAAGAAGCAGCTTCGAGAAGAATCCCA
		TCGACTTTCTGGAAGCCAAGGGCTACAAAGAAGTGAAAAAGGACCTGATCA
		TCAAGCTGCCTAAGTACTCCCTGTTCGAGCTGGAAAACGGCCGGAAGAGAA
		TGCTGGCCTCTGCCGGCGAACTGCAGAAGGGAAACGAACTGGCCCTGCCCT
		CCAAATATGTGAACTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAGG
		GCTCCCCCGAGGATAATGAGCAGAAACAGCTGTTTGTGGAACAGCACAAGC
		ACTACCTGGACGAGATCATCGAGCAGATCAGCGAGTTCTCCAAGAGAGTGA
		TCCTGGCCGACGCTAATCTGGACAAAGTGCTGTCCGCCTACAACAAGCACC
		GGGATAAGCCCATCAGAGAGCAGGCCGAGAATATCATCCACCTGTTTACCC
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		GAGGCGACAGCCCCAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCG
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		ACGTGATGCTGGAAAACTACTCAAATTTGGTGAGCGTTGGGCAGGGTGAGA
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		TAGGAGGCCAGATATGGAAGCCTAAGGACGTCAAGGAGAGCCTGAGCGCTC
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		CCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTG
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		CAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGG
		GGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTC
		CCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACA
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		CAGACGAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCCTGTTAATTAAAAA
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		AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGCTTGA
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		CCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAAT
		AAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGG
		GGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCA
		GGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCA
		GCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGG
		GCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCT
		GCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGA
		ATCAGGGGATAACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGC
		CAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCC
		CCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCC
		GACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCG
		CTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCC
		TTCGGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTC
		GGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGCACGAACCCCCCGTTCA
		GCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTCCAACCCGGT
		AAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAG
		AGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTA
		CGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGT
		TACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCGC
		TGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAA
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TABLE 7-continued

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
		CTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAG TATATATGAGTAAACTTGGTCTGACAGTTAGAAAAACTCATCGAGCATCAA ATGAAACTGCAATTTATTCATATCAGGATTATCAATACCATATTTTTGAAA AAGCCGTTTCTGTAATGAAGGAGAAAACTCACCGAGGCAGTTCCATAGGAT GGCAAGATCCTGGTATCGGTCTGCGATTCCGACTCGTCCAACATCAATACA ACCTATTAATTTCCCCTCGTCAAAAATAAGGTTATCAAGTGAGAAATCACC ATGAGTGACGACTGAATCCGGTGAGAATGGCAAAAGTTTATGCATTTCTTT CCAGACTTGTTCAACAGGCCAGCCATTACGCTCGTCATCAAAATCACTCGC ATCAACCAAACCGTTATTCATTCGTGATTGCGCCTGAGCGAAACGAAATAC GCGATCGCTGTTAAAAGGACAATTACAAACAGGAATCGAATGCAACCGGCG CAGGAACACTGCCAGCGCATCAACAATATTTTCACCTGAATCAGGATATTC TTCTAATACCTGGAATGCTGTTTTCCCAGGGATCGCAGTGGTGAGTAACCA TGCATCATCAGGAGTACGGATAAAATGCTTGATGGTCGGAAGAGGCATAAA TTCCGTCAGCCAGTTTAGTCTGACCATCTCATCTGTAACATCATTGGCAAC GCTACCTTTGCCATGTTTCAGAAACAACTCTGGCGCATCGGGCTTCCCATA CAATCGATAGATTGTCGCACCTGATTGCCCGACATTATCGCGAGCCCATTT ATACCCATATAAATCAGCATCCATGTTGGAATTTAATCGCGGCCTAGAGCA AGACGTTTCCCGTTGAATATGGCTCATACTCTTCCTTTTTCAATATTATTG AAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTAT TTAGAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCC ACCTGACGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCAC TCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCC TGCTTGTGTGTTGGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTAC AACAAGGCAAGGCTTGACCGACAATTGCATGAAGAATCTGCTTAGGGTTAG GCGTTTTGCGCTGCTTCGCGATGTACGGGCCAGATATACGCGTTGACATTG ATTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAG CCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCCTGG CTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCC CATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTT ACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTAC GCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCA GTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGT CATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGG ATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAA TGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAA CAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCT TATCGAAATTAATACGACTCACTATAAG
494	PLA003 plasmid coding sequence	ATGCCAAAAAAGAAGAGAAAGGTACCGAAGAAAAAAAGAAAGGTATACAAT CACGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAG AAGAGGAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGC CTGCTGGTGCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCC GAGGTGTGCGAGGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAG ATCATGTATGTGGGCGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAG TGGGGCCCATTCGATCTGGTGATCGGCGGCAGCCCCTGTAATGACCTGTCC ATCGTGAACCCTGCAAGGAAGGGACTGTACGAGGGAACCGGCCGGCTGTTC TTTGAGTTTTATAGACTGCTGCACGACGCCAGGCCTAAGGAGGGCGACGAT AGACCATTCTTTTGGCTGTTCGAGAATGTGGTGGCTATGGGCGTGAGCGAT AAGAGGGACATCTCCAGGTTTCTGGAGTCTAACCCCGTGATGATCGATGCA AAGGAGGTGTCCGCCGCACACAGAGCCAGGTATTTCTGGGGCAATCTGCCA GGAATGAACAGGCCACTGGCAAGCACCGTGAATGACAAGCTGGAGCTGCAG GAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAAGGTGCGCACAATC ACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCACTTCCCCGTG TTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGAGAGAGTG TTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCTGGCA AGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCTG TTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAAT GCCAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTG AGGGGCTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCT AGCATGGACGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCT CCAGGAACCGGAAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGG AACATCGAGGACATCTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAG CACCCACTGTTCGAGGGAGGAATCTGCGCACCCTGTAAGGATAAGTTCCTG GACGCCCTGTTTCTGTACGACGATGACGGCTACCAGTCCTATTGCTCTATC TGCTGTTCCGGCGAGACCCTGCTGATCTGCGGCAATCCAGATTGTACAAGG TGCTATTGTTTTGAGTGCGTGGACTCTCTGGTGGGACCAGGCACCAGCGGA AAGGTGCACGCCATGTCCAACTGGGTGTGCTACCTGTGCCTGCCATCCTCT CGCAGCGGACTGCTGCAGCGGAGAAGGAAGTGGAGATCCCAGCTGAAGGCC TTCTATGATAGGGAGTCTGAGAACCCCCTGGAGATGTTTGAGACCGTGCCA GTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTTCGAGGATATCAAG AAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGACCCCGGACAG CTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGTGGAGGAG TGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACACACA TGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCAG

TABLE 7-continued

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
		TATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTG
		GATAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTG
		GAGATGGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAAT
		GCCGTGCGCGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCA
		CTGGTGAGCGAGGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGC
		AAGCTGGCCGCCAAGTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCA
		CTGCGGGAGTACTTCAAGTATTTTTCCACCGAGCTGACATCTAGCCTGGGA
		GGACCCTCCTCTGGCGCCCCACCACCTAGCGGCGGCTCCCCTGCCGGCTCT
		CCAACCAGCACAGAGGAGGGCACCAGCGAGTCCGCCACACCAGAGTCTGGA
		CCTGGCACCAGCACAGAGCCATCCGAGGGCTCTGCCCCAGGCTCTCCTGCA
		GGCAGCCCTACCTCCACCGAAGAGGGCACCAGCACAGAGCCTTCTGAGGGC
		AGCGCCCCAGGCACCTCTACAGAGCCAAGCGAGCTCGAGGACAAGAAGTAC
		AGCATCGGCCTGGCCATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACC
		GACGAGTACAAGGTGCCCAGCAAGAAATTCAAGGTGCTGGGCAACACCGAC
		CGGCACAGCATCAAGAAGAACCTGATCGGAGCCCTGCTGTTCGACAGCGGC
		GAAACAGCCGAGGCCACCCGGCTGAAGAGAACCGCCAGAAGAAGATACACC
		AGACGGAAGAACCGGATCTGCTATCTGCAAGAGATCTTCAGCAACGAGATG
		GCCAAGGTGGACGACAGCTTCTTCCACAGACTGGAAGAGTCCTTCCTGGTG
		GAAGAGGATAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGAC
		GAGGTGGCCTACCACGAGAAGTACCCCACCATCTACCACCTGAGAAAGAAA
		CTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGATCTATCTGGCCCTG
		GCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAAC
		CCCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCAGACCTAC
		AACCAGCTGTTCGAGGAAAACCCCATCAACGCCAGCGGCGTGGACGCCAAG
		GCCATCCTGTCTGCCAGACTGAGCAAGAGCAGACGGCTGGAAAATCTGATC
		GCCCAGCTGCCCGGCGAGAAGAAGAATGGCCTGTTCGGCAACCTGATTGCC
		CTGAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAG
		GATGCCAAACTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAAC
		CTGCTGGCCCAGATCGGCGACCAGTACGCCGACCTGTTTCTGGCCGCCAAG
		AACCTGTCCGACGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAG
		ATCACCAAGGCCCCCCTGAGCGCCTCTATGATCAAGAGATACGACGAGCAC
		CACCAGGACCTGACCCTGCTGAAAGCTCTCGTGCGGCAGCAGCTGCCTGAG
		AAGTACAAAGAGATTTTCTTCGACCAGAGCAAGAACGGCTACGCCGGCTAC
		ATTGACGGCGGAGCCAGCCAGGAAGAGTTCTACAAGTTCATCAAGCCCATC
		CTGGAAAAGATGGACGGCACCGAGGAACTGCTCGTGAAGCTGAACAGAGAG
		GACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAG
		ATCCACCTGGGAGAGCTGCACGCCATTCTGCGGCGGCAGGAAGATTTTTAC
		CCATTCCTGAAGGACAACCGGGAAAAGATCGAGAAGATCCTGACCTTCCGC
		ATCCCCTACTACGTGGGCCCTCTGGCCAGGGGAAACAGCAGATTCGCCTGG
		ATGACCAGAAAGAGCGAGGAAACCATCACCCCCTGGAACTTCGAGGAAGTG
		GTGGACAAGGGCGCTTCCGCCCAGAGCTTCATCGAGCGGATGACCAACTTC
		GATAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCTGTAC
		GAGTACTTCACCGTGTATAACGAGCTGACCAAAGTGAAATACGTGACCGAG
		GGAATGAGAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTG
		GACCTGCTGTTCAAGACCAACCGGAAAGTGACCGTGAAGCAGCTGAAAGAG
		GACTACTTCAAGAAAATCGAGTGCTTCGACTCCGTGGAAATCTCCGGCGTG
		GAAGATCGGTTCAACGCCTCCCTGGGCACATACCACGATCTGCTGAAAATT
		ATCAAGGACAAGGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAA
		GATATCGTGCTGACCCTGACACTGTTTGAGGACAGAGAGATGATCGAGGAA
		CGGCTGAAAACCTATGCCCACCTGTTCGACGACAAAGTGATGAAGCAGCTG
		AAGCGGCGGAGATACACCGGCTGGGGCAGGCTGAGCCGGAAGCTGATCAAC
		GGCATCCGGGACAAGCAGTCCGGCAAGACAATCCTGGATTTCCTGAAGTCC
		GACGGCTTCGCCAACAGAAACTTCATGCAGCTGATCCACGACGACAGCCTG
		ACCTTTAAAGAGGACATCCAGAAAGCCCAGGTGTCCGGCCAGGGCGATAGC
		CTGCACGAGCACATTGCCAATCTGGCCGGCAGCCCCGCCATTAAGAAGGGC
		ATCCTGCAGACAGTGAAGGTGGTGGACGAGCTCGTGAAAGTGATGGGCCGG
		CACAAGCCCGAGAACATCGTGATCGAAATGGCCAGAGAGAACCAGACCACC
		CAGAAGGGACAGAAGAACAGCCGCGAGAGAATGAAGCGGATCGAAGAGGGC
		ATCAAAGAGCTGGGCAGCCAGATCCTGAAAGAACACCCCGTGGAAAACACC
		CAGCTGCAGAACGAGAAGCTGTACCTGTACTACCTGCAGAATGGGCGGGAT
		ATGTACGTGGACCAGGAACTGGACATCAACCGGCTGTCCGACTACGATGTG
		GACGCCATCGTGCCTCAGAGCTTTCTGAAGGACGACTCCATCGACAACAAG
		GTGCTGACCAGAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCTCC
		GAAGAGGTCGTGAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAACGCC
		AAGCTGATTACCCAGAGAAAGTTCGACAATCTGACCAAGGCCGAGAGAGGC
		GGCCTGAGCGAACTGGATAAGGCCGGCTTCATCAAGAGACAGCTGGTGGAA
		ACCCGGCAGATCACAAAGCACGTGGCACAGATCCTGGACTCCCGGATGAAC
		ACTAAGTACGACGAGAATGACAAGCTGATCCGGGAAGTGAAAGTGATCACC
		CTGAAGTCCAAGCTGGTGTCCGATTTCCGGAAGGATTTCCAGTTTTACAAA
		GTGCGCGAGATCAACAACTACCACCACGCCCACGACGCCTACCTGAACGCC
		GTCGTGGGAACCGCCCTGATCAAAAAGTACCCTAAGCTGGAAAGCGAGTTC
		GTGTACGGCGACTACAAGGTGTACGACGTGCGGAAGATGATCGCCAAGAGC
		GAGCAGGAAATCGGCAAGGCTACCGCCAAGTACTTCTTCTACAGCAACATC
		ATGAACTTTTTCAAGACCGAGATTACCCTGGCCAACGGCGAGATCCGGAAG
		CGGCCTCTGATCGAGACAAACGGCGAAACCGGGGAGATCGTGTGGGATAAG

TABLE 7-continued

sequences of exemplary epigenetic editors

SEQ ID NO	Description	Sequence
		GGCCGGGATTTTGCCACCGTGCGGAAAGTGCTGAGCATGCCCCAAGTGAAT ATCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCAGCAAAGAGTCTATC CTGCCCAAGAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTGGGAC CCTAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTATTCTGTGCTG GTGGTGGCCAAAGTGGAAAAGGGCAAGTCCAAGAAACTGAAGAGTGTGAAA GAGCTGCTGGGGATCACCATCATGGAAAGAAGCAGCTTCGAGAAGAATCCC ATCGACTTTCTGGAAGCCAAGGGCTACAAAGAAGTGAAAAAGGACCTGATC ATCAAGCTGCCTAAGTACTCCCTGTTCGAGCTGGAAAACGGCCGGAAGAGA ATGCTGGCCTCTGCCGGCGAACTGCAGAAGGGAAACGAACTGGCCCTGCCC TCCAAATATGTGAACTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAG GGCTCCCCCGAGGATAATGAGCAGAAACAGCTGTTTGTGGAACAGCACAAG CACTACCTGGACGAGATCATCGAGCAGATCAGCGAGTTCTCCAAGAGAGTG ATCCTGGCCGACGCTAATCTGGACAAAGTGCTGTCCGCCTACAACAAGCAC CGGGATAAGCCCATCAGAGAGCAGGCCGAGAATATCATCCACCTGTTTACC CTGACCAATCTGGGAGCCCCTGCCGCCTTCAAGTACTTTGACACCACCATC GACCGGAAGAGGTACACCAGCACCAAAGAGGTGCTGGACGCCACCCTGATC CACCAGAGCATCACCGGCCTGTACGAGACACGGATCGACCTGTCTCAGCTG GGAGGCGACAGCCCCAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGC GGCTCCGAGACCCCAGGCACATCTGAGAGCGCCACCCCTGAGTCCACCGGT ATGAACAATTCACAGGGGAGAGTGACATTCGAAGACGTGACCGTGAACTTC ACCCAGGGAGAATGGCAGCGCTTGAACCCAGAACAAAGGAACCTCTATCGG GACGTGATGCTGGAAAACTACTCAAATTTGGTGAGCGTTGGGCAGGGTGAG ACCACTAAGCCTGACGTGATCCTGAGATTGGAACAGGGCAAGGAGCCTTGG CTCGAGGAAGAGGAAGTCCTGGGCTCAGGGAGGGCCGAGAAAAACGGTGAT ATAGGAGGCCAGATATGGAAGCCTAAGGACGTCAAGGAGAGCCTGAGCGCT CCCAAGAAGAAAAGGAAGGTCCCAAAGAAAAAAAGAAAGGTGTGA

Table 8 below lists components of the fusion polypeptide PLA001 and their corresponding amino acid position in the fusion polypeptide sequence (SEQ ID No. 481) set forth in Table 7.

TABLE 8

annotation of PLA001 amino acid sequence

	Type	Start	End	Length
SV40 NLS	CDS	2	8	7
SV40 NLS	CDS	9	15	7
DNMT3A	CDS	17	317	301
Linker	CDS	318	344	27
DNMT3L full-length	CDS	345	730	386
XTEN80	CDS	731	810	80
dCas9	CDS	811	2180	1370
NLS	CDS	2181	2187	7
XTEN16	CDS	2188	2208	21
ZN627	CDS	2211	2290	80
FLAG	CDS	2293	2300	8
SV40 NLS	CDS	2302	2308	7
SV40 NLS	CDS	2309	2315	7

Table 9 below lists components of the polynucleotide encoding the fusion polypeptide PLA001 and their corresponding nucleotide position in the polynucleotide sequence (SEQ ID No. 482) set forth in Table 7.

TABLE 9

annotation of PLA001 polynucleotide sequence

Name	Type	Minimum	Maximum	Length
SV40 NLS	CDS	4	24	21
SV40 NLS	CDS	25	44	20
DNMT3A	CDS	49	951	903
Linker	CDS	952	1032	81

TABLE 9-continued

annotation of PLA001 polynucleotide sequence

Name	Type	Minimum	Maximum	Length
DNMT3L full-length	CDS	1033	2190	1158
XTEN80	CDS	2191	2430	240
dCas9	CDS	2431	6540	4110
NLS	CDS	6541	6561	21
XTEN16	CDS	6562	6624	63
ZN627	CDS	6631	6870	240
FLAG	CDS	6877	6900	24
SV40 NLS	CDS	6904	6924	21
SV40 NLS	CDS	6925	6945	21

Table 10 below lists components of the fusion polypeptide PLA002 and their corresponding amino acid position in the fusion polypeptide sequence (SEQ ID No. 483) set forth in Table 7.

TABLE 10

annotation of PLA002 amino acid sequence

Name	Type	Minimum	Maximum	Length
SV40 NLS	CDS	2	8	7
SV40 NLS	CDS	9	15	7
DNMT3A	CDS	17	317	301
Linker	CDS	318	344	27
DNMT3L full-length	CDS	345	730	386
XTEN80	CDS	731	810	80
dCas9	CDS	811	2180	1370
NLS	CDS	2181	2187	7
XTEN16	CDS	2188	2208	21
ZIM3	CDS	2211	2310	100
FLAG	CDS	2313	2320	8
SV40 NLS	CDS	2322	2328	7
SV40 NLS	CDS	2329	2335	7

Table 11 below lists components of the polynucleotide encoding the fusion polypeptide PLA002 and their corresponding nucleotide position in the polynucleotide sequence (SEQ ID No. 484) set forth in Table 7.

TABLE 11

annotation of PLA002 polynucleotide sequence

Name	Type	Minimum	Maximum	Length
SV40 NLS	CDS	4	24	21
SV40 NLS	CDS	25	45	21
DNMT3A	CDS	49	951	903
Linker	CDS	952	1032	81
DNMT3L full-length	CDS	1033	2190	1158

TABLE 11-continued

annotation of PLA002 polynucleotide sequence

Name	Type	Minimum	Maximum	Length
XTEN80	CDS	2191	2430	240
dCas9	CDS	2431	6540	4110
NLS	CDS	6541	6561	21
XTEN16	CDS	6562	6624	63
ZIM3	CDS	6631	6930	300
FLAG	CDS	6937	6960	24
SV40 NLS	CDS	6964	6984	21
SV40 NLS	CDS	6985	7005	21
stop	terminator	7006	7008	3

Table 12 below provides gRNA sequence tested.

TABLE 12

Exemplary gRNA sequences

SEQ IDs	Target domain sequence	SEQ IDs	gRNA sequence
333	CCTGCTGGTG GCTCCAGTTC	1093	CCUGCUGGUGGCUCCAGUUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
334	CTGAACTGGA GCCACCAGCA	1094	CUGAACUGGAGCCACCAGCAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
335	CCTGAACTGG AGCCACCAGC	1095	CCUGAACUGGAGCCACCAGCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
336	CCTCGAGAAG ATTGACGATA	1096	CCUCGAGAAGAUUGACGAUAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
337	TCGTCAATCT TCTCGAGGAT	1097	UCGUCAAUCUUCUCGAGGAUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
338	CGTCAATCTT CTCGAGGATT	1098	CGUCAAUCUUCUCGAGGAUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
339	GTCAATCTTC TCGAGGATTG	1099	GUCAAUCUUCUCGAGGAUUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
340	AACATGGAGA ACATCACATC	1100	AACAUGGAGAACAUCACAUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
341	AACATCACAT CAGGATTCCT	1101	AACAUCACAUCAGGAUUCCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
342	CTAGACTCTG CGGTATTGTG	1102	CUAGACUCUGCGGUAUUGUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
343	TACCGCAGAG TCTAGACTCG	1103	UACCGCAGAGUCUAGACUCGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
344	CGCAGAGTCT AGACTCGTGG	1104	CGCAGAGUCUAGACUCGUGGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
345	CACCACGAGT CTAGACTCTG	1105	CACCACGAGUCUAGACUCUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
346	TGGACTTCTC TCAATTTTCT	1106	UGGACUUCUCUCAAUUUUCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
347	GGACTTCTCT CAATTTTCTA	1107	GGACUUCUCUCAAUUUUCUAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
348	GACTTCTCTC AATTTTCTAG	1108	GACUUCUCUCAAUUUUCUAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
349	ACTTCTCTCA ATTTTCTAGG	1109	ACUUCUCUCAAUUUUCUAGGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
350	CGAATTTTGG CCAAGACACA	1110	CGAAUUUUGGCCAAGACACAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU

TABLE 12-continued

Exemplary qRNA sequences

SEQ IDs	Target domain sequence	SEQ IDs	gRNA sequence
351	AGGTTGGGGA CTGCGAATTT	1111	AGGUUGGGGACUGCGAAUUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
352	GGCATAGCAG CAGGATGAAG	1112	GGCAUAGCAGCAGGAUGAAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
353	AGAAGATGAG GCATAGCAGC	1113	AGAAGAUGAGGCAUAGCAGCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
354	GCTATGCCTC ATCTTCTTGT	1114	GCUAUGCCUCAUCUUCUUGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
355	GAAGAACCAA CAAGAAGATG	1115	GAAGAACCAACAAGAAGAUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
356	CATCTTCTTG TTGGTTCTTC	1116	CAUCUUCUUGUUGGUUCUUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
357	CCCGTTTGTC CTCTAATTCC	1117	CCCGUUUGUCCUCUAAUUCCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
358	CCTGGAATTA GAGGACAAAC	1118	CCUGGAAUUAGAGGACAAACGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
359	TCCTGGAATT AGAGGACAAA	1119	UCCUGGAAUUAGAGGACAAAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
360	TACTAGTGCC ATTTGTTCAG	1120	UACUAGUGCCAUUUGUUCAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
361	CCATTTGTTC AGTGGTTCGT	1121	CCAUUUGUUCAGUGGUUCGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
362	CATTTGTTCA GTGGTTCGTA	1122	CAUUUGUUCAGUGGUUCGUAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
363	CCTACGAACC ACTGAACAAA	1123	CCUACGAACCACUGAACAAAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
364	TTTCAGTTAT ATGGATGATG	1124	UUUCAGUUAUAUGGAUGAUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
365	CAAAAGAAAA TTGGTAACAG	1125	CAAAAGAAAAUUGGUAACAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
366	TACCAATTTT CTTTTGTCTT	1126	UACCAAUUUUCUUUUGUCUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
367	ACCAATTTTC TTTTGTCTTT	1127	ACCAAUUUUCUUUUGUCUUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
368	ACCCAAAGAC AAAAGAAAAT	1128	ACCCAAAGACAAAAGAAAAUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
369	TGACATACTT TCCAATCAAT	1129	UGACAUACUUUCCAAUCAAUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
370	CACTTTCTCG CCAACTTACA	1130	CACUUUCUCGCCAACUUACAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
371	CACAGAAAGG CCTTGTAAGT	1131	CACAGAAAGGCCUUGUAAGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
372	TGAACCTTTA CCCCGTTGCC	1132	UGAACCUUUACCCCGUUGCCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
373	GGGCAACGGG GTAAAGGTTC	1133	GGGCAACGGGGUAAAGGUUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
374	TTTACCCCGT TGCCCGGCAA	1134	UUUACCCCGUUGCCCGGCAAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU

TABLE 12-continued

Exemplary qRNA sequences

SEQ IDs	Target domain sequence	SEQ IDs	gRNA sequence
375	GTTGCCGGGC AACGGGGTAA	1135	GUUGCCGGGCAACGGGGUAAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
376	CCCGTTGCCC GGCAACGGCC	1136	CCCGUUGCCCGGCAACGGCCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
377	CTGGCCGTTG CCGGGCAACG	1137	CUGGCCGUUGCCGGGCAACGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
378	CCTGGCCGTT GCCGGGCAAC	1138	CCUGGCCGUUGCCGGGCAACGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
379	ACCTGGCCGT TGCCGGGCAA	1139	ACCUGGCCGUUGCCGGGCAAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
380	GCACAGACCT GGCCGTTGCC	1140	GCACAGACCUGGCCGUUGCCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
381	GGCACAGACC TGGCCGTTGC	1141	GGCACAGACCUGGCCGUUGCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
382	GCAAACACTT GGCACAGACC	1142	GCAAACACUUGGCACAGACCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
383	GGGTTGCGTC AGCAAACACT	1143	GGGUUGCGUCAGCAAACACUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
384	TTTGCTGACG CAACCCCCAC	1144	UUUGCUGACGCAACCCCCACGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
385	CTGACGCAAC CCCCACTGGC	1145	CUGACGCAACCCCCACUGGCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
386	TGACGCAACC CCCACTGGCT	1146	UGACGCAACCCCCACUGGCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
387	GACGCAACCC CCACTGGCTG	1147	GACGCAACCCCCACUGGCUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
388	AACCCCCACT GGCTGGGGCT	1148	AACCCCCACUGGCUGGGGCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
389	TCCTCTGCCG ATCCATACTG	1149	UCCUCUGCCGAUCCAUACUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
390	TCCGCAGTAT GGATCGGCAG	1150	UCCGCAGUAUGGAUCGGCAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
391	AGGAGTTCCG CAGTATGGAT	1151	AGGAGUUCCGCAGUAUGGAUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
392	CGGCTAGGAG TTCCGCAGTA	1152	CGGCUAGGAGUUCCGCAGUAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
393	TGCGAGCAAA ACAAGCGGCT	1153	UGCGAGCAAAACAAGCGGCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
394	CCGCTTGTTT TGCTCGCAGC	1154	CCGCUUGUUUUGCUCGCAGCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
395	CCTGCTGCGA GCAAAACAAG	1155	CCUGCUGCGAGCAAAACAAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
396	TGTTTTGCTC GCAGCAGGTC	1156	UGUUUUGCUCGCAGCAGGUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
397	GCAGCACAGC CTAGCAGCCA	1157	GCAGCACAGCCUAGCAGCCAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
398	TGCTAGGCTG TGCTGCCAAC	1158	UGCUAGGCUGUGCUGCCAACGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU

TABLE 12-continued

Exemplary qRNA sequences

SEQ IDs	Target domain sequence	SEQ IDs	gRNA sequence
399	GCTGCCAACT GGATCCTGCG	1159	GCUGCCAACUGGAUCCUGCGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
400	CTGCCAACTG GATCCTGCGC	1160	CUGCCAACUGGAUCCUGCGCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
401	CGTCCCGCGC AGGATCCAGT	1161	CGUCCCGCGCAGGAUCCAGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
402	AAACAAAGGA CGTCCCGCGC	1162	AAACAAAGGACGUCCCGCGCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
403	GTCCTTTGTT TACGTCCCGT	1163	GUCCUUUGUUUACGUCCCGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
404	CGCCGACGGG ACGTAAACAA	1164	CGCCGACGGGACGUAAACAAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
405	TGCCGTTCCG ACCGACCACG	1165	UGCCGUUCCGACCGACCACGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
406	AGGTGCGCCC CGTGGTCGGT	1166	AGGUGCGCCCCGUGGUCGGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
407	AGAGAGGTGC GCCCCGTGGT	1167	AGAGAGGUGCGCCCCGUGGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
408	GTAAAGAGAG GTGCGCCCCG	1168	GUAAAGAGAGGUGCGCCCCGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
409	GGGGCGCACC TCTCTTTACG	1169	GGGGCGCACCUCUCUUUACGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
410	CGGGGAGTCC GCGTAAAGAG	1170	CGGGGAGUCCGCGUAAAGAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
411	CAGATGAGAA GGCACAGACG	1171	CAGAUGAGAAGGCACAGACGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
412	GTCTGTGCCT TCTCATCTGC	1172	GUCUGUGCCUUCUCAUCUGCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
413	GGCAGATGAG AAGGCACAGA	1173	GGCAGAUGAGAAGGCACAGAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
414	GCAGATGAGA AGGCACAGAC	1174	GCAGAUGAGAAGGCACAGACGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
415	ACACGGTCCG GCAGATGAGA	1175	ACACGGUCCGGCAGAUGAGAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
416	GAAGCGAAGT GCACACGGTC	1176	GAAGCGAAGUGCACACGGUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
417	GAGGTGAAGC GAAGTGCACA	1177	GAGGUGAAGCGAAGUGCACAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
418	CTTCACCTCT GCACGTCGCA	1178	CUUCACCUCUGCACGUCGCAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
419	GGTCTCCATG CGACGTGCAG	1179	GGUCUCCAUGCGACGUGCAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
420	TGCCCAAGGT CTTACATAAG	1180	UGCCCAAGGUCUUACAUAAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
421	GTCCTCTTAT GTAAGACCTT	1181	GUCCUCUUAUGUAAGACCUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
422	AGTCCTCTTA TGTAAGACCT	1182	AGUCCUCUUAUGUAAGACCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU

TABLE 12-continued

Exemplary qRNA sequences

SEQ IDs	Target domain sequence	SEQ IDs	gRNA sequence
423	GTCTTACATA AGAGGACTCT	1183	GUCUUACAUAAGAGGACUCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
424	AATGTCAACG ACCGACCTTG	1184	AAUGUCAACGACCGACCUUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
425	TTTGAAGTAT GCCTCAAGGT	1185	UUUGAAGUAUGCCUCAAGGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
426	AGTCTTTGAA GTATGCCTCA	1186	AGUCUUUGAAGUAUGCCUCAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
427	AAGACTGTTT GTTTAAAGAC	1187	AAGACUGUUUGUUUAAAGACGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
428	AGACTGTTTG TTTAAAGACT	1188	AGACUGUUUGUUUAAAGACUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
429	CTGTTTGTTT AAAGACTGGG	1189	CUGUUUGUUUAAAGACUGGGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
430	GTTTAAAGAC TGGGAGGAGT	1190	GUUUAAAGACUGGGAGGAGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
431	TCTTTGTACT AGGAGGCTGT	1191	UCUUUGUACUAGGAGGCUGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
432	AGGAGGCTGT AGGCATAAAT	1192	AGGAGGCUGUAGGCAUAAAUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
433	GTGAAAAAGT TGCATGGTGC	1193	GUGAAAAAGUUGCAUGGUGCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
434	GCAGAGGTGA AAAAGTTGCA	1194	GCAGAGGUGAAAAAGUUGCAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
435	AACAAGAGAT GATTAGGCAG	1195	AACAAGAGAUGAUUAGGCAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
436	GACATGAACA AGAGATGATT	1196	GACAUGAACAAGAGAUGAUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
437	AGCTTGGAGG CTTGAACAGT	1197	AGCUUGGAGGCUUGAACAGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
438	CAAGCCTCCA AGCTGTGCCT	1198	CAAGCCUCCAAGCUGUGCCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
439	AAGCCTCCAA GCTGTGCCTT	1199	AAGCCUCCAAGCUGUGCCUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
440	CCTCCAAGCT GTGCCTTGGG	1200	CCUCCAAGCUGUGCCUUGGGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
441	CCACCCAAGG CACAGCTTGG	1201	CCACCCAAGGCACAGCUUGGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
442	AGCTGTGCCT TGGGTGGCTT	1202	AGCUGUGCCUUGGGUGGCUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
443	AAGCCACCCA AGGCACAGCT	1203	AAGCCACCCAAGGCACAGCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
444	GCTGTGCCTT GGGTGGCTTT	1204	GCUGUGCCUUGGGUGGCUUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
445	CTGTGCCTTG GGTGGCTTTG	1205	CUGUGCCUUGGGUGGCUUUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
446	TAGCTCCAAA TTCTTTATAA	1206	UAGCUCCAAAUUCUUUAUAAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU

TABLE 12-continued

Exemplary qRNA sequences

SEQ IDs	Target domain sequence	SEQ IDs	gRNA sequence
447	GTAGCTCCAA ATTCTTTATA	1207	GUAGCUCCAAAUUCUUUAUAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
448	TAAAGAATTT GGAGCTACTG	1208	UAAAGAAUUUGGAGCUACUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
449	ATGACTCTAG CTACCTGGGT	1209	AUGACUCUAGCUACCUGGGUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
450	CACATTTCTT GTCTCACTTT	1210	CACAUUUCUUGUCUCACUUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
451	TAGTTTCCGG AAGTGTTGAT	1211	UAGUUUCCGGAAGUGUUGAUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
452	CGTCTAACAA CAGTAGTTTC	1212	CGUCUAACAACAGUAGUUUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
453	ACTACTGTTG TTAGACGACG	1213	ACUACUGUUGUUAGACGACGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
454	CTGTTGTTAG ACGACGAGGC	1214	CUGUUGUUAGACGACGAGGCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
455	CGAGGGAGTT CTTCTTCTAG	1215	CGAGGGAGUUCUUCUUCUAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
456	GCGAGGGAGT TCTTCTTCTA	1216	GCGAGGGAGUUCUUCUUCUAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
457	GGCGAGGGAG TTCTTCTTCT	1217	GGCGAGGGAGUUCUUCUUCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
458	CTCCCTCGCC TCGCAGACGA	1218	CUCCCUCGCCUCGCAGACGAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
459	GACCTTCGTC TGCGAGGCGA	1219	GACCUUCGUCUGCGAGGCGAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
460	AGACCTTCGT CTGCGAGGCG	1220	AGACCUUCGUCUGCGAGGCGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
461	GATTGAGACC TTCGTCTGCG	1221	GAUUGAGACCUUCGUCUGCGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
462	GATTGAGATC TTCTGCGACG	1222	GAUUGAGAUCUUCUGCGACGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
463	GTCGCAGAAG ATCTCAATCT	1223	GUCGCAGAAGAUCUCAAUCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
464	TCGCAGAAGA TCTCAATCTC	1224	UCGCAGAAGAUCUCAAUCUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
465	ATATGGTGAC CCACAAAATG	1225	AUAUGGUGACCCACAAAAUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
466	TTTGTGGGTC ACCATATTCT	1226	UUUGUGGGUCACCAUAUUCUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
467	TTGTGGGTCA CCATATTCTT	1227	UUGUGGGUCACCAUAUUCUUGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
468	GCTGGATCCA ACTGGTGGTC	1228	GCUGGAUCCAACUGGUGGUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
469	CACCCCAAAA GGCCTCCGTG	1229	CACCCCAAAAGGCCUCCGUGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
470	CCTTTTGGGG TGGAGCCCTC	1230	CCUUUUGGGGUGGAGCCCUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU

TABLE 12-continued

Exemplary qRNA sequences

SEQ IDs	Target domain sequence	SEQ IDs	gRNA sequence
471	CCTGAGGGCT CCACCCCAAA	1231	CCUGAGGGCUCCACCCCAAAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
472	GGGGTGGAGC CCTCAGGCTC	1232	GGGGUGGAGCCCUCAGGCUCGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
473	GGGTGGAGCC CTCAGGCTCA	1233	GGGUGGAGCCCUCAGGCUCAGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
474	CGATTGGTGG AGGCAGGAGG	1234	CGAUUGGUGGAGGCAGGAGGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU
475	CTCATCCTCA GGCCATGCAG	1235	CUCAUCCUCAGGCCAUGCAGGUUUAAGAGCUAAGCUGGAAACAGCAUAGCAAGUUUAAAU AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU

TABLE 13

Exemplary target domain sequences and effect on HbeAg and HbsAg expression guide RNA

SEQ IDs	Associated guide RNA name (if applicable)	Target domain sequence	HbeAg (%expression of non targeting control)	HbsAg (%expression of non targeting control)
334	gRNA#001	CTGAACTGGAGCCACCAGCA	27.77203753	23.4507853
335	gRNA#002	CCTGAACTGGAGCCACCAGC	41.3794605	42.3814023
333		CCTGCTGGTGGCTCCAGTTC	65.36067834	43.2303179
336		CCTCGAGAAGATTGACGATA	82.8943107	72.648219
337		TCGTCAATCTTCTCGAGGAT	45.82985382	59.7223204
338		CGTCAATCTTCTCGAGGATT	70.38176383	73.1313979
339		GTCAATCTTCTCGAGGATTG	51.92713248	54.330978
340		AACATGGAGAACATCACATC	79.31612772	80.8981286
341		AACATCACATCAGGATTCCT	41.40633262	37.5509299
342		CTAGACTCTGCGGTATTGTG	48.56267424	41.5330827
345	gRNA#003	CACCACGAGTCTAGACTCTG	44.43853541	40.8553881
343		TACCGCAGAGTCTAGACTCG	49.18078863	56.151898
344		CGCAGAGTCTAGACTCGTGG	52.41583101	57.2264647
346		TGGACTTCTCTCAATTTTCT	49.58564481	51.1350719
347		GGACTTCTCTCAATTTTCTA	76.16671739	79.1684976
348		GACTTCTCTCAATTTTCTAG	49.79317156	54.1540479
349		ACTTCTCTCAATTTTCTAGG	69.66968253	77.4650531
350		CGAATTTTGGCCAAGACACA	53.53282063	54.0024954
371	gRNA#004	CACAGAAAGGCCTTGTAAGT	42.35590319	41.6928086
370		CACTTTCTCGCCAACTTACA	53.25960148	55.120666
373	gRNA#005	GGGCAACGGGGTAAAGGTTC	36.54111842	42.8120918
375	gRNA#006	GTTGCCGGGCAACGGGGTAA	41.20322042	38.1885911
377		CTGGCCGTTGCCGGGCAACG	57.27834882	60.830473

TABLE 13-continued

Exemplary target domain sequences and effect on HbeAg and HbsAg expression guide RNA

SEQ IDs	Associated guide RNA name (if applicable)	Target domain sequence	HbeAg (%expression of non targeting control)	HbsAg (%expression of non targeting control)
372		TGAACCTTTACCCCGTTGCC	48.16509881	60.952804
378		CCTGGCCGTTGCCGGGCAAC	56.34234102	65.50842
379		ACCTGGCCGTTGCCGGGCAA	54.10829257	53.324749
374		TTTACCCCGTTGCCCGGCAA	56.72089131	62.6906255
380		GCACAGACCTGGCCGTTGCC	42.46818432	47.3720079
381		GGCACAGACCTGGCCGTTGC	72.65381719	77.2400091
376		CCCGTTGCCCGGCAACGGCC	50.93018919	61.086777
382		GCAAACACTTGGCACAGACC	57.0196485	69.491449
383		GGGTTGCGTCAGCAAACACT	49.73518831	54.7510029
384		TTTGCTGACGCAACCCCCAC	41.79724731	50.0362297
385		CTGACGCAACCCCCACTGGC	36.90727137	36.8247762
386		TGACGCAACCCCCACTGGCT	46.49501492	59.6959921
387		GACGCAACCCCCACTGGCTG	40.09200943	51.4756937
388		AACCCCCACTGGCTGGGGCT	61.82883278	79.8761795
390	gRNA#007	TCCGCAGTATGGATCGGCAG	26.33655968	33.7255842
391	gRNA#008	AGGAGTTCCGCAGTATGGAT	28.49512897	40.080391
389	gRNA#009	TCCTCTGCCGATCCATACTG	28.45399116	42.735093
392		CGGCTAGGAGTTCCGCAGTA	56.5241517	66.9060644
393	gRNA#010	TGCGAGCAAAACAAGCGGCT	41.5479747	40.5350018
395		CCTGCTGCGAGCAAAACAAG	36.4525077	50.516964
394		CCGCTTGTTTTGCTCGCAGC	108.4014077	90.5082399
396		TGTTTTGCTCGCAGCAGGTC	68.78508191	75.7537996
397		GCAGCACAGCCTAGCAGCCA	78.73231487	68.3785588
398		TGCTAGGCTGTGCTGCCAAC	59.52249922	69.0333267
401		CGTCCCGCGCAGGATCCAGT	52.51634701	49.5876502
399		GCTGCCAACTGGATCCTGCG	75.81794218	89.0162904
400		CTGCCAACTGGATCCTGCGC	77.79441236	73.9461516
402		AAACAAAGGACGTCCCGCGC	67.52500576	72.6685954
404		CGCCGACGGGACGTAAACAA	77.77475148	70.288774
403		GTCCTTTGTTTACGTCCCGT	94.99070926	103.867949
406		AGGTGCGCCCCGTGGTCGGT	68.80565242	65.4335257
407		AGAGAGGTGCGCCCCGTGGT	42.18514493	55.1199635
408		GTAAAGAGAGGTGCGCCCCG	53.39922155	55.7151401
410		CGGGGAGTCCGCGTAAAGAG	52.63946411	66.9249801
409		GGGGCGCACCTCTCTTTACG	72.81702761	66.4993545
411	gRNA#011	CAGATGAGAAGGCACAGACG	32.31425506	44.762352

TABLE 13-continued

Exemplary target domain sequences and effect on HbeAg and HbsAg expression guide RNA

SEQ IDs	Associated guide RNA name (if applicable)	Target domain sequence	HbeAg (%expression of non targeting control)	HbsAg (%expression of non targeting control)
413		GGCAGATGAGAAGGCACAGA	59.89738685	59.5785052
415		ACACGGTCCGGCAGATGAGA	41.29188182	52.515655
412		GTCTGTGCCTTCTCATCTGC	70.71073836	72.0049046
416		GAAGCGAAGTGCACACGGTC	31.51588976	59.2847924
417		GAGGTGAAGCGAAGTGCACA	53.23795933	54.7085711
419		GGTCTCCATGCGACGTGCAG	98.80315853	94.871871
418		CTTCACCTCTGCACGTCGCA	76.66072308	76.4195077
421		GTCCTCTTATGTAAGACCTT	50.06169791	63.8903663
422		AGTCCTCTTATGTAAGACCT	54.84793515	62.0058784
420		TGCCCAAGGTCTTACATAAG	65.64906417	79.7359246
423		GTCTTACATAAGAGGACTCT	65.0201597	62.5458243
424		AATGTCAACGACCGACCTTG	53.64938718	65.5805852
425		TTTGAAGTATGCCTCAAGGT	68.9199506	80.763234
426	gRNA#012	AGTCTTTGAAGTATGCCTCA	30.45840615	47.6679105
427		AAGACTGTTTGTTTAAAGAC	75.19137394	74.1370789
428		AGACTGTTTGTTTAAAGACT	66.21290133	75.2309845
429		CTGTTTGTTTAAAGACTGGG	63.52924235	72.0972239
430		GTTTAAAGACTGGGAGGAGT	52.01423199	66.8961386
431		TCTTTGTACTAGGAGGCTGT	51.48581844	68.9533809
432		AGGAGGCTGTAGGCATAAAT	37.69681736	56.2655965
433		GTGAAAAAGTTGCATGGTGC	82.88524703	98.0043703
434		GCAGAGGTGAAAAAGTTGCA	31.73533955	53.6210823
435	gRNA#013	AACAAGAGATGATTAGGCAG	30.51551968	43.8402184
436	gRNA#014	GACATGAACAAGAGATGATT	15.37394867	25.9017005
437		AGCTTGGAGGCTTGAACAGT	84.06388656	100.433196
441	gRNA#015	CCACCCAAGGCACAGCTTGG	22.57628478	29.4502561
443		AAGCCACCCAAGGCACAGCT	38.69686132	57.447646
438		CAAGCCTCCAAGCTGTGCCT	57.03790348	55.3144232
439		AAGCCTCCAAGCTGTGCCTT	101.2197916	108.433992
442		AGCTGTGCCTTGGGTGGCTT	62.50798441	75.5245296
444		GCTGTGCCTTGGGTGGCTTT	63.60985011	68.2127614
445		CTGTGCCTTGGGTGGCTTTG	58.80930094	60.2093595
446		TAGCTCCAAATTCTTTATAA	81.50792369	102.062484
447		GTAGCTCCAAATTCTTTATA	57.5300482	84.4089935
448		TAAAGAATTTGGAGCTACTG	55.34840957	67.1682598
449		ATGACTCTAGCTACCTGGGT	70.72899714	69.314819

TABLE 13-continued

Exemplary target domain sequences and effect on HbeAg and HbsAg expression guide RNA

SEQ IDs	Associated guide RNA name (if applicable)	Target domain sequence	HbeAg (%expression of non targeting control)	HbsAg (%expression of non targeting control)
450		CACATTTCTTGTCTCACTTT	135.7647935	119.430868
451		TAGTTTCCGGAAGTGTTGAT	52.38647155	59.8621336
452		CGTCTAACAACAGTAGTTTC	84.81350809	79.1119745
453		ACTACTGTTGTTAGACGACG	50.34753433	57.5139945
454		CTGTTGTTAGACGACGAGGC	47.03375963	53.0434947
455		CGAGGGAGTTCTTCTTCTAG	36.81318989	50.1844755
456		GCGAGGGAGTTCTTCTTCTA	68.04429109	71.2738682
457	gRNA#016	GGCGAGGGAGTTCTTCTTCT	35.40374342	49.4263836
459		GACCTTCGTCTGCGAGGCGA	28.35732375	53.108582
460		AGACCTTCGTCTGCGAGGCG	41.45363172	58.2048965
461		GATTGAGACCTTCGTCTGCG	63.13599738	73.3793991
458		CTCCCTCGCCTCGCAGACGA	41.73812486	56.4066766
462		GATTGAGATCTTCTGCGACG	134.1434937	133.039909
463		GTCGCAGAAGATCTCAATCT	44.87633493	58.0732445
464		TCGCAGAAGATCTCAATCTC	70.59684886	75.0458487
465	gRNA#017	ATATGGTGACCCACAAAATG	41.36374656	46.043276
466		TTTGTGGGTCACCATATTCT	66.33644682	65.6466534
467	gRNA#018	TTGTGGGTCACCATATTCTT	48.06595023	41.7714626
468		GCTGGATCCAACTGGTGGTC	65.83430344	69.3357339
469		CACCCCAAAAGGCCTCCGTG	21.63462413	23.5507547
471	gRNA#019	CCTGAGGGCTCCACCCCAAA	45.40727826	44.6869573
470		CCTTTTGGGGTGGAGCCCTC	50.06807456	31.73417
472		GGGGTGGAGCCCTCAGGCTC	64.29444481	64.1755302
473		GGGTGGAGCCCTCAGGCTCA	44.19826805	53.1051257
474		CGATTGGTGGAGGCAGGAGG	65.52555289	60.9306557
475	gRNA#020	CTCATCCTCAGGCCATGCAG	35.40063237	17.5286587

In vitro silencing was observed in an HepG2-NTCP infection model with gRNAs targeting CpG islands with ETRs (FIG. **5**A-FIG. **5**B). A primary screen was conducted using LNPs of quality within expected parameters and a pilot experiment with a single guide (FIG. **6**-FIG. **8**). Results demonstrated that 48 gRNAs showed less than 50% expression of HBeAg at day 6 compared to non-targeting control (FIG. **9**) and 28 gRNAs showed less than 50% expression of HBsAg at day 6 compared to non-targeting control (FIG. **10**). HBsAg and HBeAg expression was positively correlated as shown in FIG. **11**.

Example 4: Zinc Finger Repressors for Silencing HBV

Zinc finger repressors targeting epigenetic target sites identified in the HBV genome were designed. Table 1 above provides amino acid sequences of zinc finger and its corresponding motif sequences and target sequences of the zinc finger.

Zinc finger repressors described in Table 1 are tested in an HBV infection model, e.g., in HepG2 cells as described herein, and efficient repression of HBV is confirmed for the zinc finger repressors provided in Table 1.

Example 5: Further In Vitro Evaluation of gRNAs

A CRISPR-Off single construct encoding PLA002, consisting of KRAB, DNMT3A, DNMT3L, and dCas9, was used in combination with one or more of the designed sgRNAs for the in vitro assays described in this example.

HepG2-NTCP cells were infected with HBV for 4 days, following procedures similar as those in Example 3, and were then transfected with CRISPR-off construct and individual exemplary gRNAs (as indicated in Table 13) formulated in a research-grade LNP. At Day 6 post-transfection HBsAg and HBeAg protein expression in the supernatant was evaluated by ELISA, as depicted in FIG. **12**A. Results from this experiment are shown in FIG. **12**B. All of the tested gRNAs led to reduction of HBsAg and HBeAg levels in the supernatant. Positive control used in this experiment is a gRNA against HBV genome that was previously shown to reduce antigens ~50%.

In another experiment, the integrated HBV cell line, PLC/PRF/5, was used to evaluate activity of gRNAs. The PLC/PRF/5 cells were transfected with CRISPR-off (PLA002) and individual gRNAs using a commercial lipid-based transfection reagent. As depicted in FIG. **13**A, four days after transfection HBsAg protein expression in the supernatant was evaluated by ELISA. Results from this experiment are shown in FIG. **13**B. Target conservation was evaluated in silico and target conservation was defined as 100% gRNA-DNA match.

In a further experiment, primary human hepatocytes (PHH) derived from humanized mice were infected with HBV for 4 days and then transfected with CRISPR-off (PLA002) and individual gRNAs formulated in a research-grade LNP, GenVoy LNPs. As depicted in FIG. **14**A, at Day 6 post-infection HBsAg and HBeAg protein expression in the supernatant was evaluated by ELISA. Results from this experiment are shown in FIG. **14**B. Positive control used in this experiment is an HBV gRNA that was previously shown to reduce antigens ~50%. The data suggested strong in vitro silencing by certain gRNAs at Day 6 after transfection. In a second PHH experiment, depicted in FIG. **14**C, post-infection HBsAg and HBeAg protein expression in the supernatant was evaluated by ELISA at Day 12 after delivery of 100 ng of payload (1:1 effector to guide RNA ratio) in research-grade LNPs. Epigenetic editors repress HBsAg and HBeAg secretion in HBV infected PHH cells at this time point, as well. Results are shown in FIG. **14**D. Sequences of the exemplary gRNAs that were tested in this example are listed in Table 13.

Example 6: In Vivo Silencing of HBV in HBV Rodent Models

Two different HBV rodent models were tested in this study. As shown in FIG. **15**, in one set of experiments, a non-transgenic model of persistent HBV infection in immunocompetent mice was used, which was established by administering an adeno-associated viral vector (AAV) that contains HBV Genotype D DNA into the mice. The administration of the AAV-HBV vector resulted in expression of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and high levels of serum HBV DNA in the mice. In another set of experiments, a transgenic mouse model of persistent HBV infection was used, whose genome was engineered to integrate HBV Genotype A DNA, resulting in expression of HBsAg and HBeAg, and circulating viral DNA in the mice.

Both mouse models were used to test 6 different treatment groups as shown in FIG. **15**. At certain times (such as 7, 14, 28, and 35 days) after single administration of 3 mg/kg of the LNPs that were loaded with the CRISPR-off construct and respective gRNAs, WT-Cas9 construct and gRNA, or control vehicle, mouse serum was extracted for analysis of HBsAg, HBeAg, and HBV DNA. Later the mice were sacrificed, and their livers were collected for further analysis.

As shown in FIG. **16**, in transgenic mouse model, durable (~1 month) and efficacious (~2 Log) DNA and HBsAg reduction was observed with CRIPSR-Off/gRNA #011 treatment. And compared to Cas9 cutter, CRISPR-Off, when administered in combination with gRNA #011, showed similar circulating viral DNA reduction, but superior HBsAg and HBeAg reduction.

Reduction of HBV markers in AAV-HBV model was also observed with administration of certain exemplary constructs. As shown in FIG. **17**, overall results in AAV8-HBV model are similar to the Tg-HBV mouse model. About 1 log DNA and HBsAg antigen reduction was observed with administration of CRISPR-Off and gRNA #011.

Effects of redosing of certain exemplary constructs were also tested. In the same experiments as above, among the six transgenic mice receiving administration of "CRISPR-off+ gRNA #016" (CRISPR-off construct and gRNA gRNA #016), three were administered with a dose of "CRISPR-off+ gRNA #016" on Day 35, and the other three were administered with "CRISPR-off+ gRNA #011" on Day 35. As shown in FIG. **18**A, redosing either with a less effective gRNA (gRNA #016 in this case) or with a more effective gRNA (gRNA #011 in this case) enhanced the silencing of all HBV marker, as shown by reduction of circulating HBV DNA, HBsAg, and HBeAg on Day 42. Redosing the gRNA #016-treated group with gRNA #011 (more effective gRNA) resulted in a more substantial reduction than redosing with gRNA #016 (less effective gRNA).

Single-dose experiments were continued to 168 days, as shown in FIG. **18**B. Results show durable and progressive reduction of viral antigens achieving −2.7 log DNA and −2.8 log HBsAg more than five months after single administration of an epigenetic editor (CRISPR-off with gRNA #011).

Five out of six animals tested had undetectable HBV DNA and HBsAg 168 days after a single dose of an epigenetic editor.

Redosing experiments were also conducted in AAV-HBV mouse model, as shown in FIG. **19**. Dosing with two different gRNAs (gRNA #016 and gRNA #011) further decreased all HBV markers. These data suggest of a potential enhanced activity when two HBV regions are targeted.

Sequences of the exemplary gRNAs that were tested in this example are listed in Table 13.

Example 7: Evaluation of ZFP in HepG2-NTCP Cells

In this example, ZF-off single constructs encoding a fusion protein consisting of KRAB, DNMT3A, DNMT3L, and an exemplary zinc finger motif of choice, were tested. Sequences of the exemplary zinc fingers that were tested in this example are listed in Table 18, as are sequences for plasmids yielding a subset of the ZF-off single construct fusion proteins.

Certain exemplary ZF-off constructs were formulated in a research-grade LNP. HepG2-NTCP cells were infected with HBV for 4 days and then transfected with the ZF-off loaded LNPs. As depicted in FIG. **20**A, at Day 6 post-infection HBsAg and HBeAg protein expression in the supernatant was evaluated by ELISA. FIG. **20**B shows the results as measured by percentage reduction in HBV antigens as compared to non-targeting control. Positive control used in this experiment is a HBV gRNA previously shown to reduce antigens ~50%. FIG. **21**A shows the results of the top ten ZF-off constructs that lead to the most reduction in HBV antigens. FIG. **21**B shows the results for all constructs in the screen.

Table 14 and 15 below show the raw data from these experiments, listed with the mRNA number yielding the zinc finger motif.

TABLE 14

% HBsAg expression relative to non-targeting control								
Trial#	1	2	3	4	5	6	7	8
Non-targ control	100	100	100	100				
Pos control	54	59	68	61	75	79	65	86
mRNA0001	10	19	25	23				
mRNA0002	12	2	8	12				
mRNA0003	10	11	14	15				
mRNA0004	10	28	13	39				
mRNA0005	3	5	1	8				
mRNA0006	4	12	8	19				
mRNA0007	97	86	60	66				
mRNA0008	68	69	65	64				
mRNA0009	65	67	74	98				
mRNA0010	84	69	66	73				
mRNA0011	67	50	60	59				
mRNA0012	59	61	70	92				
mRNA0013	97	70	66	71				
mRNA0014	60	81	66	74				
mRNA0015	81	73	77	129				
mRNA0016	120	78	71	77				
mRNA0017	75	77	82	82				
mRNA0018	78	84	93	131				
mRNA0019	107	107	77	100				
mRNA0020	77	99	60	116				
mRNA0021	32	49	68	66				
mRNA0022	71	66	51	56				
mRNA0023	65	71	76	41				
mRNA0024	109	89	86	92				
mRNA0025	86	92	90	82				
mRNA0026	77	88	81	104				

TABLE 14-continued

% HBsAg expression relative to non-targeting control								
Trial#	1	2	3	4	5	6	7	8
mRNA0027	128	77	80	81				
mRNA0028	71	67	59	66				
mRNA0029	48	47	40	57				
mRNA0030	109	82	76	75				
mRNA0031	46	32	41	27				
mRNA0032	50	59	52	73				
mRNA0033	61	62	46	50				
mRNA0034	51	24	41	25				
mRNA0035	30	25	24	34				
mRNA0036	16	22	19	19				
mRNA0037	54	43	42	46				
mRNA0038	19	23	13	29				
mRNA0039	28	46	37	36				
mRNA0040	88	78	83	80				
mRNA0041	103	92	100					
mRNA0042	99	91	99					
mRNA0043	93	89	97					
mRNA0044	98	100	95					
mRNA0045	100	96	95					
mRNA0046	94	83	92					
mRNA0047	97	77	99					
mRNA0048	96	94	90					
mRNA0049	88	87	89					
mRNA0050	87	87	85					
mRNA0051	106	104	114					
mRNA0052	104	101	107					
mRNA0053	88	86	92					
mRNA0054	98	102	91					
mRNA0055	101	96	100					
mRNA0056	99	107	108					
mRNA0057	101	102	104					
mRNA0058	110	104	102					
mRNA0059	100	91	98					
mRNA0060	94	103	100					
mRNA0061	104	96	103					
mRNA0062	106	98	104					
mRNA0063	96	86	99					

TABLE 15

% HBeAg expression relative to non-targeting control								
Trial#	100	100	100	100				
Non-targ control	100	100	100	100				
Pos control	26	36	41	53	43	43	34	54
mRNA0001	12	19	22	23				
mRNA0002	15	8	17	20				
mRNA0003	11	9	13	12				
mRNA0004	10	17	9	27				
mRNA0005	1	1	−1	3				
mRNA0006	5	8	7	13				
mRNA0007	95	78	59	65				
mRNA0008	64	67	60	65				
mRNA0009	65	64	81	98				
mRNA0010	84	68	69	70				
mRNA0011	65	51	51	67				
mRNA0012	64	61	74	96				
mRNA0013	92	74	73	79				
mRNA0014	58	85	58	76				
mRNA0015	82	83	78	124				
mRNA0016	108	81	72	80				
mRNA0017	72	77	72	80				
mRNA0018	55	55	71	93				
mRNA0019	71	79	51	87				
mRNA0020	34	36	32	52				
mRNA0021	32	40	55	55				
mRNA0022	77	64	53	65				
mRNA0023	60	69	72	43				
mRNA0024	98	76	87	84				
mRNA0025	91	86	82	92				
mRNA0026	78	97	87	102				
mRNA0027	117	62	68	74				

TABLE 15-continued

% HBeAg expression relative to non-targeting control				
Trial#	100	100	100	100
mRNA0028	75	59	58	71
mRNA0029	31	32	22	45
mRNA0030	124	86	79	77
mRNA0031	42	23	27	20
mRNA0032	46	57	57	82
mRNA0033	56	51	44	76
mRNA0034	42	21	41	18
mRNA0035	22	22	24	39
mRNA0036	13	17	16	13
mRNA0037	50	35	34	35
mRNA0038	12	16	13	25
mRNA0039	29	45	39	36
mRNA0040	93	73	80	82
mRNA0041	80	63	111	
mRNA0042	114	94	98	
mRNA0043	98	91	99	
mRNA0044	91	115	108	
mRNA0045	71	55	62	
mRNA0046	76	66	63	
mRNA0047	55	55	45	
mRNA0048	66	63	78	
mRNA0049	83	59	52	
mRNA0050	51	55	49	
mRNA0051	55	49	49	
mRNA0052	56	57	66	
mRNA0053	92	60	57	
mRNA0054	50	55	56	
mRNA0055	83	88	74	
mRNA0056	61	69	112	
mRNA0057	106	73	65	
mRNA0058	66	65	65	
mRNA0059	69	66	71	
mRNA0060	59	94	101	
mRNA0061	111	81	68	
mRNA0062	28	33	41	
mRNA0063	65	55	31	

Example 8. Dose Response Testing of Viral Antigens in HepG2-NTCP Cells

In this example, top ZF fusion proteins were tested in 5-point dose response assay for HBsAg and HBeAg. The 5 dosage points were 200ng, 150ng, 100ng, 50ng, and 25ng. Experimental schematic and results are shown in FIG. **22**.

Example 9. Testing for Durable Repression of HBsAg in HepG2.2.15 Cells

In this example, top ZF and CRISPR-off fusion proteins with guide RNAs were tested for durable repression of HBsAg. Active ZFPs and CRISPR-off editors showed durable silencing through Day 27 with 50ng treatment. Experimental schematic and results are shown in FIGS. **23**A-**23**C.

Example 10. Testing of Silencing of HBsAg in a Second Model for Int-HBV

In this example, top ZF fusion proteins were tested for repression of HBsAg in PLC/PRF/5 cells. A subset of the ZFPs silenced HBsAg in this second model. Experimental schematic and results are shown in FIG. **24**. 1. Testing ZF Fusion Proteins and CRISPR-off with guide RNAs for Specificity

In this example, ZF fusion proteins targeting HBV exhibiting significant silencing were profiled for specificity in HepG2-NTCP at day 19. All comparisons were performed against a non-targeting ZFP control. An exemplary result for the ZF fusion protein with mRNA0001 zinc finger motif is shown in FIG. **25**A. CRISPR-off with guide RNAs were similarly profiled. HepG2-NTCP cells were transfected with 100 ng of total payload using GenVoy™ LNP at a 1:1 gRNA:effector ratio. Cells were split every 3-4 days and collected at day 15 post-treatment for specificity assessments, including RNA-seq and methylation array. DESeq2 was used to identify differential gene expression. As shown in FIG. **25**B, little to no changes were observed above chosen thresholds (absolute[log 2[fold change]]>1 and −log 10[adjusted p-value]>5) as expected for effectors targeting HBV DNA. For methylation array, the Infinium MethylationEPIC v2.0 array was used, and DMRs were identified using Bumphunter. EE3, EE4, and EE5 had a result of DMR=0. Results are shown in FIGS. **25**C-**25**D.

Example 11. In Vivo Analysis of ZF-Off Constructs

Ten ZF-Off constructs as well as vehicle-only and CRISPR-Off controls were administered to AAV-HBV mice at 1 mg/kg as shown in the schematic in FIG. **26**. Table 16 shows the zinc finger motifs for each experimental group; the corresponding plasmid from Table 18, comprising the nucleic acid encoding the ZF-Off construct, was administered. Plasma from the mice was tested at Days 7, 14, 21, and 28 post dose for HBV DNA, HBsAg, and HBeAg. The livers were collected for further analysis. Results are shown in FIG. **27**. The ZF-Off construct with the ZF motif from mRNA0004 showed more than a 1.5 log reduction in HBV DNA, a >2 log reduction in HSbsAg, and a >2 log reduction of HBeAg, all sustained up to 28 days from the dose.

TABLE 16

Experimental groups for in vivo testing of ZF-Off constructs.

Group	ZF motif in construct administered	N
1	mRNA0001	6
2	mRNA0002	6
3	mRNA0003	6
4	mRNA0005	6
5	mRNA0006	6
6	mRNA0038	6
7	mRNA0004	6
8	mRNA0039	6
9	mRNA0021	6
10	mRNA0037	6

Example 12. Zinc Finger Protein Multiplexing Study in an AAV-HBV and Tg-HBV Mouse Model

AAV-HBV mice are injected with a single administration at 0.5 mg/kg of one, two, or three ZF fusion proteins, delivered as mRNA, in LNPs (schematic, FIG. **28**) in accordance with Table 17. HBV DNA, HBsAg, and HBeAg are assayed in plasma at one or more time points, and the mouse liver is collected for further analysis.

TABLE 17

Multiplexing sample groups.

Group	ZF_Off-1	ZF_Off-2	ZF_Off-3
1	mRNA0004	mRNA0021	—
2	mRNA0004	mRNA0003	—

TABLE 17-continued

Multiplexing sample groups.

Group	ZF_Off-1	ZF_Off-2	ZF_Off-3
3	mRNA0004	mRNA0038	—
4	mRNA0004	mRNA0021	mRNA0003
5	mRNA0004	mRNA0038	mRNA0003
6	mRNA0004	mRNA0021	mRNA0038
7	mRNA0004	mRNA0001	—
8	mRNA0004	mRNA0039	—
9	mRNA0004	—	—
10	Vehicle	—	—

Example 13. Dose Response for CRISPR-Off Constructs in an AAV In Vivo Model

A single dose of CRISPR-Off (SEQ ID NO: 1248) mRNA with guide RNA #008 as well as vehicle-only control was tested via 1:1 mRNA:guide RNA administration to AAV-HBV mice at 0.5 mg/kg, 1 mg/kg, or 3 mg/kg in LNPs as shown in the schematic in FIG. **29**. Plasma from the mice was tested for HBsAg at thirteen time points through 186 days after injection. Results are shown in FIG. **30**. The highest dose administered showed an approximately 3.3 log reduction in HBsAg, sustained through 186 days after the dose.

Example 14. Dose Response for CRISPR Off Constructs in Tg In Vivo Model

A single dose of CRISPR-Off (SEQ ID NO: 1248) mRNA with guide RNA #008 as well as vehicle-only control was tested via 1:1 mRNA:guide RNA administration to Tg-HBV mice at 0.5 mg/kg, 1 mg/kg, or 3 mg/kg in LNPs as shown in the schematic in FIG. **31**. Plasma from the mice was tested for HBsAg at thirteen time points through 186 days after injection. Results are shown in FIG. **32**. The highest dose administered showed an approximately 2.6 log reduction in HBsAg, sustained through 196 days after the dose.

A second dose response experiment in Tg-HBV model using CRISPR-Off (SEQ ID NO: 1248) mRNA with guide RNA #008 formulated in LNPs was conducted, with administrations at 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, or 3 mg/kg of 1:1 mRNA:guide RNA. A vehicle-only control was also used. In this experiment, plasma was tested for HBV DNA, HBsAg, and HBeAg at 13 time points through 207 days after injection. Results are shown in FIG. **32**. The HBsAg results for individual mice at the final time point of 207 days after injection are plotted in FIG. **33**. All of the mice in the 0.5 mg/kg, 1 mg/kg, and 3 mg/kg group had reduced HBsAg at Day 207 as compared to vehicle only control. Alanine transaminase (ALT) level in the mice was also tested at 207 days and found to be comparable to that of healthy untreated mice for all treatment groups.

Example 15. Guide RNA Testing in AAV-HBV Mice

Six guide RNAs were tested for relative efficacy using CRISPR-Off (SEQ ID NO: 1248) in a 28-day, single-dose study. CRISPR-Off construct mRNA and one of gRNA #003, gRNA #007, gRNA #008, gRNA #009, gRNA #011, and gRNA #015 was delivered at 1:1 mRNA:guide RNA at 1 mg/kg. Controls included vehicle only, CRISPRi with gRNA #008 (not shown), and wild type Cas9 with gRNA #011 (not shown). HBV DNA and HBsAg was measured over 28 days. Results are shown in FIG. **34**. Most of the single guide treatments tested in this experiment resulted in decreased HBV DNA and HBsAg versus vehicle only control.

Example 16. Durability Study for ZF-Off in AAV-HBV In Vivo Model: Single and Re-Dose

Mice were injected with a single dose ZF-Off construct (SEQ ID NO: 36) mRNA at 1 mg/kg in LNPs. HBV DNA and HBsAg were measured from plasma over a period of 168 days. Results are shown in FIG. **35**A. The treatment resulted in a sustained reduction of greater than 2 log in HBV DNA and similar sustained reduction in HBsAg.

In another study, mice were injected with the ZF-Off construct (SEQ ID NO: 36) mRNA at 1 mg/kg for three doses: Day 0, Day 21, and Day 42. HBV DNA and HBsAg were measured from plasma over a period of 225 days. Results are shown in FIG. **35**B. Results were similar to those of the previous single-dose experiment and in this experiment sustained over 225 days.

Example 17. Re-Dosing Studies for CRISPR-Off in AAV-HBV In Vivo Model

AAV-HBV mice were dosed with either a single dose or three doses, all at 1 mg/kg in LNPs, of CRISPR-Off (SEQ ID NO: 1248) mRNA with gRNA #008 at a 1:1 ratio of mRNA: guide RNA. For the single dose condition, the dose was administered at Day 0. For the three-dose condition, the doses were administered at Day 36, Day 57, and Day 78. A vehicle-only control was also administered. Plasma measurements of HBV DNA, HBsAg, and HBeAg were taken through Day 168 for the single-dose condition, and through Day 261 for both the three-dose condition and the vehicle control. Results are shown in FIG. **36**. Re-dosing with CRISPR-Off further improved and sustained the durability of the modulation of these HBV biomarkers.

In another study, AAV-HBV mice were dosed with either a single dose of CRISPR-Off (SEQ ID NO: 1248) mRNA with gRNA #008 with an updated modification pattern (SEQ ID NO: 1249) (1:1 ratio mRNA: guide RNA) in LNPs at 3 mg/kg, or three doses of the same epigenetic editor, each at 1 mg/kg. Both groups received a dose at Day 0, and the three-dose group also received a dose at Day 14 and at Day 28. A vehicle-only control was also administered. HBsAg and HBeAg were measured from plasma through 126 days. Results are shown in FIG. **37**. Near-additive pharmacology was demonstrated with the repeat dosing.

Example 18. Testing CRISPR-Off and Guide RNA Modifications in an AAV-HBV In Vivo Model

AAV-HBV mice were dosed with a single dose of either CRISPR-Off (SEQ ID NO: 1248) mRNA with gRNA #008 or an updated CRISPR-Off variant (SEQ ID NO: 1252) mRNA with gRNA #008 with an updated modification pattern (SEQ ID NO: 1249), with a 1:1 ratio of mRNA to guide RNA at either 0.5 mg/kg or 1 mg/kg, delivered in LNPs. A vehicle only control was also administered. HBsAg was measured in plasma over 28 days. Results are shown in FIG. **38**. The updated CRISPR-Off variant with guide RNA modifications demonstrated 1.5× potency over the previous lead epigenetic editor.

Example 19. Methylation Studies for CRISPR-Off with Various Guide RNAs

HepG2.2.15 cells were dosed at 1 nanogram (ng)/microliter (100 ng) of 1:1 CRISPR-Off (SEQ ID NO: 1248)

mRNA with various single guide RNAs in LNPs with commercial apolipoprotein E (to aid LNP entry). Methylation profiles were performed on the HBV genome samples as well as controls: for gRNA #008, untreated samples and treated with CRISPRi and wild type Cas9. For other gRNAs tested, an untreated sample (APOE only) was used as a control. Results for gRNA #008, gRNA #003, gRNA #007, gRNA #009, gRNA #011, and gRNA #015 are shown in FIGS. **39**A, **39**B, **39**C, **39**D, **39**E, and 39F, respectively. A control for the application of an off-target PCSK9 guide RNA is shown in FIG. **39**G.

Example 20. Specificity studies for CRISPR-Off and ZF Off

HepG2.2.15 cells were transfected with either ZF-Off (SEQ ID NOs: 36 and 73) mRNA or CRISPR-Off (SEQ ID NO: 1248) mRNA with gRNA #008 in research-grade LNPs. RNA-Seq was conducted to determine differentially expressed genes (DEGs), and the Twist panel was used to determine differentially methylated regions (DMRs) at CpG-enriched sites. Differentially expressed genes (DEG) and differentially methylated regions (DMR) are defined based on literature reviews, software recommendations, sequencing depth and controls DEGs are genes that have >=2-fold change and with adjusted p-value <=1e-05. DMRs are defined as regions with a minimum of 10 CpGs, with 5× coverage, p-value of <=1e-10 and min average change in methylation (beta) >=20%. Results are shown in FIG. **40**. Silencing data for same samples was also obtained. Results are shown in FIG. **41**.

Example 21. Dose Response of Guide RNAs In Vitro

An 8-point dose-response (two-fold dilution with from 4 ng/μL (400ng) to 0.031 ng/μL (3.1 ng)) was generated using HepG2.2.15 cells treated with LNPs with CRISPR-Off effector (SEQ ID NO: 1248), delivered as mRNA, and each of four gRNAs co-formulated in a 1:1 ratio. HBsAg and HBeAg were measured over six days. Results are shown in FIG. **42**.

Example 22. Dose Response of CRISPR-Off Variant In Vitro

HepG2.2.15 cells transfected via Messenger Max with CRISPR-Off effector (SEQ ID NO: 1252), delivered as mRNA, and gRNA #008 with updated modification pattern (SEQ ID NO: 1249) was used to generate a 9-point dose-response (200-0.8 ng) curve. HBsAg and HBeAg were measured over 6 days. Results are shown in FIG. **43**.

Example 23. Multiplexing Study in AAV-HBV and Tg-HBV Mouse Models

AAV-HBV and Tg-HBV mice are injected with a single administration at 0.5 mg/kg of one, two, three, or four guide RNAs targeting regions listed in Table 12 and Table 13 with CRISPR-Off (SEQ ID NO: 1248 or 1252) mRNA formulated in LNPs.

Amongst others, the following gRNAs are combined: (1) gRNA #008 and gRNA #011; (2) gRNA #008 and gRNA #003; (3) gRNA #008 and gRNA #015; (4) gRNA #008, gRNA #011, and gRNA #015; (6) gRNA #008, gRNA #011, and gRNA #003. Treatment with a single guide RNA, e.g., gRNA #008 or gRNA #011 serves as a positive control, and treatment with vehicle or with a non-targeting guide as a negative control.

One or more of HBV DNA, HBsAg, and HBeAg are assayed in plasma of the mice at one or more time points after administration, and the mouse liver is collected for further analysis. Combinations of multiple guides yield silencing at least as robust as treatment with single guides. In some cases, more robust silencing with multiple guides as compared to treatment with a single guide is observed.

Example 24. Testing mRNA: Guide RNA Ratios In Vivo

AAV-HBV mice are treated with CRISPR-Off effector (SEQ ID NO: 1252) mRNA with guide RNA (SEQ ID NO: 1249) in ratios including 1:1, 1:1.5, 2:1, 1:2, and 1:3 mRNA:guide RNA formulated into LNPs and administered at 0.5 mg/kg. 5 or 6 mice per study group are used. An optimized ratio of effector and guide RNA is identified that results in durable reduction of one or more HBV biomarkers, e.g., plasma level measurements of HBV DNA, HBsAg, and HBeAg of greater than 2 log below the observed control plasma level.

Example 25. Combination Treatment with Epigenetic Editor In Vivo

Tg-HBV mice are dosed with Entecavir (ETV) at 0.1 mg/kg for 14 days followed by CRISPR-Off with guide RNA at 1 mg/kg in a single intravenous dose. HBV DNA and HBsAg are measured in plasma for 112 days. HBV DNA levels drop after ETV treatment and there is slight synergism in the CRISPR-Off with guide with ETV group. After ETV withdrawal, the CRISPR-Off with guide maintains sustained reduction of DNA comparable to a group treated with CRISPR-Off and guide RNA alone. The addition of ETV does not affect HBsAg.

Example 26. Stable HBV Silencing Via Epigenetic Editing in Non-Transgenic Mouse Model of Persistent HBV Infection

A non-transgenic model of persistent HBV infection (AAV-HBV) in immunocompetent mice was used, which was established by administering an adeno-associated viral vector (AAV) that contains HBV Genotype D DNA into the mice. The administration of the AAV-HBV vector resulted in expression of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and high levels of serum HBV DNA in the mice.

The CRISPR-off and ZF-off constructs are tested. Constructs are delivered via IV administration of mRNA/gRNA (CRISPR-Off) or mRNA (ZF-Off) formulated into a lipid nanoparticle (LNP) at 2.5 mg/kg and 0.5 mg/kg for CRISPR-Off and ZF-Off, respectively. Some constructs are formulated in LNP compositions as described in PCT/US2014/070882, US20220402862A1, and/or US20230203480A1. A subset of the mice are re-dosed at two weeks after the first dose; a second subset are re-dosed at one month after the first dose. The readouts are circulating viral DNA, HBsAg, and HBeAg, tested using mouse plasma at one or more time points (such as 7, 14, 28, and 35 days). A durable and significant reduction in the levels of one or more of HBV DNA, HBsAg, and HBeAg is observed for some constructs.

Longer-term durability is tested over three to six months using the HBV DNA, HBsAg, and HBeAg markers. Progressive and durable reduction in one or more of these markers is seen with delivery of some constructs. The mice are sacrificed and livers are collected for further analysis, and durable silencing is confirmed by at least 2 log reduction of HBsAg and HBV DNA.

Example 27: Stable HBV Silencing Via Epigenetic Editing in Transgenic Mice Expressing Viral HBV DNA

A transgenic mouse model of persistent HBV infection (Tg-HBV) was used, whose genome was engineered to integrate HBV Genotype A DNA, resulting in expression of HBsAg and HBeAg, and circulating viral DNA in the mice.

The CRISPR-off and ZF-off constructs are tested. Constructs are delivered via IV administration of mRNA/gRNA (CRISPR-Off) or mRNA (ZF-Off) formulated into LNP at 2.5 mg/kg and 0.5 mg/kg for CRISPR-Off and ZF-Off, respectively. Some constructs are formulated in LNP compositions as described in US20220402862A1, and/or US20230203480A1. A subset of the mice are re-dosed at two weeks after the first dose; a second subset are re-dosed at one month after the first dose. The readouts are circulating viral DNA, HBsAg, and HBeAg, tested using mouse plasma at one or more time points (such as 7, 14, 28, and 35 days). A durable and significant reduction in the levels of one or more of HBV DNA, HBsAg, and HBeAg is observed for some constructs.

Longer-term durability is tested over three to six months using the HBV DNA, HBsAg, and HBeAg markers. Progressive and durable reduction in one or more of these markers is seen with delivery of some constructs. The mice are sacrificed and livers are collected for further analysis, and durable silencing is confirmed by at least 2 log reduction of HBsAg and HBV DNA.

SEQUENCES

The SEQ ID NOs (SEQ) of nucleotide (nt) and amino acid (aa) sequences described in the present disclosure are listed in Table 18 below.

TABLE 18

Sequence listing.

SEQ	Description	Sequence
1	*S. pyogenes* WT Cas9 Sequence (nt)	ATGGATAAGAAATACTCAATAGGCTTAGATATCGGCACAAATAGCGTCGGATGG GCGGTGATCACTGATGAATATAAGGTTCCGTCTAAAAAGTTCAAGGTTCTGGGA AATACAGACCGCCACAGTATCAAAAAAAATCTTATAGGGGCTCTTTTATTTGAC AGTGGAGAGACAGCGGAAGCGACTCGTCTCAAACGGACAGCTCGTAGAAGGTAT ACACGTCGGAAGAATCGTATTTGTTATCTACAGGAGATTTTTTCAAATGAGATG GCGAAAGTAGATGATAGTTTCTTTCATCGACTTGAAGAGTCTTTTTTGGTGGAA GAAGACAAGAAGCATGAACGTCATCCTATTTTTGGAAATATAGTAGATGAAGTT GCTTATCATGAGAAATATCCAACTATCTATCATCTGCGAAAAAAATTGGTAGAT TCTACTGATAAAGCGGATTTGCGCTTAATCTATTTGGCCTTAGCGCATATGATT AAGTTTCGTGGTCATTTTTTGATTGAGGGAGATTTAAATCCTGATAATAGTGAT GTGGACAAACTATTTATCCAGTTGGTACAAACCTACAATCAATTATTTGAAGAA AACCCTATTAACGCAAGTGGAGTAGATGCTAAAGCGATTCTTTCTGCACGATTG AGTAAATCAAGACGATTAGAAAATCTCATTGCTCAGCTCCCCGGTGAGAAGAAA AATGGCTTATTTGGGAATCTCATTGCTTTGTCATTGGGTTTGACCCCTAATTTT AAATCAAATTTTGATTTGGCAGAAGATGCTAAATTACAGCTTTCAAAAGATACT TACGATGATGATTTAGATAATTTATTGGCGCAAATTGGAGATCAATATGCTGAT TTGTTTTTGGCAGCTAAGAATTTATCAGATGCTATTTTACTTTCAGATATCCTA AGAGTAAATACTGAAATAACTAAGGCTCCCCTATCAGCTTCAATGATTAAACGC TACGATGAACATCATCAAGACTTGACTCTTTTAAAAGCTTTAGTTCGACAACAA CTTCCAGAAAAGTATAAAGAAATCTTTTTTGATCAATCAAAAAACGGATATGCA GGTTATATTGATGGGGGAGCTAGCCAAGAAGAATTTTATAAATTTATCAAACCA ATTTTAGAAAAAATGGATGGTACTGAGGAATTATTGGTGAAACTAAATCGTGAA GATTTGCTGCGCAAGCAACGGACCTTTGACAACGGCTCTATTCCCCATCAAATT CACTTGGGTGAGCTGCATGCTATTTTGAGAAGACAAGAAGACTTTTATCCATTT TTAAAAGACAATCGTGAGAAGATTGAAAAAATCTTGACTTTTCGAATTCCTTAT TATGTTGGTCCATTGGCGCGTGGCAATAGTCGTTTTGCATGGATGACTCGGAAG TCTGAAGAAACAATTACCCCATGGAATTTTGAAGAAGTTGTCGATAAAGGTGCT TCAGCTCAATCATTTATTGAACGCATGACAAACTTTGATAAAAATCTTCCAAAT GAAAAAGTACTACCAAAACATAGTTTGCTTTATGAGTATTTTACGGTTTATAAC GAATTGACAAAGGTCAAATATGTTACTGAAGGAATGCGAAAACCAGCATTTCTT TCAGGTGAACAGAAGAAAGCCATTGTTGATTTACTCTTCAAAACAAATCGAAAA GTAACCGTTAAGCAATTAAAAGAAGATTATTTCAAAAAAATAGAATGTTTTGAT AGTGTTGAAATTTCAGGAGTTGAAGATAGATTTAATGCTTCATTAGGTACCTAC CATGATTTGCTAAAAATTATTAAAGATAAAGATTTTTTGGATAATGAAGAAAAT GAAGATATCTTAGAGGATATTGTTTTAACATTGACCTTATTTGAAGATAGGGAG ATGATTGAGGAAAGACTTAAAACATATGCTCACCTCTTTGATGATAAGGTGATG AAACAGCTTAAACGTCGCCGTTATACTGGTTGGGGACGTTTGTCTCGAAAATTG ATTAATGGTATTAGGGATAAGCAATCTGGCAAAACAATATTAGATTTTTTGAAA TCAGATGGTTTTGCCAATCGCAATTTTATGCAGCTGATCCATGATGATAGTTTG ACATTTAAAGAAGACATTCAAAAAGCACAAGTGTCTGGACAAGGCGATAGTTTA CATGAACATATTGCAAATTTAGCTGGTAGCCCTGCTATTAAAAAAGGTATTTTA CAGACTGTAAAAGTTGTTGATGAATTGGTCAAAGTAATGGGGCGGCATAAGCCA GAAAATATCGTTATTGAAATGGCACGTGAAAATCAGACAACTCAAAAGGGCCAG AAAAATTCGCGAGAGCGTATGAAACGAATCGAAGAAGGTATCAAAGAATTAGGA AGTCAGATTCTTAAAGAGCATCCTGTTGAAAATACTCAATTGCAAAATGAAAAG CTCTATCTCTATTATCTCCAAAATGGAAGAGACATGTATGTGGACCAAGAATTA GATATTAATCGTTTAAGTGATTATGATGTCGATCACATTGTTCCACAAAGTTTC CTTAAAGACGATTCAATAGACAATAAGGTCTTAACGCGTTCTGATAAAAATCGT

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		GGTAAATCGGATAACGTTCCAAGTGAAGAAGTAGTCAAAAAGATGAAAAACTAT TGGAGACAACTTCTAAACGCCAAGTTAATCACTCAACGTAAGTTTGATAATTTA ACGAAAGCTGAACGTGGAGGTTTGAGTGAACTTGATAAAGCTGGTTTTATCAAA CGCCAATTGGTTGAAACTCGCCAAATCACTAAGCATGTGGCACAAATTTTGGAT AGTCGCATGAATACTAAATACGATGAAAATGATAAACTTATTCGAGAGGTTAAA GTGATTACCTTAAAATCTAAATTAGTTTCTGACTTCCGAAAAGATTTCCAATTC TATAAAGTACGTGAGATTAACAATTACCATCATGCCCATGATGCGTATCTAAAT GCCGTCGTTGGAACTGCTTTGATTAAGAAATATCCAAAACTTGAATCGGAGTTT GTCTATGGTGATTATAAAGTTTATGATGTTCGTAAAATGATTGCTAAGTCTGAG CAAGAAATAGGCAAAGCAACCGCAAAATATTTCTTTTACTCTAATATCATGAAC TTCTTCAAAACAGAAATTACACTTGCAAATGGAGAGATTCGCAAACGCCCTCTA ATCGAAACTAATGGGGAAACTGGAGAAATTGTCTGGGATAAAGGGCGAGATTTT GCCACAGTGCGCAAAGTATTGTCCATGCCCCAAGTCAATATTGTCAAGAAAACA GAAGTACAGACAGGCGGATTCTCCAAGGAGTCAATTTTACCAAAAAGAAATTCG GACAAGCTTATTGCTCGTAAAAAAGACTGGGATCCAAAAAAATATGGTGGTTTT GATAGTCCAACGGTAGCTTATTCAGTCCTAGTGGTTGCTAAGGTGGAAAAAGGG AAATCGAAGAAGTTAAAATCCGTTAAAGAGTTACTAGGGATCACAATTATGGAA AGAAGTTCCTTTGAAAAAAATCCGATTGACTTTTTAGAAGCTAAAGGATATAAG GAAGTTAAAAAAGACTTAATCATTAAACTACCTAAATATAGTCTTTTTGAGTTA GAAAACGGTCGTAAACGGATGCTGGCTAGTGCCGGAGAATTACAAAAAGGAAAT GAGCTGGCTCTGCCAAGCAAATATGTGAATTTTTTATATTTAGCTAGTCATTAT GAAAAGTTGAAGGGTAGTCCAGAAGATAACGAACAAAAACAATTGTTTGTGGAG CAGCATAAGCATTATTTAGATGAGATTATTGAGCAAATCAGTGAATTTTCTAAG CGTGTTATTTTAGCAGATGCCAATTTAGATAAAGTTCTTAGTGCATATAACAAA CATAGAGACAAACCAATACGTGAACAAGCAGAAAATATTATTCATTTATTTACG TTGACGAATCTTGGAGCTCCCGCTGCTTTTAAATATTTTGATACAACAATTGAT CGTAAACGATATACGTCTACAAAAGAAGTTTTAGATGCCACTCTTATCCATCAA TCCATCACTGGTCTTTATGAAACACGCATTGATTTGAGTCAGCTAGGAGGTGAC TGA
2	*S. pyogenes* WT Cas9 Sequence (aa)	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLED SGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELVE EDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMI KFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARL SKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNEDLAEDAKLQLSKDT YDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKR YDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKP ILEKMDGTEELLVKLNREDLLRKQRTEDNGSIPHQIHLGELHAILRRQEDFYPE LKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFL SGEQKKAIVDLLEKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTY HDLLKIIKDKDELDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVM KQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKP ENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEK LYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNR GKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIK RQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQF YKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSE QEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDF ATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGE DSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDELEAKGYK EVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNK HRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQ SITGLYETRIDLSQLGGD
3	SaCas9	MKRNYILGLDIGITSVGYGIIDYETRDVIDAGVRLFKEANVENNEGRRSKRGAR RLKRRRRHRIQRVKKLLFDYNLLTDHSELSGINPYEARVKGLSQKLSEEEFSAA LLHLAKRRGVHNVNEVEEDTGNELSTKEQISRNSKALEEKYVAELQLERLKKDG EVRGSINRFKTSDYVKEAKQLLKVQKAYHQLDQSFIDTYIDLLETRRTYYEGPG EGSPFGWKDIKEWYEMLMGHCTYFPEELRSVKYAYNADLYNALNDLNNLVITRD ENEKLEYYEKFQIIENVFKQKKKPTLKQIAKEILVNEEDIKGYRVTSTGKPEFT NLKVYHDIKDITARKEIIENAELLDQIAKILTIYQSSEDIQEELTNLNSELTQE EIEQISNLKGYTGTHNLSLKAINLILDELWHTNDNQIAIFNRLKLVPKKVDLSQ QKEIPTTLVDDFILSPVVKRSFIQSIKVINAIIKKYGLPNDIIIELAREKNSKD AQKMINEMQKRNRQTNERIEEIIRTTGKENAKYLIEKIKLHDMQEGKCLYSLEA IPLEDLLNNPFNYEVDHIIPRSVSEDNSFNNKVLVKQEENSKKGNRTPFQYLSS SDSKISYETFKKHILNLAKGKGRISKTKKEYLLEERDINRESVQKDFINRNLVD TRYATRGLMNLLRSYFRVNNLDVKVKSINGGFTSFLRRKWKFKKERNKGYKHHA EDALIIANADFIFKEWKKLDKAKKVMENQMFEEKQAESMPEIETEQEYKEIFIT PHQIKHIKDFKDYKYSHRVDKKPNRELINDTLYSTRKDDKGNTLIVNNLNGLYD KDNDKLKKLINKSPEKLLMYHHDPQTYQKLKLIMEQYGDEKNPLYKYYEETGNY LTKYSKKDNGPVIKKIKYYGNKLNAHLDITDDYPNSRNKVVKLSLKPYREDVYL

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		DNGVYKFVTVKNLDVIKKENYYEVNSKCYEEAKKLKKISNQAEFIASFYNNDLI KINGELYRVIGVNNDLLNRIEVNMIDITYREYLENMNDKRPPRIIKTIASKTQS IKKYSTDILGNLYEVKSKKHPQIIKKG
4	*F. novicida* WT Cpf1	MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILDDEKRAKDYKKAKQII DKYHQFFIEEILSSVCISEDLLQNYSDVYFKLKKSDDDNLQKDEKSAKDTIKKQ ISEYIKDSEKFKNLENQNLIDAKKGQESDLILWLKQSKDNGIELFKANSDITDI DEALEIIKSFKGWTTYFKGFHENRKNVYSSNDIPTSIIYRIVDDNLPKFLENKA KYESLKDKAPEAINYEQIKKDLAEELTFDIDYKTSEVNQRVESLDEVFEIANEN NYLNQSGITKENTIIGGKFVNGENTKRKGINEYINLYSQQINDKTLKKYKMSVL FKQILSDTESKSFVIDKLEDDSDVVTTMQSFYEQIAAFKTVEEKSIKETLSLLE DDLKAQKLDLSKIYFKNDKSLTDLSQQVEDDYSVIGTAVLEYITQQIAPKNLDN PSKKEQELIAKKTEKAKYLSLETIKLALEEENKHRDIDKQCRFEEILANFAAIP MIFDEIAQNKDNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQTNNLLHKL KIFHISQSEDKANILDKDEHFYLVFEECYFELANIVPLYNKIRNYITQKPYSDE KFKLNFENSTLANGWDKNKEPDNTAILFIKDDKYYLGVMNKKNNKIFDDKAIKE NKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYNPSEDILRIRNHSTHTKNGS PQKGYEKFEFNIEDCRKFIDFYKQSISKHPEWKDFGFRESDTQRYNSIDEFYRE VENQGYKLTFENISESYIDSVVNQGKLYLFQIYNKDFSAYSKGRPNLHTLYWKA LEDERNLQDVVYKLNGEAELFYRKQSIPKKITHPAKEAIANKNKDNPKKESVFE YDLIKDKRFTEDKFFFHCPITINFKSSGANKENDEINLLLKEKANDVHILSIDR GERHLAYYTLVDGKGNIIKQDTENIIGNDRMKTNYHDKLAAIEKDRDSARKDWK KINNIKEMKEGYLSQVVHEIAKLVIEYNAIVVFEDLNFGEKRGREKVEKQVYQK LEKMLIEKLNYLVFKDNEFDKTGGVLRAYQLTAPFETFKKMGKQTGIIYYVPAG FTSKICPVTGFVNQLYPKYESVSKSQEFFSKFDKICYNLDKGYFEFSFDYKNFG DKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVYPTKELEKLLKDYSIEYGHG ECIKAAICGESDKKFFAKLTSVLNTILQMRNSKTGTELDYLISPVADVNGNEED SRQAPKNMPQDADANGAYHIGLKGLMLLGRIKNNQEGKKLNLVIKNEEYFEFVQ NRNN
5	CasX	MEKRINKIRKKLSADNATKPVSRSGPMKTLLVRVMTDDLKKRLEKRRKKPEVMP QVISNNAANNLRMLLDDYTKMKEAILQVYWQEFKDDHVGLMCKFAQPASKKIDQ NKLKPEMDEKGNLTTAGFACSQCGQPLFVYKLEQVSEKGKAYTNYFGRCNVAEH EKLILLAQLKPEKDSDEAVTYSLGKFGQRALDFYSIHVTKESTHPVKPLAQIAG NRYASGPVGKALSDACMGTIASFLSKYQDIIIEHQKVVKGNQKRLESLRELAGK ENLEYPSVTLPPQPHTKEGVDAYNEVIARVRMWVNLNLWQKLKLSRDDAKPLLR LKGFPSFPVVERRENEVDWWNTINEVKKLIDAKRDMGRVFWSGVTAEKRNTILE GYNYLPNENDHKKREGSLENPKKPAKRQFGDLLLYLEKKYAGDWGKVEDEAWER IDKKIAGLTSHIEREEARNAEDAQSKAVLTDWLRAKASFVLERLKEMDEKEFYA CEIQLQKWYGDLRGNPFAVEAENRVVDISGFSIGSDGHSIQYRNLLAWKYLENG KREFYLLMNYGKKGRIRFTDGTDIKKSGKWQGLLYGGGKAKVIDLTEDPDDEQL IILPLAFGTRQGREFIWNDLLSLETGLIKLANGRVIEKTIYNKKIGRDEPALFV ALTFERREVVDPSNIKPVNLIGVDRGENIPAVIALTDPEGCPLPEFKDSSGGPT DILRIGEGYKEKQRAIQAAKEVEQRRAGGYSRKFASKSRNLADDMVRNSARDLE YHAVTHDAVLVFENLSRGFGRQGKRTEMTERQYTKMEDWLTAKLAYEGLTSKTY LSKTLAQYTSKTCSNCGFTITTADYDGMLVRLKKTSDGWATTLNNKELKAEGQI TYYNRYKRQTVEKELSAELDRLSEESGNNDISKWTKGRRDEALFLLKKRESHRP VQEQFVCLDCGHEVHADEQAALNIARSWLFLNSNSTEFKSYKSGKQPFVGAWQA FYKRRLKEVWKPNA
6	CasY	MRKKLFKGYILHNKRLVYTGKAAIRSIKYPLVAPNKTALNNLSEKIIYDYEHLF GPLNVASYARNSNRYSLVDFWIDSLRAGVIWQSKSTSLIDLISKLEGSKSPSEK IFEQIDFELKNKLDKEQFKDIILLNTGIRSSSNVRSLRGRFLKCFKEEFRDTEE VIACVDKWSKDLIVEGKSILVSKQFLYWEEEFGIKIFPHFKDNHDLPKLTFFVE PSLEFSPHLPLANCLERLKKEDISRESLLGLDNNESAFSNYENELENLLSRGEI KKIVTAVLAVSKSWENEPELEKRLHELSEKAKLLGYPKLTSSWADYRMIIGGKI KSWHSNYTEQLIKVREDLKKHQIALDKLQEDLKKVVDSSLREQIEAQREALLPL LDTMLKEKDESDDLELYRFILSDEKSLINGSYQRYIQTEEERKEDRDVTKKYKD LYSNLRNIPREFGESKKEQENKFINKSLPTIDVGLKILEDIRNALETVSVRKPP SITEEYVTKQLEKLSRKYKINAFNSNRFKQITEQVLRKYNNGELPKISEVFYRY PRESHVAIRILPVKISNPRKDISYLLDKYQISPDWKNSNPGEVVDLIEIYKLTL GWLLSCNKDESMDFSSYDLKLFPEAASLIKNFGSCLSGYYLSKMIENCITSEIK GMITLYTRDKFVVRYVTQMIGSNQKFPLLCLVGEKQTKNFSRNWGVLIEEKGDL GEEKNQEKCLIFKDKTDFAKAKEVEIFKNNIWRIRTSKYQIQFLNRLEKKTKEW DLMNLVLSEPSLVLEEEWGVSWDKDKLLPLLKKEKSCEERLYYSLPLNLVPATD YKEQSAEIEQRNTYLGLDVGEFGVAYAVVRIVRDRIELLSWGFLKDPALRKIRE RVQDMKKKQVMAVESSSSTAVARVREMAIHSLRNQIHSIALAYKAKIIYEISIS NFETGGNRMAKIYRSIKVSDVYRESGADTLVSEMIWGKKNKQMGNHISSYATSY TCCNCARTPFELVIDNDKEYEKGGDEFIFNVGDEKKVRGFLQKSLLGKTIKGKE VLKSIKEYARPPIREVLLEGEDVEQLLKRRGNSYIYRCPFCGYKTDADIQAALN IACRGYISDNAKDAVKEGERKLDYILEVRKLWEKNGAVLRSAKEL
7	CasPhi	MADTPTLFTQFLRHHLPGQRFRKDILKQAGRILANKGEDATIAFLRGKSEESPP DFQPPVKCPIIACSRPLTEWPIYQASVAIQGYVYGQSLAEFEASDPGCSKDGLL GWFDKTGVCTDYFSVQGLNLIFQNARKRYIGVQTKVTNRNEKRHKKLKRINAKR IAEGLPELTSDEPESALDETGHLIDPPGLNTNIYCYQQVSPKPLALSEVNQLPT

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		AYAGYSTSGDDPIQPMVTKDRLSISKGQPGYIPEHQRALLSQKKHRRMRGYGLK ARALLVIVRIQDDWAVIDLRSLLRNAYWRRIVQTKEPSTITKLLKLVTGDPVLD ATRMVATFTYKPGIVQVRSAKCLKNKQGSKLESERYLNETVSVTSIDLGSNNLV AVATYRLVNGNTPELLQRFTLPSHLVKDFERYKQAHDTLEDSIQKTAVASLPQG QQTEIRMWSMYGFREAQERVCQELGLADGSIPWNVMTATSTILTDLFLARGGDP KKCMFTSEPKKKKNSKQVLYKIRDRAWAKMYRTLLSKETREAWNKALWGLKRGS PDYARLSKRKEELARRCVNYTISTAEKRAQCGRTIVALEDLNIGFFHGRGKQEP GWVGLFTRKKENRWLMQALHKAFLELAHHRGYHVIEVNPAYTSQTCPVCRHCDP DNRDQHNREAFHCIGCGFRGNADLDVATHNIAMVAITGESLKRARGSVASKTPQ PLAAE
8	Cas12f1 (Cas14a)	MIKVYRYEIVKPLDLDWKEFGTILRQLQQETRFALNKATQLAWEWMGESSDYKD NHGEYPKSKDILGYTNVHGYAYHTIKTKAYRLNSGNLSQTIKRATDRFKAYQKE ILRGDMSIPSYKRDIPLDLIKENISVNRMNHGDYIASLSLLSNPAKQEMNVKRK ISVIIIVRGAGKTIMDRILSGEYQVSASQIIHDDRKNKWYLNISYDFEPQTRVL DLNKIMGIDLGVAVAVYMAFQHTPARYKLEGGEIENFRRQVESRRISMLRQGKY AGGARGGHGRDKRIKPIEQLRDKIANFRDTTNHRYSRYIVDMAIKEGCGTIQME DLTNIRDIGSRFLQNWTYYDLQQKIIYKAEEAGIKVIKIDPQYTSQRCSECGNI DSGNRIGQAIFKCRACGYEANADYNAARNIAIPNIDKIIAESIKSGGS
9	Cas 12f2 (Cas14b)	NAMIAQKTIKIKLNPTKEQIIKLNSIIEEYIKVSNFTAKKIAEIQESFTDSGLT QGTCSECGKEKTYRKYHLLKKDNKLFCITCYKRKYSQFTLQKVEFQNKTGLRNV AKLPKTYYTNAIRFASDTFSGFDEIIKKKQNRLNSIQNRLNFWKELLYNPSNRN EIKIKVVKYAPKTDTREHPHYYSEAEIKGRIKRLEKQLKKFKMPKYPEFTSETI SLQRELYSWKNPDELKISSITDKNESMNYYGKEYLKRYIDLINSQTPQILLEKE NNSFYLCFPITKNIEMPKIDDTFEPVGIDWGITRNIAVVSILDSKTKKPKFVKE YSAGYILGKRKHYKSLRKHFGQKKRQDKINKLGTKEDRFIDSNIHKLAFLIVKE IRNHSNKPIILMENITDNREEAEKSMRQNILLHSVKSRLQNYIAYKALWNNIPT NLVKPEHTSQICNRCGHQDRENRPKGSKLFKCVKCNYMSNADENASINIARKFY IGEYEPFYKDNEKMKSGVNSISM
10	Cas12f3 (Cas14c)	MEVQKTVMKTLSLRILRPLYSQEIEKEIKEEEKERRKQAGGTGELDGGFYKKLE KKHSEMFSFDRLNLLLNQLQREIAKVYNHAISELYIATIAQGNKSNKHYISSIV YNRAYGYFYNAYIALGICSKVEANFRSNELLTQQSALPTAKSDNFPIVLHKQKG AEGEDGGFRISTEGSDLIFEIPIPFYEYNGENRKEPYKWVKKGGQKPVLKLILS TFRRQRNKGWAKDEGTDAEIRKVTEGKYQVSQIEINRGKKLGEHQKWFANFSIE QPIYERKPNRSIVGGLDVGIRSPLVCAINNSFSRYSVDSNDVEKFSKQVFAFRR RLLSKNSLKRKHGHAAHKLEPITEMTEKNDKERKKIIERWAKEVTNFFVKNQVG IVQIEDLSTMKDREDHFFNQYLRGFWPYYQMQTLIENKLKEYGIEVKRVQAKYT SQLCSNPNCRYWNNYENFEYRKVNKFPKEKCEKCNLEISADYNAARNLSTPDIE KFVAKATKGINLPEK
11	C2c8	MKVLEFKIHPTEEQVSKIDQSLAACKLLWNLSIALKEESKQRYYRKKHKEDEFS PEIWGLSYSGHYDEKEFKTLKDKEKKLLIGNPCCKIAYFKKTSNGKEYTPLNSI PIRREMNAENIDKDAVNYLNRKKLAFYFRENTAKFIGEIETEFKKGFFKSVIKP AYDAAKKGIRGIPRFKGRRDKVETLVNGQPETIKIKSNGVIVSSKIGLLKIRGL DRLQGKAPRMAKITRKATGYYLQLTIETDDTIYKESDKCVGLDMGAVAIFTDDL GRQSEAKRYAKIQKKRLNRLQRQASRQKDNSNNQRKTYAKLARVHEKIARQRKG RNAQLAHKITSEYQSVILEDLNLKNMTAAAKPKEREDGDGYKQNGKKRKSGLNK ALLDNAIGQLRTFIENKANERGRKIIRVNPKHTSQTCPNCGNIDKANRVSQSKF KCVSCGYEAHADQNAAANILIRGLRDEFLRAIGSLYKFPVSMIGKYPGLAGEFT PDLDANQESIGDAPIENAEHSISKQMKQEGNRTPTQPENGSQSLIFLSAPPQPC GDSHGTNNPKALPNKASKRSSKKPRGAIPENPDQLTIWDLLD
12	dSpCas9	MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLED SGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELVE EDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMI KFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARL SKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNEKSNEDLAEDAKLQLSKDT YDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKR YDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKP ILEKMDGTEELLVKLNREDLLRKQRTEDNGSIPHQIHLGELHAILRRQEDFYPF LKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA SAQSFIERMTNEDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFL SGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTY HDLLKIIKDKDELDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVM KQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNEMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKP ENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEK LYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNR GKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIK RQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQF YKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSE QEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDE ATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGF DSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYK

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		EVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNK HRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQ SITGLYETRIDLSQLGGD
13	dSaCas9	MKRNYILGLAIGITSVGYGIIDYETRDVIDAGVRLFKEANVENNEGRRSKRGAR RLKRRRRHRIQRVKKLLFDYNLLTDHSELSGINPYEARVKGLSQKLSEEEFSAA LLHLAKRRGVHNVNEVEEDTGNELSTKEQISRNSKALEEKYVAELQLERLKKDG EVRGSINRFKTSDYVKEAKQLLKVQKAYHQLDQSFIDTYIDLLETRRTYYEGPG EGSPFGWKDIKEWYEMLMGHCTYFPEELRSVKYAYNADLYNALNDLNNLVITRD ENEKLEYYEKFQIIENVFKQKKKPTLKQIAKEILVNEEDIKGYRVTSTGKPEFT NLKVYHDIKDITARKEIIENAELLDQIAKILTIYQSSEDIQEELTNLNSELTQE EIEQISNLKGYTGTHNLSLKAINLILDELWHTNDNQIAIFNRLKLVPKKVDLSQ QKEIPTTLVDDFILSPVVKRSFIQSIKVINAIIKKYGLPNDIIIELAREKNSKD AQKMINEMQKRNRQTNERIEEIIRTTGKENAKYLIEKIKLHDMQEGKCLYSLEA IPLEDLLNNPFNYEVDHIIPRSVSFDNSFNNKVLVKQEEASKKGNRTPFQYLSS SDSKISYETFKKHILNLAKGKGRISKTKKEYLLEERDINRFSVQKDFINRNLVD TRYATRGLMNLLRSYFRVNNLDVKVKSINGGFTSFLRRKWKFKKERNKGYKHHA EDALIIANADFIFKEWKKLDKAKKVMENQMFEEKQAESMPEIETEQEYKEIFIT PHQIKHIKDFKDYKYSHRVDKKPNRELINDTLYSTRKDDKGNTLIVNNLNGLYD KDNDKLKKLINKSPEKLLMYHHDPQTYQKLKLIMEQYGDEKNPLYKYYEETGNY LTKYSKKDNGPVIKKIKYYGNKLNAHLDITDDYPNSRNKVVKLSLKPYREDVYL DNGVYKFVTVKNLDVIKKENYYEVNSKCYEEAKKLKKISNQAEFIASFYNNDLI KINGELYRVIGVNNDLLNRIEVNMIDITYREYLENMNDKRPPRIIKTIASKTQS IKKYSTDILGNLYEVKSKKHPQIIKKG
14	inactive FnCpf1	MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILDDEKRAKDYKKAKQII DKYHQFFIEEILSSVCISEDLLQNYSDVYFKLKKSDDDNLQKDEKSAKDTIKKQ ISEYIKDSEKFKNLENQNLIDAKKGQESDLILWLKQSKDNGIELFKANSDITDI DEALEIIKSFKGWTTYFKGFHENRKNVYSSNDIPTSIIYRIVDDNLPKFLENKA KYESLKDKAPEAINYEQIKKDLAEELTFDIDYKTSEVNQRVESLDEVFEIANEN NYLNQSGITKENTIIGGKFVNGENTKRKGINEYINLYSQQINDKTLKKYKMSVL FKQILSDTESKSFVIDKLEDDSDVVTTMQSFYEQIAAFKTVEEKSIKETLSLLE DDLKAQKLDLSKIYFKNDKSLTDLSQQVEDDYSVIGTAVLEYITQQIAPKNLDN PSKKEQELIAKKTEKAKYLSLETIKLALEEENKHRDIDKQCRFEEILANFAAIP MIFDEIAQNKDNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQTNNLLHKL KIFHISQSEDKANILDKDEHFYLVFEECYFELANIVPLYNKIRNYITQKPYSDE KFKLNFENSTLANGWDKNKEPDNTAILFIKDDKYYLGVMNKKNNKIFDDKAIKE NKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYNPSEDILRIRNHSTHTKNGS PQKGYEKFEFNIEDCRKFIDFYKQSISKHPEWKDFGFRESDTQRYNSIDEFYRE VENQGYKLTFENISESYIDSVVNQGKLYLFQIYNKDFSAYSKGRPNLHTLYWKA LFDERNLQDVVYKLNGEAELFYRKQSIPKKITHPAKEAIANKNKDNPKKESVFE YDLIKDKRFTEDKFFFHCPITINFKSSGANKENDEINLLLKEKANDVHILSIAR GERHLAYYTLVDGKGNIIKQDTENIIGNDRMKTNYHDKLAAIEKDRDSARKDWK KINNIKEMKEGYLSQVVHEIAKLVIEYNAIVVFEDLNFGEKRGREKVEKQVYQK LEKMLIEKLNYLVFKDNEFDKTGGVLRAYQLTAPFETFKKMGKQTGIIYYVPAG FTSKICPVTGFVNQLYPKYESVSKSQEFFSKFDKICYNLDKGYFEFSEDYKNFG DKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVYPTKELEKLLKDYSIEYGHG ECIKAAICGESDKKFFAKLTSVLNTILQMRNSKTGTELDYLISPVADVNGNEED SRQAPKNMPQDADANGAYHIGLKGLMLLGRIKNNQEGKKLNLVIKNEEYFEFVQ NRNN
15	dNmeCas9	MAAFKPNSINYILGLAIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPKT GDSLAMARRLARSVRRLTRRRAHRLLRTRRLLKREGVLQAANEDENGLIKSLPN TPWQLRAAALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGV AGNAHALQTGDFRTPAELALNKFEKESGHIRNQRSDYSHTFSRKDLQAELILLE EKQKEFGNPHVSGGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKN TYTAERFIWLTKLNNLRILEQGSERPLTDTERATLMDEPYRKSKLTYAQARKLL GLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSPEL QDEIGTAFSLFKTDEDITGRLKDRIQPEILEALLKHISFDKFVQISLKALRRIV PLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPVVLRALSQARK VINGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKAAAKFREY FPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEINLGRLNEKGYVEIDAALPESR TWDDSENNKVLVLGSENQNKGNQTPYEYENGKDNSREWQEFKARVETSREPRSK KQRILLQKFDEDGEKERNLNDTRYVNRFLCQFVADRMRLTGKGKKRVFASNGQI TNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGK TIDKETGEVLHQKTHFPQPWEFFAQEVMIRVFGKPDGKPEFEEADTLEKLRTLL AEKLSSRPEAVHEYVTPLFVSRAPNRKMSGQGHMETVKSAKRLDEGVSVLRVPL TQLKLKDLEKMVNREREPKLYEALKARLEAHKDDPAKAFAEPFYKYDKAGNRTQ QVKAVRVEQVQKTGVWVRNHNGIADNATMVRVDVFEKGDKYYLVPIYSWQVAKG ILPDRAVVQGKDEEDWQLIDDSENFKFSLHPNDLVEVITKKARMEGYFASCHRG TGNINIRIHDLDHKIGKNGILEGIGVKTALSFQKYQIDELGKEIRPCRLKKRPP VR

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
16	dCjCas9	MARILAFAIGISSIGWAFSENDELKDCGVRIFTKVENPKTGESLALPRRLARSA RKRLARRKARLNHLKHLIANEFKLNYEDYQSFDESLAKAYKGSLISPYELRFRA LNELLSKQDFARVILHIAKRRGYDDIKNSDDKEKGAILKAIKQNEEKLANYQSV GEYLYKEYFQKFKENSKEFTNVRNKKESYERCIAQSFLKDELKLIFKKQREFGF SFSKKFEEEVLSVAFYKRALKDESHLVGNCSFFTDEKRAPKNSPLAFMFVALTR IINLLNNLKNTEGILYTKDDLNALLNEVLKNGTLTYKQTKKLLGLSDDYEFKGE KGTYFIEFKKYKEFIKALGEHNLSQDDLNEIAKDITLIKDEIKLKKALAKYDLN QNQIDSLSKLEFKDHLNISFKALKLVTPLMLEGKKYDEACNELNLKVAINEDKK DELPAFNETYYKDEVTNPVVLRAIKEYRKVLNALLKKYGKVHKINIELAREVGK NHSQRAKIEKEQNENYKAKKDAELECEKLGLKINSKNILKLRLFKEQKEFCAYS GEKIKISDLQDEKMLEIDAIYPYSRSFDDSYMNKVLVFTKQNQEKLNQTPFEAF GNDSAKWQKIEVLAKNLPTKKQKRILDKNYKDKEQKNEKDRNLNDTRYIARLVL NYTKDYLDFLPLSDDENTKLNDTQKGSKVHVEAKSGMLTSALRHTWGFSAKDRN NHLHHAIDAVIIAYANNSIVKAFSDEKKEQESNSAELYAKKISELDYKNKRKFF EPFSGFRQKVLDKIDEIFVSKPERKKPSGALHEETFRKEEEFYQSYGGKEGVLK ALELGKIRKVNGKIVKNGDMFRVDIFKHKKTNKFYAVPIYTMDFALKVLPNKAV ARSKKGEIKDWILMDENYEFCFSLYKDSLILIQTKDMQEPEFVYYNAFTSSTVS LIVSKHDNKFETLSKNQKILFKNANEKEVIAKSIGIQNLKVFEKYIVSALGEVT KAEFRQREDEKK
17	dSt1Cas9	MGSDLVLGLAIGIGSVGVGILNKVTGEIIHKNSRIFPAAQAENNLVRRTNRQGR RLARRKKHRRVRLNRLFEESGLITDFTKISINLNPYQLRVKGLTDELSNEELFI ALKNMVKHRGISYLDDASDDGNSSVGDYAQIVKENSKQLETKTPGQIQLERYQT YGQLRGDFTVEKDGKKHRLINVFPTSAYRSEALRILQTQQEFNPQITDEFINRY LEILTGKRKYYHGPGNEKSRTDYGRYRTSGETLDNIFGILIGKCTFYPDEFRAA KASYTAQEFNLLNDLNNLTVPTETKKLSKEQKNQIINYVKNEKAMGPAKLFKYI AKLLSCDVADIKGYRIDKSGKAEIHTFEAYRKMKTLETLDIEQMDRETLDKLAY VLTLNTEREGIQEALEHEFADGSFSQKQVDELVQERKANSSIFGKGWHNFSVKL MMELIPELYETSEEQMTILTRLGKQKTTSSSNKTKYIDEKLLTEEIYNPVVAKS VRQAIKIVNAAIKEYGDEDNIVIEMARETNEDDEKKAIQKIQKANKDEKDAAML KAANQYNGKAELPHSVFHGHKQLATKIRLWHQQGERCLYTGKTISIHDLINNSN QFEVDAILPLSITFDDSLANKVLVYATANQEKGQRTPYQALDSMDDAWSFRELK AFVRESKTLSNKKKEYLLTEEDISKFDVRKKFIERNLVDTRYASRVVLNALQEH FRAHKIDTKVSVVRGQFTSQLRRHWGIEKTRDTYHHHAVDALIIAASSQLNLWK KQKNTLVSYSEDQLLDIETGELISDDEYKESVFKAPYQHFVDTLKSKEFEDSIL FSYQVDSKENRKISDATIYATRQAKVGKDKADETYVLGKIKDIYTQDGYDAFMK IYKKDKSKFLMYRHDPQTFEKVIEPILENYPNKQINEKGKEVPCNPFLKYKEEH GYIRKYSKKGNGPEIKSLKYYDSKLGNHIDITPKDSNNKVVLQSVSPWRADVYF NKTTGKYEILGLKYADLQFEKGTGTYKISQEKYNDIKKKEGVDSDSEFKFTLYK NDLLLVKDTETKEQQLFRELSRTMPKQKHYVELKPYDKQKFEGGEALIKVLGNV ANSGQCKKGLGKSNISIYKVRTDVLGNQHIIKNEGDKPKLDE
18	dSt3Cas9	MTKPYSIGLAIGTNSVGWAVITDNYKVPSKKMKVLGNTSKKYIKKNLLGVLLED SGITAEGRRLKRTARRRYTRRRNRILYLQEIFSTEMATLDDAFFQRLDDSELVP DDKRDSKYPIFGNLVEEKVYHDEFPTIYHLRKYLADSTKKADLRLVYLALAHMI KYRGHFLIEGEFNSKNNDIQKNFQDELDTYNAIFESDLSLENSKQLEEIVKDKI SKLEKKDRILKLFPGEKNSGIFSEFLKLIVGNQADERKCENLDEKASLHESKES YDEDLETLLGYIGDDYSDVELKAKKLYDAILLSGELTVTDNETEAPLSSAMIKR YNEHKEDLALLKEYIRNISLKTYNEVEKDDTKNGYAGYIDGKTNQEDFYVYLKN LLAEFEGADYFLEKIDREDFLRKQRTEDNGSIPYQIHLQEMRAILDKQAKFYPF LAKNKERIEKILTFRIPYYVGPLARGNSDFAWSIRKRNEKITPWNFEDVIDKES SAEAFINRMTSFDLYLPEEKVLPKHSLLYETENVYNELTKVRFIAESMRDYQFL DSKQKKDIVRLYFKDKRKVTDKDIIEYLHAIYGYDGIELKGIEKQFNSSLSTYH DLLNIINDKEFLDDSSNEAIIEEIIHTLTIFEDREMIKQRLSKFENIFDKSVLK KLSRRHYTGWGKLSAKLINGIRDEKSGNTILDYLIDDGISNRNEMQLIHDDALS FKKKIQKAQIIGDEDKGNIKEVVKSLPGSPAIKKGILQSIKIVDELVKVMGGRK PESIVVEMARENQYTNQGKSNSQQRLKRLEKSLKELGSKILKENIPAKLSKIDN NALQNDRLYLYYLQNGKDMYTGDDLDIDRLSNYDIDHIIPQAFLKDNSIDNKVL VSSASARGKSDDFPSLEVVKKRKTFWYQLLKSKLISQRKEDNLTKAERGGLLPE DKAGFIQRQLVETRQITKHVARLLDEKENNKKDENNRAVRTVKIITLKSTLVSQ FRKDFELYKVREINDFHHAHDAYLNAVIASALLKKYPKLEPEFVYGDYPKYNSF RERKSATEKVYFYSNIMNIFKKSISLADGRVIERPLIEVNEETGESVWNKESDL ATVRRVLSYPQVNVVKKVEEQNHGLDRGKPKGLFNANLSSKPKPNSNENLVGAK EYLDPKKYGGYAGISNSFAVLVKGTIEKGAKKKITNVLEFQGISILDRINYRKD KLNFLLEKGYKDIELIIELPKYSLFELSDGSRRMLASILSTNNKRGEIHKGNQI FLSQKFVKLLYHAKRISNTINENHRKYVENHKKEFEELFYYILEFNENYVGAKK NGKLLNSAFQSWQNHSIDELCSSFIGPTGSERKGLFELTSRGSAADFEFLGVKI PRYRDYTPSSLLKDATLIHQSVTGLYETRIDLAKLGEG
19	dLbCpf1	MSKLEKFTNCYSLSKTLRFKAIPVGKTQENIDNKRLLVEDEKRAEDYKGVKKLL DRYYLSFINDVLHSIKLKNLNNYISLFRKKTRTEKENKELENLEINLRKEIAKA FKGNEGYKSLFKKDIIETILPEFLDDKDEIALVNSENGFTTAFTGFFDNRENME SEEAKSTSIAFRCINENLTRYISNMDIFEKVDAIFDKHEVQEIKEKILNSDYDV EDFFEGEFFNFVLTQEGIDVYNAIIGGFVTESGEKIKGLNEYINLYNQKTKQKL PKFKPLYKQVLSDRESLSFYGEGYTSDEEVLEVERNTLNKNSEIFSSIKKLEKL

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		FKNFDEYSSAGIFVKNGPAISTISKDIFGEWNVIRDKWNAEYDDIHLKKKAVVT EKYEDDRRKSFKKIGSFSLEQLQEYADADLSVVEKLKEIIIQKVDEIYKVYGSS EKLFDADFVLEKSLKKNDAVVAIMKDLLDSVKSFENYIKAFFGEGKETNRDESE YGDFVLAYDILLKVDHIYDAIRNYVTQKPYSKDKFKLYFQNPQFMGGWDKDKET DYRATILRYGSKYYLAIMDKKYAKCLQKIDKDDVNGNYEKINYKLLPGPNKMLP KVFFSKKWMAYYNPSEDIQKIYKNGTFKKGDMENLNDCHKLIDFFKDSISRYPK WSNAYDENESETEKYKDIAGFYREVEEQGYKVSFESASKKEVDKLVEEGKLYMF QIYNKDESDKSHGTPNLHTMYFKLLEDENNHGQIRLSGGAELFMRRASLKKEEL VVHPANSPIANKNPDNPKKTTTLSYDVYKDKRESEDQYELHIPIAINKCPKNIF KINTEVRVLLKHDDNPYVIGIARGERNLLYIVVVDGKGNIVEQYSLNEIINNEN GIRIKTDYHSLLDKKEKERFEARQNWTSIENIKELKAGYISQVVHKICELVEKY DAVIALEDLNSGFKNSRVKVEKQVYQKFEKMLIDKLNYMVDKKSNPCATGGALK GYQITNKFESFKSMSTQNGFIFYIPAWLTSKIDPSTGFVNLLKTKYTSIADSKK FISSFDRIMYVPEEDLFEFALDYKNFSRTDADYIKKWKLYSYGNRIRIFRNPKK NNVFDWEEVCLTSAYKELENKYGINYQQGDIRALLCEQSDKAFYSSFMALMSLM LQMRNSITGRTDVDFLISPVKNSDGIFYDSRNYEAQENAILPKNADANGAYNIA RKVLWAIGQFKKAEDEKLDKVKIAISNKEWLEYAQTSVKH
20	inactive AsCpf1	MTQFEGFTNLYQVSKTLRFELIPQGKTLKHIQEQGFIEEDKARNDHYKELKPII DRIYKTYADQCLQLVQLDWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHD YFIGRTDNLTDAINKRHAEIYKGLFKAELFNGKVLKQLGTVTTTEHENALLRSF DKFTTYFSGFYENRKNVESAEDISTAIPHRIVQDNFPKEKENCHIFTRLITAVP SLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAG TEKIKGLNEVLNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFK SDEEVIQSFCKYKTLLRNENVLETAEALFNELNSIDLTHIFISHKKLETISSAL CDHWDTLRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEIISAAGKELS EAFKQKTSEILSHAHAALDQPLPTTLKKQEEKEILKSQLDSLLGLYHLLDWFAV DESNEVDPEFSARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKFKLNFQMPTL ASGWDVNKEKNNGAILFVKNGLYYLGIMPKQKGRYKALSFEPTEKTSEGEDKMY YDYFPDAAKMIPKCSTQLKAVTAHFQTHTTPILLSNNFIEPLEITKEIYDLNNP EKEPKKFQTAYAKKTGDQKGYREALCKWIDFTRDFLSKYTKTTSIDLSSLRPSS QYKDLGEYYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHG KPNLHTLYWTGLESPENLAKTSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKK LKDQKTPIPDTLYQELYDYVNHRLSHDLSDEARALLPNVITKEVSHEIIKDRRF TSDKFFFHVPITLNYQAANSPSKENQRVNAYLKEHPETPIIGIARGERNLIYIT VIDSTGKILEQRSLNTIQQFDYQKKLDNREKERVAARQAWSVVGTIKDLKQGYL SQVIHEIVDLMIHYQAVVVLENLNFGFKSKRTGIAEKAVYQQFEKMLIDKLNCL VLKDYPAEKVGGVLNPYQLTDQFTSFAKMGTQSGELFYVPAPYTSKIDPLTGFV DPFVWKTIKNHESRKHFLEGFDFLHYDVKTGDFILHFKMNRNLSFQRGLPGEMP AWDIVFEKNETQFDAKGTPFIAGKRIVPVIENHRFTGRYRDLYPANELIALLEE KGIVERDGSNILPKLLENDDSHAIDTMVALIRSVLQMRNSNAATGEDYINSPVR DLNGVCFDSRFQNPEWPMDADANGAYHIALKGQLLLNHLKESKDLKLQNGISNQ DWLAYIQELRN
21	inactive enAsCpf1	MTQFEGFTNLYQVSKTLRFELIPQGKTLKHIQEQGFIEEDKARNDHYKELKPII DRIYKTYADQCLQLVQLDWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHD YFIGRTDNLTDAINKRHAEIYKGLFKAELFNGKVLKQLGTVTTTEHENALLRSF DKFTTYFSGFYRNRKNVESAEDISTAIPHRIVQDNFPKFKENCHIFTRLITAVP SLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAG TEKIKGLNEVLNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFK SDEEVIQSFCKYKTLLRNENVLETAEALFNELNSIDLTHIFISHKKLETISSAL CDHWDTLRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEIISAAGKELS EAFKQKTSEILSHAHAALDQPLPTTLKKQEEKEILKSQLDSLLGLYHLLDWFAV DESNEVDPEFSARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKFKLNFQMPTL ARGWDVNREKNNGAILFVKNGLYYLGIMPKQKGRYKALSFEPTEKTSEGEDKMY YDYFPDAAKMIPKCSTQLKAVTAHFQTHTTPILLSNNFIEPLEITKEIYDLNNP EKEPKKFQTAYAKKTGDQKGYREALCKWIDFTRDELSKYTKTTSIDLSSLRPSS QYKDLGEYYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHG KPNLHTLYWTGLESPENLAKTSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKK LKDQKTPIPDTLYQELYDYVNHRLSHDLSDEARALLPNVITKEVSHEIIKDRRF TSDKFFFHVPITLNYQAANSPSKENQRVNAYLKEHPETPIIGIARGERNLIYIT VIDSTGKILEQRSLNTIQQFDYQKKLDNREKERVAARQAWSVVGTIKDLKQGYL SQVIHEIVDLMIHYQAVVVLENLNFGFKSKRTGIAEKAVYQQFEKMLIDKLNCL VLKDYPAEKVGGVLNPYQLTDQFTSFAKMGTQSGFLFYVPAPYTSKIDPLTGFV DPFVWKTIKNHESRKHFLEGFDFLHYDVKTGDFILHFKMNRNLSFQRGLPGEMP AWDIVFEKNETQFDAKGTPFIAGKRIVPVIENHRFTGRYRDLYPANELIALLEE KGIVERDGSNILPKLLENDDSHAIDTMVALIRSVLQMRNSNAATGEDYINSPVR DLNGVCFDSRFQNPEWPMDADANGAYHIALKGQLLLNHLKESKDLKLQNGISNQ DWLAYIQELRN
22	inactive HFAsCpf1	MTQFEGFTNLYQVSKTLRFELIPQGKTLKHIQEQGFIEEDKARNDHYKELKPII DRIYKTYADQCLQLVQLDWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHD YFIGRTDNLTDAINKRHAEIYKGLFKAELFNGKVLKQLGTVTTTEHENALLRSF DKFTTYFSGFYRNRKNVESAEDISTAIPHRIVQDNFPKFKENCHIFTRLITAVP SLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAG TEKIKGLNEVLALAIQKNDETAHIIASLPHRFIPLEKQILSDRNTLSFILEEFK

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		SDEEVIQSFCKYKTLLRNENVLETAEALENELNSIDLTHIFISHKKLETISSAL CDHWDTLRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEIISAAGKELS EAFKQKTSEILSHAHAALDQPLPTTLKKQEEKEILKSQLDSLLGLYHLLDWFAV DESNEVDPEFSARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKFKLNFQMPTL ARGWDVNREKNNGAILFVKNGLYYLGIMPKQKGRYKALSFEPTEKTSEGEDKMY YDYFPDAAKMIPKCSTQLKAVTAHFQTHTTPILLSNNFIEPLEITKEIYDLNNP EKEPKKFQTAYAKKTGDQKGYREALCKWIDETRDELSKYTKTTSIDLSSLRPSS QYKDLGEYYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHG KPNLHTLYWTGLESPENLAKTSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKK LKDQKTPIPDTLYQELYDYVNHRLSHDLSDEARALLPNVITKEVSHEIIKDRRF TSDKFFFHVPITLNYQAANSPSKENQRVNAYLKEHPETPIIGIARGERNLIYIT VIDSTGKILEQRSLNTIQQFDYQKKLDNREKERVAARQAWSVVGTIKDLKQGYL SQVIHEIVDLMIHYQAVVVLENLNFGFKSKRTGIAEKAVYQQFEKMLIDKLNCL VLKDYPAEKVGGVLNPYQLTDQFTSFAKMGTQSGELFYVPAPYTSKIDPLTGEV DPFVWKTIKNHESRKHFLEGFDFLHYDVKTGDFILHFKMNRNLSFQRGLPGEMP AWDIVFEKNETQFDAKGTPFIAGKRIVPVIENHRFTGRYRDLYPANELIALLEE KGIVERDGSNILPKLLENDDSHAIDTMVALIRSVLQMRNSNAATGEDYINSPVR DLNGVCFDSRFQNPEWPMDADANGAYHIALKGQLLLNHLKESKDLKLQNGISNQ DWLAYIQELRN
23	inactive RVRAsCpf1	MTQFEGFTNLYQVSKTLRFELIPQGKTLKHIQEQGFIEEDKARNDHYKELKPII DRIYKTYADQCLQLVQLDWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHD YFIGRTDNLTDAINKRHAEIYKGLFKAELFNGKVLKQLGTVTTTEHENALLRSF DKFTTYFSGFYENRKNVESAEDISTAIPHRIVQDNFPKFKENCHIFTRLITAVP SLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAG TEKIKGLNEVLNLAIQKNDETAHIIASLPHRFIPLEKQILSDRNTLSFILEEFK SDEEVIQSFCKYKTLLRNENVLETAEALENELNSIDLTHIFISHKKLETISSAL CDHWDTLRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEIISAAGKELS EAFKQKTSEILSHAHAALDQPLPTTLKKQEEKEILKSQLDSLLGLYHLLDWFAV DESNEVDPEFSARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKFKLNFQMPTL ARGWDVNVEKNRGAILFVKNGLYYLGIMPKQKGRYKALSFEPTEKTSEGEDKMY YDYFPDAAKMIPKCSTQLKAVTAHFQTHTTPILLSNNFIEPLEITKEIYDLNNP EKEPKKFQTAYAKKTGDQKGYREALCKWIDFTRDELSKYTKTTSIDLSSLRPSS QYKDLGEYYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHG KPNLHTLYWTGLFSPENLAKTSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKK LKDQKTPIPDTLYQELYDYVNHRLSHDLSDEARALLPNVITKEVSHEIIKDRRF TSDKFFFHVPITLNYQAANSPSKFNQRVNAYLKEHPETPIIGIARGERNLIYIT VIDSTGKILEQRSLNTIQQFDYQKKLDNREKERVAARQAWSVVGTIKDLKQGYL SQVIHEIVDLMIHYQAVVVLENLNFGFKSKRTGIAEKAVYQQFEKMLIDKLNCL VLKDYPAEKVGGVLNPYQLTDQFTSFAKMGTQSGELFYVPAPYTSKIDPLTGFV DPFVWKTIKNHESRKHFLEGFDFLHYDVKTGDFILHFKMNRNLSFQRGLPGFMP AWDIVFEKNETQFDAKGTPFIAGKRIVPVIENHRFTGRYRDLYPANELIALLEE KGIVERDGSNILPKLLENDDSHAIDTMVALIRSVLQMRNSNAATGEDYINSPVR DLNGVCFDSRFQNPEWPMDADANGAYHIALKGQLLLNHLKESKDLKLQNGISNQ DWLAYIQELRN
24	inactive RRAsCpf1	MTQFEGFTNLYQVSKTLRFELIPQGKTLKHIQEQGFIEEDKARNDHYKELKPII DRIYKTYADQCLQLVQLDWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHD YFIGRTDNLTDAINKRHAEIYKGLFKAELFNGKVLKQLGTVTTTEHENALLRSF DKFTTYFSGFYENRKNVESAEDISTAIPHRIVQDNFPKFKENCHIFTRLITAVP SLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAG TEKIKGLNEVLNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFK SDEEVIQSFCKYKTLLRNENVLETAEALFNELNSIDLTHIFISHKKLETISSAL CDHWDTLRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEIISAAGKELS EAFKQKTSEILSHAHAALDQPLPTTLKKQEEKEILKSQLDSLLGLYHLLDWFAV DESNEVDPEFSARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKFKLNFQMPTL ARGWDVNKEKNNGAILFVKNGLYYLGIMPKQKGRYKALSFEPTEKTSEGEDKMY YDYFPDAAKMIPRCSTQLKAVTAHFQTHTTPILLSNNFIEPLEITKEIYDLNNP EKEPKKFQTAYAKKTGDQKGYREALCKWIDFTRDELSKYTKTTSIDLSSLRPSS QYKDLGEYYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHG KPNLHTLYWTGLFSPENLAKTSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKK LKDQKTPIPDTLYQELYDYVNHRLSHDLSDEARALLPNVITKEVSHEIIKDRRF TSDKFFFHVPITLNYQAANSPSKENQRVNAYLKEHPETPIIGIARGERNLIYIT VIDSTGKILEQRSLNTIQQFDYQKKLDNREKERVAARQAWSVVGTIKDLKQGYL SQVIHEIVDLMIHYQAVVVLENLNFGFKSKRTGIAEKAVYQQFEKMLIDKLNCL VLKDYPAEKVGGVLNPYQLTDQFTSFAKMGTQSGELFYVPAPYTSKIDPLTGFV DPFVWKTIKNHESRKHFLEGEDFLHYDVKTGDFILHFKMNRNLSFQRGLPGEMP AWDIVFEKNETQFDAKGTPFIAGKRIVPVIENHRFTGRYRDLYPANELIALLEE KGIVERDGSNILPKLLENDDSHAIDTMVALIRSVLQMRNSNAATGEDYINSPVR DLNGVCFDSRFQNPEWPMDADANGAYHIALKGQLLLNHLKESKDLKLQNGISNQ DWLAYIQELRN
25	dCasX	MEKRINKIRKKLSADNATKPVSRSGPMKTLLVRVMTDDLKKRLEKRRKKPEVMP QVISNNAANNLRMLLDDYTKMKEAILQVYWQEFKDDHVGLMCKFAQPASKKIDQ NKLKPEMDEKGNLTTAGFACSQCGQPLFVYKLEQVSEKGKAYTNYFGRCNVAEH EKLILLAQLKPEKDSDEAVTYSLGKFGQRALDFYSIHVTKESTHPVKPLAQIAG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		NRYASGPVGKALSDACMGTIASFLSKYQDIIIEHQKVVKGNQKRLESLRELAGK ENLEYPSVTLPPQPHTKEGVDAYNEVIARVRMWVNLNLWQKLKLSRDDAKPLLR LKGFPSFPVVERRENEVDWWNTINEVKKLIDAKRDMGRVFWSGVTAEKRNTILE GYNYLPNENDHKKREGSLENPKKPAKRQFGDLLLYLEKKYAGDWGKVEDEAWER IDKKIAGLTSHIEREEARNAEDAQSKAVLTDWLRAKASFVLERLKEMDEKEFYA CEIQLQKWYGDLRGNPFAVEAENRVVDISGFSIGSDGHSIQYRNLLAWKYLENG KREFYLLMNYGKKGRIRFTDGTDIKKSGKWQGLLYGGGKAKVIDLTEDPDDEQL IILPLAFGTRQGREFIWNDLLSLETGLIKLANGRVIEKTIYNKKIGRDEPALFV ALTFERREVVDPSNIKPVNLIGVARGENIPAVIALTDPEGCPLPEFKDSSGGPT DILRIGEGYKEKQRAIQAAKEVEQRRAGGYSRKFASKSRNLADDMVRNSARDLF YHAVTHDAVLVFANLSRGFGRQGKRTEMTERQYTKMEDWLTAKLAYEGLTSKTY LSKTLAQYTSKTCSNCGFTITTADYDGMLVRLKKTSDGWATTLNNKELKAEGQI TYYNRYKRQTVEKELSAELDRLSEESGNNDISKWTKGRRDEALFLLKKRFSHRP VQEQFVCLDCGHEVHAAEQAALNIARSWLELNSNSTEFKSYKSGKQPFVGAWQA FYKRRLKEVWKPNA
26	dCasPhi	MPKPAVESEFSKVLKKHFPGERFRSSYMKRGGKILAAQGEEAVVAYLQGKSEEE PPNFQPPAKCHVVTKSRDFAEWPIMKASEAIQRYIYALSTTERAACKPGKSSES HAAWFAATGVSNHGYSHVQGLNLIFDHTLGRYDGVLKKVQLRNEKARARLESIN ASRADEGLPEIKAEEEEVATNETGHLLQPPGINPSFYVYQTISPQAYRPRDEIV LPPEYAGYVRDPNAPIPLGVVRNRCDIQKGCPGYIPEWQREAGTAISPKTGKAV TVPGLSPKKNKRMRRYWRSEKEKAQDALLVTVRIGTDWVVIDVRGLLRNARWRT IAPKDISLNALLDLFTGDPVIDVRRNIVTFTYTLDACGTYARKWTLKGKQTKAT LDKLTATQTVALVAIALGQTNPISAGISRVTQENGALQCEPLDRFTLPDDLLKD ISAYRIAWDRNEEELRARSVEALPEAQQAEVRALDGVSKETARTQLCADFGLDP KRLPWDKMSSNTTFISEALLSNSVSRDQVFFTPAPKKGAKKKAPVEVMRKDRTW ARAYKPRLSVEAQKLKNEALWALKRTSPEYLKLSRRKEELCRRSINYVIEKTRR RTQCQIVIPVIEDLNVRFFHGSGKRLPGWDNFFTAKKENRWFIQGLHKAFSDLR THRSFYVFEVRPERTSITCPKCGHCEVGNRDGEAFQCLSCGKTCNADLDVATHN LTQVALTGKTMPKREEPRDAQGTAPARKTKKASKSKAPPAEREDQTPAQEPSQT S
27	inactive VRER SpCas9	MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLED SGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELVE EDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMI KFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARL SKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNEKSNEDLAEDAKLQLSKDT YDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKR YDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKP ILEKMDGTEELLVKLNREDLLRKQRTEDNGSIPHQIHLGELHAILRRQEDFYPF LKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFL SGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTY HDLLKIIKDKDELDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVM KQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNEMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKP ENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEK LYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNR GKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKEDNLTKAERGGLSELDKAGFIK RQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQF YKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSE QEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDE ATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGF VSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYK EVKKDLIIKLPKYSLFELENGRKRMLASARELQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNK HRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKEYRSTKEVLDATLIHQ SITGLYETRIDLSQLGGD
28	inactive EQR SpCas9	MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLED SGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELVE EDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMI KFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARL SKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNEKSNEDLAEDAKLQLSKDT YDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKR YDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKP ILEKMDGTEELLVKLNREDLLRKQRTEDNGSIPHQIHLGELHAILRRQEDFYPE LKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFL SGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTY HDLLKIIKDKDELDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVM KQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDELKSDGFANRNEMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKP ENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEK LYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNR GKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIK

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		RQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQF YKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSE QEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDF ATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGF ESPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDELEAKGYK EVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNK HRDKPIREQAENIIHLETLTNLGAPAAFKYEDTTIDRKQYRSTKEVLDATLIHQ SITGLYETRIDLSQLGGD
29	inactive VQR SpCas9	MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLED SGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELVE EDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMI KFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARL SKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNEDLAEDAKLQLSKDT YDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKR YDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKP ILEKMDGTEELLVKLNREDLLRKQRTEDNGSIPHQIHLGELHAILRRQEDFYPF LKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA SAQSFIERMTNEDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFL SGEQKKAIVDLLEKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTY HDLLKIIKDKDELDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVM KQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKP ENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEK LYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNR GKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIK RQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQF YKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSE QEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDE ATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGF VSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYK EVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNK HRDKPIREQAENIIHLETLTNLGAPAAFKYEDTTIDRKQYRSTKEVLDATLIHQ SITGLYETRIDLSQLGGD
30	inactive SPG SpCas9	MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLED SGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELVE EDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMI KFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARL SKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNEDLAEDAKLQLSKDT YDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKR YDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKP ILEKMDGTEELLVKLNREDLLRKQRTEDNGSIPHQIHLGELHAILRRQEDFYPE LKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFL SGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTY HDLLKIIKDKDELDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVM KQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDELKSDGFANRNFMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKP ENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEK LYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNR GKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIK RQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQF YKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSE QEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDF ATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGE LWPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYK EVKKDLIIKLPKYSLFELENGRKRMLASAKQLQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNK HRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKQYRSTKEVLDATLIHQ SITGLYETRIDLSQLGGD
31	inactive SpRY Cas9	MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLED SGETAERTRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELVE EDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMI KFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARL SKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNEDLAEDAKLQLSKDT YDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKR YDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKP ILEKMDGTEELLVKLNREDLLRKQRTEDNGSIPHQIHLGELHAILRRQEDFYPF LKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFL SGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTY HDLLKIIKDKDELDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVM

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		KQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDELKSDGFANRNEMQLIHDDSL TFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKP ENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEK LYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNR GKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKEDNLTKAERGGLSELDKAGFIK RQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQF YKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSE QEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDF ATVRKVLSMPQVNIVKKTEVQTGGFSKESIRPKRNSDKLIARKKDWDPKKYGGF LWPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYK EVKKDLIIKLPKYSLFELENGRKRMLASAKQLQKGNELALPSKYVNFLYLASHY EKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNK HRDKPIREQAENIIHLFTLTRLGAPRAFKYFDTTIDPKQYRSTKEVLDATLIHQ SITGLYETRIDLSQLGGD
32	inactive KKH dSaCas9	MKRNYILGLAIGITSVGYGIIDYETRDVIDAGVRLFKEANVENNEGRRSKRGAR RLKRRRRHRIQRVKKLLEDYNLLTDHSELSGINPYEARVKGLSQKLSEEEFSAA LLHLAKRRGVHNVNEVEEDTGNELSTKEQISRNSKALEEKYVAELQLERLKKDG EVRGSINRFKTSDYVKEAKQLLKVQKAYHQLDQSFIDTYIDLLETRRTYYEGPG EGSPFGWKDIKEWYEMLMGHCTYFPEELRSVKYAYNADLYNALNDLNNLVITRD ENEKLEYYEKFQIIENVFKQKKKPTLKQIAKEILVNEEDIKGYRVTSTGKPEFT NLKVYHDIKDITARKEIIENAELLDQIAKILTIYQSSEDIQEELTNLNSELTQE EIEQISNLKGYTGTHNLSLKAINLILDELWHTNDNQIAIFNRLKLVPKKVDLSQ QKEIPTTLVDDFILSPVVKRSFIQSIKVINAIIKKYGLPNDIIIELAREKNSKD AQKMINEMQKRNRQTNERIEEIIRTTGKENAKYLIEKIKLHDMQEGKCLYSLEA IPLEDLLNNPFNYEVDHIIPRSVSEDNSENNKVLVKQEEASKKGNRTPFQYLSS SDSKISYETFKKHILNLAKGKGRISKTKKEYLLEERDINRESVQKDFINRNLVD TRYATRGLMNLLRSYFRVNNLDVKVKSINGGETSFLRRKWKFKKERNKGYKHHA EDALIIANADFIFKEWKKLDKAKKVMENQMFEEKQAESMPEIETEQEYKEIFIT PHQIKHIKDFKDYKYSHRVDKKPNRKLINDTLYSTRKDDKGNTLIVNNLNGLYD KDNDKLKKLINKSPEKLLMYHHDPQTYQKLKLIMEQYGDEKNPLYKYYEETGNY LTKYSKKDNGPVIKKIKYYGNKLNAHLDITDDYPNSRNKVVKLSLKPYREDVYL DNGVYKFVTVKNLDVIKKENYYEVNSKCYEEAKKLKKISNQAEFIASFYKNDLI KINGELYRVIGVNNDLLNRIEVNMIDITYREYLENMNDKRPPHIIKTIASKTQS IKKYSTDILGNLYEVKSKKHPQIIKKG
33	mRNA0001	SRPGERPFQCRICMRNFSKKENLLQHTRTHTGEKPFQCRICMRNFSRQDNLNSH LRTHTGSQKPFQCRICMRNFSRSHNLKLHTRTHTGEKPFQCRICMRNFSQSTTL KRHLRTHTGSQKPFQCRICMRNFSRNTNLTRHTRTHTGEKPFQCRICMRNESIK HNLARHLRTHLRGS
34	mRNA0002	SRPGERPFQCRICMRNFSKKENLLQHTRTHTGEKPFQCRICMRNFSRKDYLISH LRTHTGSQKPFQCRICMRNFSRSHNLKLHTRTHTGEKPFQCRICMRNFSQSTTL KRHLRTHTGSQKPFQCRICMRNFSRQDNLGRHLRTHTGEKPFQCRICMRNFSVV NNLNRHLKTHLRGS
35	mRNA0003	SRPGERPFQCRICMRNFSKKENLLQHTRTHTGEKPFQCRICMRNFSRKDYLISH LRTHTGSQKPFQCRICMRNFSRSHNLRLHTRTHTGEKPFQCRICMRNFSQSTTL KRHLRTHTGSQKPFQCRICMRNFSRQDNLGRHLRTHTGEKPFQCRICMRNFSVV NNLNRHLKTHLRGS
36	mRNA0004	SRPGERPFQCRICMRNFSRRHILDRHTRTHTGEKPFQCRICMRNFSRQDNLGRH LRTHTGSQKPFQCRICMRNFSQSTTLKRHLRTHTGEKPFQCRICMRNFSRRDGL AGHLKTHTGSQKPFQCRICMRNFSVHHNLVRHLRTHTGEKPFQCRICMRNESIS HNLARHLKTHLRGS
37	mRNA0005	SRPGERPFQCRICMRNFSRREVLENHLRTHTGEKPFQCRICMRNESRRDNLNRH LKTHTGSQKPFQCRICMRNFSQSTTLKRHLRTHTGEKPFQCRICMRNESRRDGL AGHLKTHTGSQKPFQCRICMRNFSVHHNLVRHLRTHTGEKPFQCRICMRNESIS HNLARHLKTHLRGS
38	mRNA0006	SRPGERPFQCRICMRNFSRRAVLDRHTRTHTGEKPFQCRICMRNFSRQDNLGRH LRTHTGSQKPFQCRICMRNFSQSTTLKRHLRTHTGEKPFQCRICMRNFSRRDGL AGHLKTHTGSQKPFQCRICMRNFSVHHNLVRHLRTHTGEKPFQCRICMRNESIS HNLARHLKTHLRGS
39	mRNA0064	SRPGERPFQCRICMRNFSRQEHLVRHLRTHTGEKPFQCRICMRNFSEGGNLMRH LKTHTGSQKPFQCRICMRNFSSDRRDLDHTRTHTGEKPFQCRICMRNESSFQSY LEHLRTHTGSQKPFQCRICMRNFSRPNHLAIHTRTHTGEKPFQCRICMRNESQS PHLKRHLRTHLRGS
40	mRNA0007	SRPGERPFQCRICMRNFSRREHLVRHLRTHTGEKPFQCRICMRNESDPSNLQRH LKTHTGSQKPFQCRICMRNFSSDRRDLDHTRTHTGEKPFQCRICMRNESSFQSY LEHLRTHTGSQKPFQCRICMRNFSRPNHLAIHTRTHTGEKPFQCRICMRNESQS PHLKRHLRTHLRGS

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
41	mRNA0008	SRPGERPFQCRICMRNFSRREHLVRHLRTHTGEKPFQCRICMRNESDMGNLGRH LKTHTGSQKPFQCRICMRNFSSDRRDLDHTRTHTGEKPFQCRICMRNESSFQSY LEHLRTHTGSQKPFQCRICMRNFSRPNHLAIHTRTHTGEKPFQCRICMRNESQS PHLKRHLRTHLRGS
42	mRNA0009	SRPGERPFQCRICMRNFSKKDHLHRHTRTHTGEKPFQCRICMRNFSQKEILTRH LRTHTGSQKPFQCRICMRNFSQSAHLKRHLRTHTGEKPFQCRICMRNFSETGSL RRHLKTHTGGGGSQKPFQCRICMRNFSQSHSLKSHLRTHTGEKPFQCRICMRNF SESGHLKRHLKTHLRGS
43	mRNA0010	SRPGERPFQCRICMRNFSKKDHLHRHTRTHTGEKPFQCRICMRNFSQKEILTRH LRTHTGSQKPFQCRICMRNFSQSAHLKRHLRTHTGEKPFQCRICMRNFSDRTPL NRHLKTHTGGGGSQKPFQCRICMRNESQSHSLKSHLRTHTGEKPFQCRICMRNE SESGHLKRHLKTHLRGS
44	mRNA0011	SRPGERPFQCRICMRNFSKTDHLARHTRTHTGEKPFQCRICMRNFSQKEILTRH LRTHTGSQKPFQCRICMRNFSQSAHLKRHLRTHTGEKPFQCRICMRNESETGSL RRHLKTHTGGGGSQKPFQCRICMRNFSQKHHLVTHLRTHTGEKPFQCRICMRNE SENSKLRRHLKTHLRGS
45	mRNA0012	SRPGERPFQCRICMRNFSQAGNLVRHLRTHTGEKPFQCRICMRNFSQNSHLRRH LKTHTGGGGSQKPFQCRICMRNFSDLSTLRRHTRTHTGEKPFQCRICMRNFSQN EHLKVHLRTHTGSQKPFQCRICMRNFSGGTALRMHTRTHTGEKPFQCRICMRNF SQRSSLVRHLRTHLRGS
46	mRNA0013	SRPGERPFQCRICMRNFSQRGNLQRHLRTHTGEKPFQCRICMRNFSQTTHLSRH LKTHTGGGGSQKPFQCRICMRNFSDGSTLRRHTRTHTGEKPFQCRICMRNFSQK THLAVHLRTHTGSQKPFQCRICMRNFSGGTALRMHTRTHTGEKPFQCRICMRNE SQRSSLVRHLRTHLRGS
47	mRNA0014	SRPGERPFQCRICMRNFSQRGNLQRHLRTHTGEKPFQCRICMRNFSQTTHLSRH LKTHTGGGGSQKPFQCRICMRNFSDLSTLRRHTRTHTGEKPFQCRICMRNESQN EHLKVHLRTHTGSQKPFQCRICMRNFSGGSALSMHTRTHTGEKPFQCRICMRNE SQRSSLVRHLRTHLRGS
48	mRNA0015	SRPGERPFQCRICMRNFSDRGNLTRHLRTHTGEKPFQCRICMRNFSQARSLRAH LKTHTGGGGSQKPFQCRICMRNESEKASLIKHTRTHTGEKPFQCRICMRNFSDH SSLKRHLRTHTGSQKPFQCRICMRNFSRRFILSRHTRTHTGEKPFQCRICMRNE SRNDSLKCHLRTHLRGS
49	mRNA0016	SRPGERPFQCRICMRNFSDRGNLTRHLRTHTGEKPFQCRICMRNFSQARSLRAH LKTHTGGGGSQKPFQCRICMRNFSDKSSLRKHTRTHTGEKPFQCRICMRNESDH SSLKRHLRTHTGSQKPFQCRICMRNESRNFILQRHTRTHTGEKPFQCRICMRNF SRNDTLIIHLRTHLRGS
50	mRNA0017	SRPGERPFQCRICMRNFSDRGNLTRHLRTHTGEKPFQCRICMRNFSQARSLRAH LKTHTGGGGSQKPFQCRICMRNFSCNGSLKKHTRTHTGEKPFQCRICMRNESDH SSLKRHLRTHTGSQKPFQCRICMRNESRNFILQRHTRTHTGEKPFQCRICMRNE SRNDTLIIHLRTHLRGS
51	mRNA0018	SRPGERPFQCRICMRNESRTDTLARHLRTHTGEKPFQCRICMRNFSRTDSLPRH LKTHTGGGGSQKPFQCRICMRNFSDHSSLKRHLRTHTGEKPFQCRICMRNFSQP HGLAHHLKTHTGSQKPFQCRICMRNFSQSAHLKRHLRTHTGEKPFQCRICMRNE SVGNSLSRHLKTHLRGS
52	mRNA0019	SRPGERPFQCRICMRNFSRTDTLARHLRTHTGEKPFQCRICMRNFSRTDSLPRH LKTHTGGGGSQKPFQCRICMRNESDHSSLKRHLRTHTGEKPFQCRICMRNFSQP HGLRHHLKTHTGSQKPFQCRICMRNFSQSAHLKRHLRTHTGEKPFQCRICMRNE SVGNSLSRHLKTHLRGS
53	mRNA0020	SRPGERPFQCRICMRNFSRTDTLARHLRTHTGEKPFQCRICMRNFSRLDMLARH LKTHTGGGGSQKPFQCRICMRNFSDHSSLKRHLRTHTGEKPFQCRICMRNFSQP HGLSTHLKTHTGSQKPFQCRICMRNFSQQAHLVRHTRTHTGEKPFQCRICMRNE SVHESLKRHLRTHLRGS
54	mRNA0021	SRPGERPFQCRICMRNFSRADNLGRHLRTHTGEKPFQCRICMRNFSRNTHLSYH LKTHTGSQKPFQCRICMRNFSRGDGLRRHLRTHTGEKPFQCRICMRNFSRRDNL NRHLKTHTGSQKPFQCRICMRNESRARNLTLHTRTHTGEKPFQCRICMRNFSDP SSLKRHLRTHLRGS
55	mRNA0022	SRPGERPFQCRICMRNFSRADNLGRHLRTHTGEKPFQCRICMRNESRNTHLSYH LKTHTGSQKPFQCRICMRNFSRKLGLLRHTRTHTGEKPFQCRICMRNFSRQDNL GRHLRTHTGSQKPFQCRICMRNFSRARNLTLHTRTHTGEKPFQCRICMRNFSDP SSLKRHLRTHLRGS

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
56	mRNA0023	SRPGERPFQCRICMRNFSRADNLGRHLRTHTGEKPFQCRICMRNESRNTHLSYH LKTHTGSQKPFQCRICMRNFSRKLGLLRHTRTHTGEKPFQCRICMRNFSRQDNL GRHLRTHTGSQKPFQCRICMRNFSRRRNLQLHTRTHTGEKPFQCRICMRNESDH SSLKRHLRTHLRGS
57	mRNA0024	SRPGERPFQCRICMRNFSQQSSLLRHTRTHTGEKPFQCRICMRNFSRREHLVRH LRTHTGSQKPFQCRICMRNFSGLTALRTHTRTHTGEKPFQCRICMRNESERAKL IRHLRTHTGGGGSQKPFQCRICMRNESAKRDLDRHTRTHTGEKPFQCRICMRNE SVNSSLTRHLRTHLRGS
58	mRNA0025	SRPGERPFQCRICMRNFSQQSSLLRHTRTHTGEKPFQCRICMRNESRREHLVRH LRTHTGSQKPFQCRICMRNFSGLTALRTHTRTHTGEKPFQCRICMRNESERAKL IRHLRTHTGGGGSQKPFQCRICMRNFSLRKDLVRHTRTHTGEKPFQCRICMRNF SVRHSLTRHLRTHLRGS
59	mRNA0026	SRPGERPFQCRICMRNFSQASALSRHTRTHTGEKPFQCRICMRNFSRREHLVRH LRTHTGSQKPFQCRICMRNFSGLTALRTHTRTHTGEKPFQCRICMRNESERAKL IRHLRTHTGGGGSQKPFQCRICMRNESAKRDLDRHTRTHTGEKPFQCRICMRNE SVNSSLTRHLRTHLRGS
60	mRNA0061	SRPGERPFQCRICMRNFSRGRNLEMHTRTHTGEKPFQCRICMRNFSDSSVLRRH LRTHTGGGGSQKPFQCRICMRNESQNANLKRHTRTHTGEKPFQCRICMRNESQK HHLAVHLRTHTGSQKPFQCRICMRNESQRSNLARHLRTHTGEKPFQCRICMRNE SQKVHLEAHLKTHLRGS
61	mRNA0027	SRPGERPFQCRICMRNFSRRRNLDVHTRTHTGEKPFQCRICMRNFSDSSVLRRH LRTHTGGGGSQKPFQCRICMRNFSQNANLKRHTRTHTGEKPFQCRICMRNESQK HHLAVHLRTHTGSQKPFQCRICMRNESQRSNLARHLRTHTGEKPFQCRICMRNE SQKVHLEAHLKTHLRGS
62	mRNA0065	SRPGERPFQCRICMRNFSRGRNLAIHTRTHTGEKPFQCRICMRNFSDSSVLRRH LRTHTGGGGSQKPFQCRICMRNESLKSNLHRHTRTHTGEKPFQCRICMRNESLK QHLVVHLRTHTGSQKPFQCRICMRNFSLKTNLARHTRTHTGEKPFQCRICMRNE SQKCHLKAHLRTHLRGS
63	mRNA0028	SRPGERPFQCRICMRNFSDGSNLRRHLRTHTGEKPFQCRICMRNFSRIDNLDGH LKTHTGSQKPFQCRICMRNESQRRYLVEHTRTHTGEKPFQCRICMRNFSQQTNL ARHLRTHTGGGGSQKPFQCRICMRNFSQRSDLTRHLRTHTGEKPFQCRICMRNE SRGDNLNRHLKTHLRGS
64	mRNA0029	SRPGERPFQCRICMRNFSDPSNLQRHLRTHTGEKPFQCRICMRNESRRDNLPKH LKTHTGSQKPFQCRICMRNFSTTFNLRVHTRTHTGEKPFQCRICMRNESQTQNL TRHLRTHTGGGGSQKPFQCRICMRNFSHKETLNRHLRTHTGEKPFQCRICMRNE SREDNLGRHLKTHLRGS
65	mRNA0030	SRPGERPFQCRICMRNFSDPSNLQRHLRTHTGEKPFQCRICMRNFSRRDNLPKH LKTHTGSQKPFQCRICMRNFSQRRYLVEHTRTHTGEKPFQCRICMRNESQQTNL ARHLRTHTGGGGSQKPFQCRICMRNFSQRSDLTRHLRTHTGEKPFQCRICMRNE SRGDNLNRHLKTHLRGS
66	mRNA0031	SRPGERPFQCRICMRNFSQQTNLTRHLRTHTGEKPFQCRICMRNESANRTLVHH LKTHTGSQKPFQCRICMRNFSEEANLRRHTRTHTGEKPFQCRICMRNESRGEHL TRHLRTHTGSQKPFQCRICMRNFSTNSSLTRHLRTHTGEKPFQCRICMRNFSRI DNLIRHLKTHLRGS
67	mRNA0032	SRPGERPFQCRICMRNFSQQTNLTRHLRTHTGEKPFQCRICMRNESANRTLVHH LKTHTGSQKPFQCRICMRNESEEANLRRHTRTHTGEKPFQCRICMRNESRREHL VRHLRTHTGSQKPFQCRICMRNESMTSSLRRHTRTHTGEKPFQCRICMRNESRQ DNLGRHLRTHLRGS
68	mRNA0033	SRPGERPFQCRICMRNFSQQTNLTRHLRTHTGEKPFQCRICMRNESANRTLVHH LKTHTGSQKPFQCRICMRNFSEEANLRRHTRTHTGEKPFQCRICMRNFSRGEHL TRHLRTHTGSQKPFQCRICMRNFSMTSSLRRHTRTHTGEKPFQCRICMRNESRQ DNLGRHLRTHLRGS
69	mRNA0034	SRPGERPFQCRICMRNFSRATHLTRHTRTHTGEKPFQCRICMRNFSRADVLKGH LRTHTGSQKPFQCRICMRNFSQRSSLVRHLRTHTGEKPFQCRICMRNESRKDAL HVHLKTHTGSQKPFQCRICMRNFSVHHNLVRHLRTHTGEKPFQCRICMRNESIS HNLARHLKTHLRGS
70	mRNA0035	SRPGERPFQCRICMRNESRATHLTRHTRTHTGEKPFQCRICMRNFSRADVLKGH LRTHTGSQKPFQCRICMRNFSQSSSLVRHLRTHTGEKPFQCRICMRNFSRKERL ATHLKTHTGSQKPFQCRICMRNFSVRHNLTRHLRTHTGEKPFQCRICMRNESIS HNLARHLKTHLRGS

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
71	mRNA0036	SRPGERPFQCRICMRNFSKKDHLHRHTRTHTGEKPFQCRICMRNFSRKESLTVH LRTHTGSQKPFQCRICMRNFSQSSSLVRHLRTHTGEKPFQCRICMRNFSRKERL ATHLKTHTGSQKPFQCRICMRNFSVHHNLVRHLRTHTGEKPFQCRICMRNESIS HNLARHLKTHLRGS
72	mRNA0037	SRPGERPFQCRICMRNFSRVDHLHRHLRTHTGEKPFQCRICMRNFSRREHLSGH LKTHTGGGGSQKPFQCRICMRNFSQSSSLVRHLRTHTGEKPFQCRICMRNFSRK ERLATHLKTHTGSQKPFQCRICMRNFSVAHNLTRHLRTHTGEKPFQCRICMRNF SISHNLARHLKTHLRGS
73	mRNA0038	SRPGERPFQCRICMRNFSRKHHLGRHTRTHTGEKPFQCRICMRNFSRREHLTIH LRTHTGGGGSQKPFQCRICMRNFSQSSSLVRHLRTHTGEKPFQCRICMRNESRK ERLATHLKTHTGSQKPFQCRICMRNESVAHNLTRHLRTHTGEKPFQCRICMRNE SISHNLARHLKTHLRGS
74	mRNA0039	SRPGERPFQCRICMRNFSRVDHLHRHLRTHTGEKPFQCRICMRNFSRSDHLSLH LKTHTGGGGSQKPFQCRICMRNFSQSSSLVRHLRTHTGEKPFQCRICMRNFSRK ERLATHLKTHTGSQKPFQCRICMRNFSVAHNLTRHLRTHTGEKPFQCRICMRNE SISHNLARHLKTHLRGS
75	mRNA0040	SRPGERPFQCRICMRNFSKTDHLARHTRTHTGEKPFQCRICMRNESQKEILTRH LRTHTGSQKPFQCRICMRNFSQSAHLKRHLRTHTGEKPFQCRICMRNESETGSL RRHLKTHTGSQKPFQCRICMRNFSQSSSLVRHLRTHTGEKPFQCRICMRNESQT NTLGRHLKTHLRGS
76	mRNA0041	SRPGERPFQCRICMRNFSKKDHLHRHTRTHTGEKPFQCRICMRNFSQKEILTRH LRTHTGSQKPFQCRICMRNFSQSAHLKRHLRTHTGEKPFQCRICMRNESETGSL RRHLKTHTGSQKPFQCRICMRNFSQSSSLVRHLRTHTGEKPFQCRICMRNFSQG GTLRRHLKTHLRGS
77	mRNA0042	SRPGERPFQCRICMRNFSKKDHLHRHTRTHTGEKPFQCRICMRNFSQKEILTRH LRTHTGSQKPFQCRICMRNFSQSAHLKRHLRTHTGEKPFQCRICMRNFSDPTSL NRHLKTHTGSQKPFQCRICMRNFSQSSSLVRHLRTHTGEKPFQCRICMRNESQT NTLGRHLKTHLRGS
78	mRNA0043	SRPGERPFQCRICMRNFSQQTNLTRHLRTHTGEKPFQCRICMRNFSVGGNLARH LKTHTGSQKPFQCRICMRNESKRYNLYQHTRTHTGEKPFQCRICMRNESRQDNL NTHLRTHTGSQKPFQCRICMRNFSRSHNLKLHTRTHTGEKPFQCRICMRNESQS TTLKRHLRTHLRGS
79	mRNA0044	SRPGERPFQCRICMRNFSQQTNLTRHLRTHTGEKPFQCRICMRNFSVGGNLSRH LKTHTGSQKPFQCRICMRNFSKRYNLYQHTRTHTGEKPFQCRICMRNESRQDNL NTHLRTHTGSQKPFQCRICMRNFSRSHNLRLHTRTHTGEKPFQCRICMRNESQS TTLKRHLRTHLRGS
80	mRNA0045	SRPGERPFQCRICMRNFSQQTNLTRHLRTHTGEKPFQCRICMRNFSVGGNLSRH LKTHTGSQKPFQCRICMRNESKKENLLQHTRTHTGEKPFQCRICMRNESRRDNL KSHLRTHTGSQKPFQCRICMRNFSRSHNLKLHTRTHTGEKPFQCRICMRNFSQS TTLKRHLRTHLRGS
81	mRNA0046	SRPGERPFQCRICMRNFSDKSSLRKHTRTHTGEKPFQCRICMRNFSDHSSLKRH LRTHTGSQKPFQCRICMRNESRNFILQRHTRTHTGEKPFQCRICMRNESRNDTL IIHLRTHTGGGGSQKPFQCRICMRNFSTSTLLKRHTRTHTGEKPFQCRICMRNE SLKEHLTRHLRTHLRGS
82	mRNA0047	SRPGERPFQCRICMRNFSCNGSLKKHTRTHTGEKPFQCRICMRNFSDHSSLKRH LRTHTGSQKPFQCRICMRNFSRNFILARHTRTHTGEKPFQCRICMRNFSRQDIL VVHLRTHTGGGGSQKPFQCRICMRNFSHKSSLTRHLRTHTGEKPFQCRICMRNE SESGHLKRHLKTHLRGS
83	mRNA0048	SRPGERPFQCRICMRNFSCNGSLKKHTRTHTGEKPFQCRICMRNFSDHSSLKRH LRTHTGSQKPFQCRICMRNFSRNFILARHTRTHTGEKPFQCRICMRNFSRQDIL VVHLRTHTGGGGSQKPFQCRICMRNFSTSTLLKRHTRTHTGEKPFQCRICMRNE SLKEHLTRHLRTHLRGS
84	mRNA0049	SRPGERPFQCRICMRNESTNNNLARHTRTHTGEKPFQCRICMRNFSRTDSLTLH LRTHTGSQKPFQCRICMRNFSQREHLTTHLRTHTGEKPFQCRICMRNESRRDNL NRHLKTHTGSQKPFQCRICMRNFSRRQKLTIHTRTHTGEKPFQCRICMRNESHK SSLTRHLRTHLRGS
85	mRNA0050	SRPGERPFQCRICMRNESTNNNLARHTRTHTGEKPFQCRICMRNESRTDSLTLH LRTHTGSQKPFQCRICMRNFSQREHLTTHLRTHTGEKPFQCRICMRNFSRGDNL KRHLKTHTGSQKPFQCRICMRNFSRRQKLTIHTRTHTGEKPFQCRICMRNESHK SSLTRHLRTHLRGS

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
86	mRNA0066	SRPGERPFQCRICMRNESTNNNLARHTRTHTGEKPFQCRICMRNFSRTDSLTLH LRTHTGSQKPFQCRICMRNESQREHLNGHLRTHTGEKPFQCRICMRNESRGDNL ARHLKTHTGSQKPFQCRICMRNFSRRQKLTIHTRTHTGEKPFQCRICMRNESHK SSLTRHLRTHLRGS
87	mRNA0051	SRPGERPFQCRICMRNFSQQTNLTRHLRTHTGEKPFQCRICMRNFSANRTLVHH LKTHTGSQKPFQCRICMRNFSDPANLRRHTRTHTGEKPFQCRICMRNFSRQEHL VRHLRTHTGGGGSQKPFQCRICMRNFSMKHHLGRHLRTHTGEKPFQCRICMRNE SQNSHLRRHLKTHLRGS
88	mRNA0052	SRPGERPFQCRICMRNFSQQTNLTRHLRTHTGEKPFQCRICMRNESANRTLVHH LKTHTGSQKPFQCRICMRNFSEEANLRRHTRTHTGEKPFQCRICMRNESRREHL VRHLRTHTGGGGSQKPFQCRICMRNFSMKHHLGRHLRTHTGEKPFQCRICMRNE SQNSHLRRHLKTHLRGS
89	mRNA0067	SRPGERPFQCRICMRNFSQQTNLTRHLRTHTGEKPFQCRICMRNFSANRTLVHH LKTHTGSQKPFQCRICMRNFSDPANLRRHTRTHTGEKPFQCRICMRNESRQEHL VRHLRTHTGGGGSQKPFQCRICMRNFSLKQHLVRHLRTHTGEKPFQCRICMRNE SQGGHLARHLKTHLRGS
90	mRNA0068	SRPGERPFQCRICMRNFSRNTHLARHTRTHTGEKPFQCRICMRNFSRADVLKGH LRTHTGSQKPFQCRICMRNFSQRSSLVRHLRTHTGEKPFQCRICMRNESRKDAL HVHLKTHTGGGGSQKPFQCRICMRNFSQNEHLKVHLRTHTGEKPFQCRICMRNE SQNSHLRRHLKTHLRGS
91	mRNA0053	SRPGERPFQCRICMRNFSRNTHLARHTRTHTGEKPFQCRICMRNFSRADVLKGH LRTHTGSQKPFQCRICMRNFSQSSSLVRHLRTHTGEKPFQCRICMRNESRKERL ATHLKTHTGGGGSQKPFQCRICMRNFSQKTHLAVHLRTHTGEKPFQCRICMRNE SQGGHLKRHLKTHLRGS
92	mRNA0054	SRPGERPFQCRICMRNFSRNTHLARHTRTHTGEKPFQCRICMRNFSRADVLKGH LRTHTGSQKPFQCRICMRNESQSSSLVRHLRTHTGEKPFQCRICMRNESRKERL ATHLKTHTGGGGSQKPFQCRICMRNFSQKTHLAVHLRTHTGEKPFQCRICMRNE SQNSHLRRHLKTHLRGS
93	mRNA0055	SRPGERPFQCRICMRNFSHKSSLTRHLRTHTGEKPFQCRICMRNESESGHLKRH LKTHTGSQKPFQCRICMRNFSRRRNLTLHTRTHTGEKPFQCRICMRNFSDRSSL KRHLRTHTGSQKPFQCRICMRNFSQPHSLAVHLRTHTGEKPFQCRICMRNESQK PHLSRHLKTHLRGS
94	mRNA0056	SRPGERPFQCRICMRNFSHKSSLTRHLRTHTGEKPFQCRICMRNFSEGGHLKRH LKTHTGSQKPFQCRICMRNFSRRRNLQLHTRTHTGEKPFQCRICMRNESDHSSL KRHLRTHTGSQKPFQCRICMRNFSRRQHLQYHTRTHTGEKPFQCRICMRNESQS AHLKRHLRTHLRGS
95	mRNA0057	SRPGERPFQCRICMRNFSHKSSLTRHLRTHTGEKPFQCRICMRNFSEGGHLKRH LKTHTGSQKPFQCRICMRNFSRRRNLTLHTRTHTGEKPFQCRICMRNESDRSSL KRHLRTHTGSQKPFQCRICMRNFSRRQHLQYHTRTHTGEKPFQCRICMRNFSQS AHLKRHLRTHLRGS
96	mRNA0058	SRPGERPFQCRICMRNFSGHTALRNHTRTHTGEKPFQCRICMRNFSQSGTLHRH LRTHTGGGGSQKPFQCRICMRNFSDHSSLKRHLRTHTGEKPFQCRICMRNESAM RSLMGHLKTHTGSQKPFQCRICMRNFSRRSRLVRHTRTHTGEKPFQCRICMRNE SRGEHLTRHLRTHLRGS
97	mRNA0059	SRPGERPFQCRICMRNFSGHTALRNHTRTHTGEKPFQCRICMRNFSQSTTLKRH LRTHTGGGGSQKPFQCRICMRNESDHSSLKRHLRTHTGEKPFQCRICMRNESQQ RSLVGHLKTHTGSQKPFQCRICMRNFSEAHHLSRHLRTHTGEKPFQCRICMRNE SRTEHLARHLKTHLRGS
98	mRNA0060	SRPGERPFQCRICMRNFSGHTALRNHTRTHTGEKPFQCRICMRNFSQSTTLKRH LRTHTGGGGSQKPFQCRICMRNFSDHSSLKRHLRTHTGEKPFQCRICMRNESAM RSLMGHLKTHTGSQKPFQCRICMRNESRQSRLQRHTRTHTGEKPFQCRICMRNE SRREHLVRHLRTHLRGS
99	mRNA0062	SRPGERPFQCRICMRNFSQGETLKRHLRTHTGEKPFQCRICMRNFSRADNLRRH LKTHTGSQKPFQCRICMRNFSDKANLTRHLRTHTGEKPFQCRICMRNFSDQGNL IRHLKTHTGGGGSQKPFQCRICMRNFSHRHVLINHTRTHTGEKPFQCRICMRNE STNSSLTRHLRTHLRGS
100	mRNA0063	SRPGERPFQCRICMRNFSQGETLKRHLRTHTGEKPFQCRICMRNESRADNLRRH LKTHTGSQKPFQCRICMRNFSDSSNLRRHLRTHTGEKPFQCRICMRNFSDQGNL IRHLKTHTGGGGSQKPFQCRICMRNFSHKSSLTRHLRTHTGEKPFQCRICMRNE SIRTSLKRHLKTHLRGS

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
101	mRNA0069	SRPGERPFQCRICMRNFSQGETLKRHLRTHTGEKPFQCRICMRNFSRADNLRRH LKTHTGSQKPFQCRICMRNFSEQGNLLRHLRTHTGEKPFQCRICMRNFSDGGNL GRHLKTHTGGGGSQKPFQCRICMRNFSHRHVLINHTRTHTGEKPFQCRICMRNE STNSSLTRHLRTHLRGS
102	HBV target sequence	GATGAGGCATAGCAGCAG
103	HBV target sequence	GATGATTAGGCAGAGGTG
104	HBV target sequence	GGATTCAGCGCCGACGGG
105	HBV target sequence	GGCAGTAGTCGGAACAGGG
106	HBV target sequence	GTAAACTGAGCCAGGAGAA
107	HBV target sequence	ACGGTGGTCTCCATGCGAC
108	HBV target sequence	GCTGGATGTGTCTGCGGCG
109	HBV target sequence	GTCTGCGAGGCGAGGGAG
110	HBV target sequence	GTTGCCGGGCAACGGGGTA
111	HBV target sequence	CGAGAAAGTGAAAGCCTGC
112	HBV target sequence	GAGGCTTGAACAGTAGGAC
113	HBV target sequence	GAGGTTGGGGACTGCGAA
114	HBV target sequence	GATGATGTGGTATTGGGG
115	HBV target sequence	GATGATGTGGTATTGGGGG
116	HBV target sequence	GCAGTAGTCGGAACAGGG
117	HBV target sequence	GCATAGCAGCAGGATGAA
118	HBV target sequence	GGCGTTCACGGTGGTCTCC
119	HBV target sequence	GTTGGTGAGTGATTGGAG
120	HBV target sequence	GGAGGTTGGGGACTGCGAA
121	HBV target sequence	GGATGATGTGGTATTGGGG
122	HBV target sequence	GGATGTGTCTGCGGCGTT
123	HBV target sequence	GGGGGTTGCGTCAGCAAAC
124	HBV target sequence	GTTGTTAGACGACGAGGCA
125	F1	KKENLLQ

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
126	F1	RRHILDR
127	F1	RREVLEN
128	F1	RRAVLDR
129	F1	RQEHLVR
130	F1	RREHLVR
131	F1	KKDHLHR
132	F1	KTDHLAR
133	F1	QAGNLVR
134	F1	QRGNLQR
135	F1	DRGNLTR
136	F1	RTDTLAR
137	F1	RADNLGR
138	F1	QQSSLLR
139	F1	QASALSR
140	F1	RGRNLEM
141	F1	RRRNLDV
142	F1	RGRNLAI
143	F1	DGSNLRR
144	F1	DPSNLQR
145	F1	QQTNLTR
146	F1	RATHLTR
147	F1	RVDHLHR
148	F1	RKHHLGR
149	F1	DKSSLRK
150	F1	CNGSLKK
151	F1	TNNNLAR
152	F1	RNTHLAR
153	F1	HKSSLTR
154	F1	GHTALRN
155	F1	QGETLKR
156	F2	RQDNLNS
157	F2	RKDYLIS
158	F2	RQDNLGR
159	F2	RRDNLNR
160	F2	EGGNLMR
161	F2	DPSNLQR
162	F2	DMGNLGR
163	F2	QKEILTR

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
164	F2	QNSHLRR
165	F2	QTTHLSR
166	F2	QARSLRA
167	F2	RTDSLPR
168	F2	RLDMLAR
169	F2	RNTHLSY
170	F2	RREHLVR
171	F2	DSSVLRR
172	F2	RIDNLDG
173	F2	RRDNLPK
174	F2	ANRTLVH
175	F2	RADVLKG
176	F2	RKESLTV
177	F2	RREHLSG
178	F2	RREHLTI
179	F2	RSDHLSL
180	F2	VGGNLAR
181	F2	VGGNLSR
182	F2	DHSSLKR
183	F2	RTDSLTL
184	F2	ESGHLKR
185	F2	EGGHLKR
186	F2	QSGTLHR
187	F2	QSTTLKR
188	F2	RADNLRR
189	F3	RSHNLKL
190	F3	RSHNLRL
191	F3	QSTTLKR
192	F3	SDRRDLD
193	F3	QSAHLKR
194	F3	DLSTLRR
195	F3	DGSTLRR
196	F3	EKASLIK
197	F3	DKSSLRK
198	F3	CNGSLKK
199	F3	DHSSLKR
200	F3	RGDGLRR
201	F3	RKLGLLR

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
202	F3	GLTALRT
203	F3	QNANLKR
204	F3	LKSNLHR
205	F3	QRRYLVE
206	F3	TTENLRV
207	F3	EEANLRR
208	F3	QRSSLVR
209	F3	QSSSLVR
210	F3	KRYNLYQ
211	F3	KKENLLQ
212	F3	RNFILQR
213	F3	RNFILAR
214	F3	QREHLTT
215	F3	QREHLNG
216	F3	DPANLRR
217	F3	RRRNLTL
218	F3	RRRNLQL
219	F3	DKANLTR
220	F3	DSSNLRR
221	F3	EQGNLLR
222	F4	QSTTLKR
223	F4	RRDGLAG
224	F4	SFQSYLE
225	F4	ETGSLRR
226	F4	DRTPLNR
227	F4	QNEHLKV
228	F4	QKTHLAV
229	F4	DHSSLKR
230	F4	QPHGLAH
231	F4	QPHGLRH
232	F4	QPHGLST
233	F4	RRDNLNR
234	F4	RQDNLGR
235	F4	ERAKLIR
236	F4	QKHHLAV
237	F4	LKQHLVV
238	F4	QQTNLAR
239	F4	QTQNLTR

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
240	F4	RGEHLTR
241	F4	RREHLVR
242	F4	RKDALHV
243	F4	RKERLAT
244	F4	DPTSLNR
245	F4	RQDNLNT
246	F4	RRDNLKS
247	F4	RNDTLII
248	F4	RQDILVV
249	F4	RGDNLKR
250	F4	RGDNLAR
251	F4	RQEHLVR
252	F4	DRSSLKR
253	F4	AMRSLMG
254	F4	QQRSLVG
255	F4	DQGNLIR
256	F4	DGGNLGR
257	F5	RNTNLTR
258	F5	RQDNLGR
259	F5	VHHNLVR
260	F5	RPNHLAI
261	F5	QSHSLKS
262	F5	QKHHLVT
263	F5	GGTALRM
264	F5	GGSALSM
265	F5	RRFILSR
266	F5	RNFILQR
267	F5	QSAHLKR
268	F5	QQAHLVR
269	F5	RARNLTL
270	F5	RRRNLQL
271	F5	AKRDLDR
272	F5	LRKDLVR
273	F5	QRSNLAR
274	F5	LKTNLAR
275	F5	QRSDLTR
276	F5	HKETLNR
277	F5	TNSSLTR

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
278	F5	MTSSLRR
279	F5	VRHNLTR
280	F5	VAHNLTR
281	F5	QSSSLVR
282	F5	RSHNLKL
283	F5	RSHNLRL
284	F5	TSTLLKR
285	F5	HKSSLTR
286	F5	RRQKLTI
287	F5	MKHHLGR
288	F5	LKQHLVR
289	F5	QNEHLKV
290	F5	QKTHLAV
291	F5	QPHSLAV
292	F5	RRQHLQY
293	F5	RRSRLVR
294	F5	EAHHLSR
295	F5	RQSRLQR
296	F5	HRHVLIN
297	F6	IKHNLAR
298	F6	VVNNLNR
299	F6	ISHNLAR
300	F6	QSPHLKR
301	F6	ESGHLKR
302	F6	ENSKLRR
303	F6	QRSSLVR
304	F6	RNDSLKC
305	F6	RNDTLII
306	F6	VGNSLSR
307	F6	VHESLKR
308	F6	DPSSLKR
309	F6	DHSSLKR
310	F6	VNSSLTR
311	F6	VRHSLTR
312	F6	QKVHLEA
313	F6	QKCHLKA
314	F6	RGDNLNR
315	F6	REDNLGR

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
316	F6	RIDNLIR
317	F6	RQDNLGR
318	F6	QTNTLGR
319	F6	QGGTLRR
320	F6	QSTTLKR
321	F6	LKEHLTR
322	F6	HKSSLTR
323	F6	QNSHLRR
324	F6	QGGHLAR
325	F6	QGGHLKR
326	F6	QKPHLSR
327	F6	QSAHLKR
328	F6	RGEHLTR
329	F6	RTEHLAR
330	F6	RREHLVR
331	F6	TNSSLTR
332	F6	IRTSLKR
327	F6	QSAHLKR
328	F6	RGEHLTR
329	F6	RTEHLAR
330	F6	RREHLVR
331	F6	TNSSLTR
332	F6	IRTSLKR
495	ZIM3	MNNSQGRVTFEDVTVNFTQGEWQRLNPEQRNLYRDVMLENYSNLVSVGQGETTK PDVILRLEQGKEPWLEEEEVLGSGRAEKNGDIGGQIWKPKDVKESL
496	ZNF436	MAATLLMAGSQAPVTFEDMAMYLTREEWRPLDAAQRDLYRDVMQENYGNVVSLD FEIRSENEVNPKQEISEDVQFGTTSERPAENAEENPESEEGFESGDRSERQW
497	ZNF257	MLENYRNLVFLGIAVSKPDLITCLEQGKEPCNMKRHEMVAKPPVMCSHIAEDLC PERDIKYFFQKVILRRYDKCEHENLQLRKGCKSVDECKVCK
498	ZNF675	MGLLTERDVAIEFSLEEWQCLDTAQRNLYKNVILENYRNLVELGIAVSKQDLIT CLEQEKEPLTVKRHEMVNEPPVMCSHFAQEFWPEQNIKDSF
499	ZNF490	MLQMQNSEHHGQSIKTQTDSISLEDVAVNFTLEEWALLDPGQRNIYRDVMRATE KNLACIGEKWKDQDIEDEHKNQGRNLRSPMVEALCENKEDCPCGKSTSQIPDLN TNLETPTG
500	ZNF320	MALSQGLLTFRDVAIEFSQEEWKCLDPAQRTLYRDVMLENYRNLVSLDISSKCM MNTLSSTGQGNTEVIHTGTLQRQASYHIGAFCSQEIEKDIHDFVFQ
501	ZNF331	MAQGLVTFADVAIDFSQEEWACLNSAQRDLYWDVMLENYSNLVSLDLESAYENK SLPTKKNIHEIRASKRNSDRRSKSLGRNWICEGTLERPQRSRGR
502	ZNF816	MLREEATKKSKEKEPGMALPQGRLTERDVAIEFSLEEWKCLNPAQRALYRAVML ENYRNLEFVDSSLKSMMEFSSTRHSITGEVIHTGTLQRHKSHHIGDFCFPEMKK DIHHFEFQWQ
503	ZNF680	MPGPPGSLEMGPLTFRDVAIEFSLEEWQCLDTAQRNLYRKVMFENYRNLVFLGI AVSKPHLITCLEQGKEPWNRKRQEMVAKPPVIYSHFTEDLWPEHSIKDSF

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
504	ZNF41	MSPPWSPALAAEGRGSSCEASVSFEDVTVDESKEEWQHLDPAQRRLYWDVTLEN YSHLLSVGYQIPKSEAAFKLEQGEGPWMLEGEAPHQSCSGEAIGKMQQQGIPGG IFFHC
505	ZNF189	MASPSPPPESKEEWDYLDPAQRSLYKDVMMENYGNLVSLDVLNRDKDEEPTVKQ EIEEIEEEVEPQGVIVTRIKSEIDQDPMGRETFELVGRLDKQRGIFLWEIPRES L
506	ZNF528	MALTQGPLKFMDVAIEFSQEEWKCLDPAQRTLYRDVMLENYRNLVSLGICLPDL SVTSMLEQKRDPWTLQSEEKIANDPDGRECIKGVNTERSSKLGSN
507	ZNF543	MAASAQVSVTFEDVAVTFTQEEWGQLDAAQRTLYQEVMLETCGLLMSLGCPLEK PELIYQLDHRQELWMATKDLSQSSYPGDNTKPKTTEPTFSHLALPE
508	ZNF554	MFSQEERMAAGYLPRWSQELVTFEDVSMDESQEEWELLEPAQKNLYREVMLENY RNVVSLEALKNQCTDVGIKEGPLSPAQTSQVTSLSSWTGYLLFQPVASSHLEQR EALWIEEKGTPQASCSDWMTVLRNQDSTYKKVALQE
509	ZNF140	MSQGSVTFRDVAIDESQEEWKWLQPAQRDLYRCVMLENYGHLVSLGLSISKPDV VSLLEQGKEPWLGKREVKRDLFSVSESSGEIKDESPKNVIYDD
510	ZNF610	MEEAQKRKAKESGMALPQGRLTEMDVAIEFSQEEWKSLDPGQRALYRDVMLENY RNLVFLGRSCVLGSNAENKPIKNQLGLTLESHLSELQLFQAGRKIYRSNQVEKE TNHR
511	ZNF264	MAAAVLTDRAQVSVTFDDVAVTFTKEEWGQLDLAQRTLYQEVMLENCGLLVSLG CPVPKAELICHLEHGQEPWTRKEDLSQDTCPGDKGKPKTTEPTTCEPALSE
512	ZNF350	MIQAQESITLEDVAVDFTWEEWQLLGAAQKDLYRDVMLENYSNLVAVGYQASKP DALFKLEQGEQLWTIEDGIHSGACSDIWKVDHVLERLQSESLVNR
513	ZNF8	MEGVAGVMSVGPPAARLQEPVTFRDVAVDFTQEEWGQLDPTQRILYRDVMLETF GHLLSIGPELPKPEVISQLEQGTELWVAERGTTQGCHPAWEPRSESQASRKEEG LPEE
514	ZNF582	MSLGSELFRDVAIVFSQEEWQWLAPAQRDLYRDVMLETYSNLVSLGLAVSKPDV ISFLEQGKEPWMVERVVSGGLCPVLESRYDTKELFPKQHVYEV
515	ZNF30	MAHKYVGLQYHGSVTFEDVAIAFSQQEWESLDSSQRGLYRDVMLENYRNLVSMA GHSRSKPHVIALLEQWKEPEVTVRKDGRRWCTDLQLEDDTIGCKEMPTSEN
516	ZNF324	MAFEDVAVYFSQEEWGLLDTAQRALYRRVMLDNFALVASLGLSTSRPRVVIQLE RGEEPWVPSGTDTTLSRTTYRRRNPGSWSLTEDRDVSG
517	ZNF98	MLENYRNLVFVGIAASKPDLITCLEQGKEPWNVKRHEMVTEPPVVYSYFAQDLW PKQGKKNYFQKVILRTYKKCGRENLQLRKYCKSMDECKVHKECYNGLNQC
518	ZNF669	MHERRPDPCREPLASPIQDSVAFEDVAVNETQEEWALLDSSQKNLYREVMQETC RNLASVGSQWKDQNIEDHFEKPGKDIRNHIVQRLCESKEDGQYGEVVSQIPNLD LNENISTGLKPCECSICGK
519	ZNF677	MALSQGLFTFKDVAIEFSQEEWECLDPAQRALYRDVMLENYRNLLSLDEDNIPP EDDISVGFTSKGLSPKENNKEELYHLVILERKESHGINNFDLKEVWENMPKEDS LW
520	ZNF596	MTFEDIIVDETQEEWALLDTSQRKLFQDVMLENISHLVSIGKQLCKSVVLSQLE QVEKLSTQRISLLQGREVGIKHQEIPFIHHIYQKGTSTISTMRS
521	ZNF214	MAVTFEDVTIIFTWEEWKFLDSSQKRLYREVMWENYTNVMSVENWNESYKSQEE KFRYLEYENFSYWQGWWNAGAQMYENQNYGETVQGTDSKDLTQQDRSQC
522	ZNF37A	MITSQGSVSFRDVTVGFTQEEWQHLDPAQRTLYRDVMLENYSHLVSVGYCIPKP EVILKLEKGEEPWILEEKFPSQSHLELINTSRNYSIMKENEENKG
523	ZNF34	MFEDVAVYLSREEWGRLGPAQRGLYRDVMLETYGNLVSLGVGPAGPKPGVISQL ERGDEPWVLDVQGTSGKEHLRVNSPALGTRTEYKELTSQETFGEEDPQGSEPVE ACDHIS
524	ZNF250	METYGNVVSLGLPGSKPDIISQLERGEDPWVLDRKGAKKSQGLWSDYSDNLKYD HTTACTQQDSLSCPWECETKGESQNTDLSPKPLISEQTVILGKTPLGRIDQENN ETKQ
525	ZNF547	MAEMNPAQGHVVFEDVAIYESQEEWGHLDEAQRLLYRDVMLENLALLSSLGCCH GAEDEEAPLEPGVSVGVSQVMAPKPCLSTQNTQPCETCSSLLKDILRL

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
526	ZNF273	MLDNYRNLVFLGIAVSKPDLITCLEQGKEPCNMKRHAMVAKPPVVCSHFAQDLW PKQGLKDS
527	ZNF354A	MAAGQREARPQVSLTFEDVAVLFTRDEWRKLAPSQRNLYRDVMLENYRNLVSLG LPFTKPKVISLLQQGEDPWEVEKDGSGVSSLGSKSSHKTTKSTQTQDSSFQ
528	ZFP82	MALRSVMESDVSIDESPEEWEYLDLEQKDLYRDVMLENYSNLVSLGCFISKPDV ISSLEQGKEPWKVVRKGRRQYPDLETKYETKKLSLENDIYEIN
529	ZNF224	MTTFKEAMTFKDVAVVFTEEELGLLDLAQRKLYRDVMLENERNLLSVGHQAFHR DTFHELREEKIWMMKTAIQREGNSGDKIQTEMETVSEAGTHQEW
530	ZNF33A	MFQVEQKSQESVSFKDVTVGETQEEWQHLDPSQRALYRDVMLENYSNLVSVGYC VHKPEVIFRLQQGEEPWKQEEEFPSQSFPEVWTADHLKERSQENQSKHL
531	ZNF45	MTKSKEAVTFKDVAVVFSEEELQLLDLAQRKLYRDVMLENFRNVVSVGHQSTPD GLPQLEREEKLWMMKMATQRDNSSGAKNLKEMETLQEVGLRYLP
532	ZNF175	MSQKPQVLGPEKQDGSCEASVSFEDVTVDESREEWQQLDPAQRCLYRDVMLELY SHLFAVGYHIPNPEVIFRMLKEKEPRVEEAEVSHQRCQEREFGLEIPQKEISKK ASFQ
533	ZNF595	MELVTFRDVAIEFSPEEWKCLDPAQQNLYRDVMLENYRNLVSLGFVISNPDLVT CLEQIKEPCNLKIHETAAKPPAICSPFSQDLSPVQGIEDSE
534	ZNF184	MSTLLQGGHNLLSSASFQESVTFKDVIVDFTQEEWKQLDPGQRDLERDVTLENY THLVSIGLQVSKPDVISQLEQGTEPWIMEPSIPVGTCADWETRLENSVSAPEPD ISEE
535	ZNF419	MDPAQVPVAADLLTDHEEGYVTFEDVAVYFSQEEWRLLDDAQRLLYRNVMLENE TLLASLGLASSKTHEITQLESWEEPFMPAWEVVTSAIPRGCWHGAEAEEAPEQI ASVG
536	ZFP28-1	MKKLEAVGTGIEPKAMSQGLVTFGDVAVDESQEEWEWLNPIQRNLYRKVMLENY RNLASLGLCVSKPDVISSLEQGKEPWTVKRKMTRAWCPDLKAVWKIKELPLKKD FCEG
537	ZFP28-2	MSLLGEHWDYDALFETQPGLVTIKNLAVDERQQLHPAQKNFCKNGIWENNSDLG SAGHCVAKPDLVSLLEQEKEPWMVKRELTGSLFSGQRSVHETQELFPKQDSYAE
538	ZNF18	MLALAASQPARLEERLIRDRDLGASLLPAAPQEQWRQLDSTQKEQYWDLILETY GKMVSGAGISHPKSDLTNSIEFGEELAGIYLHVNEKIPRPTCIGDRQENDKENL NLENH
539	ZNF213	MEGRPGETTDTCFVSGVHGPVALGDIPFYFSREEWGTLDPAQRDLEWDIKRENS RNTTLGFGLKGQSEKSLLQEMVPVVPGQTGSDVTVSWSPEEAEAWESENRPRAA LGPVVGARRGRPPTRRRQFRDLA
540	ZNF394	MVAVVRALQRALDGTSSQGMVTFEDTAVSLTWEEWERLDPARRDFCRESAQKDS GSTVPPSLESRVENKELIPMQQILEEAEPQGQLQEAFQGKRPLESKCGSTHEDR VEKQSGDP
541	ZFP1	MNKSQGSVSFTDVTVDFTQEEWEQLDPSQRILYMDVMLENYSNLLSVEVWKADD QMERDHRNPDEQARQFLILKNQTPIEERGDLFGKALNLNTDFVSLRQVPYKYDL YEKTL
542	ZFP14	MAHGSVTFRDVAIDESQEEWEFLDPAQRDLYRDVMWENYSNFISLGPSISKPDV ITLLDEERKEPGMVVREGTRRYCPDLESRYRTNTLSPEKDIYEIYSFQWDIMER
543	ZNF416	MAAAVLRDSTSVPVTAEAKLMGFTQGCVTFEDVAIYFSQEEWGLLDEAQRLLYR DVMLENFALITALVCWHGMEDEETPEQSVSVEGVPQVRTPEASPSTQKIQSCDM CVPFLTDILHLTDLPGQELYLTGACAVEHQDQK
544	ZNF557	MLPPTAASQREGHTEGGELVNELLKSWLKGLVTFEDVAVEFTQEEWALLDPAQR TLYRDVMLENCRNLASLGNQVDKPRLISQLEQEDKVMTEERGILSGTCPDVENP FKAKGLTPKLHVERKEQSRNMKMER
545	ZNF566	MAQESVMFSDVSVDESQEEWECLNDDQRDLYRDVMLENYSNLVSMGHSISKPNV ISYLEQGKEPWLADRELTRGQWPVLESRCETKKLELKKEIYEIESTQWEIMEK
546	ZNF729	MPGAPGSLEMGPLTFRDVTIEFSLEEWQCLDTVQQNLYRDVMLENYRNLVELGM AVFKPDLITCLKQGKEPWNMKRHEMVTKPPVMRSHFTQDLWPDQSTKDSFQEVI LRTYAR
547	ZIM2	MAGSQFPDFKHLGTFLVFEELVTFEDVLVDESPEELSSLSAAQRNLYREVMLEN YRNLVSLGHQFSKPDIISRLEEEESYAMETDSRHTVICQGE

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
548	ZNF254	MPGPPRSLEMGLLTFRDVAIEFSLEEWQHLDIAQQNLYRNVMLENYRNLAFLGI AVSKPDLITCLEQGKEPWNMKRHE
549	ZNF764	MAPPLAPLPPRDPNGAGPEWREPGAVSFADVAVYFCREEWGCLRPAQRALYRDV MRETYGHLSALGIGGNKPALISWVEEEAELWGPAAQDPE
550	ZNF785	MGPPLAPRPAHVPGEAGPRRTRESRPGAVSFADVAVYESPEEWECLRPAQRALY RDVMRETFGHLGALGFSVPKPAFISWVEGEVEAWSPEAQDPDGESS
551	ZNF10 (KOX1)	MDAKSLTAWSRTLVTFKDVFVDFTREEWKLLDTAQQIVYRNVMLENYKNLVSLG YQLTKPDVILRLEKGEEPWLVEREIHQETHPDSETAFEIKSSVSSRSIFKDKQS CDIKMEGMARNDLWYLSLEEVWKCRDQLDKYQENPERHLRQVAFTQKKVLTQER VSESGKYGGNCLLPAQLVLREYFHKRDSHTKSLKHDLVLNGHQDSCASNSNECG QTFCQNIHLIQFARTHTGDKSYKCPDNDNSLTHGSSLGISKGIHREKPYECKEC GKFFSWRSNLTRHQLIHTGEKPYECKECGKSFSRSSHLIGHQKTHTGEEPYECK ECGKSFSWFSHLVTHQRTHTGDKLYTCNQCGKSFVHSSRLIRHQRTHTGEKPYE CPECGKSFRQSTHLILHQRTHVRVRPYECNECGKSYSQRSHLVVHHRIHTGLKP FECKDCGKCFSRSSHLYSHQRTHTGEKPYECHDCGKSFSQSSALIVHQRIHTGE KPYECCQCGKAFIRKNDLIKHQRIHVGEETYKCNQCGIIFSQNSPFIVHQIAHT GEQFLTCNQCGTALVNTSNLIGYQTNHIRENAY
552	CBX5 (chromoshadow domain)	MGKKTKRTADSSSSEDEEEYVVEKVLDRRVVKGQVEYLLKWKGESEEHNTWEPE KNLDCPELISEFMKKYKKMKEGENNKPREKSESNKRKSNESNSADDIKSKKKRE QSNDIARGFERGLEPEKIIGATDSCGDLMFLMKWKDTDEADLVLAKEANVKCPQ IVIAFYEERLTWHAYPEDAENKEKETAKS
553	RYBP (YAF2_RYBP component of PRC1)	MTMGDKKSPTRPKRQAKPAADEGFWDCSVCTERNSAEAFKCSICDVRKGTSTRK PRINSQLVAQQVAQQYATPPPPKKEKKEKVEKQDKEKPEKDKEISPSVTKKNTN KKTKPKSDILKDPPSEANSIQSANATTKTSETNHTSRPRLKNVDRSTAQQLAVT VGNVTVIITDFKEKTRSSSTSSSTVTSSAGSEQQNQSSSGSESTDKGSSRSSTP KGDMSAVNDESF
554	YAF2 (YAF2_RYBP component of PRC1)	MGDKKSPTRPKRQPKPSSDEGYWDCSVCTERNSAEAFKCMMCDVRKGTSTRKPR PVSQLVAQQVTQQFVPPTQSKKEKKDKVEKEKSEKETTSKKNSHKKTRPRLKNV DRSSAQHLEVTVGDLTVIITDFKEKTKSPPASSAASADQHSQSGSSSDNTERGM SRSSSPRGEASSLNGESH
555	MGA (component of PRC1.6)	MEEKQQIILANQDGGTVAGAAPTFFVILKQPGNGKTDQGILVTNQDACALASSV SSPVKSKGKICLPADCTVGGITVTLDNNSMWNEFYHRSTEMILTKQGRRMFPYC RYWITGLDSNLKYILVMDISPVDNHRYKWNGRWWEPSGKAEPHVLGRVFIHPES PSTGHYWMHQPVSFYKLKLTNNTLDQEGHIILHSMHRYLPRLHLVPAEKAVEVI QLNGPGVHTFTFPQTEFFAVTAYQNIQITQLKIDYNPFAKGERDDGLNNKPQRD GKQKNSSDQEGNNISSSSGHRVRLTEGQGSEIQPGDLDPLSRGHETSGKGLEKT SLNIKRDELGEMDTDSALSEVPQLKQEISECLIASSFEDDSRVASPLDQNGSEN VVIKEEPLDDYDYELGECPEGVTVKQEETDEETDVYSNSDDDPILEKQLKRHNK VDNPEADHLSSKWLPSSPSGVAKAKMEKLDTGKMPVVYLEPCAVTRSTVKISEL PDNMLSTSRKDKSSMLAELEYLPTYIENSNETAFCLGKESENGLRKHSPDLRVV QKYPLLKEPQWKYPDISDSISTERILDDSKDSVGDSLSGKEDLGRKRTTMLKIA TAAKVVNANQNASPNVPGKRGRPRKLKLCKAGRPPKNTGKSLISTKNTPVSPGS TFPDVKPDLEDVDGVLEVSFESKEALDIHAVDGTTEESSSLQASTTNDSGYRAR ISQLEKELIEDLKTLRHKQVIHPGLQEVGLKLNSVDPTMSIDLKYLGVQLPLAP ATSFPFWNLTGTNPASPDAGFPFVSRTGKINDFTKIKGWRGKFHSASASRNEGG NSESSLKNRSAFCSDKLDEYLENEGKLMETSMGFSSNAPTSPVVYQLPTKSTSY VRTLDSVLKKQSTISPSTSYSLKPHSVPPVSRKAKSQNRQATFSGRTKSSYKSI LPYPVSPKQKYSHVILGDKVTKNSSGIISENQANNFVVPTLDENIFPKQISLRQ AQQQQQQQQGSRPPGLSKSQVKLMDLEDCALWEGKPRTYITEERADVSLTTLLT AQASLKTKPIHTIIRKRAPPCNNDFCRLGCVCSSLALEKRQPAHCRRPDCMFGC TCLKRKVVLVKGGSKTKHFQRKAAHRDPVFYDTLGEEAREEEEGIREEEEQLKE KKKRKKLEYTICETEPEQPVRHYPLWVKVEGEVDPEPVYIPTPSVIEPMKPLLL PQPEVLSPTVKGKLLTGIKSPRSYTPKPNPVIREEDKDPVYLYFESMMTCARVR VYERKKEDQRQPSSSSSPSPSFQQQTSCHSSPENHNNAKEPDSEQQPLKQLTCD LEDDSDKLQEKSWKSSCNEGESSSTSYMHQRSPGGPTKLIEIISDCNWEEDRNK ILSILSQHINSNMPQSLKVGSFIIELASQRKSRGEKNPPVYSSRVKISMPSCQD QDDMAEKSGSETPDGPLSPGKMEDISPVQTDALDSVRERLHGGKGLPFYAGLSP AGKLVAYKRKPSSSTSGLIQVASNAKVAASRKPRTLLPSTSNSKMASSSGTATN RPGKNLKAFVPAKRPIAARPSPGGVFTQFVMSKVGALQQKIPGVSTPQTLAGTQ KFSIRPSPVMVVTPVVSSEPVQVCSPVTAAVTTTTPQVELENTTAVTPMTAISD VETKETTYSSGATTTGVVEVSETNTSTSVTSTQSTATVNLTKTTGITTPVASVA FPKSLVASPSTITLPVASTASTSLVVVTAAASSSMVTTPTSSLGSVPIILSGIN GSPPVSQRPENAAQIPVATPQVSPNTVKRAGPRLLLIPVQQGSPTLRPVSNTQL QGHRMVLQPVRSPSGMNLFRHPNGQIVQLLPLHQLRGSNTQPNLQPVMERNPGS VMGIRLPAPSKPSETPPSSTSSSAFSVMNPVIQAVGSSSAVNVITQAPSLLSSG ASFVSQAGTLTLRISPPEPQSFASKTGSETKITYSSGGQPVGTASLIPLQSGSF ALLQLPGQKPVPSSILQHVASLQMKRESQNPDQKDETNSIKREQETKKVLQSEG EAVDPEANVIKQNSGAATSEETLNDSLEDRGDHLDEECLPEEGCATVKPSEHSC

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		ITGSHTDQDYKDVNEEYGARNRKSSKEKVAVLEVRTISEKASNKTVQNLSKVQH QKLGDVKVEQQKGFDNPEENSSEFPVTEKEESKFELSGSKVMEQQSNLQPEAKE KECGDSLEKDRERWRKHLKGPLTRKCVGASQECKKEADEQLIKETKTCQENSDV FQQEQGISDLLGKSGITEDARVLKTECDSWSRISNPSAFSIVPRRAAKSSRGNG HFQGHLLLPGEQIQPKQEKKGGRSSADFTVLDLEEDDEDDNEKTDDSIDEIVDV VSDYQSEEVDDVEKNNCVEYIEDDEEHVDIETVEELSEEINVAHLKTTAAHTQS FKQPSCTHISADEKAAERSRKAPPIPLKLKPDYWSDKLQKEAEAFAYYRRTHTA NERRRRGEMRDLFEKLKITLGLLHSSKVSKSLILTRAFSEIQGLTDQADKLIGQ KNLLTRKRNILIRKVSSLSGKTEEVVLKKLEYIYAKQQALEAQKRKKKMGSDEF DISPRISKQQEGSSASSVDLGQMFINNRRGKPLILSRKKDQATENTSPLNTPHT SANLVMTPQGQLLTLKGPLFSGPVVAVSPDLLESDLKPQVAGSAVALPENDDLE MMPRIVNVTSLATEGGLVDMGGSKYPHEVPDSKPSDHLKDTVRNEDNSLEDKGR ISSRGNRDGRVTLGPTQVFLANKDSGYPQIVDVSNMQKAQEFLPKKISGDMRGI QYKWKESESRGERVKSKDSSFHKLKMKDLKDSSIEMELRKVTSAIEEAALDSSE LLTNMEDEDDTDETLTSLLNEIAFLNQQLNDDSVGLAELPSSMDTEFPGDARRA FISKVPPGSRATFQVEHLGTGLKELPDVQGESDSISPLLLHLEDDDESENEKQL AEPASEPDVLKIVIDSEIKDSLLSNKKAIDGGKNTSGLPAEPESVSSPPTLHMK TGLENSNSTDTLWRPMPKLAPLGLKVANPSSDADGQSLKVMPCLAPIAAKVGSV GHKMNLTGNDQEGRESKVMPTLAPVVAKLGNSGASPSSAGK
556	CBX1 (chromoshadow)	MGKKQNKKKVEEVLEEEEEEYVVEKVLDRRVVKGKVEYLLKWKGFSDEDNTWEP EENLDCPDLIAEFLQSQKTAHETDKSEGGKRKADSDSEDKGEESKPKKKKEESE KPRGFARGLEPERIIGATDSSGELMFLMKWKNSDEADLVPAKEANVKCPQVVIS FYEERLTWHSYPSEDDDKKDDKN
557	SCMH1 (SAM_1/SPM)	MLVCYSVLACEILWDLPCSIMGSPLGHFTWDKYLKETCSVPAPVHCFKQSYTPP SNEFKISMKLEAQDPRNTTSTCIATVVGLTGARLRLRLDGSDNKNDFWRLVDSA EIQPIGNCEKNGGMLQPPLGFRLNASSWPMFLLKTLNGAEMAPIRIFHKEPPSP SHNFFKMGMKLEAVDRKNPHFICPATIGEVRGSEVLVTFDGWRGAFDYWCRFDS RDIFPVGWCSLTGDNLQPPGTKVVIPKNPYPASDVNTEKPSIHSSTKTVLEHQP GQRGRKPGKKRGRTPKTLISHPISAPSKTAEPLKFPKKRGPKPGSKRKPRTLLN PPPASPTTSTPEPDTSTVPQDAATIPSSAMQAPTVCIYLNKNGSTGPHLDKKKV QQLPDHFGPARASVVLQQAVQACIDCAYHQKTVESFLKQGHGGEVISAVEDREQ HTLNLPAVNSITYVLRFLEKLCHNLRSDNLFGNQPFTQTHLSLTAIEYSHSHDR YLPGETFVLGNSLARSLEPHSDSMDSASNPTNLVSTSQRHRPLLSSCGLPPSTA SAVRRLCSRGVLKGSNERRDMESFWKLNRSPGSDRYLESRDASRLSGRDPSSWT VEDVMQFVREADPQLGPHADLFRKHEIDGKALLLLRSDMMMKYMGLKLGPALKL SYHIDRLKQGKF
558	MPP8 (Chromodomain)	MEQVAEGARVTAVPVSAADSTEELAEVEEGVGVVGEDNDAAARGAEAFGDSEED GEDVFEVEKILDMKTEGGKVLYKVRWKGYTSDDDTWEPEIHLEDCKEVLLEFRK KIAENKAKAVRKDIQRLSLNNDIFEANSDSDQQSETKEDTSPKKKKKKLRQREE KSPDDLKKKKAKAGKLKDKSKPDLESSLESLVEDLRTKKRISEAKEELKESKKP KKDEVKETKELKKVKKGEIRDLKTKTREDPKENRKTKKEKFVESQVESESSVLN DSPFPEDDSEGLHSDSREEKQNTKSARERAGQDMGLEHGFEKPLDSAMSAEEDT DVRGRRKKKTPRKAEDTRENRKLENKNAFLEKKTVPKKQRNQDRSKSAAELEKL MPVSAQTPKGRRLSGEERGLWSTDSAEEDKETKRNESKEKYQKRHDSDKEEKGR KEPKGLKTLKEIRNAFDLFKLTPEEKNDVSENNRKREEIPLDEKTIDDHKTKEN KQSLKERRNTRDETDTWAYIAAEGDQEVLDSVCQADENSDGRQQILSLGMDLQL EWMKLEDFQKHLDGKDENFAATDAIPSNVLRDAVKNGDYITVKVALNSNEEYNL DQEDSSGMTLVMLAAAGGQDDLLRLLITKGAKVNGRQKNGTTALIHAAEKNELT TVAILLEAGAFVNVQQSNGETALMKACKRGNSDIVRLVIECGADCNILSKHQNS ALHFAKQSNNVLVYDLLKNHLETLSRVAEETIKDYFEARLALLEPVFPIACHRL CEGPDFSTDENYKPPQNIPEGSGILLFIFHANFLGKEVIARLCGPCSVQAVVLN DKFQLPVELDSHFVYSFSPVAGPNKLFIRLTEAPSAKVKLLIGAYRVQLQ
559	SUMO3 (Rad60- SLD)	MSEEKPKEGVKTENDHINLKVAGQDGSVVQFKIKRHTPLSKLMKAYCERQGLSM RQIRFRFDGQPINETDTPAQLEMEDEDTIDVFQQQTGGVPESSLAGHSE
560	HERC2 (Cyt-b5)	MPSESFCLAAQARLDSKWLKTDIQLAFTRDGLCGLWNEMVKDGEIVYTGTESTQ NGELPPRKDDSVEPSGTKKEDLNDKEKKDEEETPAPIYRAKSILDSWVWGKQPD VNELKECLSVLVKEQQALAVQSATTTLSALRLKQRLVILERYFIALNRTVFQEN VKVKWKSSGISLPPVDKKSSRPAGKGVEGLARVGSRAALSFAFAFLRRAWRSGE DADLCSELLQESLDALRALPEASLEDESTVSSVWLEVVERATRELRSVVTGDVH GTPATKGPGSIPLQDQHLALAILLELAVQRGTLSQMLSAILLLLQLWDSGAQET DNERSAQGTSAPLLPLLQRFQSIICRKDAPHSEGDMHLLSGPLSPNESFLRYLT LPQDNELAIDLRQTAVVVMAHLDRLATPCMPPLCSSPTSHKGSLQEVIGWGLIG WKYYANVIGPIQCEGLANLGVTQIACAEKRFLILSRNGRVYTQAYNSDTLAPQL VQGLASRNIVKIAAHSDGHHYLALAATGEVYSWGCGDGGRLGHGDTVPLEEPKV ISAFSGKQAGKHVVHIACGSTYSAAITAEGELYTWGRGNYGRLGHGSSEDEAIP MLVAGLKGLKVIDVACGSGDAQTLAVTENGQVWSWGDGDYGKLGRGGSDGCKTP KLIEKLQDLDVVKVRCGSQFSIALTKDGQVYSWGKGDNQRLGHGTEEHVRYPKL LEGLQGKKVIDVAAGSTHCLALTEDSEVHSWGSNDQCQHFDTLRVTKPEPAALP GLDTKHIVGIACGPAQSFAWSSCSEWSIGLRVPFVVDICSMTFEQLDLLLRQVS EGMDGSADWPPPQEKECVAVATLNLLRLQLHAAISHQVDPEFLGLGLGSILLNS LKQTVVTLASSAGVLSTVQSAAQAVLQSGWSVLLPTAEERARALSALLPCAVSG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		NEVNISPGRREMIDLLVGSLMADGGLESALHAAITAEIQDIEAKKEAQKEKEID EQEANASTFHRSRTPLDKDLINTGICESSGKQCLPLVQLIQQLLRNIASQTVAR LKDVARRISSCLDFEQHSRERSASLDLLLRFQRLLISKLYPGESIGQTSDISSP ELMGVGSLLKKYTALLCTHIGDILPVAASIASTSWRHFAEVAYIVEGDFTGVLL PELVVSIVLLLSKNAGLMQEAGAVPLLGGLLEHLDRENHLAPGKERDDHEELAW PGIMESFFTGQNCRNNEEVTLIRKADLENHNKDGGFWTVIDGKVYDIKDFQTQS LTGNSILAQFAGEDPVVALEAALQFEDTRESMHAFCVGQYLEPDQEIVTIPDLG SLSSPLIDTERNLGLLLGLHASYLAMSTPLSPVEIECAKWLQSSIFSGGLQTSQ IHYSYNEEKDEDHCSSPGGTPASKSRLCSHRRALGDHSQAFLQAIADNNIQDHN VKDFLCQIERYCRQCHLTTPIMFPPEHPVEEVGRLLLCCLLKHEDLGHVALSLV HAGALGIEQVKHRTLPKSVVDVCRVVYQAKCSLIKTHQEQGRSYKEVCAPVIER LRFLFNELRPAVCNDLSIMSKEKLLSSLPRWRRIAQKIIRERRKKRVPKKPEST DDEEKIGNEESDLEEACILPHSPINVDKRPIAIKSPKDKWQPLLSTVTGVHKYK WLKQNVQGLYPQSPLLSTIAEFALKEEPVDVEKMRKCLLKQLERAEVRLEGIDT ILKLASKNFLLPSVQYAMFCGWQRLIPEGIDIGEPLTDCLKDVDLIPPENRMLL EVTFGKLYAWAVQNIRNVLMDASAKFKELGIQPVPLQTITNENPSGPSLGTIPQ ARFLLVMLSMLTLQHGANNLDLLLNSGMLALTQTALRLIGPSCDNVEEDMNASA QGASATVLEETRKETAPVQLPVSGPELAAMMKIGTRVMRGVDWKWGDQDGPPPG LGRVIGELGEDGWIRVQWDTGSTNSYRMGKEGKYDLKLAELPAAAQPSAEDSDT EDDSEAEQTERNIHPTAMMFTSTINLLQTLCLSAGVHAEIMQSEATKTLCGLLR MLVESGTTDKTSSPNRLVYREQHRSWCTLGFVRSIALTPQVCGALSSPQWITLL MKVVEGHAPFTATSLQRQILAVHLLQAVLPSWDKTERARDMKCLVEKLEDELGS LLTTCSSDVPLLRESTLRRRRVRPQASLTATHSSTLAEEVVALLRTLHSLTQWN GLINKYINSQLRSITHSFVGRPSEGAQLEDYFPDSENPEVGGLMAVLAVIGGID GRLRLGGQVMHDEFGEGTVTRITPKGKITVQFSDMRTCRVCPLNQLKPLPAVAF NVNNLPFTEPMLSVWAQLVNLAGSKLEKHKIKKSTKQAFAGQVDLDLLRCQQLK LYILKAGRALLSHQDKLRQILSQPAVQETGTVHTDDGAVVSPDLGDMSPEGPQP PMILLQQLLASATQPSPVKAIFDKQELEAAALAVCQCLAVESTHPSSPGFEDCS SSEATTPVAVQHIRPARVKRRKQSPVPALPIVVQLMEMGFSRRNIEFALKSLTG ASGNASSLPGVEALVGWLLDHSDIQVTELSDADTVSDEYSDEEVVEDVDDAAYS MSTGAVVTESQTYKKRADFLSNDDYAVYVRENIQVGMMVRCCRAYEEVCEGDVG KVIKLDRDGLHDLNVQCDWQQKGGTYWVRYIHVELIGYPPPSSSSHIKIGDKVR VKASVTTPKYKWGSVTHQSVGVVKAFSANGKDIIVDFPQQSHWTGLLSEMELVP SIHPGVTCDGCQMFPINGSRFKCRNCDDEDFCETCFKTKKHNTRHTFGRINEPG QSAVFCGRSGKQLKRCHSSQPGMLLDSWSRMVKSLNVSSSVNQASRLIDGSEPC WQSSGSQGKHWIRLEIFPDVLVHRLKMIVDPADSSYMPSLVVVSGGNSLNNLIE LKTININPSDTTVPLLNDCTEYHRYIEIAIKQCRSSGIDCKIHGLILLGRIRAE EEDLAAVPFLASDNEEEEDEKGNSGSLIRKKAAGLESAATIRTKVFVWGLNDKD QLGGLKGSKIKVPSFSETLSALNVVQVAGGSKSLFAVTVEGKVYACGEATNGRL GLGISSGTVPIPRQITALSSYVVKKVAVHSGGRHATALTVDGKVFSWGEGDDGK LGHFSRMNCDKPRLIEALKTKRIRDIACGSSHSAALTSSGELYTWGLGEYGRLG HGDNTTQLKPKMVKVLLGHRVIQVACGSRDAQTLALTDEGLVESWGDGDFGKLG RGGSEGCNIPQNIERLNGQGVCQIECGAQFSLALTKSGVVWTWGKGDYFRLGHG SDVHVRKPQVVEGLRGKKIVHVAVGALHCLAVTDSGQVYAWGDNDHGQQGNGTT TVNRKPTLVQGLEGQKITRVACGSSHSVAWTTVDVATPSVHEPVLFQTARDPLG ASYLGVPSDADSSAASNKISGASNSKPNRPSLAKILLSLDGNLAKQQALSHILT ALQIMYARDAVVGALMPAAMIAPVECPSESSAAPSDASAMASPMNGEECMLAVD IEDRLSPNPWQEKREIVSSEDAVTPSAVTPSAPSASARPFIPVTDDLGAASIIA ETMTKTKEDVESQNKAAGPEPQALDEFTSLLIADDTRVVVDLLKLSVCSRAGDR GRDVLSAVLSGMGTAYPQVADMLLELCVTELEDVATDSQSGRLSSQPVVVESSH PYTDDTSTSGTVKIPGAEGLRVEFDRQCSTERRHDPLTVMDGVNRIVSVRSGRE WSDWSSELRIPGDELKWKFISDGSVNGWGWRFTVYPIMPAAGPKELLSDRCVLS CPSMDLVTCLLDERLNLASNRSIVPRLAASLAACAQLSALAASHRMWALQRLRK LLTTEFGQSININRLLGENDGETRALSFTGSALAALVKGLPEALQRQFEYEDPI VRGGKQLLHSPFFKVLVALACDLELDTLPCCAETHKWAWERRYCMASRVAVALD KRTPLPRLFLDEVAKKIRELMADSENMDVLHESHDIFKREQDEQLVQWMNRRPD DWTLSAGGSGTIYGWGHNHRGQLGGIEGAKVKVPTPCEALATLRPVQLIGGEQT LFAVTADGKLYATGYGAGGRLGIGGTESVSTPTLLESIQHVFIKKVAVNSGGKH CLALSSEGEVYSWGEAEDGKLGHGNRSPCDRPRVIESLRGIEVVDVAAGGAHSA CVTAAGDLYTWGKGRYGRLGHSDSEDQLKPKLVEALQGHRVVDIACGSGDAQTL CLTDDDTVWSWGDGDYGKLGRGGSDGCKVPMKIDSLTGLGVVKVECGSQFSVAL TKSGAVYTWGKGDYHRLGHGSDDHVRRPRQVQGLQGKKVIAIATGSLHCVCCTE DGEVYTWGDNDEGQLGDGTTNAIQRPRLVAALQGKKVNRVACGSAHTLAWSTSK PASAGKLPAQVPMEYNHLQEIPIIALRNRLLLLHHLSELFCPCIPMEDLEGSLD ETGLGPSVGEDTLRGILISQGKEAAFRKVVQATMVRDRQHGPVVELNRIQVKRS RSKGGLAGPDGTKSVFGQMCAKMSSFGPDSLLLPHRVWKVKFVGESVDDCGGGY SESIAEICEELQNGLTPLLIVTPNGRDESGANRDCYLLSPAARAPVHSSMEREL GVLLGIAIRTGSPLSLNLAEPVWKQLAGMSLTIADLSEVDKDFIPGLMYIRDNE ATSEEFEAMSLPFTVPSASGQDIQLSSKHTHITLDNRAEYVRLAINYRLHEFDE QVAAVREGMARVVPVPLLSLFTGYELETMVCGSPDIPLHLLKSVATYKGIEPSA SLIQWFWEVMESESNTERSLFLRFVWGRTRLPRTIADERGRDFVIQVLDKYNPP DHFLPESYTCFFLLKLPRYSCKQVLEEKLKYAIHFCKSIDTDDYARIALTGEPA ADDSSDDSDNEDVDSFASDSTQDYLTGH

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
561	BIN1 (SH3_9)	MAEMGSKGVTAGKIASNVQKKLTRAQEKVLQKLGKADETKDEQFEQCVQNENKQ LTEGTRLQKDLRTYLASVKAMHEASKKLNECLQEVYEPDWPGRDEANKIAENND LLWMDYHQKLVDQALLTMDTYLGQFPDIKSRIAKRGRKLVDYDSARHHYESLQT AKKKDEAKIAKPVSLLEKAAPQWCQGKLQAHLVAQTNLLRNQAEEELIKAQKVF EEMNVDLQEELPSLWNSRVGFYVNTFQSIAGLEENFHKEMSKLNQNLNDVLVGL EKQHGSNTFTVKAQPSDNAPAKGNKSPSPPDGSPAATPEIRVNHEPEPAGGATP GATLPKSPSQLRKGPPVPPPPKHTPSKEVKQEQILSLFEDTFVPEISVTTPSQF EAPGPFSEQASLLDLDEDPLPPVTSPVKAPTPSGQSIPWDLWEPTESPAGSLPS GEPSAAEGTFAVSWPSQTAEPGPAQPAEASEVAGGTQPAAGAQEPGETAASEAA SSSLPAVVVETFPATVNGTVEGGSGAGRLDLPPGEMFKVQAQHDYTATDTDELQ LKAGDVVLVIPFQNPEEQDEGWLMGVKESDWNQHKELEKCRGVFPENFTERVP
562	PCGF2 (RING finger protein domain)	MHRTTRIKITELNPHLMCALCGGYFIDATTIVECLHSFCKTCIVRYLETNKYCP MCDVQVHKTRPLLSIRSDKTLQDIVYKLVPGLFKDEMKRRRDFYAAYPLTEVPN GSNEDRGEVLEQEKGALSDDEIVSLSIEFYEGARDRDEKKGPLENGDGDKEKTG VRFLRCPAAMTVMHLAKFLRNKMDVPSKYKVEVLYEDEPLKEYYTLMDIAYIYP WRRNGPLPLKYRVQPACKRLTLATVPTPSEGTNTSGASECESVSDKAPSPATLP ATSSSLPSPATPSHGSPSSHGPPATHPTSPTPPSTASGATTAANGGSLNCLQTP SSTSRGRKMTVNGAPVPPLT
563	TOX (HMG box)	MDVRFYPPPAQPAAAPDAPCLGPSPCLDPYYCNKEDGENMYMSMTEPSQDYVPA SQSYPGPSLESEDFNIPPITPPSLPDHSLVHLNEVESGYHSLCHPMNHNGLLPF HPQNMDLPEITVSNMLGQDGTLLSNSISVMPDIRNPEGTQYSSHPQMAAMRPRG QPADIRQQPGMMPHGQLTTINQSQLSAQLGLNMGGSNVPHNSPSPPGSKSATPS PSSSVHEDEGDDTSKINGGEKRPASDMGKKPKTPKKKKKKDPNEPQKPVSAYAL FFRDTQAAIKGQNPNATFGEVSKIVASMWDGLGEEQKQVYKKKTEAAKKEYLKQ LAAYRASLVSKSYSEPVDVKTSQPPQLINSKPSVFHGPSQAHSALYLSSHYHQQ PGMNPHLTAMHPSLPRNIAPKPNNQMPVTVSIANMAVSPPPPLQISPPLHQHLN MQQHQPLTMQQPLGNQLPMQVQSALHSPTMQQGFTLQPDYQTIINPTSTAAQVV TQAMEYVRSGCRNPPPQPVDWNNDYCSSGGMQRDKALYLT
564	FOXA1 (HNF3A C-terminal domain)	MLGTVKMEGHETSDWNSYYADTQEAYSSVPVSNMNSGLGSMNSMNTYMTMNTMT TSGNMTPASFNMSYANPGLGAGLSPGAVAGMPGGSAGAMNSMTAAGVTAMGTAL SPSGMGAMGAQQAASMNGLGPYAAAMNPCMSPMAYAPSNLGRSRAGGGGDAKTF KRSYPHAKPPYSYISLITMAIQQAPSKMLTLSEIYQWIMDLFPYYRQNQQRWQN SIRHSLSFNDCFVKVARSPDKPGKGSYWTLHPDSGNMFENGCYLRRQKRFKCEK QPGAGGGGGSGSGGSGAKGGPESRKDPSGASNPSADSPLHRGVHGKTGQLEGAP APGPAASPQTLDHSGATATGGASELKTPASSTAPPISSGPGALASVPASHPAHG LAPHESQLHLKGDPHYSENHPESINNLMSSSEQQHKLDFKAYEQALQYSPYGST LPASLPLGSASVTTRSPIEPSALEPAYYQGVYSRPVLNTS
565	FOXA2 (HNF3B C-terminal domain)	MLGAVKMEGHEPSDWSSYYAEPEGYSSVSNMNAGLGMNGMNTYMSMSAAAMGSG SGNMSAGSMNMSSYVGAGMSPSLAGMSPGAGAMAGMGGSAGAAGVAGMGPHLSP SLSPLGGQAAGAMGGLAPYANMNSMSPMYGQAGLSRARDPKTYRRSYTHAKPPY SYISLITMAIQQSPNKMLTLSEIYQWIMDLEPEYRQNQQRWQNSIRHSLSENDC FLKVPRSPDKPGKGSFWTLHPDSGNMFENGCYLRRQKRFKCEKQLALKEAAGAA GSGKKAAAGAQASQAQLGEAAGPASETPAGTESPHSSASPCQEHKRGGLGELKG TPAAALSPPEPAPSPGQQQQAAAHLLGPPHHPGLPPEAHLKPEHHYAFNHPFSI NNLMSSEQQHHHSHHHHQPHKMDLKAYEQVMHYPGYGSPMPGSLAMGPVTNKTG LDASPLAADTSYYQGVYSRPIMNSS
566	IRF2BP1 (IRF-2BP1 2 N-terminal domain)	MASVQASRRQWCYLCDLPKMPWAMVWDESEAVCRGCVNFEGADRIELLIDAARQ LKRSHVLPEGRSPGPPALKHPATKDLAAAAAQGPQLPPPQAPQPQPSGTGGGVSG QDRYDRATSSGRLPLPSPALEYTLGSRLANGLGREEAVAEGARRALLGSMPGLM PPGLLAAAVSGLGSRGLTLAPGLSPARPLFGSDFEKEKQQRNADCLAELNEAMR GRAEEWHGRPKAVREQLLALSACAPFNVREKKDHGLVGRVFAFDATARPPGYEF ELKLFTEYPCGSGNVYAGVLAVARQMFHDALREPGKALASSGFKYLEYERRHGS GEWRQLGELLTDGVRSFREPAPAEALPQQYPEPAPAALCGPPPRAPSRNLAPTP RRRKASPEPEGEAAGKMTTEEQQQRHWVAPGGPYSAETPGVPSPIAALKNVAEA LGHSPKDPGGGGGPVRAGGASPAASSTAQPPTQHRLVARNGEAEVSPTAGAEAV SGGGSGTGATPGAPLCCTLCRERLEDTHFVQCPSVPGHKFCFPCSREFIKAQGP AGEVYCPSGDKCPLVGSSVPWAFMQGEIATILAGDIKVKKERDP
567	IRF2BP2 (IRF-2BP1 2 N-terminal domain)	MAAAVAVAAASRRQSCYLCDLPRMPWAMIWDFTEPVCRGCVNYEGADRVEFVIE TARQLKRAHGCFPEGRSPPGAAASAAAKPPPLSAKDILLQQQQQLGHGGPEAAP RAPQALERYPLAAAAERPPRLGSDFGSSRPAASLAQPPTPQPPPVNGILVPNGE SKLEEPPELNRQSPNPRRGHAVPPTLVPLMNGSATPLPTALGLGGRAAASLAAV SGTAAASLGSAQPTDLGAHKRPASVSSSAAVEHEQREAAAKEKQPPPPAHRGPA DSLSTAAGAAELSAEGAGKSRGSGEQDWVNRPKTVRDTLLALHQHGHSGPFESK FKKEPALTAGRLLGFEANGANGSKAVARTARKRKPSPEPEGEVGPPKINGEAQP WLSTSTEGLKIPMTPTSSFVSPPPPTASPHSNRTTPPEAAQNGQSPMAALILVA DNAGGSHASKDANQVHSTTRRNSNSPPSPSSMNQRRLGPREVGGQGAGNTGGLE PVHPASLPDSSLATSAPLCCTLCHERLEDTHEVQCPSVPSHKFCFPCSRQSIKQ QGASGEVYCPSGEKCPLVGSNVPWAFMQGEIATILAGDVKVKKERDS

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
568	IRF2BPL IRF-2BP1 2 N-terminal domain	MSAAQVSSSRRQSCYLCDLPRMPWAMIWDESEPVCRGCVNYEGADRIEFVIETA RQLKRAHGCFQDGRSPGPPPPVGVKTVALSAKEAAAAAAAAAAAAAAAQQQQQQ QQQQQQQQQQQQQQQQQQLNHVDGSSKPAVLAAPSGLERYGLSAAAAAAAAAA AAVEQRSRFEYPPPPVSLGSSSHTARLPNGLGGPNGFPKPTPEEGPPELNRQSP NSSSAAASVASRRGTHGGLVTGLPNPGGGGGPQLTVPPNLLPQTLLNGPASAAV LPPPPPHALGSRGPPTPAPPGAPGGPACLGGTPGVSATSSSASSSTSSSVAEVG VGAGGKRPGSVSSTDQERELKEKQRNAEALAELSESLRNRAEEWASKPKMVRDT LLTLAGCTPYEVRFKKDHSLLGRVFAFDAVSKPGMDYELKLFIEYPTGSGNVYS SASGVAKQMYQDCMKDFGRGLSSGFKYLEYEKKHGSGDWRLLGDLLPEAVRFFK EGVPGADMLPQPYLDASCPMLPTALVSLSRAPSAPPGTGALPPAAPSGRGAAAS LRKRKASPEPPDSAEGALKLGEEQQRQQWMANQSEALKLTMSAGGFAAPGHAAG GPPPPPPPLGPHSNRTTPPESAPQNGPSPMAALMSVADTLGTAHSPKDGSSVHS TTASARRNSSSPVSPASVPGQRRLASRNGDLNLQVAPPPPSAHPGMDQVHPQNI PDSPMANSGPLCCTICHERLEDTHFVQCPSVPSHKFCFPCSRESIKAQGATGEV YCPSGEKCPLVGSNVPWAFMQGEIATILAGDVKVKKERDP
569	HOXA13 (homeodomain)	MTASVLLHPRWIEPTVMFLYDNGGGLVADELNKNMEGAAAAAAAAAAAAAAAGAG GGGFPHPAAAAAGGNFSVAAAAAAAAAAAAANQCRNLMAHPAPLAPGAASAYSSA PGEAPPSAAAAAAAAAAAAAAAAAAASSSGGPGPAGPAGAEAAKQCSPCSAAAQS SSGPAALPYGYFGSGYYPCARMGPHPNAIKSCAQPASAAAAAAFADKYMDTAGP AAEEFSSRAKEFAFYHQGYAAGPYHHHQPMPGYLDMPVVPGLGGPGESRHEPLG LPMESYQPWALPNGWNGQMYCPKEQAQPPHLWKSTLPDVVSHPSDASSYRRGRK KRVPYTKVQLKELEREYATNKFITKDKRRRISATTNLSERQVTIWFQNRRVKEK KVINKLKTTS
570	HOXB13 (homeodomain)	MEPGNYATLDGAKDIEGLLGAGGGRNLVAHSPLTSHPAAPTLMPAVNYAPLDLP GSAEPPKQCHPCPGVPQGTSPAPVPYGYFGGGYYSCRVSRSSLKPCAQAATLAA YPAETPTAGEEYPSRPTEFAFYPGYPGTYQPMASYLDVSVVQTLGAPGEPRHDS LLPVDSYQSWALAGGWNSQMCCQGEQNPPGPEWKAAFADSSGQHPPDACAFRRG RKKRIPYSKGQLRELEREYAANKFITKDKRRKISAATSLSERQITIWFQNRRVK EKKVLAKVKNSATP
571	HOXC13 (homeodomain)	MTTSLLLHPRWPESLMYVYEDSAAESGIGGGGGGGGGGTGGAGGGCSGASPGKA PSMDGLGSSCPASHCRDLLPHPVLGRPPAPLGAPQGAVYTDIPAPEAARQCAPP PAPPTSSSATLGYGYPFGGSYYGCRLSHNVNLQQKPCAYHPGDKYPEPSGALPG DDLSSRAKEFAFYPSFASSYQAMPGYLDVSVVPGISGHPEPRHDALIPVEGYQH WALSNGWDSQVYCSKEQSQSAHLWKSPFPDVVPLQPEVSSYRRGRKKRVPYTKV QLKELEKEYAASKFITKEKRRRISATTNLSERQVTIWFQNRRVKEKKVVSKSKA PHLHST
572	HOXA11 (homeodomain)	MDFDERGPCSSNMYLPSCTYYVSGPDFSSLPSFLPQTPSSRPMTYSYSSNLPQV QPVREVTFREYAIEPATKWHPRGNLAHCYSAEELVHRDCLQAPSAAGVPGDVLA KSSANVYHHPTPAVSSNFYSTVGRNGVLPQAFDQFFETAYGTPENLASSDYPGD KSAEKGPPAATATSAAAAAAATGAPATSSSDSGGGGGCRETAAAAEEKERRRRP ESSSSPESSSGHTEDKAGGSSGQRTRKKRCPYTKYQIRELEREFFFSVYINKEK RLQLSRMLNLTDRQVKIWFQNRRMKEKKINRDRLQYYSANPLL
573	HOXC11 (homeodomain)	MENSVNLGNFCSPSRKERGADEGERGSCASNLYLPSCTYYMPEFSTVSSFLPQA PSRQISYPYSAQVPPVREVSYGLEPSGKWHHRNSYSSCYAAADELMHRECLPPS TVTEILMKNEGSYGGHHHPSAPHATPAGFYSSVNKNSVLPQAFDRFEDNAYCGG GDPPAEPPCSGKGEAKGEPEAPPASGLASRAEAGAEAEAEEENTNPSSSGSAHS VAKEPAKGAAPNAPRTRKKRCPYSKFQIRELEREFFENVYINKEKRLQLSRMLN LTDRQVKIWFQNRRMKEKKLSRDRLQYFSGNPLL
574	HOXC10 (homeodomain)	MTCPRNVTPNSYAEPLAAPGGGERYSRSAGMYMQSGSDENCGVMRGCGLAPSLS KRDEGSSPSLALNTYPSYLSQLDSWGDPKAAYRLEQPVGRPLSSCSYPPSVKEE NVCCMYSAEKRAKSGPEAALYSHPLPESCLGEHEVPVPSYYRASPSYSALDKTP HCSGANDFEAPFEQRASLNPRAEHLESPQLGGKVSFPETPKSDSQTPSPNEIKT EQSLAGPKGSPSESEKERAKAADSSPDTSDNEAKEEIKAENTTGNWLTAKSGRK KRCPYTKHQTLELEKEFLENMYLTRERRLEISKTINLTDRQVKIWFQNRRMKLK KMNRENRIRELTSNENFT
575	HOXA10 (homeodomain)	MSARKGYLLPSPNYPTTMSCSESPAANSFLVDSLISSGRGEAGGGGGGAGGGGG GGYYAHGGVYLPPAADLPYGLQSCGLFPTLGGKRNEAASPGSGGGGGGLGPGAH GYGPSPIDLWLDAPRSCRMEPPDGPPPPPQQQPPPPPQPPQPAPQATSCSFAQN IKEESSYCLYDSADKCPKVSATAAELAPFPRGPPPDGCALGTSSGVPVPGYERL SQAYGTAKGYGSGGGGAQQLGAGPFPAQPPGRGEDLPPALASGSADAARKERAL DSPPPPTLACGSGGGSQGDEEAHASSSAAEELSPAPSESSKASPEKDSLGNSKG ENAANWLTAKSGRKKRCPYTKHQTLELEKEFLENMYLTRERRLEISRSVHLTDR QVKIWFQNRRMKLKKMNRENRIRELTANENFS
576	HOXB9 (homeodomain)	MSISGTLSSYYVDSIISHESEDAPPAKFPSGQYASSRQPGHAEHLEFPSCSFQP KAPVEGASWAPLSPHASGSLPSVYHPYIQPQGVPPAESRYLRTWLEPAPRGEAA PGQGQAAVKAEPLLGAPGELLKQGTPEYSLETSAGREAVLSNQRPGYGDNKICE GSEDKERPDQTNPSANWLHARSSRKKRCPYTKYQTLELEKEFLENMYLTRDRRH EVARLLNLSERQVKIWFQNRRMKMKKMNKEQGKE

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
577	HOXA9 (homeodomain)	MATTGALGNYYVDSFLLGADAADELSVGRYAPGTLGQPPRQAATLAEHPDFSPC SFQSKATVEGASWNPVHAAGANAVPAAVYHHHHHHPYVHPQAPVAAAAPDGRYM RSWLEPTPGALSFAGLPSSRPYGIKPEPLSARRGDCPTLDTHTLSLTDYACGSP PVDREKQPSEGAFSENNAENESGGDKPPIDPNNPAANWLHARSTRKKRCPYTKH QTLELEKEFLENMYLTRDRRYEVARLLNLTERQVKIWFQNRRMKMKKINKDRAK DE
578	ZFP28_HUMAN	NKKLEAVGTGIEPKAMSQGLVTFGDVAVDFSQEEWEWLNPIQRNLYRKVMLENY RNLASLGLCVSKPDVISSLEQGKEPW
579	ZN334_HUMAN	KMKKFQIPVSFQDLTVNFTQEEWQQLDPAQRLLYRDVMLENYSNLVSVGYHVSK PDVIFKLEQGEEPWIVEEFSNQNYPD
580	ZN568_HUMAN	CSQESALSEEEEDTTRPLETVTFKDVAVDLTQEEWEQMKPAQRNLYRDVMLENY SNLVTVGCQVTKPDVIFKLEQEEEPW
581	ZN37A_HUMAN	ITSQGSVSFRDVTVGFTQEEWQHLDPAQRTLYRDVMLENYSHLVSVGYCIPKPE VILKLEKGEEPWILEEKFPSQSHLEL
582	ZN181_HUMAN	PQVTFNDVAIDFTHEEWGWLSSAQRDLYKDVMVQNYENLVSVAGLSVTKPYVIT LLEDGKEPWMMEKKLSKGMIPDWESR
583	ZN510_HUMAN	PLRFSTLFQEQQKMNISQASVSFKDVTIEFTQEEWQQMAPVQKNLYRDVMLENY SNLVSVGYCCFKPEVIFKLEQGEEPW
584	ZN862_HUMAN	QDPSAEGLSEEVPVVFEELPVVFEDVAVYFTREEWGMLDKRQKELYRDVMRMNY ELLASLGPAAAKPDLISKLERRAAPW
585	ZN140_HUMAN	SQGSVTFRDVAIDFSQEEWKWLQPAQRDLYRCVMLENYGHLVSLGLSISKPDVV SLLEQGKEPWLGKREVKRDLFSVSES
586	ZN208_HUMAN	GSLTFRDVAIEFSLEEWQCLDTAQQNLYRNVMLENYRNLVELGIAAFKPDLIIF LEEGKESWNMKRHEMVEESPVICSHF
587	ZN248_HUMAN	NKSQEQVSFKDVCVDFTQEEWYLLDPAQKILYRDVILENYSNLVSVGYCITKPE VIFKIEQGEEPWILEKGFPSQCHPER
588	ZN571_HUMAN	PHLLVTFRDVAIDESQEEWECLDPAQRDLYRDVMLENYSNLISLDLESSCVTKK LSPEKEIYEMESLQWENMGKRINHHL
589	ZN699_HUMAN	EEERKTAELQKNRIQDSVVFEDVAVDETQEEWALLDLAQRNLYRDVMLENFQNL ASLGYPLHTPHLISQWEQEEDLQTVK
590	ZN726_HUMAN	GLLTFRDVAIEFSLEEWQCLDTAQKNLYRNVMLENYRNLAFLGIAVSKPDLIIC LEKEKEPWNMKRDEMVDEPPGICPHF
591	ZIK1_HUMAN	RAPTQVTVSPETHMDLTKGCVTFEDIAIYFSQDEWGLLDEAQRLLYLEVMLENE ALVASLGCGHGTEDEETPSDQNVSVG
592	ZNF2_HUMAN	AAVSPTTRCQESVTFEDVAVVETDEEWSRLVPIQRDLYKEVMLENYNSIVSLGL PVPQPDVIFQLKRGDKPWMVDLHGSE
593	Z705F_HUMAN	HSLEKVTFEDVAIDFTQEEWDMMDTSKRKLYRDVMLENISHLVSLGYQISKSYI ILQLEQGKELWREGRVFLQDQNPDRE
594	ZNF14_HUMAN	DSVSFEDVAVNETLEEWALLDSSQKKLYEDVMQETFKNLVCLGKKWEDQDIEDD HRNQGKNRRCHMVERLCESRRGSKCG
595	ZN471_HUMAN	NVEVVKVMPQDLVTFKDVAIDESQEEWQWMNPAQKRLYRSMMLENYQSLVSLGL CISKPYVISLLEQGREPWEMTSEMTR
596	ZN624_HUMAN	TQPDEDLHLQAEETQLVKESVTFKDVAIDFTLEEWRLMDPTQRNLHKDVMLENY RNLVSLGLAVSKPDMISHLENGKGPW
597	ZNF84_HUMAN	TMLQESFSFDDLSVDFTQKEWQLLDPSQKNLYKDVMLENYSSLVSLGYEVMKPD VIFKLEQGEEPWVGDGEIPSSDSPEV
598	ZNF7_HUMAN	EVVTFGDVAVHFSREEWQCLDPGQRALYREVMLENHSSVAGLAGELVEKPELIS RLEQGEEPWVLDLQGAEGTEAPRTSK
599	ZN891_HUMAN	RNAEEERMIAVFLTTWLQEPMTEKDVAVEFTQEEWMMLDSAQRSLYRDVMLENY RNLTSVEYQLYRLTVISPLDQEEIRN
600	ZN337_HUMAN	GPQGARRQAFLAFGDVTVDFTQKEWRLLSPAQRALYREVTLENYSHLVSLGILH SKPELIRRLEQGEVPWGEERRRRPGP

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
601	Z705G_HUMAN	HSLKKLTFEDVAIDFTQEEWAMMDTSKRKLYRDVMLENISHLVSLGYQISKSYI ILQLEQGKELWREGRVFLQDQNPNRE
602	ZN529_HUMAN	MPEVEFPDQFFTVLTMDHELVTLRDVVINESQEEWEYLDSAQRNLYWDVMMENY SNLLSLDLESRNETKHLSVGKDIIQN
603	ZN729_HUMAN	PGAPGSLEMGPLTFRDVTIEFSLEEWQCLDTVQQNLYRDVMLENYRNLVELGMA VFKPDLITCLKQGKEPWNMKRHEMVT
604	ZN419_HUMAN	RDPAQVPVAADLLTDHEEGYVTFEDVAVYFSQEEWRLLDDAQRLLYRNVMLENE TLLASLGLASSKTHEITQLESWEEPF
605	Z705A_HUMAN	HSLKKVTFEDVAIDETQEEWAMMDTSKRKLYRDVMLENISHLVSLGYQISKSYI ILQLEQGKELWREGREFLQDQNPDRE
606	ZNF45_HUMAN	TKSKEAVTFKDVAVVFSEEELQLLDLAQRKLYRDVMLENFRNVVSVGHQSTPDG LPQLEREEKLWMMKMATQRDNSSGAK
607	ZN302_HUMAN	SQVTFSDVAIDFSHEEWACLDSAQRDLYKDVMVQNYENLVSVGLSVTKPYVIML LEDGKEPWMMEKKLSKAYPFPLSHSV
608	ZN486_HUMAN	PGPLRSLEMESLQFRDVAVEFSLEEWHCLDTAQQNLYRDVMLENYRHLVELGII VSKPDLITCLEQGIKPLTMKRHEMIA
609	ZN621_HUMAN	LQTTWPQESVTFEDVAVYFTQNQWASLDPAQRALYGEVMLENYANVASLVAFPF PKPALISHLERGEAPWGPDPWDTEIL
610	ZN688_HUMAN	APLLAPRPGETRPGCRKPGTVSFADVAVYFSPEEWGCLRPAQRALYRDVMQETY GHLGALGFPGPKPALISWMEQESEAW
611	ZN33A_HUMAN	NKVEQKSQESVSFKDVTVGFTQEEWQHLDPSQRALYRDVMLENYSNLVSVGYCV HKPEVIFRLQQGEEPWKQEEEFPSQS
612	ZN554_HUMAN	CFSQEERMAAGYLPRWSQELVTFEDVSMDFSQEEWELLEPAQKNLYREVMLENY RNVVSLEALKNQCTDVGIKEGPLSPA
613	ZN878_HUMAN	DSVAFEDVAVNFTQEEWALLDPSQKNLYREVMQETLRNLTSIGKKWNNQYIEDE HQNPRRNLRRLIGERLSESKESHQHG
614	ZN772_HUMAN	MGPAQVPMNSEVIVDPIQGQVNFEDVEVYFSQEEWVLLDEAQRLLYRDVMLENE ALMASLGHTSFMSHIVASLVMGSEPW
615	ZN224_HUMAN	TTFKEAMTFKDVAVVFTEEELGLLDLAQRKLYRDVMLENFRNLLSVGHQAFHRD TFHFLREEKIWMMKTAIQREGNSGDK
616	ZN184_HUMAN	DSTLLQGGHNLLSSASFQEAVTFKDVIVDETQEEWKQLDPGQRDLERDVTLENY THLVSIGLQVSKPDVISQLEQGTEPW
617	ZN544_HUMAN	EARSMLVPPQASVCFEDVAMAFTQEEWEQLDLAQRTLYREVTLETWEHIVSLGL FLSKSDVISQLEQEEDLCRAEQEAPR
618	ZNF57_HUMAN	DSVVFEDVAVDFTLEEWALLDSAQRDLYRDVMLETERNLASVDDGTQFKANGSV SLQDMYGQEKSKEQTIPNETGNNSCA
619	ZN283_HUMAN	EESHGALISSCNSRTMTDGLVTERDVAIDESQEEWECLDPAQRDLYVDVMLENY SNLVSLDLESKTYETKKIFSENDIFE
620	ZN549_HUMAN	VITPQIPMVTEEFVKPSQGHVTFEDIAVYFSQEEWGLLDEAQRCLYHDVMLENE SLMASVGCLHGIEAEEAPSEQTLSAQ
621	ZN211_HUMAN	VQLRPQTRMATALRDPASGSVTFEDVAVYFSWEEWDLLDEAQKHLYFDVMLENE ALTSSLGCWCGVEHEETPSEQRISGE
622	ZN615_HUMAN	MQAQESLTLEDVAVDFTWEEWQFLSPAQKDLYRDVMLENYSNLVAVGYQASKPD ALSKLERGEETCTTEDEIYSRICSEI
623	ZN253_HUMAN	GPLQFRDVAIEFSLEEWHCLDTAQRNLYRDVMLENYRNLVFLGIVVSKPDLVTC LEQGKKPLTMERHEMIAKPPVMSSHF
624	ZN226_HUMAN	NMFKEAVTFKDVAVAFTEEELGLLGPAQRKLYRDVMVENFRNLLSVGHPPFKQD VSPIERNEQLWIMTTATRRQGNLGEK
625	ZN730_HUMAN	GALTERDVAIEFSLEEWQCLDTEQQNLYRNVMLDNYRNLVELGIAVSKPDLITC LEQEKEPWNLKTHDMVAKPPVICSHI

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
626	Z585A_HUMAN	SPQKSSALAPEDHGSSYEGSVSFRDVAIDESREEWRHLDPSQRNLYRDVMLETY SHLLSVGYQVPEAEVVMLEQGKEPWA
627	ZN732_HUMAN	ELLTFRDVAIEFSPEEWKCLDPAQQNLYRDVMLENYRNLISLGVAISNPDLVIY LEQRKEPYKVKIHETVAKHPAVCSHE
628	ZN681_HUMAN	EPLKERDVAIEFSLEEWQCLDTIQQNLYRNVMLENYRNLVFLGIVVSKPDLITC LEQEKEPWTRKRHRMVAEPPVICSHE
629	ZN667_HUMAN	PSARGKSKSKAPITFGDLAIYFSQEEWEWLSPIQKDLYEDVMLENYRNLVSLGL SFRRPNVITLLEKGKAPWMVEPVRRR
630	ZN649_HUMAN	TKAQESLTLEDVAVDFTWEEWQFLSPAQKDLYRDVMLENYSNLVSVGYQAGKPD ALTKLEQGEPLWTLEDEIHSPAHPEI
631	ZN470_HUMAN	SQEEVEVAGIKLCKAMSLGSVTFTDVAIDESQDEWEWLNLAQRSLYKKVMLENY RNLVSVGLCISKPDVISLLEQEKDPW
632	ZN484_HUMAN	TKSLESVSFKDVTVDESRDEWQQLDLAQKSLYREVMLENYENLISVGCQVPKPE VIFSLEQEEPCMLDGEIPSQSRPDGD
633	ZN431_HUMAN	SGCPGAERNLLVYSYFEKETLTERDVAIEFSLEEWECLNPAQQNLYMNVMLENY KNLVELGVAVSKQDPVTCLEQEKEPW
634	ZN382_HUMAN	PLQGSVSFKDVTVDETQEEWQQLDPAQKALYRDVMLENYCHFVSVGFHMAKPDM IRKLEQGEELWTQRIFPSYSYLEEDG
635	ZN254_HUMAN	PGPPRSLEMGLLTFRDVAIEFSLEEWQHLDIAQQNLYRNVMLENYRNLAFLGIA VSKPDLITCLEQGKEPWNMKRHEMVD
636	ZN124_HUMAN	SGHPGSWEMNSVAFEDVAVNFTQEEWALLDPSQKNLYRDVMQETERNLASIGNK GEDQSIEDQYKNSSRNLRHIISHSGN
637	ZN607_HUMAN	SYGSITFGDVAIDESHQEWEYLSLVQKTLYQEVMMENYDNLVSLAGHSVSKPDL ITLLEQGKEPWMIVREETRGECTDLD
638	ZN317_HUMAN	DLFVCSGLEPHTPSVGSQESVTFQDVAVDFTEKEWPLLDSSQRKLYKDVMLENY SNLTSLGYQVGKPSLISHLEQEEEPR
639	ZN620_HUMAN	FQTAWRQEPVTFEDVAVYFTQNEWASLDSVQRALYREVMLENYANVASLAFPFT TPVLVSQLEQGELPWGLDPWEPMGRE
640	ZN141_HUMAN	ELLTFRDVAIEFSPEEWKCLDPDQQNLYRDVMLENYRNLVSLGVAISNPDLVTC LEQRKEPYNVKIHKIVARPPAMCSHF
641	ZN584_HUMAN	AGEAEAQLDPSLQGLVMFEDVTVYFSREEWGLLNVTQKGLYRDVMLENFALVSS LGLAPSRSPVFTQLEDDEQSWVPSWV
642	ZN540_HUMAN	AHALVTERDVAIDFSQKEWECLDTTQRKLYRDVMLENYNNLVSLGYSGSKPDVI TLLEQGKEPCVVARDVTGRQCPGLLS
643	ZN75D_HUMAN	KRIKHWKMASKLILPESLSLLTFEDVAVYFSEEEWQLLNPLEKTLYNDVMQDIY ETVISLGLKLKNDTGNDHPISVSTSE
644	ZN555_HUMAN	DSVVFEDVAVDETLEEWALLDSAQRDLYRDVMLETFQNLASVDDETQFKASGSV SQQDIYGEKIPKESKIATFTRNVSWA
645	ZN658_HUMAN	NMSQASVSFQDVTVEFTREEWQHLGPVERTLYRDVMLENYSHLISVGYCITKPK VISKLEKGEEPWSLEDEFLNQRYPGY
646	ZN684_HUMAN	ISFQESVTFQDVAVDETAEEWQLLDCAERTLYWDVMLENYRNLISVGCPITKTK VILKVEQGQEPWMVEGANPHESSPES
647	RBAK_HUMAN	NTLQGPVSFKDVAVDETQEEWQQLDPDEKITYRDVMLENYSHLVSVGYDTTKPN VIIKLEQGEEPWIMGGEFPCQHSPEA
648	ZN829_HUMAN	HPEEEERMHDELLQAVSKGPVMFRDVSIDESQEEWECLDADQMNLYKEVMLENF SNLVSVGLSNSKPAVISLLEQGKEPW
649	ZN582_HUMAN	SLGSELERDVAIVESQEEWQWLAPAQRDLYRDVMLETYSNLVSLGLAVSKPDVI SFLEQGKEPWMVERVVSGGLCPVLES
650	ZN112_HUMAN	TKFQEMVTFKDVAVVFTEEELGLLDSVQRKLYRDVMLENERNLLLVAHQPFKPD LISQLEREEKLLMVETETPRDGCSGR

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
651	ZN716_HUMAN	AKRPGPPGSREMGLLTFRDIAIEFSLAEWQCLDHAQQNLYRDVMLENYRNLVSL GIAVSKPDLITCLEQNKEPQNIKRNE
652	HKR1_HUMAN	TCMVHRQTMSCSGAGGITAFVAFRDVAVYFTQEEWRLLSPAQRTLHREVMLETY NHLVSLEIPSSKPKLIAQLERGEAPW
653	ZN350_HUMAN	IQAQESITLEDVAVDFTWEEWQLLGAAQKDLYRDVMLENYSNLVAVGYQASKPD ALFKLEQGEQLWTIEDGIHSGACSDI
654	ZN480_HUMAN	AQKRRKRKAKESGMALPQGHLTFRDVAIEFSQAEWKCLDPAQRALYKDVMLENY RNLVSLGISLPDLNINSMLEQRREPW
655	ZN416_HUMAN	DSTSVPVTAEAKLMGFTQGCVTFEDVAIYESQEEWGLLDEAQRLLYRDVMLENF ALITALVCWHGMEDEETPEQSVSVEG
656	ZNF92_HUMAN	GPLTFRDVKIEFSLEEWQCLDTAQRNLYRDVMLENYRNLVFLGIAVSKPDLITW LEQGKEPWNLKRHEMVDKTPVMCSHE
657	ZN100_HUMAN	SGCPGAERSLLVQSYFEKGPLTFRDVAIEFSLEEWQCLDSAQQGLYRKVMLENY RNLVFLAGIALTKPDLITCLEQGKEP
658	ZN736_HUMAN	GVLTFRDVAVEFSPEEWECLDSAQQRLYRDVMLENYGNLVSLGLAIFKPDLMTC LEQRKEPWKVKRQEAVAKHPAGSFHF
659	ZNF74_HUMAN	KENLEDISGWGLPEARSKESVSFKDVAVDETQEEWGQLDSPQRALYRDVMLENY QNLLALGPPLHKPDVISHLERGEEPW
660	CBX1_HUMAN	EESEKPRGFARGLEPERIIGATDSSGELMELMKWKNSDEADLVPAKEANVKCPQ VVISFYEERLTWHSYPSEDDDKKDDK
661	ZN443_HUMAN	ASVALEDVAVNFTREEWALLGPCQKNLYKDVMQETIRNLDCVVMKWKDQNIEDQ YRYPRKNLRCRMLERFVESKDGTQCG
662	ZN195_HUMAN	TLLTERDVAIEFSLEEWKCLDLAQQNLYRDVMLENYRNLESVGLTVCKPGLITC LEQRKEPWNVKRQEAADGHPEMGFHH
663	ZN530_HUMAN	AAALRAPTQQVEVAFEDVAIYFSQEEWELLDEMQRLLYRDVMLENFAVMASLGC WCGAVDEGTPSAESVSVEELSQGRTP
664	ZN782_HUMAN	NTFQASVSFQDVTVEFSQEEWQHMGPVERTLYRDVMLENYSHLVSVGYCFTKPE LIFTLEQGEDPWLLEKEKGELSRNSP
665	ZN791_HUMAN	DSVAFEDVSVSESQEEWALLAPSQKKLYRDVMQETFKNLASIGEKWEDPNVEDQ HKNQGRNLRSHTGERLCEGKEGSQCA
666	ZN331_HUMAN	AQGLVTFADVAIDFSQEEWACLNSAQRDLYWDVMLENYSNLVSLDLESAYENKS LPTEKNIHEIRASKRNSDRRSKSLGR
667	Z354C_HUMAN	AVDLLSAQEPVTFRDVAVFFSQDEWLHLDSAQRALYREVMLENYSSLVSLGIPF SMPKLIHQLQQGEDPCMVEREVPSDT
668	ZN157_HUMAN	SPQRFPALIPGEPGRSFEGSVSFEDVAVDETRQEWHRLDPAQRTMHKDVMLETY SNLASVGLCVAKPEMIFKLERGEELW
669	ZN727_HUMAN	RVLTFRDVAVEFSPEEWECLDSAQQRLYRDVMLENYGNLFSLGLAIFKPDLITY LEQRKEPWNARRQKTVAKHPAGSLHE
670	ZN550_HUMAN	AETKDAAQMLVTFKDVAVTFTREEWRQLDLAQRTLYREVMLETCGLLVSLGHRV PKPELVHLLEHGQELWIVKRGLSHAT
671	ZN793_HUMAN	IEYQIPVSFKDVVVGFTQEEWHRLSPAQRALYRDVMLETYSNLVSVGYEGTKPD VILRLEQEEAPWIGEAACPGCHCWED
672	ZN235_HUMAN	TKFQEAVTEKDVAVAFTEEELGLLDSAQRKLYRDVMLENERNLVSVGHQSFKPD MISQLEREEKLWMKELQTQRGKHSGD
673	ZNF8_HUMAN	DEGVAGVMSVGPPAARLQEPVTERDVAVDETQEEWGQLDPTQRILYRDVMLETF GHLLSIGPELPKPEVISQLEQGTELW
674	ZN724_HUMAN	GPLTEMDVAIEFSVEEWQCLDTAQQNLYRNVMLENYRNLVELGIAVSKPDLITC LEQGKEPWNMERHEMVAKPPGMCCYF
675	ZN573_HUMAN	HQVGLIRSYNSKTMTCFQELVTERDVAIDESRQEWEYLDPNQRDLYRDVMLENY RNLVSLGGHSISKPVVVDLLERGKEP

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
676	ZN577_HUMAN	NATIVMSVRREQGSSSGEGSLSFEDVAVGFTREEWQFLDQSQKVLYKEVMLENY INLVSIGYRGTKPDSLFKLEQGEPPG
677	ZN789_HUMAN	FPPARGKELLSFEDVAMYFTREEWGHLNWGQKDLYRDVMLENYRNMVLLGFQFP KPEMICQLENWDEQWILDLPRTGNRK
678	ZN718_HUMAN	ELLTFKDVAIEFSPEEWKCLDTSQQNLYRDVMLENYRNLVSLGVSISNPDLVTS LEQRKEPYNLKIHETAARPPAVCSHE
679	ZN300_HUMAN	MKSQGLVSFKDVAVDFTQEEWQQLDPSQRTLYRDVMLENYSHLVSMGYPVSKPD VISKLEQGEEPWIIKGDISNWIYPDE
680	ZN383_HUMAN	AEGSVMFSDVSIDESQEEWDCLDPVQRDLYRDVMLENYGNLVSMGLYTPKPQVI SLLEQGKEPWMVGRELTRGLCSDLES
681	ZN429_HUMAN	GPLTFTDVAIEFSLEEWQCLDTAQQNLYRNVMLENYRNLVELGIAVSKPDLITC LEKEKEPCKMKRHEMVDEPPVVCSHF
682	ZN677_HUMAN	ALSQGLFTFKDVAIEFSQEEWECLDPAQRALYRDVMLENYRNLLSLDEDNIPPE DDISVGFTSKGLSPKENNKEELYHLV
683	ZN850_HUMAN	NMEGLVMFQDLSIDESQEEWECLDAAQKDLYRDVMMENYSSLVSLGLSIPKPDV ISLLEQGKEPWMVSRDVLGGWCRDSE
684	ZN454_HUMAN	AVSHLPTMVQESVTFKDVAILFTQEEWGQLSPAQRALYRDVMLENYSNLVSLGL LGPKPDTFSQLEKREVWMPEDTPGGF
685	ZN257_HUMAN	GPLTIRDVTVEFSLEEWHCLDTAQQNLYRDVMLENYRNLVFLGIAVSKPDLITC LEQGKEPCNMKRHEMVAKPPVMCSHI
686	ZN264_HUMAN	AAAVLTDRAQVSVTFDDVAVTFTKEEWGQLDLAQRTLYQEVMLENCGLLVSLGC PVPKAELICHLEHGQEPWTRKEDLSQ
687	ZFP82_HUMAN	ALRSVMESDVSIDESPEEWEYLDLEQKDLYRDVMLENYSNLVSLGCFISKPDVI SSLEQGKEPWKVVRKGRRQYPDLETK
688	ZFP14_HUMAN	AHGSVTFRDVAIDFSQEEWEFLDPAQRDLYRDVMWENYSNFISLGPSISKPDVI TLLDEERKEPGMVVREGTRRYCPDLE
689	ZN485_HUMAN	APRAQIQGPLTFGDVAVAFTRIEWRHLDAAQRALYRDVMLENYGNLVSVGLLSS KPKLITQLEQGAEPWTEVREAPSGTH
690	ZN737_HUMAN	GPLQFRDVAIEFSLEEWHCLDTAQRNLYRNVMLENYRNLVFLGIVVSKPDLITC LEQGKKPLTMKKHEMVANPSVTCSHE
691	ZNF44_HUMAN	TLPRGQPEVLEWGLPKDQDSVAFEDVAVNFTHEEWALLGPSQKNLYRDVMRETI RNLNCIGMKWENQNIDDQHQNLRRNP
692	ZN596_HUMAN	PSPDSMTFEDIIVDFTQEEWALLDTSQRKLFQDVMLENISHLVSIGKQLCKSVV LSQLEQVEKLSTQRISLLQGREVGIK
693	ZN565_HUMAN	EESREIRAGQIVLKAMAQGLVTERDVAIEFSLEEWKCLEPAQRDLYREVTLENF GHLASLGLSISKPDVVSLLEQGKEPW
694	ZN543_HUMAN	AASAQVSVTFEDVAVTFTQEEWGQLDAAQRTLYQEVMLETCGLLMSLGCPLFKP ELIYQLDHRQELWMATKDLSQSSYPG
695	ZFP69_HUMAN	RESLEDEVTPGLPTAESQELLTFKDISIDFTQEEWGQLAPAHQNLYREVMLENY SNLVSVGYQLSKPSVISQLEKGEEPW
696	SUMO1_HUMAN	EGEYIKLKVIGQDSSEIHFKVKMTTHLKKLKESYCQRQGVPMNSLRELFEGQRI ADNHTPKELGMEEEDVIEVYQEQTGG
697	ZNF12_HUMAN	NKSLGPVSFKDVAVDFTQEEWQQLDPEQKITYRDVMLENYSNLVSVGYHIIKPD VISKLEQGEEPWIVEGEFLLQSYPDE
698	ZN169_HUMAN	SPGLLTTRKEALMAFRDVAVAFTQKEWKLLSSAQRTLYREVMLENYSHLVSLGI AFSKPKLIEQLEQGDEPWREENEHLL
699	ZN433_HUMAN	MFQDSVAFEDVAVTFTQEEWALLDPSQKNLCRDVMQETERNLASIGKKWKPQNI YVEYENLRRNLRIVGERLFESKEGHQ
700	SUMO3_HUMAN	ENDHINLKVAGQDGSVVQFKIKRHTPLSKLMKAYCERQGLSMRQIRFREDGQPI NETDTPAQLEMEDEDTIDVEQQQTGG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
701	ZNF98_HUMAN	PGPLGSLEMGVLTFRDVALEFSLEEWQCLDTAQQNLYRNVMLENYRNLVFVGIA ASKPDLITCLEQGKEPWNVKRHEMVT
702	ZN175_HUMAN	LSQKPQVLGPEKQDGSCEASVSFEDVTVDESREEWQQLDPAQRCLYRDVMLELY SHLFAVGYHIPNPEVIERMLKEKEPR
703	ZN347_HUMAN	ALTQGQVTFRDVAIEFSQEEWTCLDPAQRTLYRDVMLENYRNLASLGISCEDLS IISMLEQGKEPFTLESQVQIAGNPDG
704	ZNF25_HUMAN	NKFQGPVTLKDVIVEFTKEEWKLLTPAQRTLYKDVMLENYSHLVSVGYHVNKPN AVFKLKQGKEPWILEVEFPHRGFPED
705	ZN519_HUMAN	ELLTFRDVAIEFSPEEWKCLDPAQQNLYRDVMLENYRNLVSLAVYSYYNQGILP EQGIQDSFKKATLGRYGSCGLENICL
706	Z585B_HUMAN	SPQKSSALAPEDHGSSYEGSVSERDVAIDESREEWRHLDLSQRNLYRDVMLETY SHLLSVGYQVPKPEVVMLEQGKEPWA
707	ZIM3_HUMAN	NNSQGRVTFEDVTVNFTQGEWQRLNPEQRNLYRDVMLENYSNLVSVGQGETTKP DVILRLEQGKEPWLEEEEVLGSGRAE
708	ZN517_HUMAN	AMALPMPGPQEAVVFEDVAVYFTRIEWSCLAPDQQALYRDVMLENYGNLASLGE LVAKPALISLLEQGEEPGALILQVAE
709	ZN846_HUMAN	DSSQHLVTFEDVAVDFTQEEWTLLDQAQRDLYRDVMLENYKNLIILAGSELFKR SLMSGLEQMEELRTGVTGVLQELDLQ
710	ZN230_HUMAN	TTFKEAVTEKDVAVFFTEEELGLLDPAQRKLYQDVMLENFTNLLSVGHQPFHPF HFLREEKFWMMETATQREGNSGGKTI
711	ZNF66_HUMAN	GPLQFRDVAIEFSLEEWHCLDMAQRNLYRDVMLENYRNLVELGIVVSKPDLITH LEQGKKPSTMQRHEMVANPSVLCSHE
712	ZFP1_HUMAN	NKSQGSVSFTDVTVDFTQEEWEQLDPSQRILYMDVMLENYSNLLSVEVWKADDQ MERDHRNPDEQARQFLILKNQTPIEE
713	ZN713_HUMAN	EEEEMNDGSQMVRSQESLTFQDVAVDETREEWDQLYPAQKNLYRDVMLENYRNL VALGYQLCKPEVIAQLELEEEWVIER
714	ZN816_HUMAN	EEATKKSKEKEPGMALPQGRLTERDVAIEFSLEEWKCLNPAQRALYRAVMLENY RNLEFVDSSLKSMMEFSSTRHSITGE
715	ZN426_HUMAN	EKTPAGRIVADCLTDCYQDSVTFDDVAVDETQEEWTLLDSTQRSLYSDVMLENY KNLATVGGQIIKPSLISWLEQEESRT
716	ZN674_HUMAN	AMSQESLTFKDVFVDFTLEEWQQLDSAQKNLYRDVMLENYSHLVSVGHLVGKPD VIFRLGPGDESWMADGGTPVRTCAGE
717	ZN627_HUMAN	DSVAFEDVAVNFTLEEWALLDPSQKNLYRDVMRETFRNLASVGKQWEDQNIEDP FKIPRRNISHIPERLCESKEGGQGEE
718	ZNF20_HUMAN	MFQDSVAFEDVAVSFTQEEWALLDPSQKNLYRDVMQETFKNLTSVGKTWKVQNI EDEYKNPRRNLSLMREKLCESKESHH
719	Z587B_HUMAN	AVVATLRLSAQGTVTFEDVAVKFTQEEWNLLSEAQRCLYRDVTLENLALMSSLG CWCGVEDEAAPSKQSIYIQRETQVRT
720	ZN316_HUMAN	EEEEEDEDEDDLLTAGCQELVTFEDVAVYFSLEEWERLEADQRGLYQEVMQENY GILVSLGYPIPKPDLIFRLEQGEEPW
721	ZN233_HUMAN	TKFQEMVTFKDVAVVFTREELGLLDLAQRKLYQDVMLENFRNLLSVGYQPFKLD VILQLGKEDKLRMMETEIQGDGCSGH
722	ZN611_HUMAN	EEAAQKRKGKEPGMALPQGRLTERDVAIEFSLAEWKCLNPSQRALYREVMLENY RNLEAVDISSKCMMKEVLSTGQGNTE
723	ZN556_HUMAN	DTVVFEDVVVDFTLEEWALLNPAQRKLYRDVMLETFKHLASVDNEAQLKASGSI SQQDTSGEKLSLKQKIEKFTRKNIWA
724	ZN234_HUMAN	TTFKEGLTFKDVAVVFTEEELGLLDPVQRNLYQDVMLENFRNLLSVGHHPFKHD VFLLEKEKKLDIMKTATQRKGKSADK
725	ZN560_HUMAN	SALQQEFWKIQTSNGIQMDLVTFDSVAVEFTQEEWTLLDPAQRNLYSDVMLENY KNLSSVGYQLFKPSLISWLEEEEELS

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
726	ZNF77_HUMAN	DCVIFEEVAVNETPEEWALLDHAQRSLYRDVMLETCRNLASLDCYIYVRTSGSS SQRDVFGNGISNDEEIVKFTGSDSWS
727	ZN682_HUMAN	ELLTFRDVTIEFSLEEWEFLNPAQQSLYRKVMLENYRNLVSLGLTVSKPELISR LEQRQEPWNVKRHETIAKPPAMSSHY
728	ZN614_HUMAN	IKTQESLTLEDVAVEFSWEEWQLLDTAQKNLYRDVMVENYNHLVSLGYQTSKPD VLSKLAHGQEPWTTDAKIQNKNCPGI
729	ZN785_HUMAN	PAHVPGEAGPRRTRESRPGAVSFADVAVYFSPEEWECLRPAQRALYRDVMRETE GHLGALGFSVPKPAFISWVEGEVEAW
730	ZN445_HUMAN	GCPGDQVTPTRSLTAQLQETMTFKDVEVTFSQDEWGWLDSAQRNLYRDVMLENY RNMASLVGPFTKPALISWLEAREPWG
731	ZFP30_HUMAN	ARDLVMERDVAVDESQEEWECLNSYQRNLYRDVILENYSNLVSLAGCSISKPDV ITLLEQGKEPWMVVRDEKRRWTLDLE
732	ZN225_HUMAN	TTLKEAVTEKDVAVVFTEEELRLLDLAQRKLYREVMLENFRNLLSVGHQSLHRD TFHFLKEEKFWMMETATQREGNLGGK
733	ZN551_HUMAN	SPPSPRSSMAAVALRDSAQGMTFEDVAIYFSQEEWELLDESQRFLYCDVMLENE AHVTSLGYCHGMENEAIASEQSVSIQ
734	ZN610_HUMAN	DEEAQKRKAKESGMALPQGRLTEMDVAIEFSQEEWKSLDPGQRALYRDVMLENY RNLVFLGICLPDLSIISMLKQRREPL
735	ZN528_HUMAN	ALTQGPLKFMDVAIEFSQEEWKCLDPAQRTLYRDVMLENYRNLVSLGICLPDLS VTSMLEQKRDPWTLQSEEKIANDPDG
736	ZN284_HUMAN	TMFKEAVTFKDVAVVFTEEELGLLDVSQRKLYRDVMLENFRNLLSVGHQLSHRD TFHFQREEKFWIMETATQREGNSGGK
737	ZN418_HUMAN	QGTVAFEDVAVNFSQEEWSLLSEVQRCLYHDVMLENWVLISSLGCWCGSEDEEA PSKKSISIQRVSQVSTPGAGVSPKKA
738	MPP8_HUMAN	AEAFGDSEEDGEDVEEVEKILDMKTEGGKVLYKVRWKGYTSDDDTWEPEIHLED CKEVLLEFRKKIAENKAKAVRKDIQR
739	ZN490_HUMAN	VLQMQNSEHHGQSIKTQTDSISLEDVAVNFTLEEWALLDPGQRNIYRDVMRATE KNLACIGEKWKDQDIEDEHKNQGRNL
740	ZN805_HUMAN	AMALTDPAQVSVTEDDVAVTFTQEEWGQLDLAQRTLYQEVMLENCGLLVSLGCP VPRPELIYHLEHGQEPWTRKEDLSQG
741	Z780B_HUMAN	VHGSVTFRDVAIDESQEEWECLQPDQRTLYRDVMLENYSHLISLGSSISKPDVI TLLEQEKEPWIVVSKETSRWYPDLES
742	ZN763_HUMAN	DPVACEDVAVNETQEEWALLDISQRKLYREVMLETERNLTSIGKKWKDQNIEYE YQNPRRNFRSLIEGNVNEIKEDSHCG
743	ZN285_HUMAN	IKFQERVTFKDVAVVFTKEELALLDKAQINLYQDVMLENFRNLMLVRDGIKNNI LNLQAKGLSYLSQEVLHCWQIWKQRI
744	ZNF85_HUMAN	GPLTFRDVAIEFSLKEWQCLDTAQRNLYRNVMLENYRNLVELGITVSKPDLITC LEQGKEAWSMKRHEIMVAKPTVMCSH
745	ZN223_HUMAN	TMSKEAVTFKDVAVVFTEEELGLLDLAQRKLYRDVMLENFRNLLSVGHQPFHRD TFHFLREEKFWMMDIATQREGNSGGK
746	ZNF90_HUMAN	GPLEFRDVAIEFSLEEWHCLDTAQQNLYRDVMLENYRHLVELGIVVTKPDLITC LEQGKKPFTVKRHEMIAKSPVMCFHF
747	ZN557_HUMAN	GHTEGGELVNELLKSWLKGLVTFEDVAVEFTQEEWALLDPAQRTLYRDVMLENC RNLASLGNQVDKPRLISQLEQEDKVM
748	ZN425_HUMAN	AEPASVTVTEDDVALYFSEQEWEILEKWQKQMYKQEMKTNYETLDSLGYAFSKP DLITWMEQGRMLLISEQGCLDKTRRT
749	ZN229_HUMAN	HSQASAISQDREEKIMSQEPLSFKDVAVVFTEEELELLDSTQRQLYQDVMQENE RNLLSVGERNPLGDKNGKDTEYIQDE
750	ZN606_HUMAN	GSLEEGRRATGLPAAQVQEPVTFKDVAVDFTQEEWGQLDLVQRTLYRDVMLETY GHLLSVGNQIAKPEVISLLEQGEEPW

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
751	ZN155_HUMAN	TTFKEAVTFKDVAVVFTEEELGLLDPAQRKLYRDVMLENFRNLLSVGHQPFHQD TCHFLREEKFWMMGTATQREGNSGGK
752	ZN222_HUMAN	AKLYEAVTFKDVAVIFTEEELGLLDPAQRKLYRDVMLENERNLLSVGGKIQTEM ETVPEAGTHEEFSCKQIWEQIASDLT
753	ZN442_HUMAN	RSDLFLPDSQTNEERKQYDSVAFEDVAVNFTQEEWALLGPSQKSLYRDVMWETI RNLDCIGMKWEDTNIEDQHRNPRRSL
754	ZNF91_HUMAN	PGTPGSLEMGLLTFRDVAIEFSPEEWQCLDTAQQNLYRNVMLENYRNLAFLGIA LSKPDLITYLEQGKEPWNMKQHEMVD
755	ZN135_HUMAN	TPGVRVSTDPEQVTFEDVVVGESQEEWGQLKPAQRTLYRDVMLDTFRLLVSVGH WLPKPNVISLLEQEAELWAVESRLPQ
756	ZN778_HUMAN	EQTQAAGMVAGWLINCYQDAVTEDDVAVDETQEEWTLLDPSQRDLYRDVMLENY ENLASVEWRLKTKGPALRQDRSWFRA
757	RYBP_HUMAN	PSEANSIQSANATTKTSETNHTSRPRLKNVDRSTAQQLAVTVGNVTVIITDEKE KTRSSSTSSSTVTSSAGSEQQNQSSS
758	ZN534_HUMAN	ALTQGQLSESDVAIEFSQEEWKCLDPGQKALYRDVMLENYRNLVSLGEDNVRPE ACICSGICLPDLSVTSMLEQKRDPWT
759	ZN586_HUMAN	AAAAALRAPAQSSVTFEDVAVNESLEEWSLLNEAQRCLYRDVMLETLTLISSLG CWHGGEDEAAPSKQSTCIHIYKDQGG
760	ZN567_HUMAN	AQGSVSFNDVTVDFTQEEWQHLDHAQKTLYMDVMLENYCHLISVGCHMTKPDVI LKLERGEEPWTSFAGHTCLEENWKAE
761	ZN440_HUMAN	DPVAFKDVAVNFTQEEWALLDISQRKLYREVMLETERNLTSLGKRWKDQNIEYE HQNPRRNERSLIEEKVNEIKDDSHCG
762	ZN583_HUMAN	SKDLVTFGDVAVNESQEEWEWLNPAQRNLYRKVMLENYRSLVSLGVSVSKPDVI SLLEQGKEPWMVKKEGTRGPCPDWEY
763	ZN441_HUMAN	DSVAFEDVAINFTCEEWALLGPSQKSLYRDVMQETIRNLDCIGMIWQNHDIEED QYKDLRRNLRCHMVERACEIKDNSQC
764	ZNF43_HUMAN	GPLTEMDVAIEFCLEEWQCLDIAQQNLYRNVMLENYRNLVELGIAVSKPDLITC LEQEKEPWEPMRRHEMVAKPPVMCSH
765	CBX5_HUMAN	QSNDIARGFERGLEPEKIIGATDSCGDLMFLMKWKDTDEADLVLAKEANVKCPQ IVIAFYEERLTWHAYPEDAENKEKET
766	ZN589_HUMAN	ALPAKDSAWPWEEKPRYLGPVTFEDVAVLFTEAEWKRLSLEQRNLYKEVMLENL RNLVSLAESKPEVHTCPSCPLAFGSQ
767	ZNF10_HUMAN	DAKSLTAWSRTLVTFKDVFVDFTREEWKLLDTAQQIVYRNVMLENYKNLVSLGY QLTKPDVILRLEKGEEPWLVEREIHQ
768	ZN563_HUMAN	DAVAFEDVAVNETQEEWALLGPSQKNLYRYVMQETIRNLDCIRMIWEEQNTEDQ YKNPRRNLRCHMVERFSESKDSSQCG
769	ZN561_HUMAN	EKTKVERMVEDYLASGYQDSVTFDDVAVDETPEEWALLDTTEKYLYRDVMLENY MNLASVEWEIQPRTKRSSLQQGFLKN
770	ZN136_HUMAN	DSVAFEDVDVNFTQEEWALLDPSQKNLYRDVMWETMRNLASIGKKWKDQNIKDH YKHRGRNLRSHMLERLYQTKDGSQRG
771	ZN630_HUMAN	IESQEPVTFEDVAVDETQEEWQQLNPAQKTLHRDVMLETYNHLVSVGCSGIKPD VIFKLEHGKDPWIIESELSRWIYPDR
772	ZN527_HUMAN	AVGLCKAMSQGLVTERDVALDESQEEWEWLKPSQKDLYRDVMLENYRNLVWLGL SISKPNMISLLEQGKEPWMVERKMSQ
773	ZN333_HUMAN	DKVEEEAMAPGLPTACSQEPVTFADVAVVETPEEWVELDSTQRSLYRDVMLENY RNLASVADQLCKPNALSYLEERGEQW
774	Z324B_HUMAN	TFEDVAVYFSQEEWGLLDTAQRALYRHVMLENFTLVTSLGLSTSRPRVVIQLER GEEPWVPSGKDMTLARNTYGRLNSGS
775	ZN786_HUMAN	AEPPRLPLTFEDVAIYFSEQEWQDLEAWQKELYKHVMRSNYETLVSLDDGLPKP ELISWIEHGGEPERKWRESQKSGNII

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
776	ZN709_HUMAN	DSVVFEDVAVNETQEEWALLGPSQKKLYRDVMQETFVNLASIGENWEEKNIEDH KNQGRKLRSHMVERLCERKEGSQFGE
777	ZN792_HUMAN	AAAALRDPAQGCVTFEDVTIYFSQEEWVLLDEAQRLLYCDVMLENFALIASLGL ISFRSHIVSQLEMGKEPWVPDSVDMT
778	ZN599_HUMAN	AAPALALVSFEDVVVTFTGEEWGHLDLAQRTLYQEVMLETCRLLVSLGHPVPKP ELIYLLEHGQELWTVKRGLSQSTCAG
779	ZN613_HUMAN	IKSQESLTLEDVAVEFTWEEWQLLGPAQKDLYRDVMLENYSNLVSVGYQASKPD ALFKLEQGEPWTVENEIHSQICPEIK
780	ZF69B_HUMAN	GESLESRVTLGSLTAESQELLTFKDVSVDFTQEEWGQLAPAHRNLYREVMLENY GNLVSVGCQLSKPGVISQLEKGEEPW
781	ZN799_HUMAN	ASVALEDVAVNFTREEWALLGPCQKNLYKDVMQETIRNLDCVGMKWKDQNIEDQ YRYPRKNLRCRMLERFVESKDGTQCG
782	ZN569_HUMAN	TESQGTVTFKDVAIDFTQEEWKRLDPAQRKLYRNVMLENYNNLITVGYPFTKPD VIFKLEQEEEPWVMEEEVLRRHWQGE
783	ZN564_HUMAN	DSVASEDVAVNETLEEWALLDPSQKKLYRDVMRETFRNLACVGKKWEDQSIEDW YKNQGRILRNHMEEGLSESKEYDQCG
784	ZN546_HUMAN	EETQGELTSSCGSKTMANVSLAFRDVSIDLSQEEWECLDAVQRDLYKDVMLENY SNLVSLGYTIPKPDVITLLEQEKEPW
785	ZFP92_HUMAN	AAILLTTRPKVPVSFEDVSVYFTKTEWKLLDLRQKVLYKRVMLENYSHLVSLGF SFSKPHLISQLERGEGPWVADIPRTW
786	YAF2_HUMAN	KDKVEKEKSEKETTSKKNSHKKTRPRLKNVDRSSAQHLEVTVGDLTVIITDEKE KTKSPPASSAASADQHSQSGSSSDNT
787	ZN723_HUMAN	GPLTFTDVAIKESLEEWQFLDTAQQNLYRDVMLENYRNLVFLGVGVSKPDLITC LEQGKEPWNMKRHKMVAKPPVVCSHE
788	ZNF34_HUMAN	RKPNPQAMAALFLSAPPQAEVTFEDVAVYLSREEWGRLGPAQRGLYRDVMLETY GNLVSLGVGPAGPKPGVISQLERGDE
789	ZN439_HUMAN	LSLSPILLYTCEMFQDPVAFKDVAVNETQEEWALLDISQKNLYREVMLETFWNL TSIGKKWKDQNIEYEYQNPRRNERSV
790	ZFP57_HUMAN	AAGEPRSLLFFQKPVTFEDVAVNFTQEEWDCLDASQRVLYQDVMSETEKNLTSV ARIFLHKPELITKLEQEEEQWRETRV
791	ZNF19_HUMAN	AAMPLKAQYQEMVTFEDVAVHFTKTEWTGLSPAQRALYRSVMLENEGNLTALGY PVPKPALISLLERGDMAWGLEAQDDP
792	ZN404_HUMAN	ARVPLTESDVAIDESQEEWEYLNSDQRDLYRDVMLENYTNLVSLDENFTTESNK LSSEKRNYEVNAYHQETWKRNKTENL
793	ZN274_HUMAN	ASRLPTAWSCEPVTFEDVTLGFTPEEWGLLDLKQKSLYREVMLENYRNLVSVEH QLSKPDVVSQLEEAEDFWPVERGIPQ
794	CBX3_HUMAN	SKKKRDAADKPRGFARGLDPERIIGATDSSGELMFLMKWKDSDEADLVLAKEAN MKCPQIVIAFYEERLTWHSCPEDEAQ
795	ZNF30_HUMAN	AHKYVGLQYHGSVTFEDVAIAFSQQEWESLDSSQRGLYRDVMLENYRNLVSMGH SRSKPHVIALLEQWKEPEVTVRKDGR
796	ZN250_HUMAN	AAARLLPVPAGPQPLSFQAKLTFEDVAVLLSQDEWDRLCPAQRGLYRNVMMETY GNVVSLGLPGSKPDIISQLERGEDPW
797	ZN570_HUMAN	AVGLLKAMYQELVTERDVAVDESQEEWDCLDSSQRHLYSNVMLENYRILVSLGL CFSKPSVILLLEQGKAPWMVKRELTK
798	ZN675_HUMAN	GLLTERDVAIEFSLEEWQCLDTAQRNLYKNVILENYRNLVELGIAVSKQDLITC LEQEKEPLTVKRHEMVNEPPVMCSHF
799	ZN695_HUMAN	GLLAFRDVALEFSPEEWECLDPAQRSLYRDVMLENYRNLISLGEDSENMQFLFH SLAMSKPELIICLEARKEPWNVNTEK
800	ZN548_HUMAN	NLTEGRVVFEDVAIYFSQEEWGHLDEAQRLLYRDVMLENLALLSSLGSWHGAED EEAPSQQGFSVGVSEVTASKPCLSSQ

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
801	ZN132_HUMAN	GPAQHTSWPCGSAVPTLKSMVTFEDVAVYFSQEEWELLDAAQRHLYHSVMLENL ELVTSLGSWHGVEGEGAHPKQNVSVE
802	ZN738_HUMAN	SGYPGAERNLLEYSYFEKGPLTFRDVVIEFSQEEWQCLDTAQQDLYRKVMLENF RNLVFLGIDVSKPDLITCLEQGKDPW
803	ZN420_HUMAN	ARKLVMFRDVAIDESQEEWECLDSAQRDLYRDVMLENYSNLVSLDLPSRCASKD LSPEKNTYETELSQWEMSDRLENCDL
804	ZN626_HUMAN	GPLQFRDVAIEFSLEEWHCLDTAQRNLYRNVMLENYSNLVELGITVSKPDLITC LEQGRKPLTMKRNEMIAKPSVMCSHF
805	ZN559_HUMAN	VAGWLTNYSQDSVTFEDVAVDETQEEWTLLDQTQRNLYRDVMLENYKNLVAVDW ESHINTKWSAPQQNFLQGKTSSVVEM
806	ZN460_HUMAN	AAAWMAPAQESVTFEDVAVTFTQEEWGQLDVTQRALYVEVMLETCGLLVALGDS TKPETVEPIPSHLALPEEVSLQEQLA
807	ZN268_HUMAN	VLEWLFISQEQPKITKSWGPLSFMDVFVDFTWEEWQLLDPAQKCLYRSVMLENY SNLVSLGYQHTKPDIIFKLEQGEELC
808	ZN304_HUMAN	AAAVLMDRVQSCVTFEDVEVYFSREEWELLEEAQRFLYRDVMLENFALVATLGE WCEAEHEAPSEQSVSVEGVSQVRTAE
809	ZIM2_HUMAN	AGSQFPDFKHLGTFLVFEELVTFEDVLVDESPEELSSLSAAQRNLYREVMLENY RNLVSLGHQFSKPDIISRLEEEESYA
810	ZN605_HUMAN	IQSQISFEDVAVDFTLEEWQLLNPTQKNLYRDVMLENYSNLVELEVWLDNPKMW LRDNQDNLKSMERGHKYDVFGKIENS
811	ZN844_HUMAN	DLVAFEDVAVNFTQEEWSLLDPSQKNLYREVMQETLRNLASIGEKWKDQNIEDQ YKNPRNNLRSLLGERVDENTEENHCG
812	SUMO5_HUMAN	KDEDIKLRVIGQDSSEIHFKVKMTTPLKKLKKSYCQRQGVPVNSLRELFEGQRI ADNHTPEELGMEEEDVIEVYQEQIGG
813	ZN101_HUMAN	DSVAFEDVAVNFTQEEWALLSPSQKNLYRDVTLETERNLASVGIQWKDQDIENL YQNLGIKLRSLVERLCGRKEGNEHRE
814	ZN783_HUMAN	RNFWILRLPPGSKGEAPKVPVTEDDVAVYFSELEWGKLEDWQKELYKHVMRGNY ETLVSLDYAISKPDILTRIERGEEPC
815	ZN417_HUMAN	AAAAPRRPTQQGTVTFEDVAVNFSQEEWCLLSEAQRCLYRDVMLENLALISSLG CWCGSKDEEAPCKQRISVQRESQSRT
816	ZN182_HUMAN	SGEDSGSFYSWQKAKREQGLVTFEDVAVDETQEEWQYLNPPQRTLYRDVMLETY SNLVFVGQQVTKPNLILKLEVEECPA
817	ZN823_HUMAN	DSVAFEDVAVNFTQEEWALLGPSQKSLYRNVMQETIRNLDCIEMKWEDQNIGDQ CQNAKRNLRSHTCEIKDDSQCGETFG
818	ZN177_HUMAN	AAGWLTTWSQNSVTFQEVAVDFSQEEWALLDPAQKNLYKDVMLENERNLASVGY QLCRHSLISKVDQEQLKTDERGILQG
819	ZN197_HUMAN	ENPRNQLMALMLLTAQPQELVMFEEVSVCFTSEEWACLGPIQRALYWDVMLENY GNVTSLEWETMTENEEVTSKPSSSQR
820	ZN717_HUMAN	LETYNSLVSLQELVSFEEVAVHFTWEEWQDLDDAQRTLYRDVMLETYSSLVSLG HCITKPEMIFKLEQGAEPWIVEETPN
821	ZN669_HUMAN	RHFRRPEPCREPLASPIQDSVAFEDVAVNFTQEEWALLDSSQKNLYREVMQETC RNLASVGSQWKDQNIEDHFEKPGKDI
822	ZN256_HUMAN	AAAELTAPAQGIVTFEDVAVYFSWKEWGLLDEAQKCLYHDVMLENLTLTTSLGG SGAGDEEAPYQQSTSPQRVSQVRIPK
823	ZN251_HUMAN	AATFQLPGHQEMPLTFQDVAVYFSQAEGRQLGPQQRALYRDVMLENYGNVASLG FPVPKPELISQLEQGKELWVLNLLGA
824	CBX4_HUMAN	RSEAGEPPSSLQVKPETPASAAVAVAAAAAPTTTAEKPPAEAQDEPAESLSEFK PFFGNIIITDVTANCLTVTFKEYVTV
825	PCGF2_HUMAN	HRTTRIKITELNPHLMCALCGGYFIDATTIVECLHSFCKTCIVRYLETNKYCPM CDVQVHKTRPLLSIRSDKTLQDIVYK

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
826	CDY2_HUMAN	ASQEFEVEAIVDKRQDKNGNTQYLVRWKGYDKQDDTWEPEQHLMNCEKCVHDEN RRQTEKQKKLTWTTTSRIFSNNARRR
827	CDYL2_HUMAN	ASGDLYEVERIVDKRKNKKGKWEYLIRWKGYGSTEDTWEPEHHLLHCEEFIDEF NGLHMSKDKRIKSGKQSSTSKLLRDS
828	HERC2_HUMAN	TLIRKADLENHNKDGGFWTVIDGKVYDIKDFQTQSLTGNSILAQFAGEDPVVAL EAALQFEDTRESMHAFCVGQYLEPDQ
829	ZN562_HUMAN	EKTKIGTMVEDHRSNSYQDSVTEDDVAVEFTPEEWALLDTTQKYLYRDVMLENY MNLASVDFFFCLTSEWEIQPRTKRSS
830	ZN461_HUMAN	AHELVMERDVAIDVSQEEWECLNPAQRNLYKEVMLENYSNLVSLGLSVSKPAVI SSLEQGKEPWMVVREETGRWCPGTWK
831	Z324A HUMAN	AFEDVAVYFSQEEWGLLDTAQRALYRRVMLDNFALVASLGLSTSRPRVVIQLER GEEPWVPSGTDTTLSRTTYRRRNPGS
832	ZN766_HUMAN	AQLRRGHLTFRDVAIEFSQEEWKCLDPVQKALYRDVMLENYRNLVSLGICLPDL SIISMMKQRTEPWTVENEMKVAKNPD
833	ID2_HUMAN	SDHSLGISRSKTPVDDPMSLLYNMNDCYSKLKELVPSIPQNKKVSKMEILQHVI DYILDLQIALDSHPTIVSLHHQRPGQ
834	TOX_HUMAN	KDPNEPQKPVSAYALFFRDTQAAIKGQNPNATFGEVSKIVASMWDGLGEEQKQV YKKKTEAAKKEYLKQLAAYRASLVSK
835	ZN274_HUMAN	QEEKQEDAAICPVTVLPEEPVTFQDVAVDESREEWGLLGPTQRTEYRDVMLETE GHLVSVGWETTLENKELAPNSDIPEE
836	SCMH1_HUMAN	DASRLSGRDPSSWTVEDVMQFVREADPQLGPHADLERKHEIDGKALLLLRSDMM MKYMGLKLGPALKLSYHIDRLKQGKE
837	ZN214_HUMAN	AVTFEDVTIIFTWEEWKFLDSSQKRLYREVMWENYTNVMSVENWNESYKSQEEK FRYLEYENFSYWQGWWNAGAQMYENQ
838	CBX7_HUMAN	ELSAIGEQVFAVESIRKKRVRKGKVEYLVKWKGWPPKYSTWEPEEHILDPRLVM AYEEKEERDRASGYRKRGPKPKRLLL
839	ID1_HUMAN	GGAGARLPALLDEQQVNVLLYDMNGCYSRLKELVPTLPQNRKVSKVEILQHVID YIRDLQLELNSESEVGTPGGRGLPVR
840	CREM_HUMAN	VVMAASPGSLHSPQQLAEEATRKRELRLMKNREAAKECRRRKKEYVKCLESRVA VLEVQNKKLIEELETLKDICSPKTDY
841	SCX_HUMAN	GGGPGGRPGREPRQRHTANARERDRTNSVNTAFTALRTLIPTEPADRKLSKIET LRLASSYISHLGNVLLAGEACGDGQP
842	ASCL1_HUMAN	SGFGYSLPQQQPAAVARRNERERNRVKLVNLGFATLREHVPNGAANKKMSKVET LRSAVEYIRALQQLLDEHDAVSAAFQ
843	ZN764_HUMAN	APLPPRDPNGAGPEWREPGAVSFADVAVYFCREEWGCLRPAQRALYRDVMRETY GHLSALGIGGNKPALISWVEEEAELW
844	SCML2_HUMAN	KQGFSKDPSTWSVDEVIQFMKHTDPQISGPLADLERQHEIDGKALFLLKSDVMM KYMGLKLGPALKLCYYIEKLKEGKYS
845	TWST1_HUMAN	SGGGSPQSYEELQTQRVMANVRERQRTQSLNEAFAALRKIIPTLPSDKLSKIQT LKLAARYIDFLYQVLQSDELDSKMAS
846	CREB1_HUMAN	IAPGVVMASSPALPTQPAEEAARKREVRLMKNREAARECRRKKKEYVKCLENRV AVLENQNKTLIEELKALKDLYCHKSD
847	TERF1_HUMAN	SRIPVSKSQPVTPEKHRARKRQAWLWEEDKNLRSGVRKYGEGNWSKILLHYKEN NRTSVMLKDRWRTMKKLKLISSDSED
848	ID3_HUMAN	SLAIARGRGKGPAAEEPLSLLDDMNHCYSRLRELVPGVPRGTQLSQVEILQRVI DYILDLQVVLAEPAPGPPDGPHLPIQ
849	CBX8_HUMAN	GSGPPSSGGGLYRDMGAQGGRPSLIARIPVARILGDPEEESWSPSLTNLEKVVV TDVTSNFLTVTIKESNTDQGFFKEKR
850	CBX4_HUMAN	ELPAVGEHVFAVESIEKKRIRKGRVEYLVKWRGWSPKYNTWEPEENILDPRLLI AFQNRERQEQLMGYRKRGPKPKPLVV

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
851	GSX1_HUMAN	VDSSSNQLPSSKRMRTAFTSTQLLELEREFASNMYLSRLRRIEIATYLNLSEKQ VKIWFQNRRVKHKKEGKGSNHRGGGG
852	NKX22_HUMAN	TPGGGGDAGKKRKRRVLFSKAQTYELERRFRQQRYLSAPEREHLASLIRLTPTQ VKIWFQNHRYKMKRARAEKGMEVTPL
853	ATF1_HUMAN	QTVVMTSPVTLTSQTTKTDDPQLKREIRLMKNREAARECRRKKKEYVKCLENRV AVLENQNKTLIEELKTLKDLYSNKSV
854	TWST2_HUMAN	KGSPSAQSFEELQSQRILANVRERQRTQSLNEAFAALRKIIPTLPSDKLSKIQT LKLAARYIDFLYQVLQSDEMDNKMTS
855	ZNF17_HUMAN	NLTEDYMVFEDVAIHFSQEEWGILNDVQRHLHSDVMLENFALLSSVGCWHGAKD EEAPSKQCVSVGVSQVTTLKPALSTQ
856	TOX3_HUMAN	KDPNEPQKPVSAYALFFRDTQAAIKGQNPNATFGEVSKIVASMWDSLGEEQKQV YKRKTEAAKKEYLKALAAYRASLVSK
857	TOX4_HUMAN	KDPNEPQKPVSAYALFERDTQAAIKGQNPNATFGEVSKIVASMWDSLGEEQKQV YKRKTEAAKKEYLKALAAYKDNQECQ
858	ZMYM3_HUMAN	LDGSTWDFCSEDCKSKYLLWYCKAARCHACKRQGKLLETIHWRGQIRHFCNQQC LLRFYSQQNQPNLDTQSGPESLLNSQ
859	12BP1_HUMAN	ASVQASRRQWCYLCDLPKMPWAMVWDESEAVCRGCVNFEGADRIELLIDAARQL KRSHVLPEGRSPGPPALKHPATKDLA
860	RHXF1_HUMAN	MEGPQPENMQPRTRRTKFTLLQVEELESVFRHTQYPDVPTRRELAENLGVTEDK VRVWFKNKRARCRRHQRELMLANELR
861	SSX2_HUMAN	PKIMPKKPAEEGNDSEEVPEASGPQNDGKELCPPGKPTTSEKIHERSGPKRGEH AWTHRLRERKQLVIYEEISDPEEDDE
862	12BPL_HUMAN	SAAQVSSSRRQSCYLCDLPRMPWAMIWDESEPVCRGCVNYEGADRIEFVIETAR QLKRAHGCFQDGRSPGPPPPVGVKTV
863	ZN680_HUMAN	PGPPGSLEMGPLTFRDVAIEFSLEEWQCLDTAQRNLYRKVMFENYRNLVELGIA VSKPHLITCLEQGKEPWNRKRQEMVA
864	CBX1_HUMAN	NKKKVEEVLEEEEEEYVVEKVLDRRVVKGKVEYLLKWKGFSDEDNTWEPEENLD CPDLIAEFLQSQKTAHETDKSEGGKR
865	TRI68 HUMAN	LANVVEKVRLLRLHPGMGLKGDLCERHGEKLKMFCKEDVLIMCEACSQSPEHEA HSVVPMEDVAWEYKWELHEALEHLKK
866	HXA13_HUMAN	VVSHPSDASSYRRGRKKRVPYTKVQLKELEREYATNKFITKDKRRRISATTNLS ERQVTIWFQNRRVKEKKVINKLKTTS
867	PHC3_HUMAN	ENSDLLPVAQTEPSIWTVDDVWAFIHSLPGCQDIADEFRAQEIDGQALLLLKED HLMSAMNIKLGPALKICARINSLKES
868	TCF24_HUMAN	AGPGGGSRSGSGRPAAANAARERSRVQTLRHAFLELQRTLPSVPPDTKLSKLDV LLLATTYIAHLTRSLQDDAEAPADAG
869	CBX3_HUMAN	QNGKSKKVEEAEPEEFVVEKVLDRRVVNGKVEYFLKWKGFTDADNTWEPEENLD CPELIEAFLNSQKAGKEKDGTKRKSL
870	HXB13_HUMAN	QHPPDACAFRRGRKKRIPYSKGQLRELEREYAANKFITKDKRRKISAATSLSER QITIWFQNRRVKEKKVLAKVKNSATP
871	HEY1_HUMAN	SMSPTTSSQILARKRRRGIIEKRRRDRINNSLSELRRLVPSAFEKQGSAKLEKA EILQMTVDHLKMLHTAGGKGYFDAHA
872	PHC2_HUMAN	LVGMGHHELPSEPTKWNVEDVYEFIRSLPGCQEIAEEFRAQEIDGQALLLLKED HLMSAMNIKLGPALKIYARISMLKDS
873	ZNF81_HUMAN	PANEDAPQPGEHGSACEVSVSFEDVTVDESREEWQQLDSTQRRLYQDVMLENYS HLLSVGFEVPKPEVIFKLEQGEGPWT
874	FIGLA_HUMAN	GYSSTENLQLVLERRRVANAKERERIKNLNRGFARLKALVPFLPQSRKPSKVDI LKGATEYIQVLSDLLEGAKDSKKQDP
875	SAM11_HUMAN	EEAPAPEDVTKWTVDDVCSFVGGLSGCGEYTRVFREQGIDGETLPLLTEEHLLT NMGLKLGPALKIRAQVARRLGRVFYV

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
876	KMT2B_HUMAN	GGTLAHTPRRSLPSHHGKKMRMARCGHCRGCLRVQDCGSCVNCLDKPKFGGPNT KKQCCVYRKCDKIEARKMERLAKKGR
877	HEY2_HUMAN	LNSPTTTSQIMARKKRRGIIEKRRRDRINNSLSELRRLVPTAFEKQGSAKLEKA EILQMTVDHLKMLQATGGKGYFDAHA
878	JDP2_HUMAN	QPVKSELDEEEERRKRRREKNKVAAARCRNKKKERTEFLQRESERLELMNAELK TQIEELKQERQQLILMLNRHRPTCIV
879	HXC13_HUMAN	LQPEVSSYRRGRKKRVPYTKVQLKELEKEYAASKFITKEKRRRISATTNLSERQ VTIWFQNRRVKEKKVVSKSKAPHLHS
880	ASCL4_HUMAN	LPVPLDSAFEPAFLRKRNERERQRVRCVNEGYARLRDHLPRELADKRLSKVETL RAAIDYIKHLQELLERQAWGLEGAAG
881	HHEX_HUMAN	SPFLQRPLHKRKGGQVRESNDQTIELEKKFETQKYLSPPERKRLAKMLQLSERQ VKTWFQNRRAKWRRLKQENPQSNKKE
882	HERC2_HUMAN	IAIATGSLHCVCCTEDGEVYTWGDNDEGQLGDGTTNAIQRPRLVAALQGKKVNR VACGSAHTLAWSTSKPASAGKLPAQV
883	GSX2_HUMAN	GGSDASQVPNGKRMRTAFTSTQLLELEREFSSNMYLSRLRRIEIATYLNLSEKQ VKIWFQNRRVKHKKEGKGTQRNSHAG
884	BIN1_HUMAN	RLDLPPGFMFKVQAQHDYTATDTDELQLKAGDVVLVIPFQNPEEQDEGWLMGVK ESDWNQHKELEKCRGVFPENFTERVP
885	ETV7_HUMAN	GICKLPGRLRIQPALWSREDVLHWLRWAEQEYSLPCTAEHGFEMNGRALCILTK DDERHRAPSSGDVLYELLQYIKTQRR
886	ASCL3_HUMAN	PNYRGCEYSYGPAFTRKRNERERQRVKCVNEGYAQLRHHLPEEYLEKRLSKVET LRAAIKYINYLQSLLYPDKAETKNNP
887	PHC1_HUMAN	LHGINPVFLSSNPSRWSVEEVYEFIASLQGCQEIAEEFRSQEIDGQALLLLKEE HLMSAMNIKLGPALKICAKINVLKET
888	OTP_HUMAN	QAGQQQGQQKQKRHRTRFTPAQLNELERSFAKTHYPDIFMREELALRIGLTESR VQVWFQNRRAKWKKRKKTTNVFRAPG
889	12BP2_HUMAN	AAAVAVAAASRRQSCYLCDLPRMPWAMIWDFTEPVCRGCVNYEGADRVEFVIET ARQLKRAHGCFPEGRSPPGAAASAAA
890	VGLL2_HUMAN	FSSQTPASIKEEEGSPEKERPPEAEYINSRCVLFTYFQGDISSVVDEHESRALS QPSSYSPSCTSSKAPRSSGPWRDCSF
891	HXA11_HUMAN	DKAGGSSGQRTRKKRCPYTKYQIRELEREFFFSVYINKEKRLQLSRMLNLTDRQ VKIWFQNRRMKEKKINRDRLQYYSAN
892	PDLI4_HUMAN	GAPLSGLQGLPECTRCGHGIVGTIVKARDKLYHPECFMCSDCGLNLKQRGYFFL DERLYCESHAKARVKPPEGYDVVAVY
893	ASCL2_HUMAN	RRPATAETGGGAAAVARRNERERNRVKLVNLGFQALRQHVPHGGASKKLSKVET LRSAVEYIRALQRLLAEHDAVRNALA
894	CDX4_HUMAN	TVQVTGKTRTKEKYRVVYTDHQRLELEKEFHCNRYITIQRKSELAVNLGLSERQ VKIWFQNRRAKERKMIKKKISQFENS
895	ZN860_HUMAN	EEAAQKRKEKEPGMALPQGHLTFRDVAIEFSLEEWKCLDPTQRALYRAMMLENY RNLHSVDISSKCMMKKESSTAQGNTE
896	LMBL4_HUMAN	DIRASQVARWTVDEVAEFVQSLLGCEEHAKCFKKEQIDGKAFLLLTQTDIVKVM KIKLGPALKIYNSILMFRHSQELPEE
897	PDIP3_HUMAN	LSPLEGTKMTVNNLHPRVTEEDIVELFCVCGALKRARLVHPGVAEVVFVKKDDA ITAYKKYNNRCLDGQPMKCNLHMNGN
898	NKX25_HUMAN	DNAERPRARRRRKPRVLESQAQVYELERRFKQQRYLSAPERDQLASVLKLTSTQ VKIWFQNRRYKCKRQRQDQTLELVGL
899	CEBPB_HUMAN	SQVKSKAKKTVDKHSDEYKIRRERNNIAVRKSRDKAKMRNLETQHKVLELTAEN ERLQKKVEQLSRELSTLRNLFKQLPE
900	ISL1_HUMAN	KRDYIRLYGIKCAKCSIGFSKNDFVMRARSKVYHIECFRCVACSRQLIPGDEFA LREDGLFCRADHDVVERASLGAGDPL

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
901	CDX2_HUMAN	SLGSQVKTRTKDKYRVVYTDHQRLELEKEFHYSRYITIRRKAELAATLGLSERQ VKIWFQNRRAKERKINKKKLQQQQQQ
902	PROP1_HUMAN	QGGQRGRPHSRRRHRTTESPVQLEQLESAFGRNQYPDIWARESLARDTGLSEAR IQVWFQNRRAKQRKQERSLLQPLAHL
903	SIN3B_HUMAN	DALTYLDQVKIRFGSDPATYNGFLEIMKEFKSQSIDTPGVIRRVSQLFHEHPDL IVGFNAFLPLGYRIDIPKNGKLNIQS
904	SMBT1_HUMAN	RLHLDSNPLKWSVADVVRFIRSTDCAPLARIFLDQEIDGQALLLLTLPTVQECM DLKLGPAIKLCHHIERIKFAFYEQFA
905	HXC11_HUMAN	AKGAAPNAPRTRKKRCPYSKFQIRELEREFFENVYINKEKRLQLSRMLNLTDRQ VKIWFQNRRMKEKKLSRDRLQYFSGN
906	HXC10_HUMAN	TTGNWLTAKSGRKKRCPYTKHQTLELEKEFLENMYLTRERRLEISKTINLTDRQ VKIWFQNRRMKLKKMNRENRIRELTS
907	PRS6A_HUMAN	YLVSNVIELLDVDPNDQEEDGANIDLDSQRKGKCAVIKTSTRQTYFLPVIGLVD AEKLKPGDLVGVNKDSYLILETLPTE
908	VSX1_HUMAN	KASPTLGKRKKRRHRTVFTAHQLEELEKAFSEAHYPDVYAREMLAVKTELPEDR IQVWFQNRRAKWRKREKRWGGSSVMA
909	NKX23_HUMAN	EESERPKPRSRRKPRVLESQAQVFELERRFKQQRYLSAPEREHLASSLKLTSTQ VKIWFQNRRYKCKRQRQDKSLELGAH
910	MTG16_HUMAN	VVPGSRQEEVIDHKLTEREWAEEWKHLNNLLNCIMDMVEKTRRSLTVLRRCQEA DREELNHWARRYSDAEDTKKGPAPAA
911	HMX3_HUMAN	ESPEKKPACRKKKTRTVFSRSQVFQLESTFDMKRYLSSSERAGLAASLHLTETQ VKIWFQNRRNKWKRQLAAELEAANLS
912	HMX1_HUMAN	RGGVGVGGGRKKKTRTVESRSQVFQLESTEDLKRYLSSAERAGLAASLQLTETQ VKIWFQNRRNKWKRQLAAELEAASLS
913	KIF22_HUMAN	ELLAHGRQKILDLLNEGSARDLRSLQRIGPKKAQLIVGWRELHGPESQVEDLER VEGITGKQMESFLKANILGLAAGQRC
914	CSTF2_HUMAN	ESPYGETISPEDAPESISKAVASLPPEQMFELMKQMKLCVQNSPQEARNMLLQN PQLAYALLQAQVVMRIVDPEIALKIL
915	CEBPE_HUMAN	AGPLHKGKKAVNKDSLEYRLRRERNNIAVRKSRDKAKRRILETQQKVLEYMAEN ERLRSRVEQLTQELDTLRNLFRQIPE
916	DLX2_HUMAN	IRIVNGKPKKVRKPRTIYSSFQLAALQRRFQKTQYLALPERAELAASLGLTQTQ VKIWFQNRRSKFKKMWKSGEIPSEQH
917	ZMYM3_HUMAN	TVYQFCSPSCWTKFQRTSPEGGIHLSCHYCHSLFSGKPEVLDWQDQVFQFCCRD CCEDFKRLRGVVSQCEHCRQEKLLHE
918	PPARG_HUMAN	TMVDTEMPFWPTNFGISSVDLSVMEDHSHSFDIKPFTTVDESSISTPHYEDIPF TRTDPVVADYKYDLKLQEYQSAIKVE
919	PRIC1_HUMAN	GRHHAELLKPRCSACDEIIFADECTEAEGRHWHMKHFCCLECETVLGGQRYIMK DGRPFCCGCFESLYAEYCETCGEHIG
920	UNC4_HUMAN	DPDKESPGCKRRRTRTNFTGWQLEELEKAFNESHYPDVEMREALALRLDLVESR VQVWFQNRRAKWRKKENTKKGPGRPA
921	BARX2_HUMAN	TEQPTPRQKKPRRSRTIFTELQLMGLEKKFQKQKYLSTPDRLDLAQSLGLTQLQ VKTWYQNRRMKWKKMVLKGGQEAPTK
922	ALX3_HUMAN	SMELAKNKSKKRRNRTTFSTFQLEELEKVFQKTHYPDVYAREQLALRTDLTEAR VQVWFQNRRAKWRKRERYGKIQEGRN
923	TCF15_HUMAN	GGGGGAGPVVVVRQRQAANARERDRTQSVNTAFTALRTLIPTEPVDRKLSKIET VRLASSYIAHLANVLLLGDSADDGQP
924	TERA_HUMAN	IDDTVEGITGNLFEVYLKPYFLEAYRPIRKGDIFLVRGGMRAVEFKVVETDPSP YCIVAPDTVIHCEGEPIKREDEEESL
925	VSX2_HUMAN	SALNQTKKRKKRRHRTIFTSYQLEELEKAFNEAHYPDVYAREMLAMKTELPEDR IQVWFQNRRAKWRKREKCWGRSSVMA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
926	HXD12_HUMAN	DGLPWGAAPGRARKKRKPYTKQQIAELENEFLVNEFINRQKRKELSNRLNLSDQ QVKIWFQNRRMKKKRVVLREQALALY
927	CDX1_HUMAN	GGGGSGKTRTKDKYRVVYTDHQRLELEKEFHYSRYITIRRKSELAANLGLTERQ VKIWFQNRRAKERKVNKKKQQQQQPP
928	TCF23_HUMAN	TRAGGLALGRSEASPENAARERSRVRTLRQAFLALQAALPAVPPDTKLSKLDVL VLAASYIAHLTRTLGHELPGPAWPPE
929	ALX1_HUMAN	KCDSNVSSSKKRRHRTTFTSLQLEELEKVFQKTHYPDVYVREQLALRTELTEAR VQVWFQNRRAKWRKRERYGQIQQAKS
930	HXA10_HUMAN	NAANWLTAKSGRKKRCPYTKHQTLELEKEFLENMYLTRERRLEISRSVHLTDRQ VKIWFQNRRMKLKKMNRENRIRELTA
931	RX_HUMAN	LSEEEQPKKKHRRNRTTFTTYQLHELERAFEKSHYPDVYSREELAGKVNLPEVR VQVWFQNRRAKWRRQEKLEVSSMKLQ
932	CXXC5_HUMAN	HMAGLAEYPMQGELASAISSGKKKRKRCGMCAPCRRRINCEQCSSCRNRKTGHQ ICKFRKCEELKKKPSAALEKVMLPTG
933	SCML1_HUMAN	SITKHPSTWSVEAVVLELKQTDPLALCPLVDLERSHEIDGKALLLLTSDVLLKH LGVKLGTAVKLCYYIDRLKQGKCFEN
934	NFIL3_HUMAN	ACRRKREFIPDEKKDAMYWEKRRKNNEAAKRSREKRRLNDLVLENKLIALGEEN ATLKAELLSLKLKFGLISSTAYAQEI
935	DLX6_HUMAN	EIRFNGKGKKIRKPRTIYSSLQLQALNHRFQQTQYLALPERAELAASLGLTQTQ VKIWFQNKRSKFKKLLKQGSNPHESD
936	MTG8_HUMAN	GLHGTRQEEMIDHRLTDREWAEEWKHLDHLLNCIMDMVEKTRRSLTVLRRCQEA DREELNYWIRRYSDAEDLKKGGGSSS
937	CBX8_HUMAN	ELSAVGERVFAAEALLKRRIRKGRMEYLVKWKGWSQKYSTWEPEENILDARLLA AFEEREREMELYGPKKRGPKPKTELL
938	CEBPD_HUMAN	AREKSAGKRGPDRGSPEYRQRRERNNIAVRKSRDKAKRRNQEMQQKLVELSAEN EKLHQRVEQLTRDLAGLRQFFKQLPS
939	SEC13_HUMAN	SGGCDNLIKLWKEEEDGQWKEEQKLEAHSDWVRDVAWAPSIGLPTSTIASCSQD GRVFIWTCDDASSNTWSPKLLHKEND
940	FIP1_HUMAN	VKGVDLDAPGSINGVPLLEVDLDSFEDKPWRKPGADLSDYENYGENEDTWKAYC EKQKRIRMGLEVIPVTSTINKITAED
941	ALX4_HUMAN	KADSESNKGKKRRNRTTFTSYQLEELEKVFQKTHYPDVYAREQLAMRTDLTEAR VQVWFQNRRAKWRKRERFGQMQQVRT
942	LHX3_HUMAN	TAKQREAEATAKRPRTTITAKQLETLKSAYNTSPKPARHVREQLSSETGLDMRV VQVWFQNRRAKEKRLKKDAGRQRWGQ
943	PRIC2_HUMAN	GRHHAECLKPRCAACDEIIFADECTEAEGRHWHMKHFCCFECETVLGGQRYIMK EGRPYCCHCFESLYAEYCDTCAQHIG
944	MAGI3_HUMAN	IIGGDRPDEFLQVKNVLKDGPAAQDGKIAPGDVIVDINGNCVLGHTHADVVQME QLVPVNQYVNLTLCRGYPLPDDSEDP
945	NELL1_HUMAN	CCPECDTRVTSQCLDQNGHKLYRSGDNWTHSCQQCRCLEGEVDCWPLTCPNLSC EYTAILEGECCPRCVSDPCLADNITY
946	PRRX1_HUMAN	LNSEEKKKRKQRRNRTTENSSQLQALERVFERTHYPDAFVREDLARRVNLTEAR VQVWFQNRRAKERRNERAMLANKNAS
947	MTG8R_HUMAN	GLNGGYQDELVDHRLTEREWADEWKHLDHALNCIMEMVEKTRRSMAVLRRCQES DREELNYWKRRYNENTELRKTGTELV
948	RAX2_HUMAN	GPGEEAPKKKHRRNRTTFTTYQLHQLERAFEASHYPDVYSREELAAKVHLPEVR VQVWFQNRRAKWRRQERLESGSGAVA
949	DLX3_HUMAN	VRMVNGKPKKVRKPRTIYSSYQLAALQRRFQKAQYLALPERAELAAQLGLTQTQ VKIWFQNRRSKFKKLYKNGEVPLEHS
950	DLX1_HUMAN	EVRENGKGKKIRKPRTIYSSLQLQALNRRFQQTQYLALPERAELAASLGLTQTQ VKIWFQNKRSKFKKLMKQGGAALEGS

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
951	NKX26_HUMAN	GRSEQPKARQRRKPRVLFSQAQVLALERRFKQQRYLSAPEREHLASALQLTSTQ VKIWFQNRRYKCKRQRQDKSLELAGH
952	NAB1_HUMAN	LPRTLGELQLYRILQKANLLSYFDAFIQQGGDDVQQLCEAGEEEFLEIMALVGM ASKPLHVRRLQKALRDWVTNPGLENQ
953	SAMD7_HUMAN	NLSLDEDIQKWTVDDVHSFIRSLPGCSDYAQVFKDHAIDGETLPLLTEEHLRGT MGLKLGPALKIQSQVSQHVGSMFYKK
954	PITX3_HUMAN	SPEDGSLKKKQRRQRTHFTSQQLQELEATFQRNRYPDMSTREEIAVWTNLTEAR VRVWFKNRRAKWRKRERSQQAELCKG
955	WDR5_HUMAN	SNLLVSASDDKTLKIWDVSSGKCLKTLKGHSNYVFCCNENPQSNLIVSGSFDES VRIWDVKTGKCLKTLPAHSDPVSAVH
956	MEOX2_HUMAN	GNYKSEVNSKPRKERTAFTKEQIRELEAEFAHHNYLTRLRRYEIAVNLDLTERQ VKVWFQNRRMKWKRVKGGQQGAAARE
957	NAB2_HUMAN	LPRTLGELQLYRVLQRANLLSYYETFIQQGGDDVQQLCEAGEEEFLEIMALVGM ATKPLHVRRLQKALREWATNPGLESQ
958	DHX8_HUMAN	PEEPTIGDIYNGKVTSIMQFGCFVQLEGLRKRWEGLVHISELRREGRVANVADV VSKGQRVKVKVLSFTGTKTSLSMKDV
959	FOXA2 HUMAN	YAFNHPFSINNLMSSEQQHHHSHHHHQPHKMDLKAYEQVMHYPGYGSPMPGSLA MGPVTNKTGLDASPLAADTSYYQGVY
960	CBX6_HUMAN	TAAAGPAPPTAPEPAGASSEPEAGDWRPEMSPCSNVVVTDVTSNLLTVTIKEFC NPEDFEKVAAGVAGAAGGGGSIGASK
961	EMX2_HUMAN	FLLHNALARKPKRIRTAFSPSQLLRLEHAFEKNHYVVGAERKQLAHSLSLTETQ VKVWFQNRRTKFKRQKLEEEGSDSQQ
962	CPSF6_HUMAN	KRIALYIGNLTWWTTDEDLTEAVHSLGVNDILEIKFFENRANGQSKGFALVGVG SEASSKKLMDLLPKRELHGQNPVVTP
963	HXC12_HUMAN	SGAPWYPINSRSRKKRKPYSKLQLAELEGEFLVNEFITRQRRRELSDRINLSDQ QVKIWFQNRRMKKKRLLLREQALSFF
964	KDM4B_HUMAN	SDNLYPESITSRDCVQLGPPSEGELVELRWTDGNLYKAKFISSVTSHIYQVEFE DGSQLTVKRGDIFTLEEELPKRVRSR
965	LMBL3_HUMAN	GIPASKVSKWSTDEVSEFIQSLPGCEEHGKVFKDEQIDGEAFLLMTQTDIVKIM SIKLGPALKIENSILMEKAAEKNSHN
966	PHX2A_HUMAN	EPSGLHEKRKQRRIRTTFTSAQLKELERVFAETHYPDIYTREELALKIDLTEAR VQVWFQNRRAKFRKQERAASAKGAAG
967	EMX1_HUMAN	LLLHGPFARKPKRIRTAFSPSQLLRLERAFEKNHYVVGAERKQLAGSLSLSETQ VKVWFQNRRTKYKRQKLEEEGPESEQ
968	NC2B_HUMAN	SSGNDDDLTIPRAAINKMIKETLPNVRVANDARELVVNCCTEFIHLISSEANEI CNKSEKKTISPEHVIQALESLGFGSY
969	DLX4_HUMAN	ERRPQAPAKKLRKPRTIYSSLQLQHLNQRFQHTQYLALPERAQLAAQLGLTQTQ VKIWFQNKRSKYKKLLKQNSGGQEGD
970	SRY_HUMAN	NVQDRVKRPMNAFIVWSRDQRRKMALENPRMRNSEISKQLGYQWKMLTEAEKWP FFQEAQKLQAMHREKYPNYKYRPRRK
971	ZN777_HUMAN	EITRLAVWAAVQAVERKLEAQAMRLLTLEGRTGTNEKKIADCEKTAVEFANHLE SKWVVLGTLLQEYGLLQRRLENMENL
972	NELL1_HUMAN	CEKDIDECSEGIIECHNHSRCVNLPGWYHCECRSGFHDDGTYSLSGESCIDIDE CALRTHTCWNDSACINLAGGEDCLCP
973	ZN398_HUMAN	AAISLWTVVAAVQAIERKVEIHSRRLLHLEGRTGTAEKKLASCEKTVTELGNQL EGKWAVLGTLLQEYGLLQRRLENLEN
974	GATA3_HUMAN	GQNRPLIKPKRRLSAARRAGTSCANCQTTTTTLWRRNANGDPVCNACGLYYKLH NINRPLTMKKEGIQTRNRKMSSKSKK
975	BSH_HUMAN	HAELPGKHCRRRKARTVESDSQLSGLEKRFEIQRYLSTPERVELATALSLSETQ VKTWFQNRRMKHKKQLRKSQDEPKAP

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
976	SF3B4_HUMAN	QDATVYVGGLDEKVSEPLLWELFLQAGPVVNTHMPKDRVTGQHQGYGFVEFLSE EDADYAIKIMNMIKLYGKPIRVNKAS
977	TEAD1_HUMAN	PIDNDAEGVWSPDIEQSFQEALAIYPPCGRRKIILSDEGKMYGRNELIARYIKL RTGKTRTRKQVSSHIQVLARRKSRDE
978	TEAD3_HUMAN	GLDNDAEGVWSPDIEQSFQEALAIYPPCGRRKIILSDEGKMYGRNELIARYIKL RTGKTRTRKQVSSHIQVLARKKVREY
979	RGAP1_HUMAN	DSVGTPQSNGGMRLHDFVSKTVIKPESCVPCGKRIKFGKLSLKCRDCRVVSHPE CRDRCPLPCIPTLIGTPVKIGEGMLA
980	PHF1_HUMAN	SAPHSMTASSSSVSSPSPGLPRRSAPPSPLCRSLSPGTGGGVRGGVGYLSRGDP VRVLARRVRPDGSVQYLVEWGGGGIF
981	FOXA1_HUMAN	GDPHYSENHPESINNLMSSSEQQHKLDFKAYEQALQYSPYGSTLPASLPLGSAS VTTRSPIEPSALEPAYYQGVYSRPVL
982	GATA2_HUMAN	GQNRPLIKPKRRLSAARRAGTCCANCQTTTTTLWRRNANGDPVCNACGLYYKLH NVNRPLTMKKEGIQTRNRKMSNKSKK
983	FOXO3_HUMAN	DSLSGSSLYSTSANLPVMGHEKFPSDLDLDMENGSLECDMESIIRSELMDADGL DENFDSLISTQNVVGLNVGNFTGAKQ
984	ZN212_HUMAN	TEISLWTVVAAIQAVEKKMESQAARLQSLEGRTGTAEKKLADCEKMAVEFGNQL EGKWAVLGTLLQEYGLLQRRLENVEN
985	IRX4_HUMAN	MDSGTRRKNATRETTSTLKAWLQEHRKNPYPTKGEKIMLAIITKMTLTQVSTWE ANARRRLKKENKMTWPPRNKCADEKR
986	ZBED6_HUMAN	NIEKQIYLPSTRAKTSIVWHFFHVDPQYTWRAICNLCEKSVSRGKPGSHLGTST LQRHLQARHSPHWTRANKFGVASGEE
987	LHX4_HUMAN	AKQNDDSEAGAKRPRTTITAKQLETLKNAYKNSPKPARHVREQLSSETGLDMRV VQVWFQNRRAKEKRLKKDAGRHRWGQ
988	SIN3A_HUMAN	DALSYLDQVKLQFGSQPQVYNDFLDIMKEFKSQSIDTPGVISRVSQLFKGHPDL IMGFNTFLPPGYKIEVQTNDMVNVTT
989	RBBP7_HUMAN	DDHTVCLWDINAGPKEGKIVDAKAIFTGHSAVVEDVAWHLLHESLEGSVADDQK LMIWDTRSNTTSKPSHLVDAHTAEVN
990	NKX61_HUMAN	GSILLDKDGKRKHTRPTFSGQQIFALEKTFEQTKYLAGPERARLAYSLGMTESQ VKVWFQNRRTKWRKKHAAEMATAKKK
991	TRI68_HUMAN	DPTALVEAIVEEVACPICMTFLREPMSIDCGHSFCHSCLSGLWEIPGESQNWGY TCPLCRAPVQPRNLRPNWQLANVVEK
992	R51A1_HUMAN	QSLPKKVSLSSDTTRKPLEIRSPSAESKKPKWVPPAASGGSRSSSSPLVVVSVK SPNQSLRLGLSRLARVKPLHPNATST
993	MB3L1_HUMAN	AKSSQRKQRDCVNQCKSKPGLSTSIPLRMSSYTFKRPVTRITPHPGNEVRYHQW EESLEKPQQVCWQRRLQGLQAYSSAG
994	DLX5_HUMAN	VRMVNGKPKKVRKPRTIYSSFQLAALQRRFQKTQYLALPERAELAASLGLTQTQ VKIWFQNKRSKIKKIMKNGEMPPEHS
995	NOTC1_HUMAN	LQCNNHACGWDGGDCSLNENDPWKNCTQSLQCWKYFSDGHCDSQCNSAGCLEDG FDCQRAEGQCNPLYDQYCKDHFSDGH
996	TERF2_HUMAN	ETWVEEDELFQVQAAPDEDSTTNITKKQKWTVEESEWVKAGVQKYGEGNWAAIS KNYPFVNRTAVMIKDRWRTMKRLGMN
997	ZN282_HUMAN	AEISLWTVVAAIQAVERKVDAQASQLLNLEGRTGTAEKKLADCEKTAVEFGNHM ESKWAVLGTLLQEYGLLQRRLENLEN
998	RGS12_HUMAN	LEKRTLFRLDLVPINRSVGLKAKPTKPVTEVLRPVVARYGLDLSGLLVRLSGEK EPLDLGAPISSLDGQRVVLEEKDPSR
999	ZN840_HUMAN	PNCLSSSMQLPHGGGRHQELVRERDVAVVESPEEWDHLTPEQRNLYKDVMLDNC KYLASLGNWTYKAHVMSSLKQGKEPW
1000	SPI2B_HUMAN	DDYKEGDLRIMPESSESPPTEREPGGVVDGLIGKHVEYTKEDGSKRIGMVIHQV EAKPSVYFIKFDDDFHIYVYDLVKKS

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
1001	PAX7_HUMAN	SEPDLPLKRKQRRSRTTFTAEQLEELEKAFERTHYPDIYTREELAQRTKLTEAR VQVWFSNRRARWRKQAGANQLAAFNH
1002	NKX62_HUMAN	AGGVLDKDGKKKHSRPTFSGQQIFALEKTFEQTKYLAGPERARLAYSLGMTESQ VKVWFQNRRTKWRKRHAVEMASAKKK
1003	ASXL2_HUMAN	DVMSFSVTVTTIPASQAMNPSSHGQTIPVQAFSEENSIEGTPSKCYCRLKAMIM CKGCGAFCHDDCIGPSKLCVSCLVVR
1004	FOXO1_HUMAN	GGYSSVSSCNGYGRMGLLHQEKLPSDLDGMFIERLDCDMESIIRNDLMDGDTLD FNFDNVLPNQSFPHSVKTTTHSWVSG
1005	GATA3_HUMAN	GGSPTGFGCKSRPKARSSTGRECVNCGATSTPLWRRDGTGHYLCNACGLYHKMN GQNRPLIKPKRRLSAARRAGTSCANC
1006	GATA1_HUMAN	GQNRPLIRPKKRLIVSKRAGTQCTNCQTTTTTLWRRNASGDPVCNACGLYYKLH QVNRPLTMRKDGIQTRNRKASGKGKK
1007	ZMYM5_HUMAN	PVALLRKQNFQPTAQQQLTKPAKITCANCKKPLQKGQTAYQRKGSAHLFCSTTC LSSFSHKRTQNTRSIICKKDASTKKA
1008	ZN783_HUMAN	TEITLWTVVAAIQALEKKVDSCLTRLLTLEGRTGTAEKKLADCEKTAVEFGNQL EGKWAVLGTLLQEYGLLQRRLENVEN
1009	SPI2B_HUMAN	KKQRGRPSSQPRRNIVGCRISHGWKEGDEPITQWKGTVLDQVPINPSLYLVKYD GIDCVYGLELHRDERVLSLKILSDRV
1010	LRP1_HUMAN	WTCDLDDDCGDRSDESASCAYPTCFPLTQFTCNNGRCININWRCDNDNDCGDNS DEAGCSHSCSSTQFKCNSGRCIPEHW
1011	MIXL1_HUMAN	PKGAAAPSASQRRKRTSFSAEQLQLLELVERRTRYPDIHLRERLAALTLLPESR IQVWFQNRRAKSRRQSGKSFQPLARP
1012	SGT1_HUMAN	KIKYDWYQTESQVVITLMIKNVQKNDVNVEFSEKELSALVKLPSGEDYNLKLEL LHPIIPEQSTFKVLSTKIEIKLKKPE
1013	LMCD1_HUMAN	DPSKEVEYVCELCKGAAPPDSPVVYSDRAGYNKQWHPTCFVCAKCSEPLVDLIY FWKDGAPWCGRHYCESLRPRCSGCDE
1014	CEBPA HUMAN	GSGAGKAKKSVDKNSNEYRVRRERNNIAVRKSRDKAKQRNVETQQKVLELTSDN DRLRKRVEQLSRELDTLRGIFRQLPE
1015	GATA2_HUMAN	GPASSFTPKQRSKARSCSEGRECVNCGATATPLWRRDGTGHYLCNACGLYHKMN GQNRPLIKPKRRLSAARRAGTCCANC
1016	SOX14_HUMAN	KPSDHIKRPMNAFMVWSRGQRRKMAQENPKMHNSEISKRLGAEWKLLSEAEKRP YIDEAKRLRAQHMKEHPDYKYRPRRK
1017	WTIP_HUMAN	LYSGFQQTADKCSVCGHLIMEMILQALGKSYHPGCFRCSVCNECLDGVPFTVDV ENNIYCVRDYHTVFAPKCASCARPIL
1018	PRP19_HUMAN	HPSQDLVESASPDATIRIWSVPNASCVQVVRAHESAVTGLSLHATGDYLLSSSD DQYWAFSDIQTGRVLTKVTDETSGCS
1019	CBX6_HUMAN	ELSAVGERVFAAESIIKRRIRKGRIEYLVKWKGWAIKYSTWEPEENILDSRLIA AFEQKERERELYGPKKRGPKPKTELL
1020	NKX11_HUMAN	RTGSDSKSGKPRRARTAFTYEQLVALENKFKATRYLSVCERLNLALSLSLTETQ VKIWFQNRRTKWKKQNPGADTSAPTG
1021	RBBP4_HUMAN	VWDLSKIGEEQSPEDAEDGPPELLFIHGGHTAKISDESWNPNEPWVICSVSEDN IMQVWQMAENIYNDEDPEGSVDPEGQ
1022	DMRT2_HUMAN	ERCTPAGGGAEPRKLSRTPKCARCRNHGVVSCLKGHKRFCRWRDCQCANCLLVV ERQRVMAAQVALRRQQATEDKKGLSG
1023	SMCA2_HUMAN	SQPGALIPGDPQAMSQPNRGPSPFSPVQLHQLRAQILAYKMLARGQPLPETLQL AVQGKRTLPGLQQQQQQQQQQQQQQQ
1024	ZNF10	MDAKSLTAWSRTLVTFKDVFVDFTREEWKLLDTAQQIVYRNVMLENYKNLVSLG YQLTKPDVILRLEKGEEPWLVEREIHQETHPDSETAFEIKSSVSSRSIFKDKQS CDIKMEGMARNDLWYLSLEEVWKCRDQLDKYQENPERHLRQVAFTQKKVLTQER VSESGKYGGNCLLPAQLVLREYFHKRDSHTKSLKHDLVLNGHQDSCASNSNECG QTFCQNIHLIQFARTHTGDKSYKCPDNDNSLTHGSSLGISKGIHREKPYECKEC GKFFSWRSNLTRHQLIHTGEKPYECKECGKSESRSSHLIGHQKTHTGEEPYECK

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		ECGKSFSWFSHLVTHQRTHTGDKLYTCNQCGKSFVHSSRLIRHQRTHTGEKPYE CPECGKSFRQSTHLILHQRTHVRVRPYECNECGKSYSQRSHLVVHHRIHTGLKP FECKDCGKCESRSSHLYSHQRTHTGEKPYECHDCGKSFSQSSALIVHQRIHTGE KPYECCQCGKAFIRKNDLIKHQRIHVGEETYKCNQCGIIFSQNSPFIVHQIAHT GEQFLTCNQCGTALVNTSNLIGYQTNHIRENAY
1025	EED_HUMAN	MSEREVSTAPAGTDMPAAKKQKLSSDENSNPDLSGDENDDAVSIESGINTERPD TPTNTPNAPGRKSWGKGKWKSKKCKYSFKCVNSLKEDHNQPLFGVQFNWHSKEG DPLVFATVGSNRVTLYECHSQGEIRLLQSYVDADADENFYTCAWTYDSNTSHPL LAVAGSRGIIRIINPITMQCIKHYVGHGNAINELKFHPRDPNLLLSVSKDHALR LWNIQTDTLVAIFGGVEGHRDEVLSADYDLLGEKIMSCGMDHSLKLWRINSKRM MNAIKESYDYNPNKTNRPFISQKIHFPDFSTRDIHRNYVDCVRWLGDLILSKSC ENAIVCWKPGKMEDDIDKIKPSESNVTILGREDYSQCDIWYMRESMDFWQKMLA LGNQVGKLYVWDLEVEDPHKAKCTTLTHHKCGAAIRQTSESRDSSILIAVCDDA SIWRWDRLR
1026	RCOR1_HUMAN	MPAMVEKGPEVSGKRRGRNNAAASASAAAASAAASAACASPAATAASGAAASSA SAAAASAAAAPNNGQNKSLAAAAPNGNSSSNSWEEGSSGSSSDEEHGGGGMRVG PQYQAVVPDFDPAKLARRSQERDNLGMLVWSPNQNLSEAKLDEYIAIAKEKHGY NMEQALGMLFWHKHNIEKSLADLPNFTPFPDEWTVEDKVLFEQAFSFHGKTFHR IQQMLPDKSIASLVKFYYSWKKTRTKTSVMDRHARKQKREREESEDELEEANGN NPIDIEVDQNKESKKEVPPTETVPQVKKEKHSTQAKNRAKRKPPKGMFLSQEDV EAVSANATAATTVLRQLDMELVSVKRQIQNIKQTNSALKEKLDGGIEPYRLPEV IQKCNARWTTEEQLLAVQAIRKYGRDFQAISDVIGNKSVVQVKNFFVNYRRREN IDEVLQEWEAEHGKEETNGPSNQKPVKSPDNSIKMPEEEDEAPVLDVRYASAS
1027	human DNMT1	MPARTAPARVPTLAVPAISLPDDVRRRLKDLERDSLTEKECVKEKLNLLHEFLQ TEIKNQLCDLETKLRKEELSEEGYLAKVKSLLNKDLSLENGAHAYNREVNGRLE NGNQARSEARRVGMADANSPPKPLSKPRTPRRSKSDGEAKPEPSPSPRITRKST RQTTITSHFAKGPAKRKPQEESERAKSDESIKEEDKDQDEKRRRVTSRERVARP LPAEEPERAKSGTRTEKEEERDEKEEKRLRSQTKEPTPKQKLKEEPDREARAGV QADEDEDGDEKDEKKHRSQPKDLAAKRRPEEKEPEKVNPQISDEKDEDEKEEKR RKTTPKEPTEKKMARAKTVMNSKTHPPKCIQCGQYLDDPLKYGQHPPDAVDEPQ MLTNEKLSIFDANESGFESYEALPQHKLTCFSVYCKHGHLCPIDTGLIEKNIEL FFSGSAKPIYDDDPSLEGGVNGKNLGPINEWWITGEDGGEKALIGESTSFAEYI LMDPSPEYAPIFGLMQEKIYISKIVVEFLQSNSDSTYEDLINKIETTVPPSGLN LNRFTEDSLLRHAQFVVEQVESYDEAGDSDEQPIFLTPCMRDLIKLAGVTLGQR RAQARRQTIRHSTREKDRGPTKATTTKLVYQIFDTFFAEQIEKDDREDKENAFK RRRCGVCEVCQQPECGKCKACKDMVKFGGSGRSKQACQERRCPNMAMKEADDDE EVDDNIPEMPSPKKMHQGKKKKQNKNRISWVGEAVKTDGKKSYYKKVCIDAETL EVGDCVSVIPDDSSKPLYLARVTALWEDSSNGQMFHAHWFCAGTDTVLGATSDP LELFLVDECEDMQLSYIHSKVKVIYKAPSENWAMEGGMDPESLLEGDDGKTYFY QLWYDQDYARFESPPKTQPTEDNKFKFCVSCARLAEMRQKEIPRVLEQLEDLDS RVLYYSATKNGILYRVGDGVYLPPEAFTENIKLSSPVKRPRKEPVDEDLYPEHY RKYSDYIKGSNLDAPEPYRIGRIKEIFCPKKSNGRPNETDIKIRVNKFYRPENT HKSTPASYHADINLLYWSDEEAVVDFKAVQGRCTVEYGEDLPECVQVYSMGGPN RFYFLEAYNAKSKSFEDPPNHARSPGNKGKGKGKGKGKPKSQACEPSEPEIEIK LPKLRTLDVFSGCGGLSEGFHQAGISDTLWAIEMWDPAAQAFRLNNPGSTVETE DCNILLKLVMAGETTNSRGQRLPQKGDVEMLCGGPPCQGFSGMNRENSRTYSKE KNSLVVSFLSYCDYYRPRFFLLENVRNFVSFKRSMVLKLTLRCLVRMGYQCTFG VLQAGQYGVAQTRRRAIILAAAPGEKLPLFPEPLHVFAPRACQLSVVVDDKKEV SNITRLSSGPERTITVRDTMSDLPEVRNGASALEISYNGEPQSWFQRQLRGAQY QPILRDHICKDMSALVAARMRHIPLAPGSDWRDLPNIEVRLSDGTMARKLRYTH HDRKNGRSSSGALRGVCSCVEAGKACDPAARQENTLIPWCLPHTGNRHNHWAGL YGRLEWDGFFSTTVTNPEPMGKQGRVLHPEQHRVVSVRECARSQGFPDTYRLFG NILDKHRQVGNAVPPPLAKAIGLEIKLCMLAKARESASAKIKEEEAAKD
1028	human DNMT3A	MPAMPSSGPGDTSSSAAEREEDRKDGEEQEEPRGKEERQEPSTTARKVGRPGRK RKHPPVESGDTPKDPAVISKSPSMAQDSGASELLPNGDLEKRSEPQPEEGSPAG GQKGGAPAEGEGAAETLPEASRAVENGCCTPKEGRGAPAEAGKEQKETNIESMK MEGSRGRLRGGLGWESSLRQRPMPRLTFQAGDPYYISKRKRDEWLARWKREAEK KAKVIAGMNAVEENQGPGESQKVEEASPPAVQQPTDPASPTVATTPEPVGSDAG DKNATKAGDDEPEYEDGRGFGIGELVWGKLRGFSWWPGRIVSWWMTGRSRAAEG TRWVMWFGDGKFSVVCVEKLMPLSSFCSAFHQATYNKQPMYRKAIYEVLQVASS RAGKLFPVCHDSDESDTAKAVEVQNKPMIEWALGGFQPSGPKGLEPPEEEKNPY KEVYTDMWVEPEAAAYAPPPPAKKPRKSTAEKPKVKEIIDERTRERLVYEVRQK CRNIEDICISCGSLNVTLEHPLFVGGMCQNCKNCFLECAYQYDDDGYQSYCTIC CGGREVLMCGNNNCCRCFCVECVDLLVGPGAAQAAIKEDPWNCYMCGHKGTYGL LRRREDWPSRLQMFFANNHDQEFDPPKVYPPVPAEKRKPIRVLSLEDGIATGLL VLKDLGIQVDRYIASEVCEDSITVGMVRHQGKIMYVGDVRSVTQKHIQEWGPED LVIGGSPCNDLSIVNPARKGLYEGTGRLFFEFYRLLHDARPKEGDDRPFFWLFE NVVAMGVSDKRDISRFLESNPVMIDAKEVSAAHRARYFWGNLPGMNRPLASTVN DKLELQECLEHGRIAKFSKVRTITTRSNSIKQGKDQHFPVEMNEKEDILWCTEM ERVFGFPVHYTDVSNMSRLARQRLLGRSWSVPVIRHLFAPLKEYFACV

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
1029	human DNMT3A catalytic domain	NHDQEFDPPKVYPPVPAEKRKPIRVLSLFDGIATGLLVLKDLGIQVDRYIASEV CEDSITVGMVRHQGKIMYVGDVRSVTQKHIQEWGPFDLVIGGSPCNDLSIVNPA RKGLYEGTGRLFFEFYRLLHDARPKEGDDRPFFWLFENVVAMGVSDKRDISREL ESNPVMIDAKEVSAAHRARYFWGNLPGMNRPLASTVNDKLELQECLEHGRIAKF SKVRTITTRSNSIKQGKDQHFPVEMNEKEDILWCTEMERVFGFPVHYTDVSNMS RLARQRLLGRSWSVPVIRHLFAPLKEYFACV
1030	human DNMT3B	MKGDTRHLNGEEDAGGREDSILVNGACSDQSSDSPPILEAIRTPEIRGRRSSSR LSKREVSSLLSYTQDLTGDGDGEDGDGSDTPVMPKLFRETRTRSESPAVRTRNN NSVSSRERHRPSPRSTRGRQGRNHVDESPVEFPATRSLRRRATASAGTPWPSPP SSYLTIDLTDDTEDTHGTPQSSSTPYARLAQDSQQGGMESPQVEADSGDGDSSE YQDGKEFGIGDLVWGKIKGFSWWPAMVVSWKATSKRQAMSGMRWVQWFGDGKES EVSADKLVALGLESQHENLATENKLVSYRKAMYHALEKARVRAGKTFPSSPGDS LEDQLKPMLEWAHGGFKPTGIEGLKPNNTQPVVNKSKVRRAGSRKLESRKYENK TRRRTADDSATSDYCPAPKRLKTNCYNNGKDRGDEDQSREQMASDVANNKSSLE DGCLSCGRKNPVSFHPLFEGGLCQTCRDRFLELFYMYDDDGYQSYCTVCCEGRE LLLCSNTSCCRCFCVECLEVLVGTGTAAEAKLQEPWSCYMCLPQRCHGVLRRRK DWNVRLQAFFTSDTGLEYEAPKLYPAIPAARRRPIRVLSLEDGIATGYLVLKEL GIKVGKYVASEVCEESIAVGTVKHEGNIKYVNDVRNITKKNIEEWGPFDLVIGG SPCNDLSNVNPARKGLYEGTGRLFFEFYHLLNYSRPKEGDDRPFFWMFENVVAM KVGDKRDISRELECNPVMIDAIKVSAAHRARYFWGNLPGMNRPVIASKNDKLEL QDCLEYNRIAKLKKVQTITTKSNSIKQGKNQLFPVVMNGKEDVLWCTELERIFG FPVHYTDVSNMGRGARQKLLGRSWSVPVIRHLFAPLKDYFACE
1031	mouse DNMT3C	MRGGSRHLSNEEDVSGCEDCIIISGTCSDQSSDPKTVPLTQVLEAVCTVENRGC RTSSQPSKRKASSLISYVQDLTGDGDEDRDGEVGGSSGSGTPVMPQLFCETRIP SKTPAPLSWQANTSASTPWLSPASPYPIIDLTDEDVIPQSISTPSVDWSQDSHQ EGMDTTQVDAESRDGGNIEYQVSADKLLLSQSCILAAFYKLVPYRESTYRTLEK ARVRAGKACPSSPGESLEDQLKPMLEWAHGGFKPTGIEGLKPNKKQPENKSRRR TTNDPAASESSPPKRLKTNSYGGKDRGEDEESREQMASDVTNNKGNLEDHCLSC GRKDPVSFHPLFEGGLCQSCRDRELELFYMYDEDGYQSYCTVCCEGRELLLCSN TSCCRCFCVECLEVLVGAGTAEDVKLQEPWSCYMCLPQRCHGVLRRRKDWNMRL QDFFTTDPDLEEFEPPKLYPAIPAAKRRPIRVLSLEDGIATGYLVLKELGIKVE KYIASEVCAESIAVGTVKHEGQIKYVDDIRNITKEHIDEWGPFDLVIGGSPCND LSCVNPVRKGLFEGTGRLFFEFYRLLNYSCPEEEDDRPFFWMFENVVAMEVGDK RDISRFLECNPVMIDAIKVSAAHRARYFWGNLPGMNRPVMASKNDKLELQDCLE FSRTAKLKKVQTITTKSNSIRQGKNQLFPVVMNGKDDVLWCTELERIFGFPEHY TDVSNMGRGARQKLLGRSWSVPVIRHLFAPLKDHFACE
1032	human DNMT3L	MAAIPALDPEAEPSMDVILVGSSELSSSVSPGTGRDLIAYEVKANQRNIEDICI CCGSLQVHTQHPLFEGGICAPCKDKFLDALFLYDDDGYQSYCSICCSGETLLIC GNPDCTRCYCFECVDSLVGPGTSGKVHAMSNWVCYLCLPSSRSGLLQRRRKWRS QLKAFYDRESENPLEMFETVPVWRRQPVRVLSLFEDIKKELTSLGFLESGSDPG QLKHVVDVTDTVRKDVEEWGPFDLVYGATPPLGHTCDRPPSWYLEQFHRLLQYA RPKPGSPRPFFWMFVDNLVLNKEDLDVASRFLEMEPVTIPDVHGGSLQNAVRVW SNIPAIRSSRHWALVSEEELSLLAQNKQSSKLAAKWPTKLVKNCELPLREYFKY FSTELTSSL
1033	human DNMT3L catalytic domain	NPLEMFETVPVWRRQPVRVLSLFEDIKKELTSLGFLESGSDPGQLKHVVDVTDT VRKDVEEWGPFDLVYGATPPLGHTCDRPPSWYLFQFHRLLQYARPKPGSPRPFF WMFVDNLVLNKEDLDVASRFLEMEPVTIPDVHGGSLQNAVRVWSNIPAIRSRHW ALVSEEELSLLAQNKQSSKLAAKWPTKLVKNCFLPLREYFKYFSTELTSSL
1034	mouse DNMT3L	MGSRETPSSCSKTLETLDLETSDSSSPDADSPLEEQWLKSSPALKEDSVDVVLE DCKEPLSPSSPPTGREMIRYEVKVNRRSIEDICLCCGTLQVYTRHPLFEGGLCA PCKDKFLESLFLYDDDGHQSYCTICCSGGTLFICESPDCTRCYCFECVDILVGP GTSERINAMACWVCFLCLPFSRSGLLQRRKRWRHQLKAFHDQEGAGPMEIYKTV SAWKRQPVRVLSLERNIDKVLKSLGFLESGSGSGGGTLKYVEDVTNVVRRDVEK WGPFDLVYGSTQPLGSSCDRCPGWYMFQFHRILQYALPRQESQRPFFWIEMDNL LLTEDDQETTTRELQTEAVTLQDVRGRDYQNAMRVWSNIPGLKSKHAPLTPKEE EYLQAQVRSRSKLDAPKVDLLVKNCLLPLREYFKYFSQNSLPL
1035	mouse DNMT3L catalytic domain	GPMEIYKTVSAWKRQPVRVLSLERNIDKVLKSLGFLESGSGSGGGTLKYVEDVT NVVRRDVEKWGPFDLVYGSTQPLGSSCDRCPGWYMFQFHRILQYALPRQESQRP FFWIEMDNLLLTEDDQETTTRFLQTEAVTLQDVRGRDYQNAMRVWSNIPGLKSK HAPLTPKEEEYLQAQVRSRSKLDAPKVDLLVKNCLLPLREYFKYFSQNSLPL
1036	human TRDMT1 (DNMT2)	MEPLRVLELYSGVGGMHHALRESCIPAQVVAAIDVNTVANEVYKYNFPHTQLLA KTIEGITLEEFDRLSFDMILMSPPCQPFTRIGRQGDMTDSRTNSFLHILDILPR LQKLPKYILLENVKGFEVSSTRDLLIQTIENCGFQYQEFLLSPTSLGIPNSRLR YFLIAKLQSEPLPFQAPGQVLMEFPKIESVHPQKYAMDVENKIQEKNVEPNISE DGSIQCSGKDAILFKLETAEEIHRKNQQDSDLSVKMLKDFLEDDTDVNQYLLPP KSLLRYALLLDIVQPTCRRSVCFTKGYGSYIEGTGSVLQTAEDVQVENIYKSLT NLSQEEQITKLLILKLRYFTPKEIANLLGFPPEFGFPEKITVKQRYRLLGNSLN VHVVAKLIKILYE

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
1037	*M. penetrans* M MpeI	MNSNKDKIKVIKVFEAFAGIGSQFKALKNIARSKNWEIQHSGMVEWFVDAIVSY VAIHSKNFNPKIEQLDKDILSISNDSKMPISEYGIKKINNTIKASYLNYAKKHF NNLFDIKKVNKDNFPKNIDIFTYSFPCQDLSVQGLQKGIDKELNTRSGLLWEIE RILEEIKNSFSKEEMPKYLLMENVKNLLSHKNKKNYNTWLKQLEKFGYKSKTYL LNSKNEDNCQNRERVFCLSIRDDYLEKTGFKFKELEKVKNPPKKIKDILVDSSN YKYLNLNKYETTTFRETKSNIISRSLKNYTTENSENYVYNINGIGPTLTASGAN SRIKIETQQGVRYLTPLECFKYMQFDVNDFKKVQSTNLISENKMIYIAGNSIPV KILEAIENTLEFVNNEE
1038	*S. monobiae* M SssI	MSKVENKTKKLRVFEAFAGIGAQRKALEKVRKDEYEIVGLAEWYVPAIVMYQAI HNNFHTKLEYKSVSREEMIDYLENKTLSWNSKNPVSNGYWKRKKDDELKIIYNA IKLSEKEGNIFDIRDLYKRTLKNIDLLTYSFPCQDLSQQGIQKGMKRGSGTRSG LLWEIERALDSTEKNDLPKYLLMENVGALLHKKNEEELNQWKQKLESLGYQNSI EVLNAADFGSSQARRRVEMISTLNEFVELPKGDKKPKSIKKVLNKIVSEKDILN NLLKYNLTEFKKTKSNINKASLIGYSKENSEGYVYDPEFTGPTLTASGANSRIK IKDGSNIRKMNSDETFLYIGFDSQDGKRVNEIEFLTENQKIFVCGNSISVEVLE AIIDKIGG
1039	*H. parainfluenzae* M HpaII	MKDVLDDNLLEEPAAQYSLFEPESNPNLREKFTFIDLFAGIGGFRIAMQNLGGK CIFSSEWDEQAQKTYEANFGDLPYGDITLEETKAFIPEKFDILCAGEPCQAFSI AGKRGGFEDTRGTLFFDVAEIIRRHQPKAFFLENVKGLKNHDKGRTLKTILNVL REDLGYFVPEPAIVNAKNFGVPQNRERIYIVGFHKSTGVNSESYPEPLDKIVTE ADIREEKTVPTKYYLSTQYIDTLRKHKERHESKGNGFGYEIIPDDGIANAIVVG GMGRERNLVIDHRITDETPTTNIKGEVNREGIRKMTPREWARLQGFPDSYVIPV SDASAYKQFGNSVAVPAIQATGKKILEKLGNLYD
1040	*A. luteus* M AluI	MSKANAKYSFVDLFAGIGGFHAALAATGGVCEYAVEIDREAAAVYERNWNKPAL GDITDDANDEGVTLRGYDGPIDVLTGGFPCQPFSKSGAQHGMAETRGTLFWNIA RIIEEREPTVLILENVRNLVGPRHRHEWLTIIETLRFFGYEVSGAPAIFSPHLL PAWMGGTPQVRERVFITATLVPERMRDERIPRTETGEIDAEAIGPKPVATMNDR FPIKKGGTELFHPGDRKSGWNLLTSGIIREGDPEPSNVDLRLTETETLWIDAWD DLESTIRRATGRPLEGEPYWADSWTDFRELSRLVVIRGFQAPEREVVGDRKRYV ARTDMPEGFVPASVTRPAIDETLPAWKQSHLRRNYDFFERHFAEVVAWAYRWGV YTDLFPASRRKLEWQAQDAPRLWDTVMHFRPSGIRAKRPTYLPALVAITQTSIV GPLERRLSPRETARLQGLPEWFDFGEQRAAATYKQMGNGVNVGVVRHILREHVR RDRALLKLTPAGQRIINAVLADEPDATVGALGAAE
1041	*H. aegyptius* M HaeIII	MNLISLESGAGGLDLGFQKAGFRIICANEYDKSIWKTYESNHSAKLIKGDISKI SSDEFPKCDGIIGGPPCQSWSEGGSLRGIDDPRGKLFYEYIRILKQKKPIFFLA ENVKGMMAQRHNKAVQEFIQEFDNAGYDVHIILLNANDYGVAQDRKRVFYIGER KELNINYLPPIPHLIKPTFKDVIWDLKDNPIPALDKNKTNGNKCIYPNHEYFIG SYSTIFMSRNRVRQWNEPAFTVQASGRQCQLHPQAPVMLKVSKNLNKFVEGKEH LYRRLTVRECARVQGFPDDFIFHYESLNDGYKMIGNAVPVNLAYEIAKTIKSAL EICKGN
1042	H. haemolyticus M HhaI	MIEIKDKQLTGLRFIDLFAGLGGFRLALESCGAECVYSNEWDKYAQEVYEMNFG EKPEGDITQVNEKTIPDHDILCAGFPCQAFSISGKQKGFEDSRGTLFFDIARIV REKKPKVVFMENVKNFASHDNGNTLEVVKNTMNELDYSFHAKVLNALDYGIPQK RERIYMICFRNDLNIQNFQFPKPFELNTFVKDLLLPDSEVEHLVIDRKDLVMTN QEIEQTTPKTVRLGIVGKGGQGERIYSTRGIAITLSAYGGGIFAKTGGYLVNGK TRKLHPRECARVMGYPDSYKVHPSTSQAYKQFGNSVVINVLQYIAYNIGSSLNE KPY
1043	Moraxella M MspI	MKPEILKLIRSKLDLTQKQASEIIEVSDKTWQQWESGKTEMHPAYYSFLQEKLK DKINFEELSAQKTLQKKIFDKYNQNQITKNAEELAEITHIEERKDAYSSDFKFI DLFSGIGGIRQSFEVNGGKCVESSEIDPFAKFTYYTNFGVVPFGDITKVEATTI PQHDILCAGEPCQPFSHIGKREGFEHPTQGTMFHEIVRIIETKKTPVLFLENVP GLINHDDGNTLKVIIETLEDMGYKVHHTVLDASHFGIPQKRKRFYLVAFLNQNI HFEFPKPPMISKDIGEVLESDVTGYSISEHLQKSYLFKKDDGKPSLIDKNTTGA VKTLVSTYHKIQRLTGTFVKDGETGIRLLTTNECKAIMGFPKDFVIPVSRTQMY RQMGNSVVVPVVTKIAEQISLALKTVNQQSPQENFELELV
1044	Ascobolus Masc1	MSERRYEAGMTVALHEGSFLKIQRVYIRQYHADNRREHMLVGPLFRRTKYLKAL SKKVNEVAIVHESIHVPVQDVIGVRELIITNRPFPECRKGDEHTGRLVCRWVYN LDERAKGREYKKQRYIRRITEAEADPEYRVEDRVLRRRWFQEGYIGDEISYKEH GNGDIVDIRSESPLQVLDGWGGDLVDLENGEETSIPGPCRSASSYGRLMKPPLA QAADSNTSRKYTFGDTFCGGGGVSLGARQAGLEVKWAFDMNPNAGANYRRNEPN TDFFLAEAEQFIQLSVGISQHVDILHLSPPCQTFSRAHTIAGKNDENNEASFFA VVNLIKAVRPRLFTVEETDGIMDRQSRQFIDTALMGITELGYSFRICVLNAIEY GVCQNRKRLIIIGAAPGEELPPFPLPTHQDFFSKDPRRDLLPAVTLDDALSTIT PESTDHHLNHVWQPAEWKTPYDAHRPFKNAIRAGGGEYDIYPDGRRKFTVRELA CIQGFPDEYEFVGTLTDKRRIIGNAVPPPLSAAIMSTLRQWMTEKDFERME
1045	*Arabidopsis* MET1	MVENGAKAAKRKKRPLPEIQEVEDVPRTRRPRRAAACTSFKEKSIRVCEKSATI EVKKQQIVEEEFLALRLTALETDVEDRPTRRLNDFVLEDSDGVPQPLEMLEIHD

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		IFVSGAILPSDVCTDKEKEKGVRCTSFGRVEHWSISGYEDGSPVIWISTELADY DCRKPAASYRKVYDYFYEKARASVAVYKKLSKSSGGDPDIGLEELLAAVVRSMS SGSKYFSSGAAIIDFVISQGDFIYNQLAGLDETAKKHESSYVEIPVLVALREKS SKIDKPLQRERNPSNGVRIKEVSQVAESEALTSDQLVDGTDDDRRYAILLQDEE NRKSMQQPRKNSSSGSASNMFYIKINEDEIANDYPLPSYYKTSEEETDELILYD ASYEVQSEHLPHRMLHNWALYNSDLRFISLELLPMKQCDDIDVNIFGSGVVTDD NGSWISLNDPDSGSQSHDPDGMCIFLSQIKEWMIEFGSDDIISISIRTDVAWYR LGKPSKLYAPWWKPVLKTARVGISILTFLRVESRVARLSFADVTKRLSGLQAND KAYISSDPLAVERYLVVHGQIILQLFAVYPDDNVKRCPFVVGLASKLEDRHHTK WIIKKKKISLKELNLNPRAGMAPVASKRKAMQATTTRLVNRIWGEFYSNYSPED PLQATAAENGEDEVEEEGGNGEEEVEEEGENGLTEDTVPEPVEVQKPHTPKKIR GSSGKREIKWDGESLGKTSAGEPLYQQALVGGEMVAVGGAVTLEVDDPDEMPAI YFVEYMFESTDHCKMLHGRFLQRGSMTVLGNAANERELFLTNECMTTQLKDIKG VASFEIRSRPWGHQYRKKNITADKLDWARALERKVKDLPTEYYCKSLYSPERGG FFSLPLSDIGRSSGFCTSCKIREDEEKRSTIKLNVSKTGFFINGIEYSVEDEVY VNPDSIGGLKEGSKTSFKSGRNIGLRAYVVCQLLEIVPKESRKADLGSEDVKVR RFYRPEDVSAEKAYASDIQELYFSQDTVVLPPGALEGKCEVRKKSDMPLSREYP ISDHIFFCDLFFDTSKGSLKQLPANMKPKFSTIKDDTLLRKKKGKGVESEIESE IVKPVEPPKEIRLATLDIFAGCGGLSHGLKKAGVSDAKWAIEYEEPAGQAFKQN HPESTVFVDNCNVILRAIMEKGGDQDDCVSTTEANELAAKLTEEQKSTLPLPGQ VDFINGGPPCQGFSGMNRFNQSSWSKVQCEMILAFLSFADYFRPRYFLLENVRT FVSFNKGQTFQLTLASLLEMGYQVRFGILEAGAYGVSQSRKRAFIWAAAPEEVL PEWPEPMHVFGVPKLKISLSQGLHYAAVRSTALGAPFRPITVRDTIGDLPSVEN GDSRTNKEYKEVAVSWFQKEIRGNTIALTDHICKAMNELNLIRCKLIPTRPGAD WHDLPKRKVTLSDGRVEEMIPFCLPNTAERHNGWKGLYGRLDWQGNFPTSVTDP QPMGKVGMCFHPEQHRILTVRECARSQGFPDSYEFAGNINHKHRQIGNAVPPPL AFALGRKLKEALHLKKSPQHQP
1046	*Ascobolus* Masc2	MELTPELSGVSTDLGGGGSIFAHWRMKEESPAPTEILDDLNVLEWEKTTRDYSK EDLRIADQLFSIEDEHQSLPFETADAEDGTPTEEEEEKELPMRTLDNEVLYDAS DLELAALDLIGTELNIHAVGTVGPIYTEGEEDEQEDEDEDVSPPVRTGTQATSA SVTQMTVELYIRNIVQYEFCFNDDGTVETWIQTTNAHYKLLQPAKCYTSLYRPV NDCLNVITAIITLAPESTTMSLKDLLKVMDDKAQAVSYEEVERMSEFIVQHLDQ WMETAPKKKSKLIEKSKVYIDLNNLAGIDMVSGVRPPPVRRVTGRSSAPKKRIV RNMNDAVLLHQNETTVTNWIHQLSAGMFGRALNVLGAETADVENLTCDPASAKF VVPQRRLHKRLKWETRGHIPVSEEEYKHIYQGKKYAKFFEAVRAVDESKLTIKL GDLVYVLDQDPKVTQTQFATAGREGRKKGAEKEKIQVRFGRVLSIRQPDSNSKD AQNVFIHVQWLVLGCDTILQEMASRRELFLTDSCDTVFADVIYGVAKLTPLGAK DIPTVEFHESMATMMGENEFFVRFKYNYQDGSFTDLKDVDAEQIGTLQPRVNTH RNPGYCSNCRIKYDNERTGDKWIYENDTEGEPRLFRSSKGWCIYAQEFVYLQPV EKQPGTTFRVGYISEINKSSVIVELLARVDDDDKSGHISYSDPRHLYFTGTDIK VTFDKIIRKCFVFHDSGDQKAKAPLMYGTLQRDLYYYRYEKRKGKAELVPVREI RSIHEQTLNDWESRTQIERHGAVSGKKLKGLDIFAGCGGLTLGLDLSGAVDTKW DIEFAPSAANTLALNEPDAQVENQCANVLLSRAIQSEDEGSLDIEYDLQGRVLP DLPKKGEVDFIYGGPPCQGFSGVNRYKKGNDIKNSLVATFLSYVDHYKPRFVLL ENVKGLITTKLGNSKNAEGKWEGGISNGVVKFIYRTLISMNYQCRIGLVQSGEY GVPQSRPRVIFLAARMGERLPDLPEPMHAFEVLDSQYALPHIKRYHTTQNGVAP LPRITIGEAVSDLPKFQYANPGVWPRHDPYSSAKAQPSDKTIEKFSVSKATSFV GYLLQPYHSRPQSEFQRRLRTKLVPSDEPAEKTSLLTTKLVTAHVTRLENKETT QRIVCVPMWPGADHRSLPKEMRPWCLVDPNSQAEKHRFWPGLFGRLGMEDFEST ALTDVQPCGKQGKVLHPTQRRVYTVRELARAQGFPDWFAFTDGDADSGLGGVKK WHRNIGNAVPVPLGEQIGRCIGYSVWWKDDMIAQLREDGADEDEEMIDGNDQWV EELNTQMAADMPGLPLLVTHLLNLCVYRRLYGPNAKEFLPARVYDKKLEGGRRR LVWAML
1047	*Neurospora* Dim2	MDSPDRSHGGMFIDVPAETMGFQEDYLDMFASVLSQGLAKEGDYAHHQPLPAGK EECLEPIAVATTITPSPDDPQLQLQLELEQQFQTESGLNGVDPAPAPESEDEAD LPDGFSDESPDDDFVVQRSKHITVDLPVSTLINPRSTFQRIDENDNLVPPPQST PERVAVEDLLKAAKAAGKNKEDYIEFELHDENFYVNYAYHPQEMRPIQLVATKV LHDKYYFDGVLKYGNTKHYVTGMQVLELPVGNYGASLHSVKGQIWVRSKHNAKK EIYYLLKKPAFEYQRYYQPFLWIADLGKHVVDYCTRMVERKREVTLGCFKSDFI QWASKAHGKSKAFQNWRAQHPSDDERTSVAANIGYIWKEINGVAGAKRAAGDQL FRELMIVKPGQYFRQEVPPGPVVTEGDRTVAATIVTPYIKECFGHMILGKVLRL AGEDAEKEKEVKLAKRLKIENKNATKADTKDDMKNDTATESLPTPLRSLPVQVL EATPIESDIVSIVSSDLPPSENNPPPLINGSVKPKAKANPKPKPSTQPLHAAHV KYLSQELVNKIKVGDVISTPRDDSSNTDTKWKPTDTDDHRWFGLVQRVHTAKTK SSGRGLNSKSFDVIWFYRPEDTPCCAMKYKWRNELFLSNHCTCQEGHHARVKGN EVLAVHPVDWFGTPESNKGEFFVRQLYESEQRRWITLQKDHLTCYHNQPPKPPT APYKPGDTVLATLSPSDKESDPYEVVEYFTQGEKETAFVRLRKLLRRRKVDRQD APANELVYTEDLVDVRAERIVGKCIMRCFRPDERVPSPYDRGGTGNMFFITHRQ DHGRCVPLDTLPPTLRQGENPLGNLGKPKLRGMDLYCGGGNFGRGLEEGGVVEM RWANDIWDKAIHTYMANTPDPNKTNPFLGSVDDLLRLALEGKESDNVPRPGEVD FIAAGSPCPGFSLLTQDKKVLNQVKNQSLVASFASFVDFYRPKYGVLENVSGIV QTFVNRKQDVLSQLFCALVGMGYQAQLILGDAWAHGAPQSRERVELYFAAPGLP LPDPPLPSHSHYRVKNRNIGFLCNGESYVQRSFIPTAFKFVSAGEGTADLPKIG DGKPDACVRFPDHRLASGITPYIRAQYACIPTHPYGMNFIKAWNNGNGVMSKSD

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		RDLFPSEGKTRTSDASVGWKRLNPKTLFPTVTTTSNPSDARMGPGLHWDEDRPY TVQEMRRAQGYLDEEVLVGRTTDQWKLVGNSVSRHMALAIGLKFREAWLGTLYD ESAVVATATATATTAAAVGVTVPVMEEPGIGTTESSRPSRSPVHTAVDLDDSKS ERSRSTTPATVLSTSSAAGDGSANAAGLEDDDNDDMEMMEVTRKRSSPAVDEEG MRPSKVQKVEVTVASPASRRSSRQASRNPTASPSSKASKATTHEAPAPEELESD AESYSETYDKEGFDGDYHSGHEDQYSEEDEEEEYAEPETMTVNGMTIVKL
1048	*Drosophila* dDnmt2	MVFRVLELFSGIGGMHYAFNYAQLDGQIVAALDVNTVANAVYAHNYGSNLVKTR NIQSLSVKEVTKLQANMLLMSPPCQPHTRQGLQRDTEDKRSDALTHLCGLIPEC QELEYILMENVKGFESSQARNQFIESLERSGFHWREFILTPTQFNVPNTRYRYY CIARKGADFPFAGGKIWEEMPGAIAQNQGLSQIAEIVEENVSPDFLVPDDVLTK RVLVMDIIHPAQSRSMCFTKGYTHYTEGTGSAYTPLSEDESHRIFELVKEIDTS NQDASKSEKILQQRLDLLHQVRLRYFTPREVARLMSFPENFEFPPETTNRQKYR LLGNSINVKVVGELIKLLTIK
1049	*S. pombe* Pmt1	MLSTKRLRVLELYSGIGGMHYALNLANIPADIVCAIDINPQANEIYNLNHGKLA KHMDISTLTAKDFDAFDCKLWTMSPSCQPFTRIGNRKDILDPRSQAFLNILNVL PHVNNLPEYILIENVQGFEESKAAEECRKVLRNCGYNLIEGILSPNQFNIPNSR SRWYGLARLNEKGEWSIDDVFQFSEVAQKEGEVKRIRDYLEIERDWSSYMVLES VLNKWGHQFDIVKPDSSSCCCFTRGYTHLVQGAGSILQMSDHENTHEQFERNRM ALQLRYFTAREVARLMGFPESLEWSKSNVTEKCMYRLLGNSINVKVVSYLISLL LEPLNE
1050	*Arabidopsis* DRM1	MVMSHIFLISQIQEVEHGDSDDVNWNTDDDELAIDNFQFSPSPVHISATSPNSI QNRISDETVASFVEMGESTQMIARAIEETAGANMEPMMILETLENYSASTEASS SKSKVINHFIAMGFPEEHVIKAMQEHGDEDVGEITNALLTYAEVDKLRESEDMN ININDDDDDNLYSLSSDDEEDELNNSSNEDRILQALIKMGYLREDAAIAIERCG EDASMEEVVDFICAAQMARQFDEIYAEPDKKELMNNNKKRRTYTETPRKPNTDQ LISLPKEMIGFGVPNHPGLMMHRPVPIPDIARGPPFFYYENVAMTPKGVWAKIS SHLYDIVPEFVDSKHFCAAARKRGYIHNLPIQNRFQIQPPQHNTIQEAFPLTKR WWPSWDGRTKLNCLLTCIASSRLTEKIREALERYDGETPLDVQKWVMYECKKWN LVWVGKNKLAPLDADEMEKLLGFPRDHTRGGGISTTDRYKSLGNSFQVDTVAYH LSVLKPLFPNGINVLSLFTGIGGGEVALHRLQIKMNVVVSVEISDANRNILRSF WEQTNQKGILREFKDVQKLDDNTIERLMDEYGGFDLVIGGSPCNNLAGGNRHHR VGLGGEHSSLFFDYCRILEAVRRKARHMRR
1051	*Arabadopsis* DRM2	MVIWNNDDDDFLEIDNFQSSPRSSPIHAMQCRVENLAGVAVTTSSLSSPTETTD LVQMGFSDEVFATLEDMGFPVEMISRAIKETGPNVETSVIIDTISKYSSDCEAG SSKSKAIDHELAMGFDEEKVVKAIQEHGEDNMEAIANALLSCPEAKKLPAAVEE EDGIDWSSSDDDTNYTDMLNSDDEKDPNSNENGSKIRSLVKMGESELEASLAVE RCGENVDIAELTDELCAAQMAREFSEFYTEHEEQKPRHNIKKRRFESKGEPRSS VDDEPIRLPNPMIGFGVPNEPGLITHRSLPELARGPPFFYYENVALTPKGVWET ISRHLFEIPPEFVDSKYFCVAARKRGYIHNLPINNRFQIQPPPKYTIHDAFPLS KRWWPEWDKRTKLNCILTCTGSAQLTNRIRVALEPYNEEPEPPKHVQRYVIDQC KKWNLVWVGKNKAAPLEPDEMESILGFPKNHTRGGGMSRTERFKSIGNSFQVDT VAYHLSVLKPIFPHGINVLSLFTGIGGGEVALHRLQIKMKLVVSVEISKVNRNI LKDFWEQTNQTGELIEFSDIQHLTNDTIEGLMEKYGGEDLVIGGSPCNNLAGGN RVSRVGLEGDQSSLFFEYCRILEVVRARMRGS
1052	*Arabadopsis* CMT1	MAARNKQKKRAEPESDLCFAGKPMSVVESTIRWPHRYQSKKTKLQAPTKKPANK GGKKEDEEIIKQAKCHFDKALVDGVLINLNDDVYVTGLPGKLKFIAKVIELFEA DDGVPYCRERWYYRPEDTLIERFSHLVQPKRVFLSNDENDNPLTCIWSKVNIAK VPLPKITSRIEQRVIPPCDYYYDMKYEVPYLNFTSADDGSDASSSLSSDSALNC FENLHKDEKELLDLYSGCGAMSTGFCMGASISGVKLITKWSVDINKFACDSLKL NHPETEVRNEAAEDELALLKEWKRLCEKESLVSSTEPVESISELEDEEVEENDD IDEASTGAELEPGEFEVEKFLGIMFGDPQGTGEKTLQLMVRWKGYNSSYDTWEP YSGLGNCKEKLKEYVIDGFKSHLLPLPGTVYTVCGGPPCQGISGYNRYRNNEAP LEDQKNQQLLVELDIIDELKPNYVLMENVVDLLRESKGFLARHAVASFVAMNYQ TRLGMMAAGSYGLPQLRNRVFLWAAQPSEKLPPYPLPTHEVAKKENTPKEFKDL QVGRIQMEFLKLDNALTLADAISDLPPVTNYVANDVMDYNDAAPKTEFENFISL KRSETLLPAFGGDPTRRLEDHQPLVLGDDDLERVSYIPKQKGANYRDMPGVLVH NNKAEINPRFRAKLKSGKNVVPAYAISFIKGKSKKPFGRLWGDEIVNTVVTRAE PHNQCVIHPMQNRVLSVRENARLQGFPDCYKLCGTIKEKYIQVGNAVAVPVGVA LGYAFGMASQGLTDDEPVIKLPFKYPECMQAKDQI
1053	*Arabadopsis* CMT2	MLSPAKCESEEAQAPLDLHSSSRSEPECLSLVLWCPNPEEAAPSSTRELIKLPD NGEMSLRRSTTLNCNSPEENGGEGRVSQRKSSRGKSQPLLMLTNGCQLRRSPRF RALHANFDNVCSVPVTKGGVSQRKFSRGKSQPLLTLTNGCQLRRSPRFRAVDGN FDSVCSVPVTGKFGSRKRKSNSALDKKESSDSEGLTFKDIAVIAKSLEMEIISE CQYKNNVAEGRSRLQDPAKRKVDSDTLLYSSINSSKQSLGSNKRMRRSQREMKG TENEGEENLGKSKGKGMSLASCSFRRSTRLSGTVETGNTETLNRRKDCGPALCG AEQVRGTERLVQISKKDHCCEAMKKCEGDGLVSSKQELLVFPSGCIKKTVNGCR DRTLGKPRSSGLNTDDIHTSSLKISKNDTSNGLTMTTALVEQDAMESLLQGKTS ACGAADKGKTREMHVNSTVIYLSDSDEPSSIEYLNGDNLTQVESGSALSSGGNE GIVSLDLNNPTKSTKRKGKRVTRTAVQEQNKRSICFFIGEPLSCEEAQERWRWR YELKERKSKSRGQQSEDDEDKIVANVECHYSQAKVDGHTFSLGDFAYIKGEEEE

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		THVGQIVEFFKTTDGESYFRVQWFYRATDTIMERQATNHDKRRLFYSTVMNDNP VDCLISKVTVLQVSPRVGLKPNSIKSDYYFDMEYCVEYSTFQTLRNPKTSENKL ECCADVVPTESTESILKKKSFSGELPVLDLYSGCGGMSTGLSLGAKISGVDVVT KWAVDQNTAACKSLKLNHPNTQVRNDAAGDFLQLLKEWDKLCKRYVENNDQRTD TLRSVNSTKETSGSSSSSDDDSDSEEYEVEKLVDICFGDHDKTGKNGLKFKVHW KGYRSDEDTWELAEELSNCQDAIREFVTSGFKSKILPLPGRVGVICGGPPCQGI SGYNRHRNVDSPLNDERNQQIIVEMDIVEYLKPSYVLMENVVDILRMDKGSLGR YALSRLVNMRYQARLGIMTAGCYGLSQFRSRVEMWGAVPNKNLPPFPLPTHDVI VRYGLPLEFERNVVAYAEGQPRKLEKALVLKDAISDLPHVSNDEDREKLPYESL PKTDFQRYIRSTKRDLTGSAIDNCNKRTMLLHDHRPFHINEDDYARVCQIPKRK GANFRDLPGLIVRNNTVCRDPSMEPVILPSGKPLVPGYVFTFQQGKSKRPEARL WWDETVPTVLTVPTCHSQALLHPEQDRVLTIRESARLQGFPDYFQFCGTIKERY CQIGNAVAVSVSRALGYSLGMAFRGLARDEHLIKLPQNFSHSTYPQLQETIPH
1054	*Arabadopsis* CMT3	MAPKRKRPATKDDTTKSIPKPKKRAPKRAKTVKEEPVTVVEEGEKHVARELDEP IPESEAKSTWPDRYKPIEVQPPKASSRKKTKDDEKVEIIRARCHYRRAIVDERQ IYELNDDAYVQSGEGKDPFICKIIEMFEGANGKLYFTARWFYRPSDTVMKEFEI LIKKKRVFFSEIQDTNELGLLEKKLNILMIPLNENTKETIPATENCDFFCDMNY FLPYDTFEAIQQETMMAISESSTISSDTDIREGAAAISEIGECSQETEGHKKAT LLDLYSGCGAMSTGLCMGAQLSGLNLVTKWAVDMNAHACKSLQHNHPETNVRNM TAEDFLFLLKEWEKLCIHFSLRNSPNSEEYANLHGLNNVEDNEDVSEESENEDD GEVFTVDKIVGISFGVPKKLLKRGLYLKVRWLNYDDSHDTWEPIEGLSNCRGKI EEFVKLGYKSGILPLPGGVDVVCGGPPCQGISGHNRERNLLDPLEDQKNKQLLV YMNIVEYLKPKFVLMENVVDMLKMAKGYLARFAVGRLLQMNYQVRNGMMAAGAY GLAQFRLRFFLWGALPSEIIPQFPLPTHDLVHRGNIVKEFQGNIVAYDEGHTVK LADKLLLKDVISDLPAVANSEKRDEITYDKDPTTPFQKFIRLRKDEASGSQSKS KSKKHVLYDHHPLNLNINDYERVCQVPKRKGANFRDEPGVIVGPGNVVKLEEGK ERVKLESGKTLVPDYALTYVDGKSCKPFGRLWWDEIVPTVVTRAEPHNQVIIHP EQNRVLSIRENARLQGFPDDYKLFGPPKQKYIQVGNAVAVPVAKALGYALGTAF QGLAVGKDPLLTLPEGFAFMKPTLPSELA
1055	*Neurospora* Rid	MAEQNPFVIDDEDDVIQIHDEEEVEEEVAEVIDITEDDIEPSELDRAFGSRPKE ETLPSLLLRDQGFIVRPGMTVELKAPIGRFAISFVRVNSIVKVRQAHVNNVTIR GHGFTRAKEMNGMLPKQLNECCLVASIDTRDPRP
1056	*E. coli* strain 12 hsdM	MNNNDLVAKLWKLCDNLRDGGVSYQNYVNELASLLFLKMCKETGQEAEYLPEGY RWDDLKSRIGQEQLQFYRKMLVHLGEDDKKLVQAVFHNVSTTITEPKQITALVS NMDSLDWYNGAHGKSRDDFGDMYEGLLQKNANETKSGAGQYFTPRPLIKTIIHL LKPQPREVVQDPAAGTAGFLIEADRYVKSQTNDLDDLDGDTQDFQIHRAFIGLE LVPGTRRLALMNCLLHDIEGNLDHGGAIRLGNTLGSDGENLPKAHIVATNPPFG SAAGTNITRTFVHPTSNKQLCFMQHIIETLHPGGRAAVVVPDNVLFEGGKGTDI RRDLMDKCHLHTILRLPTGIFYAQGVKTNVLFFTKGTVANPNQDKNCTDDVWVY DLRTNMPSFGKRTPFTDEHLQPFERVYGEDPHGLSPRTEGEWSENAEETEVADS EENKNTDQHLATSRWRKFSREWIRTAKSDSLDISWLKDKDSIDADSLPEPDVLA AEAMGELVQALSELDALMRELGASDEADLQRQLLEEAFGGVKE
1057	*E. coli* strain 12 hsdS	MSAGKLPEGWVIAPVSTVTTLIRGVTYKKEQAINYLKDDYLPLIRANNIQNGKE DTTDLVFVPKNLVKESQKISPEDIVIAMSSGSKSVVGKSAHQHLPFECSEGAFC GVLRPEKLIFSGFIAHFTKSSLYRNKISSLSAGANINNIKPASFDLINIPIPPL AEQKIIAEKLDTLLAQVDSTKARFEQIPQILKRERQAVLGGAVNGKLTEKWRNF EPQHSVEKKLNFESILTELRNGLSSKPNESGVGHPILRISSVRAGHVDQNDIRE LECSESELNRHKLQDGDLLFTRYNGSLEFVGVCGLLKKLQHQNLLYPDKLIRAR LTKDALPEYIEIFFSSPSARNAMMNCVKTTSGQKGISGKDIKSQVVLLPPVKEQ AEIVRRVEQLFAYADTIEKQVNNALARVNNLTQSILAKAFRGELTAQWRAENPD LISGENSAAALLEKIKAERAASGGKKASRKKS
1058	*T. aquaticus* M TaqI	MGLPPLLSLPSNSAPRSLGRVETPPEVVDEMVSLAEAPRGGRVLEPACAHGPEL RAFREAHGTAYRFVGVEIDPKALDLPPWAEGILADELLWEPGEAFDLILGNPPY GIVGEASKYPIHVFKAVKDLYKKAFSTWKGKYNLYGAFLEKAVRLLKPGGVLVE VVPATWLVLEDFALLREFLAREGKTSVYYLGEVFPQKKVSAVVIRFQKSGKGLS LWDTQESESGFTPILWAEYPHWEGEIIRFETEETRKLEISGMPLGDLFHIRFAA RSPEFKKHPAVRKEPGPGLVPVLTGRNLKPGWVDYEKNHSGLWMPKERAKELRD FYATPHLVVAHTKGTRVVAAWDERAYPWREEFHLLPKEGVRLDPSSLVQWLNSE AMQKHVRTLYRDFVPHLTLRMLERLPVRREYGEHTSPESARNE
1059	*E. coli* M EcoDam	MKKNRAFLKWAGGKYPLLDDIKRHLPKGECLVEPFVGAGSVELNTDESRYILAD INSDLISLYNIVKMRTDEYVQAARELFVPETNCAEVYYQFREEENKSQDPERRA VLFLYLNRYGYNGLCRYNLRGEFNVPFGRYKKPYFPEAELYHFAEKAQNAFFYC ESYADSMARADDASVVYCDPPYAPLSATANFTAYHTNSFTLEQQAHLAEIAEGL VERHIPVLISNHDTMLTREWYQRAKLHVVKVRRSISSNGGTRKKVDELLALYKP GVVSPAKK
1060	*C. crescentus* M CcrMI	MKFGPETIIHGDCIEQMNALPEKSVDLIFADPPYNLQLGGDLLRPDNSKVDAVD DHWDQFESFAAYDKFTREWLKAARRVLKDDGAIWVIGSYHNIFRVGVAVQDLGE WILNDIVWRKSNPMPNEKGTRFANAHETLIWASKSQNAKRYTENYDALKMANDE VQMRSDWTIPLCTGEERIKGADGQKAHPTQKPEALLYRVILSTTKPGDVILDPF

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		FGVGTTGAAAKRLGRKFIGIEREAEYLEHAKARIAKVVPIAPEDLDVMGSKRAE PRVPFGTIVEAGLLSPGDTLYCSKGTHVAKVRPDGSITVGDLSGSIHKIGALVQ SAPACNGWTYWHFKTDAGLAPIDVLRAQVRAGMN
1061	*C. difficile* CamA	MDDISQDNFLLSKEYENSLDVDTKKASGIYYTPKIIVDYIVKKTLKNHDIIKNP YPRILDISCGCGNFLLEVYDILYDLFEENIYELKKKYDENYWTVDNIHRHILNY CIYGADIDEKAISILKDSLTNKKVVNDLDESDIKINLFCCDSLKKKWRYKEDYI VGNPPYIGHKKLEKKYKKFLLEKYSEVYKDKADLYFCFYKKIIDILKQGGIGSV ITPRYFLESLSGKDLREYIKSNVNVQEIVDELGANIFKNIGVSSCILTFDKKKT KETYIDVFKIKNEDICINKFETLEELLKSSKFEHFNINQRLLSDEWILVNKDDE TFYNKIQEKCKYSLEDIAISFQGIITGCDKAFILSKDDVKLNLVDDKELKCWIK SKNINKYIVDKSEYRLIYSNDIDNENTNKRILDEIIGLYKTKLENRRECKSGIR KWYELQWGREKLFFERKKIMYPYKSNENRFAIDYDNNESSADVYSFFIKEEYLD KFSYEYLVGILNSSVYDKYFKITAKKMSKNIYDYYPNKVMKIRIFRDNNYEEIE NLSKQIISILLNKSIDKGKVEKLQIKMDNLIMDSLGI
1062	KAP1	MAASAAAASAAAASAASGSPGPGEGSAGGEKRSTAPSAAASASASAAASSPAGG GAEALELLEHCGVCRERLRPEREPRLLPCLHSACSACLGPAAPAAANSSGDGGA AGDGTVVDCPVCKQQCFSKDIVENYFMRDSGSKAATDAQDANQCCTSCEDNAPA TSYCVECSEPLCETCVEAHQRVKYTKDHTVRSTGPAKSRDGERTVYCNVHKHEP LVLFCESCDTLTCRDCQLNAHKDHQYQFLEDAVRNQRKLLASLVKRLGDKHATL QKSTKEVRSSIRQVSDVQKRVQVDVKMAILQIMKELNKRGRVLVNDAQKVTEGQ QERLERQHWTMTKIQKHQEHILRFASWALESDNNTALLLSKKLIYFQLHRALKM IVDPVEPHGEMKFQWDLNAWTKSAEAFGKIVAERPGTNSTGPAPMAPPRAPGPL SKQGSGSSQPMEVQEGYGFGSGDDPYSSAEPHVSGVKRSRSGEGEVSGLMRKVP RVSLERLDLDLTADSQPPVFKVFPGSTTEDYNLIVIERGAAAAATGQPGTAPAG TPGAPPLAGMAIVKEEETEAAIGAPPTATEGPETKPVLMALAEGPGAEGPRLAS PSGSTSSGLEVVAPEGTSAPGGGPGTLDDSATICRVCQKPGDLVMCNQCEFCFH LDCHLPALQDVPGEEWSCSLCHVLPDLKEEDGSLSLDGADSTGVVAKLSPANQR KCERVLLALFCHEPCRPLHQLATDSTFSLDQPGGTLDLTLIRARLQEKLSPPYS SPQEFAQDVGRMFKQFNKLTEDKADVQSIIGLQRFFETRMNEAFGDTKFSAVLV EPPPMSLPGAGLSSQELSGGPGDGP
1063	MECP2	MVAGMLGLREEKSEDQDLQGLKDKPLKFKKVKKDKKEEKEGKHEPVQPSAHHSA EPAEAGKAETSEGSGSAPAVPEASASPKQRRSIIRDRGPMYDDPTLPEGWTRKL KQRKSGRSAGKYDVYLINPQGKAFRSKVELIAYFEKVGDTSLDPNDEDFTVTGR GSPSRREQKPPKKPKSPKAPGTGRGRGRPKGSGTTRPKAATSEGVQVKRVLEKS PGKLLVKMPFQTSPGGKAEGGGATTSTQVMVIKRPGRKRKAEADPQAIPKKRGR KPGSVVAAAAAEAKKKAVKESSIRSVQETVLPIKKRKTRETVSIEVKEVVKPLL VSTLGEKSGKGLKTCKSPGRKSKESSPKGRSSSASSPPKKEHHHHHHHSESPKA PVPLLPPLPPPPPEPESSEDPTSPPEPQDLSSSVCKEEKMPRGGSLESDGCPKE PAKTQPAVATAATAAEKYKHRGEGERKDIVSSSMPRPNREEPVDSRTPVTERVS
1064	linker	SGSETPGTSESATPES
1065	linker	SGGS
1066	linker	SGGSSGSETPGTSESATPESSGGS
1067	linker	SGGSSGGSSGSETPGTSESATPESSGGSSGGS
1068	linker	GGSGGSPGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTE EGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGPGSEPATSGGSGGS
1069	XTEN linker (XTEN16)	SGSETPGTSESATPES
1070	XTEN linker	SGGSSGGSSGSETPGTSESATPES
1071	XTEN linker	SGGSSGGSSGSETPGTSESATPESSGGSSGGSSGGSSGGS
1072	XTEN linker	SGGSSGGSSGSETPGTSESATPESSGGSSGGSSGGSSGGSSGSETPGTSESATP ESSGGSSGGS
1073	XTEN linker	PGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSTE PSEGSAPGTSTEPSEGSAPGTSESATPESGPGSEPATS
1074	NLS	PKKKRKV
1075	NLS	AVKRPAATKKAGQAKKKKLD
1076	NLS	MSRRRKANPTKLSENAKKLAKEVEN
1077	NLS	PAAKRVKLD
1078	NLS	KLKIKRPVK

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
1079	NLS	MDSLLMNRRKFLYQFKNVRWAKGRRETYLC
1092	XTEN linker (XTEN80)	GGPSSGAPPPSGGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGS PTSTEEGTSTEPSEGSAPGTSTEPSE
1236	Plasmid for fusion protein with mRNA001	CGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTAC AATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTT GGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTT GACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCG CGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATA GTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTAC ATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATT GACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC CTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCG TAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTAT CGAAATTAATACGACTCACTATAAGGAGACCCAAGCTACCGGTGCCACCATGTA CCCATACGATGTTCCAGATTACGCTTCGCCGAAGAAAAAGCGCAAGGTCAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGA CGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGG AAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACAT CTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGG AGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGA CGATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCT GATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTC TCTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTG CTACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTG GAGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGAT GTTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTT CGAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGA CCCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGT GGAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACA CACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCA GTATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGA TAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGAT GGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCG CGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGA GGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAA GTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAA GTATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCC ACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCAC CAGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGA GGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCAC CAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGA GCTCGAGTCCCGGCCAGGGGAACGGCCCTTCCAGTGTCGGATCTGCATGAGAAA CTTTTCAAAGAAGTTCAATCTCCTTCAGCATACCCGGACCCACACTGGAGAGAA ACCCTTTCAGTGCAGGATATGTATGCGGAATTTTTCCCGGCAAGATAATTTGAA TTCCCATTTGAGAACACATACCGGGAGTCAGAAGCCTTTCCAATGCCGGATTTG CATGAGGAACTTCTCCCGAAGCCATAATTTGAAACTCCATACTAGAACACATAC AGGCGAGAAGCCATTCCAGTGTAGGATCTGCATGCGCAATTTTAGCCAATCAAC CACTCTTAAACGCCATCTGAGAACGCATACAGGTAGTCAGAAGCCTTTTCAGTG CAGGATCTGCATGAGGAATTTTAGTCGCAACACGAACTTGACTAGACACACAAG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		AACGCATACTGGAGAGAAGCCCTTTCAGTGTAGGATTTGTATGCGGAACTTCAG CATTAAACACAACCTGGCAAGGCATCTGAGGACTCATTTGCGCGGGTCTAGCCC CAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGAGACCCCAGG CACATCTGAGAGCGCCACCCCTGAGTCCCGGACCCTGGTGACATTCAAGGACGT GTTCGTGGACTTCACCCGGGAGGAGTGGAAGCTGCTGGACACAGCCCAGCAGAT CGTGTACAGGAACGTGATGCTGGAGAACTATAAGAATCTGGTGTCTCTGGGCTA CCAGCTGACAAAGCCAGATGTGATCCTGCGGCTGGAGAAGGGAGAGGAGCCCTG GCTGGTGTAGTCTAGAAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGAC TGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAAT GCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTA TAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACG TGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGC CACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCAC GGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTT GGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCT GCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCC TTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCG GCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGC CGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAACTAGTGGCGCCTGATGCGGTATTTTCTCCTTACGCA TCTGTGCGGTATTTCACACCGCATAATCCAGCACAGTGGCGGCCCGTTTAAACC CGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCC TCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAA TAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGG GGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCAT GCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGCATT AATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCG CTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTAT CAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAG GAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCG CGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATC GACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGT TTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCG GATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCAC GCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGC ACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTG AGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACA GGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGC CTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTCTGCTGAAGC CAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCG CTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGAT CTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAA ACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGA TCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAA CTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCT GTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGA TACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCAC GCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGC GCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCC GGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCA TTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCT CCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAG CGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGT TATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCG TAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGT GTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGC CACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAA AACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTG CACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAA AAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTT GAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATT GTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGG TTCCGCGCACATTTCCCCGAAAAGTGCCACCTGA
1237	Plasmid for fusion protein with mRNA002	CGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTAC AATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTT GGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTT GACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCG CGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATA GTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTAC ATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATT GACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC CTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCG TAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTAT CGAAATTAATACGACTCACTATAAGGAGACCCAAGCTACCGGTGCCACCATGTA CCCATACGATGTTCCAGATTACGCTTCGCCGAAGAAAAAGCGCAAGGTCAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGA CGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGG AAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACAT CTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGG AGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGA CGATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCT GATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTC TCTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTG CTACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTG GAGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGAT GTTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTT CGAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGA CCCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGT GGAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACA CACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCA GTATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGA TAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGAT GGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCG CGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGA GGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAA GTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAA GTATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCC ACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCAC CAGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGA GGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCAC CAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGA GCTCGAGTCCCGGCCAGGGGAACGGCCCTTCCAGTGTCGGATCTGCATGAGAAA CTTTTCAAAGAAGTTCAATCTGCTTCAGCACACCCGGACCCACACTGGAGAGAA ACCCTTTCAGTGCAGGATATGTATGCGGAATTTTTCCCGAAAAGATTACTTGAT TAGCCACCTCCGAACACATACCGGGAGTCAGAAGCCTTTCCAATGCCGGATTTG CATGAGGAACTTCTCCAGGAGCCACAACCTTAAACTGCACACAAGAACACATAC AGGCGAGAAGCCATTCCAGTGTAGGATCTGCATGCGCAATTTTAGCCAATCCAC AACATTGAAAAGACATCTTCGGACGCATACAGGTAGTCAGAAGCCTTTTCAGTG CAGGATCTGCATGAGGAATTTTAGTCGACAAGATAATCTTGGCCGACATCTTCG AACGCATACTGGAGAGAAGCCCTTTCAGTGTAGGATTTGTATGCGGAACTTCAG CGTAGTAAACAACTTGAACAGACACTTGAAAACTCATTTGCGCGGGTCTAGCCC CAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGAGACCCCAGG CACATCTGAGAGCGCCACCCCTGAGTCCCGGACCCTGGTGACATTCAAGGACGT GTTCGTGGACTTCACCCGGGAGGAGTGGAAGCTGCTGGACACAGCCCAGCAGAT CGTGTACAGGAACGTGATGCTGGAGAACTATAAGAATCTGGTGTCTCTGGGCTA CCAGCTGACAAAGCCAGATGTGATCCTGCGGCTGGAGAAGGGAGAGGAGCCCTG GCTGGTGTAGTCTAGAAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGAC TGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAAT GCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTA TAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACG TGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGC CACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCAC GGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTT GGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCT GCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCC TTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCG GCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGC

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		CGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAACTAGTGGCGCCTGATGCGGTATTTTCTCCTTACGCA TCTGTGCGGTATTTCACACCGCATAATCCAGCACAGTGGCGGCCCGTTTAAACC CGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCC TCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAA TAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGG GGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCAT GCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGCATT AATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCG CTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTAT CAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAG GAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCG CGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATC GACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGT TTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCG GATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCAC GCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGC ACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTG AGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACA GGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGC CTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTCTGCTGAAGC CAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCG CTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGAT CTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAA ACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGA TCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAA CTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCT GTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGA TACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCAC GCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGC GCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCC GGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCA TTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCT CCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAG CGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGT TATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCG TAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGT GTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGC CACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAA AACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTG CACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAA AAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTT GAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATT GTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGG TTCCGCGCACATTTCCCCGAAAAGTGCCACCTGA
1238	Plasmid for fusion protein with mRNA0003	CGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTAC AATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTT GGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTT GACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCG CGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATA GTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTAC ATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATT GACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC CTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCG TAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTAT CGAAATTAATACGACTCACTATAAGGAGACCCAAGCTACCGGTGCCACCATGTA CCCATACGATGTTCCAGATTACGCTTCGCCGAAGAAAAAGCGCAAGGTCAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGA CGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGG AAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACAT CTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGG AGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGA CGATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCT GATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTC TCTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTG CTACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTG GAGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGAT GTTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTT CGAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGA CCCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGT GGAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACA CACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCA GTATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGA TAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGAT GGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCG CGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGA GGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAA GTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAA GTATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCC ACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCAC CAGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGA GGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCAC CAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGA GCTCGAGTCCCGGCCAGGGGAACGGCCCTTCCAGTGTCGGATCTGCATGAGAAA CTTTTCAAAAAAGTTTAACCTTCTCCAACACACACGAACCCACACTGGAGAGAA ACCCTTTCAGTGCAGGATATGTATGCGGAATTTTTCCAGAAAAGATTATTTGAT CAGTCATCTGCGAACACATACCGGGAGTCAGAAGCCTTTCCAATGCCGGATTTG CATGAGGAACTTCTCCAGGAGTCATAACCTCCGGTTGCACACACGCACACATAC AGGCGAGAAGCCATTCCAGTGTAGGATCTGCATGCGCAATTTTAGCCAGAGTAC GACCCTGAAGAGACATCTGCGGACGCATACAGGTAGTCAGAAGCCTTTTCAGTG CAGGATCTGCATGAGGAATTTTAGTCGGCAAGATAATTTGGGGAGACACTTGAG AACGCATACTGGAGAGAAGCCCTTTCAGTGTAGGATTTGTATGCGGAACTTCAG CGTTGTGAATAATTTGAATCGGCATCTCAAAACTCATTTGCGCGGGTCTAGCCC CAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGAGACCCCAGG CACATCTGAGAGCGCCACCCCTGAGTCCCGGACCCTGGTGACATTCAAGGACGT GTTCGTGGACTTCACCCGGGAGGAGTGGAAGCTGCTGGACACAGCCCAGCAGAT CGTGTACAGGAACGTGATGCTGGAGAACTATAAGAATCTGGTGTCTCTGGGCTA CCAGCTGACAAAGCCAGATGTGATCCTGCGGCTGGAGAAGGGAGAGGAGCCCTG GCTGGTGTAGTCTAGAAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGAC TGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAAT GCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTA TAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACG TGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGC CACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCAC GGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTT GGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCT GCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCC TTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCG GCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGC CGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAACTAGTGGCGCCTGATGCGGTATTTTCTCCTTACGCA TCTGTGCGGTATTTCACACCGCATAATCCAGCACAGTGGCGGCCCGTTTAAACC CGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCC TCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAA TAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGG GGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCAT GCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGCATT AATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCG CTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTAT CAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAG GAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCG CGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATC GACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGT TTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCG GATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCAC GCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGC ACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		AGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACA GGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGC CTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTCTGCTGAAGC CAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCG CTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGAT CTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAA ACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGA TCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAA CTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCT GTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGA TACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCAC GCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGC GCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCC GGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCA TTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCT CCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAG CGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGT TATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCG TAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGT GTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGC CACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAA AACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTG CACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAA AAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTT GAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATT GTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGG TTCCGCGCACATTTCCCCGAAAAGTGCCACCTGA
1239	Plasmid for fusion protein with mRNA0004	CGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTAC AATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTT GGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTT GACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCG CGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATA GTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTAC ATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATT GACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC CTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCG TAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTAT CGAAATTAATACGACTCACTATAAGGAGACCCAAGCTACCGGTGCCACCATGTA CCCATACGATGTTCCAGATTACGCTTCGCCGAAGAAAAAGCGCAAGGTCAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGA CGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGG AAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACAT CTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGG AGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGA CGATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCT GATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTC TCTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTG CTACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTG GAGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGAT GTTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTT CGAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		CCCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGT GGAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACA CACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCA GTATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGA TAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGAT GGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCG CGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGA GGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAA GTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAA GTATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCC ACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCAC CAGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGA GGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCAC CAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGA GCTCGAGTCCCGGCCAGGGGAACGGCCCTTCCAGTGTCGGATCTGCATGAGAAA CTTTTCACGACGCCACATTTTGGACAGACATACTCGGACCCACACTGGAGAGAA ACCCTTTCAGTGCAGGATATGTATGCGGAATTTTTCCCGCCAGGACAACTTGGG GCGGCATCTGCGCACACATACCGGGAGTCAGAAGCCTTTCCAATGCCGGATTTG CATGAGGAACTTCTCCCAATCTACCACTCTTAAACGACACTTGCGCACACATAC AGGCGAGAAGCCATTCCAGTGTAGGATCTGCATGCGCAATTTTAGCCGCCGGGA CGGCCTGGCAGGGCACCTTAAGACGCATACAGGTAGTCAGAAGCCTTTTCAGTG CAGGATCTGCATGAGGAATTTTAGTGTTCATCATAACCTCGTTAGGCATCTGAG AACGCATACTGGAGAGAAGCCCTTTCAGTGTAGGATTTGTATGCGGAACTTCAG CATCAGTCACAATTTGGCGCGGCACCTTAAGACTCATTTGCGCGGGTCTAGCCC CAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGAGACCCCAGG CACATCTGAGAGCGCCACCCCTGAGTCCCGGACCCTGGTGACATTCAAGGACGT GTTCGTGGACTTCACCCGGGAGGAGTGGAAGCTGCTGGACACAGCCCAGCAGAT CGTGTACAGGAACGTGATGCTGGAGAACTATAAGAATCTGGTGTCTCTGGGCTA CCAGCTGACAAAGCCAGATGTGATCCTGCGGCTGGAGAAGGGAGAGGAGCCCTG GCTGGTGTAGTCTAGAAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGAC TGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAAT GCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTA TAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACG TGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGC CACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCAC GGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTT GGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCT GCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCC TTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCG GCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGC CGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAACTAGTGGCGCCTGATGCGGTATTTTCTCCTTACGCA TCTGTGCGGTATTTCACACCGCATAATCCAGCACAGTGGCGGCCCGTTTAAACC CGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCC TCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAA TAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGG GGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCAT GCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGCATT AATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCG CTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTAT CAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAG GAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCG CGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATC GACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGT TTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCG GATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCAC GCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGC ACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTG AGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACA GGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGC CTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTCTGCTGAAGC CAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCG CTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGAT CTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAA ACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGA TCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAA CTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCT GTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGA TACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCAC GCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGC GCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCC GGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCA TTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCT CCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAG CGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGT TATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		TAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGT GTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGC CACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAA AACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTG CACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAA AAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTT GAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATT GTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGG TTCCGCGCACATTTCCCCGAAAAGTGCCACCTGA
1240	Plasmid for fusion protein with mRNA0005	CGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTAC AATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTT GGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTT GACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCG CGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATA GTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTAC ATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATT GACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC CTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCG TAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTAT CGAAATTAATACGACTCACTATAAGGAGACCCAAGCTACCGGTGCCACCATGTA CCCATACGATGTTCCAGATTACGCTTCGCCGAAGAAAAAGCGCAAGGTCAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGA CGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGG AAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACAT CTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGG AGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGA CGATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCT GATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTC TCTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTG CTACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTG GAGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGAT GTTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTT CGAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGA CCCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGT GGAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACA CACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCA GTATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGA TAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGAT GGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCG CGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGA GGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAA GTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAA GTATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCC ACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCAC CAGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGA GGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCAC CAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGA GCTCGAGTCCCGGCCAGGGGAACGGCCCTTCCAGTGTCGGATCTGCATGAGAAA CTTTTCACGCCGGGAGGTATTGGAAAACCATTTGCGAACCCACACTGGAGAGAA ACCCTTTCAGTGCAGGATATGTATGCGGAATTTTTCCCGGCGGGATAATCTCAA TCGGCACTTGAAAACACATACCGGGAGTCAGAAGCCTTTCCAATGCCGGATTTG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		CATGAGGAACTTCTCCCAATCCACTACCCTCAAGCGACATCTGCGGACACATAC AGGCGAGAAGCCATTCCAGTGTAGGATCTGCATGCGCAATTTTAGCCGAAGGGA TGGGCTGGCGGGCCATCTTAAGACGCATACAGGTAGTCAGAAGCCTTTTCAGTG CAGGATCTGCATGAGGAATTTTAGTGTCCATCACAACCTGGTCAGACACCTTAG GACGCATACTGGAGAGAAGCCCTTTCAGTGTAGGATTTGTATGCGGAACTTCAG CATATCACATAACCTTGCCCGACACTTGAAGACTCATTTGCGCGGGTCTAGCCC CAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGAGACCCCAGG CACATCTGAGAGCGCCACCCCTGAGTCCCGGACCCTGGTGACATTCAAGGACGT GTTCGTGGACTTCACCCGGGAGGAGTGGAAGCTGCTGGACACAGCCCAGCAGAT CGTGTACAGGAACGTGATGCTGGAGAACTATAAGAATCTGGTGTCTCTGGGCTA CCAGCTGACAAAGCCAGATGTGATCCTGCGGCTGGAGAAGGGAGAGGAGCCCTG GCTGGTGTAGTCTAGAAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGAC TGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAAT GCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTA TAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACG TGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGC CACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCAC GGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTT GGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCT GCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCC TTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCG GCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGC CGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAACTAGTGGCGCCTGATGCGGTATTTTCTCCTTACGCA TCTGTGCGGTATTTCACACCGCATAATCCAGCACAGTGGCGGCCCGTTTAAACC CGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCC TCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAA TAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGG GGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCAT GCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGCATT AATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCG CTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTAT CAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAG GAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCG CGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATC GACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGT TTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCG GATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCAC GCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGC ACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTG AGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACA GGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGC CTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTCTGCTGAAGC CAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCG CTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGAT CTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAA ACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGA TCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAA CTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCT GTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGA TACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCAC GCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGC GCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCC GGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCA TTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCT CCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAG CGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGT TATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCG TAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGT GTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGC CACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAA AACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTG CACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAA AAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTT GAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATT GTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGG TTCCGCGCACATTTCCCCGAAAAGTGCCACCTGA
1241	Plasmid for fusion fusion protein with mRNA0006	CGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTAC AATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTT GGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTT GACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCG CGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATA GTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTAC ATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATT GACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC CTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCG TAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTAT CGAAATTAATACGACTCACTATAAGGAGACCCAAGCTACCGGTGCCACCATGTA CCCATACGATGTTCCAGATTACGCTTCGCCGAAGAAAAAGCGCAAGGTCAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGA CGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGG AAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACAT CTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGG AGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGA CGATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCT GATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTC TCTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTG CTACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTG GAGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGAT GTTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTT CGAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGA CCCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGT GGAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACA CACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCA GTATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGA TAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGAT GGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCG CGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGA GGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAA GTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAA GTATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCC ACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCAC CAGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGA GGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCAC CAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGA GCTCGAGTCCCGGCCAGGGGAACGGCCCTTCCAGTGTCGGATCTGCATGAGAAA CTTTTCACGCAGGGCAGTGTTGGATAGACATACCCGGACCCACACTGGAGAGAA ACCCTTTCAGTGCAGGATATGTATGCGGAATTTTTCCCGACAAGATAATCTGGG GAGGCATCTGCGGACACATACCGGGAGTCAGAAGCCTTTCCAATGCCGGATTTG CATGAGGAACTTCTCCCAATCAACTACCCTGAAGCGACATCTGCGCACACATAC AGGCGAGAAGCCATTCCAGTGTAGGATCTGCATGCGCAATTTTAGCCGCCGCGA TGGGCTGGCTGGACACCTGAAGACGCATACAGGTAGTCAGAAGCCTTTTCAGTG CAGGATCTGCATGAGGAATTTTAGTGTTCATCACAACTTGGTCCGACACCTTCG GACGCATACTGGAGAGAAGCCCTTTCAGTGTAGGATTTGTATGCGGAACTTCAG CATTTCACACAACCTCGCGCGCCACTTGAAAACTCATTTGCGCGGGTCTAGCCC CAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGAGACCCCAGG CACATCTGAGAGCGCCACCCCTGAGTCCCGGACCCTGGTGACATTCAAGGACGT GTTCGTGGACTTCACCCGGGAGGAGTGGAAGCTGCTGGACACAGCCCAGCAGAT CGTGTACAGGAACGTGATGCTGGAGAACTATAAGAATCTGGTGTCTCTGGGCTA CCAGCTGACAAAGCCAGATGTGATCCTGCGGCTGGAGAAGGGAGAGGAGCCCTG GCTGGTGTAGTCTAGAAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGAC TGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAAT GCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTA TAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACG TGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGC CACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCAC GGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTT

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		GGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCT GCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCC TTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCG GCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGC CGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAACTAGTGGCGCCTGATGCGGTATTTTCTCCTTACGCA TCTGTGCGGTATTTCACACCGCATAATCCAGCACAGTGGCGGCCCGTTTAAACC CGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCC TCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAA TAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGG GGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCAT GCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGCATT AATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCG CTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTAT CAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAG GAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCG CGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATC GACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGT TTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCG GATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCAC GCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGC ACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTG AGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACA GGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGC CTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTCTGCTGAAGC CAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCG CTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGAT CTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAA ACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGA TCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAA CTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCT GTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGA TACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCAC GCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGC GCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCC GGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCA TTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCT CCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAG CGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGT TATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCG TAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGT GTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGC CACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAA AACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTG CACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAA AAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTT GAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATT GTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGG TTCCGCGCACATTTCCCCGAAAAGTGCCACCTGA
1242	Plasmid for fusion protein with mRNA0021	CGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTAC AATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTT GGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTT GACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCG CGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATA GTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTAC ATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATT GACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC CTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCG TAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTAT CGAAATTAATACGACTCACTATAAGGAGACCCAAGCTACCGGTGCCACCATGTA CCCATACGATGTTCCAGATTACGCTTCGCCGAAGAAAAAGCGCAAGGTCAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGA CGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGG AAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACAT CTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGG AGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGA CGATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCT GATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTC TCTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTG CTACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTG GAGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGAT GTTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTT CGAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGA CCCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGT GGAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACA CACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCA GTATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGA TAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGAT GGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCG CGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGA GGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAA GTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAA GTATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCC ACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCAC CAGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGA GGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCAC CAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGA GCTCGAGTCCCGGCCAGGGGAACGGCCCTTCCAGTGTCGGATCTGCATGAGAAA CTTTTCAAGAGCAGATAATCTGGGTCGGCACCTCCGCACCCACACTGGAGAGAA ACCCTTTCAGTGCAGGATATGTATGCGGAATTTTTCCCGCAACACGCATCTCAG TTATCACCTTAAAACACATACCGGGAGTCAGAAGCCTTTCCAATGCCGGATTTG CATGAGGAACTTCTCCAGGGGCGACGGCTTGAGGCGGCATCTTCGCACACATAC AGGCGAGAAGCCATTCCAGTGTAGGATCTGCATGCGCAATTTTAGCCGCAGAGA CAATTTGAACAGACATCTCAAAACGCATACAGGTAGTCAGAAGCCTTTTCAGTG CAGGATCTGCATGAGGAATTTTAGTCGAGCAAGAAACTTGACGCTGCACACCCG GACGCATACTGGAGAGAAGCCCTTTCAGTGTAGGATTTGTATGCGGAACTTCAG CGACCCTTCATCTTTGAAGCGCCATCTTCGCACTCATTTGCGCGGGTCTAGCCC CAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGAGACCCCAGG CACATCTGAGAGCGCCACCCCTGAGTCCCGGACCCTGGTGACATTCAAGGACGT GTTCGTGGACTTCACCCGGGAGGAGTGGAAGCTGCTGGACACAGCCCAGCAGAT CGTGTACAGGAACGTGATGCTGGAGAACTATAAGAATCTGGTGTCTCTGGGCTA CCAGCTGACAAAGCCAGATGTGATCCTGCGGCTGGAGAAGGGAGAGGAGCCCTG GCTGGTGTAGTCTAGAAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGAC TGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAAT GCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTA TAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACG TGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGC CACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCAC GGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTT GGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCT GCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCC TTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCG GCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGC CGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAACTAGTGGCGCCTGATGCGGTATTTTCTCCTTACGCA TCTGTGCGGTATTTCACACCGCATAATCCAGCACAGTGGCGGCCCGTTTAAACC CGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCC TCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAA TAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGG GGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCAT GCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGCATT AATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCG CTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTAT CAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAG GAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCG CGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATC GACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGT

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		TTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCG GATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCAC GCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGC ACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTG AGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACA GGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGC CTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTCTGCTGAAGC CAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCG CTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGAT CTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAA ACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGA TCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAA CTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCT GTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGA TACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCAC GCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGC GCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCC GGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCA TTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCT CCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAG CGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGT TATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCG TAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGT GTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGC CACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAA AACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTG CACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAA AAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTT GAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATT GTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGG TTCCGCGCACATTTCCCCGAAAAGTGCCACCTGA
1243	Plasmid for fusion protein with mRNA0037	CGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTAC AATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTT GGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTT GACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCG CGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATA GTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTAC ATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATT GACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC CTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCG TAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTAT CGAAATTAATACGACTCACTATAAGGAGACCCAAGCTACCGGTGCCACCATGTA CCCATACGATGTTCCAGATTACGCTTCGCCGAAGAAAAAGCGCAAGGTCAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGA CGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGG AAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACAT CTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGG AGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGA CGATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCT GATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTC TCTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		CTACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTG GAGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGAT GTTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTT CGAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGA CCCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGT GGAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACA CACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCA GTATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGA TAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGAT GGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCG CGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGA GGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAA GTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAA GTATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCC ACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCAC CAGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGA GGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCAC CAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGA GCTCGAGTCCCGGCCAGGGGAACGGCCCTTCCAGTGTCGGATCTGCATGAGAAA CTTTTCAAGAGTGGATCATCTCCATCGACACCTCCGGACCCACACTGGAGAGAA ACCCTTTCAGTGCAGGATATGTATGCGGAATTTTTCCCGGAGGGAACATTTGTC CGGACATCTCAAGACACATACCGGGGGAGGCGGTAGTCAGAAGCCTTTCCAATG CCGGATTTGCATGAGGAACTTCTCCCAAAGTTCCAGCCTCGTCCGCCATCTTCG CACACATACAGGCGAGAAGCCATTCCAGTGTAGGATCTGCATGCGCAATTTTAG CCGCAAGGAGCGATTGGCAACCCACCTCAAGACGCATACAGGTAGTCAGAAGCC TTTTCAGTGCAGGATCTGCATGAGGAATTTTAGTGTCGCACATAACCTCACAAG GCATCTGCGCACGCATACTGGAGAGAAGCCCTTTCAGTGTAGGATTTGTATGCG GAACTTCAGCATTAGTCATAACCTGGCAAGGCATCTCAAAACTCATTTGCGCGG GTCTAGCCCCAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGA GACCCCAGGCACATCTGAGAGCGCCACCCCTGAGTCCCGGACCCTGGTGACATT CAAGGACGTGTTCGTGGACTTCACCCGGGAGGAGTGGAAGCTGCTGGACACAGC CCAGCAGATCGTGTACAGGAACGTGATGCTGGAGAACTATAAGAATCTGGTGTC TCTGGGCTACCAGCTGACAAAGCCAGATGTGATCCTGCGGCTGGAGAAGGGAGA GGAGCCCTGGCTGGTGTAGTCTAGAAATCAACCTCTGGATTACAAAATTTGTGA AAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGC TGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTC CTCCTTGTATAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGT CAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTG GGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCC TATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGC TCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTT TCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTG CTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCC GGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTC CCTTTGGGCCGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAACTAGTGGCGCCTGATGCGGTATTTTCT CCTTACGCATCTGTGCGGTATTTCACACCGCATAATCCAGCACAGTGGCGGCCC GTTTAAACCCGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTT GTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTC CTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCT ATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAAT AGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACC AGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGC GCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGC GAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGG ATAACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTA AAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATC ACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGAT ACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGC CGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTC ATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGG GCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACT ATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCA CTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGA AGTGGTGGCCTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTC TGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAAC AAACCACCGCTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAA AAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGT GGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCT TCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATAT ATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCT CAGCGATCTGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGA TAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGC GAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAA GGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTA ATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		TTGTTGCCATTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTT CATTCAGCTCCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGT GCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGG CCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCA TGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCT GAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATA ATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTT CGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAAC CCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTG GGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACAC GGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATC AGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAAC AAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACCTGA
1244	Plasmid for fusion protein with mRNA0038	CGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTAC AATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTT GGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTT GACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCG CGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATA GTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTAC ATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATT GACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC CTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCG TAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTAT CGAAATTAATACGACTCACTATAAGGAGACCCAAGCTACCGGTGCCACCATGTA CCCATACGATGTTCCAGATTACGCTTCGCCGAAGAAAAAGCGCAAGGTCAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGA CGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGG AAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACAT CTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGG AGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGA CGATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCT GATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTC TCTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTG CTACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTG GAGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGAT GTTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTT CGAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGA CCCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGT GGAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACA CACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCA GTATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGA TAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGAT GGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCG CGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGA GGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAA GTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAA GTATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCC ACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCAC CAGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGA GGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCAC CAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		GCTCGAGTCCCGGCCAGGGGAACGGCCCTTCCAGTGTCGGATCTGCATGAGAAA CTTTTCACGCAAGCACCACCTTGGGAGACATACCAGAACCCACACTGGAGAGAA ACCCTTTCAGTGCAGGATATGTATGCGGAATTTTTCCCGACGGGAACACCTCAC GATTCATTTGCGGACACATACCGGGGGAGGCGGTAGTCAGAAGCCTTTCCAATG CCGGATTTGCATGAGGAACTTCTCCCAGAGCTCATCTCTCGTGCGGCACCTGCG GACACATACAGGCGAGAAGCCATTCCAGTGTAGGATCTGCATGCGCAATTTTAG CCGGAAGGAGCGATTGGCGACGCACCTGAAAACGCATACAGGTAGTCAGAAGCC TTTTCAGTGCAGGATCTGCATGAGGAATTTTAGTGTAGCCCACAACCTGACTAG GCATTTGAGGACGCATACTGGAGAGAAGCCCTTTCAGTGTAGGATTTGTATGCG GAACTTCAGCATTTCTCACAATCTCGCGCGACATTTGAAAACTCATTTGCGCGG GTCTAGCCCCAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGA GACCCCAGGCACATCTGAGAGCGCCACCCCTGAGTCCCGGACCCTGGTGACATT CAAGGACGTGTTCGTGGACTTCACCCGGGAGGAGTGGAAGCTGCTGGACACAGC CCAGCAGATCGTGTACAGGAACGTGATGCTGGAGAACTATAAGAATCTGGTGTC TCTGGGCTACCAGCTGACAAAGCCAGATGTGATCCTGCGGCTGGAGAAGGGAGA GGAGCCCTGGCTGGTGTAGTCTAGAAATCAACCTCTGGATTACAAAATTTGTGA AAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGC TGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTC CTCCTTGTATAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGT CAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTG GGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCC TATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGC TCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTT TCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTG CTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCC GGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTC CCTTTGGGCCGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAACTAGTGGCGCCTGATGCGGTATTTTCT CCTTACGCATCTGTGCGGTATTTCACACCGCATAATCCAGCACAGTGGCGGCCC GTTTAAACCCGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTT GTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTC CTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCT ATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAAT AGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACC AGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGC GCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGC GAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGG ATAACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTA AAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATC ACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGAT ACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGC CGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTC ATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGG GCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACT ATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCA CTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGA AGTGGTGGCCTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTC TGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAAC AAACCACCGCTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAA AAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGT GGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCT TCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATAT ATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCT CAGCGATCTGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGA TAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGC GAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAA GGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTA ATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACG TTGTTGCCATTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTT CATTCAGCTCCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGT GCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGG CCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCA TGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCT GAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATA ATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTT CGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAAC CCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTG GGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACAC GGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATC AGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAAC AAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACCTGA
1245	Plasmid for fusion protein with mRNA0039	CGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTAC AATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTT GGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTT GACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		CGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATA GTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTAC ATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATT GACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC CTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCG TAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT CTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTAT CGAAATTAATACGACTCACTATAAGGAGACCCAAGCTACCGGTGCCACCATGTA CCCATACGATGTTCCAGATTACGCTTCGCCGAAGAAAAAGCGCAAGGTCAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGA CGTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGG AAGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACAT CTGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGG AGGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGA CGATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCT GATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTC TCTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTG CTACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTG GAGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGAT GTTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTT CGAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGA CCCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGT GGAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACA CACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCA GTATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGA TAATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGAT GGAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCG CGTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGA GGAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAA GTGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAA GTATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCC ACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCAC CAGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGA GGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCAC CAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGA GCTCGAGTCCCGGCCAGGGGAACGGCCCTTCCAGTGTCGGATCTGCATGAGAAA CTTTTCACGAGTCGATCACCTCCACCGCCACCTGCGAACCCACACTGGAGAGAA ACCCTTTCAGTGCAGGATATGTATGCGGAATTTTTCCAGGTCCGACCACCTCAG CTTGCACTTGAAGACACATACCGGGGGAGGCGGTAGTCAGAAGCCTTTCCAATG CCGGATTTGCATGAGGAACTTCTCCCAATCTAGTTCATTGGTACGACATCTTAG GACACATACAGGCGAGAAGCCATTCCAGTGTAGGATCTGCATGCGCAATTTTAG CCGAAAAGAGCGGCTGGCGACCCACTTGAAAACGCATACAGGTAGTCAGAAGCC TTTTCAGTGCAGGATCTGCATGAGGAATTTTAGTGTAGCGCATAACTTGACACG GCACTTGCGCACGCATACTGGAGAGAAGCCCTTTCAGTGTAGGATTTGTATGCG GAACTTCAGCATTTCCCATAATCTGGCGCGGCACCTGAAGACTCATTTGCGCGG GTCTAGCCCCAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGA GACCCCAGGCACATCTGAGAGCGCCACCCCTGAGTCCCGGACCCTGGTGACATT CAAGGACGTGTTCGTGGACTTCACCCGGGAGGAGTGGAAGCTGCTGGACACAGC CCAGCAGATCGTGTACAGGAACGTGATGCTGGAGAACTATAAGAATCTGGTGTC TCTGGGCTACCAGCTGACAAAGCCAGATGTGATCCTGCGGCTGGAGAAGGGAGA GGAGCCCTGGCTGGTGTAGTCTAGAAATCAACCTCTGGATTACAAAATTTGTGA AAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGC TGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTC

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		CTCCTTGTATAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGT CAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTG GGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCC TATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGC TCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTT TCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTG CTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCC GGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTC CCTTTGGGCCGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAACTAGTGGCGCCTGATGCGGTATTTTCT CCTTACGCATCTGTGCGGTATTTCACACCGCATAATCCAGCACAGTGGCGGCCC GTTTAAACCCGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTT GTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTC CTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCT ATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAAT AGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACC AGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGC GCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGC GAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGG ATAACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTA AAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATC ACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGAT ACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGC CGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTC ATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGG GCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACT ATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCA CTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGA AGTGGTGGCCTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTC TGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAAC AAACCACCGCTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAA AAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGT GGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCT TCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATAT ATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCT CAGCGATCTGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGA TAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGC GAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAA GGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTA ATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACG TTGTTGCCATTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTT CATTCAGCTCCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGT GCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGG CCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCA TGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCT GAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATA ATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTT CGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAAC CCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTG GGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACAC GGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATC AGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAAC AAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACCTGA
1246	Plasmid for expression of CRISPR-Off fusion protein (nt)	GGGCGCTCGAGCAGGTTCAGAAGGAGATCAAAAACCCCCAAGGATCAAACATGC CAAAAAAGAAGAGAAAGGTACCGAAGAAAAAAAGAAAGGTATACAATCACGATC AGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAGGAAGC CAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGTGCTGA AGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGAGGATT CTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGGCGACG TGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCTGGTGA TCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAAGGGAC TGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCACGACG CCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAATGTGG TGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTCTAACC CCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTATTTCT GGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGACAAGC TGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAAGGTGC GCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCACTTCC CCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGAGAGAG TGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCTGGCAA GGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCTGTTCG CCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGCCAACA GCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGGCTCCC ACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGACGTGA TCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGGAAGGG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		ATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACATCTGTA TCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGGAGGAA TCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGACGATG ACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCTGATCT GCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTCTCTGG TGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTGCTACC TGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTGGAGAT CCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGATGTTTG AGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTTCGAGG ATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGACCCCG GACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGTGGAGG AGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACACACAT GCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCAGTATG CAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGATAATC TGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGATGGAGC CAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCGCGTGT GGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGAGGAGG AGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAAGTGGC CTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAAGTATT TTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCCACCAC CTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCACCAGCG AGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGAGGGCT CTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCACCAGCA CAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGAGCTCG AGGACAAGAAGTACAGCATCGGCCTGGCCATCGGCACCAACTCTGTGGGCTGGG CCGTGATCACCGACGAGTACAAGGTGCCCAGCAAGAAATTCAAGGTGCTGGGCA ACACCGACCGGCACAGCATCAAGAAGAACCTGATCGGAGCCCTGCTGTTCGACA GCGGCGAAACAGCCGAGGCCACCCGGCTGAAGAGAACCGCCAGAAGAAGATACA CCAGACGGAAGAACCGGATCTGCTATCTGCAAGAGATCTTCAGCAACGAGATGG CCAAGGTGGACGACAGCTTCTTCCACAGACTGGAAGAGTCCTTCCTGGTGGAAG AGGATAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGG CCTACCACGAGAAGTACCCCACCATCTACCACCTGAGAAAGAAACTGGTGGACA GCACCGACAAGGCCGACCTGCGGCTGATCTATCTGGCCCTGGCCCACATGATCA AGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACAGCGACG TGGACAAGCTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGAAA ACCCCATCAACGCCAGCGGCGTGGACGCCAAGGCCATCCTGTCTGCCAGACTGA GCAAGAGCAGACGGCTGGAAAATCTGATCGCCCAGCTGCCCGGCGAGAAGAAGA ATGGCCTGTTCGGCAACCTGATTGCCCTGAGCCTGGGCCTGACCCCCAACTTCA AGAGCAACTTCGACCTGGCCGAGGATGCCAAACTGCAGCTGAGCAAGGACACCT ACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTACGCCGACC TGTTTCTGGCCGCCAAGAACCTGTCCGACGCCATCCTGCTGAGCGACATCCTGA GAGTGAACACCGAGATCACCAAGGCCCCCCTGAGCGCCTCTATGATCAAGAGAT ACGACGAGCACCACCAGGACCTGACCCTGCTGAAAGCTCTCGTGCGGCAGCAGC TGCCTGAGAAGTACAAAGAGATTTTCTTCGACCAGAGCAAGAACGGCTACGCCG GCTACATTGACGGCGGAGCCAGCCAGGAAGAGTTCTACAAGTTCATCAAGCCCA TCCTGGAAAAGATGGACGGCACCGAGGAACTGCTCGTGAAGCTGAACAGAGAGG ACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAGATCC ACCTGGGAGAGCTGCACGCCATTCTGCGGCGGCAGGAAGATTTTTACCCATTCC TGAAGGACAACCGGGAAAAGATCGAGAAGATCCTGACCTTCCGCATCCCCTACT ACGTGGGCCCTCTGGCCAGGGGAAACAGCAGATTCGCCTGGATGACCAGAAAGA GCGAGGAAACCATCACCCCCTGGAACTTCGAGGAAGTGGTGGACAAGGGCGCTT CCGCCCAGAGCTTCATCGAGCGGATGACCAACTTCGATAAGAACCTGCCCAACG AGAAGGTGCTGCCCAAGCACAGCCTGCTGTACGAGTACTTCACCGTGTATAACG AGCTGACCAAAGTGAAATACGTGACCGAGGGAATGAGAAAGCCCGCCTTCCTGA GCGGCGAGCAGAAAAAGGCCATCGTGGACCTGCTGTTCAAGACCAACCGGAAAG TGACCGTGAAGCAGCTGAAAGAGGACTACTTCAAGAAAATCGAGTGCTTCGACT CCGTGGAAATCTCCGGCGTGGAAGATCGGTTCAACGCCTCCCTGGGCACATACC ACGATCTGCTGAAAATTATCAAGGACAAGGACTTCCTGGACAATGAGGAAAACG AGGACATTCTGGAAGATATCGTGCTGACCCTGACACTGTTTGAGGACAGAGAGA TGATCGAGGAACGGCTGAAAACCTATGCCCACCTGTTCGACGACAAAGTGATGA AGCAGCTGAAGCGGCGGAGATACACCGGCTGGGGCAGGCTGAGCCGGAAGCTGA TCAACGGCATCCGGGACAAGCAGTCCGGCAAGACAATCCTGGATTTCCTGAAGT CCGACGGCTTCGCCAACAGAAACTTCATGCAGCTGATCCACGACGACAGCCTGA CCTTTAAAGAGGACATCCAGAAAGCCCAGGTGTCCGGCCAGGGCGATAGCCTGC ACGAGCACATTGCCAATCTGGCCGGCAGCCCCGCCATTAAGAAGGGCATCCTGC AGACAGTGAAGGTGGTGGACGAGCTCGTGAAAGTGATGGGCCGGCACAAGCCCG AGAACATCGTGATCGAAATGGCCAGAGAGAACCAGACCACCCAGAAGGGACAGA AGAACAGCCGCGAGAGAATGAAGCGGATCGAAGAGGGCATCAAAGAGCTGGGCA GCCAGATCCTGAAAGAACACCCCGTGGAAAACACCCAGCTGCAGAACGAGAAGC TGTACCTGTACTACCTGCAGAATGGGGGGGATATGTACGTGGACCAGGAACTGG ACATCAACCGGCTGTCCGACTACGATGTGGACGCCATCGTGCCTCAGAGCTTTC TGAAGGACGACTCCATCGACAACAAGGTGCTGACCAGAAGCGACAAGAACCGGG GCAAGAGCGACAACGTGCCCTCCGAAGAGGTCGTGAAGAAGATGAAGAACTACT GGCGGCAGCTGCTGAACGCCAAGCTGATTACCCAGAGAAAGTTCGACAATCTGA CCAAGGCCGAGAGAGGCGGCCTGAGCGAACTGGATAAGGCCGGCTTCATCAAGA GACAGCTGGTGGAAACCCGGCAGATCACAAAGCACGTGGCACAGATCCTGGACT

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		CCCGGATGAACACTAAGTACGACGAGAATGACAAGCTGATCCGGGAAGTGAAAG TGATCACCCTGAAGTCCAAGCTGGTGTCCGATTTCCGGAAGGATTTCCAGTTTT ACAAAGTGCGCGAGATCAACAACTACCACCACGCCCACGACGCCTACCTGAACG CCGTCGTGGGAACCGCCCTGATCAAAAAGTACCCTAAGCTGGAAAGCGAGTTCG TGTACGGCGACTACAAGGTGTACGACGTGCGGAAGATGATCGCCAAGAGCGAGC AGGAAATCGGCAAGGCTACCGCCAAGTACTTCTTCTACAGCAACATCATGAACT TTTTCAAGACCGAGATTACCCTGGCCAACGGCGAGATCCGGAAGCGGCCTCTGA TCGAGACAAACGGCGAAACCGGGGAGATCGTGTGGGATAAGGGCCGGGATTTTG CCACCGTGCGGAAAGTGCTGAGCATGCCCCAAGTGAATATCGTGAAAAAGACCG AGGTGCAGACAGGCGGCTTCAGCAAAGAGTCTATCCTGCCCAAGAGGAACAGCG ATAAGCTGATCGCCAGAAAGAAGGACTGGGACCCTAAGAAGTACGGCGGCTTCG ACAGCCCCACCGTGGCCTATTCTGTGCTGGTGGTGGCCAAAGTGGAAAAGGGCA AGTCCAAGAAACTGAAGAGTGTGAAAGAGCTGCTGGGGATCACCATCATGGAAA GAAGCAGCTTCGAGAAGAATCCCATCGACTTTCTGGAAGCCAAGGGCTACAAAG AAGTGAAAAAGGACCTGATCATCAAGCTGCCTAAGTACTCCCTGTTCGAGCTGG AAAACGGCCGGAAGAGAATGCTGGCCTCTGCCGGCGAACTGCAGAAGGGAAACG AACTGGCCCTGCCCTCCAAATATGTGAACTTCCTGTACCTGGCCAGCCACTATG AGAAGCTGAAGGGCTCCCCCGAGGATAATGAGCAGAAACAGCTGTTTGTGGAAC AGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGCGAGTTCTCCAAGA GAGTGATCCTGGCCGACGCTAATCTGGACAAAGTGCTGTCCGCCTACAACAAGC ACCGGGATAAGCCCATCAGAGAGCAGGCCGAGAATATCATCCACCTGTTTACCC TGACCAATCTGGGAGCCCCTGCCGCCTTCAAGTACTTTGACACCACCATCGACC GGAAGAGGTACACCAGCACCAAAGAGGTGCTGGACGCCACCCTGATCCACCAGA GCATCACCGGCCTGTACGAGACACGGATCGACCTGTCTCAGCTGGGAGGCGACA GCCCCAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGAGACCC CAGGCACATCTGAGAGCGCCACCCCTGAGTCCACCGGTATGAACAATTCACAGG GGAGAGTGACATTCGAAGACGTGACCGTGAACTTCACCCAGGGAGAATGGCAGC GCTTGAACCCAGAACAAAGGAACCTCTATCGGGACGTGATGCTGGAAAACTACT CAAATTTGGTGAGCGTTGGGCAGGGTGAGACCACTAAGCCTGACGTGATCCTGA GATTGGAACAGGGCAAGGAGCCTTGGCTCGAGGAAGAGGAAGTCCTGGGCTCAG GGAGGGCCGAGAAAAACGGTGATATAGGAGGCCAGATATGGAAGCCTAAGGACG TCAAGGAGAGCCTGAGCGCTCCCAAGAAGAAAAGGAAGGTCCCAAAGAAAAAAA GAAAGGTGTGAGGATCCTGAGTCTAGAAATCAACCTCTGGATTACAAAATTTGT GAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATAC GCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTC TCCTCCTTGTATAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTT GTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGT TGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTC CCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGG GCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCC TTTCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTC TGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTG CCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATC TCCCTTTGGGCCGCCTCCCCGCCTGTTAATTAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAGCTTGAAGAGCCTAGTGGCGCCTGATGCGG TATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATAATCCAGCACAGT GGCGGCCCGTTTAAACCCGCTGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGC CATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTC CCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGT GTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGG AAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGG AAAGAACCAGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCG TATTGGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCG GCTGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGA ATCAGGGGATAACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAG GAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGA CGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACT ATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCC GACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGC GCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTC CAAGCTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATC CGGTAACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGC AGCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGA GTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGAACAGTATTTGGTAT CTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATC CGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGAT TACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTC TGACGCTCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATC AAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAAT CTAAAGTATATATGAGTAAACTTGGTCTGACAGTTAGAAAAACTCATCGAGCAT CAAATGAAACTGCAATTTATTCATATCAGGATTATCAATACCATATTTTTGAAA AAGCCGTTTCTGTAATGAAGGAGAAAACTCACCGAGGCAGTTCCATAGGATGGC AAGATCCTGGTATCGGTCTGCGATTCCGACTCGTCCAACATCAATACAACCTAT TAATTTCCCCTCGTCAAAAATAAGGTTATCAAGTGAGAAATCACCATGAGTGAC GACTGAATCCGGTGAGAATGGCAAAAGTTTATGCATTTCTTTCCAGACTTGTTC

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		AACAGGCCAGCCATTACGCTCGTCATCAAAATCACTCGCATCAACCAAACCGTT ATTCATTCGTGATTGCGCCTGAGCGAAACGAAATACGCGATCGCTGTTAAAAGG ACAATTACAAACAGGAATCGAATGCAACCGGCGCAGGAACACTGCCAGCGCATC AACAATATTTTCACCTGAATCAGGATATTCTTCTAATACCTGGAATGCTGTTTT CCCAGGGATCGCAGTGGTGAGTAACCATGCATCATCAGGAGTACGGATAAAATG CTTGATGGTCGGAAGAGGCATAAATTCCGTCAGCCAGTTTAGTCTGACCATCTC ATCTGTAACATCATTGGCAACGCTACCTTTGCCATGTTTCAGAAACAACTCTGG CGCATCGGGCTTCCCATACAATCGATAGATTGTCGCACCTGATTGCCCGACATT ATCGCGAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCG CGGCCTAGAGCAAGACGTTTCCCGTTGAATATGGCTCATACTCTTCCTTTTTCA ATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGA ATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGT GCCACCTGACGTCGATCGACGGATCGGGAGATCTCCCGATCCCCTATGGTGCAC TCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGC TTGTGTGTTGGAGGTCGCTGAGTAGTGCGCGAGCAAAATTTAAGCTACAACAAG GCAAGGCTTGACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGC GCTGCTTCGCGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAG TTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTT CCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCC CCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGAC TTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGT ACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAA ATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTG GCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCA GTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCA CCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCC AAAATGTCGTAACAACTCCGCCCCATTGACGCAAATGGGGGGTAGGCGTGTACG GTGGGAGGTCTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTA CTGGCTTATCGAAATTAATACGACTCACTATAAG
1247	Coding region of plasmid for expression of CRISPR-Off fusion protein (nt)	ATGCCAAAAAAGAAGAGAAAGGTACCGAAGAAAAAAAGAAAGGTATACAATCAC GATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAGG AAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGTG CTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGAG GATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGGC GACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCTG GTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAAG GGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCAC GACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAAT GTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTCT AACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTAT TTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGAC AAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAAG GTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCAC TTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGAG AGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCTG GCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCTG TTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGCC AACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGGC TCCCACATGGCAGCAATCCCCGCCCTGGACCCCGAGGCCGAGCCTAGCATGGAC GTGATCCTGGTGGGCTCTAGCGAGCTGTCCTCTAGCGTGTCTCCAGGAACCGGA AGGGATCTGATCGCATACGAGGTGAAGGCCAATCAGCGGAACATCGAGGACATC TGTATCTGCTGTGGCAGCCTGCAGGTGCACACACAGCACCCACTGTTCGAGGGA GGAATCTGCGCACCCTGTAAGGATAAGTTCCTGGACGCCCTGTTTCTGTACGAC GATGACGGCTACCAGTCCTATTGCTCTATCTGCTGTTCCGGCGAGACCCTGCTG ATCTGCGGCAATCCAGATTGTACAAGGTGCTATTGTTTTGAGTGCGTGGACTCT CTGGTGGGACCAGGCACCAGCGGAAAGGTGCACGCCATGTCCAACTGGGTGTGC TACCTGTGCCTGCCATCCTCTCGCAGCGGACTGCTGCAGCGGAGAAGGAAGTGG AGATCCCAGCTGAAGGCCTTCTATGATAGGGAGTCTGAGAACCCCCTGGAGATG TTTGAGACCGTGCCAGTGTGGCGCCGGCAGCCCGTGAGGGTGCTGAGCCTGTTC GAGGATATCAAGAAGGAGCTGACATCCCTGGGCTTTCTGGAGTCCGGCTCTGAC CCCGGACAGCTGAAGCACGTGGTGGATGTGACCGACACAGTGCGGAAGGATGTG GAGGAGTGGGGCCCTTTCGACCTGGTGTACGGAGCAACCCCTCCACTGGGACAC ACATGCGACAGACCCCCTTCTTGGTACCTGTTCCAGTTTCACCGCCTGCTGCAG TATGCAAGGCCAAAGCCAGGCAGCCCTAGACCATTCTTTTGGATGTTCGTGGAT AATCTGGTGCTGAACAAGGAGGATCTGGACGTGGCCAGCAGGTTTCTGGAGATG GAGCCAGTGACCATCCCAGACGTGCACGGCGGCTCCCTGCAGAATGCCGTGCGC GTGTGGTCTAACATCCCTGCCATCAGAAGCAGGCACTGGGCACTGGTGAGCGAG GAGGAGCTGTCCCTGCTGGCCCAGAATAAGCAGAGCAGCAAGCTGGCCGCCAAG TGGCCTACAAAGCTGGTGAAGAACTGCTTCCTGCCACTGCGGGAGTACTTCAAG TATTTTTCCACCGAGCTGACATCTAGCCTGGGAGGACCCTCCTCTGGCGCCCCA CCACCTAGCGGCGGCTCCCCTGCCGGCTCTCCAACCAGCACAGAGGAGGGCACC AGCGAGTCCGCCACACCAGAGTCTGGACCTGGCACCAGCACAGAGCCATCCGAG GGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCCTACCTCCACCGAAGAGGGCACC AGCACAGAGCCTTCTGAGGGCAGCGCCCCAGGCACCTCTACAGAGCCAAGCGAG CTCGAGGACAAGAAGTACAGCATCGGCCTGGCCATCGGCACCAACTCTGTGGGC

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		TGGGCCGTGATCACCGACGAGTACAAGGTGCCCAGCAAGAAATTCAAGGTGCTG GGCAACACCGACCGGCACAGCATCAAGAAGAACCTGATCGGAGCCCTGCTGTTC GACAGCGGCGAAACAGCCGAGGCCACCCGGCTGAAGAGAACCGCCAGAAGAAGA TACACCAGACGGAAGAACCGGATCTGCTATCTGCAAGAGATCTTCAGCAACGAG ATGGCCAAGGTGGACGACAGCTTCTTCCACAGACTGGAAGAGTCCTTCCTGGTG GAAGAGGATAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAG GTGGCCTACCACGAGAAGTACCCCACCATCTACCACCTGAGAAAGAAACTGGTG GACAGCACCGACAAGGCCGACCTGCGGCTGATCTATCTGGCCCTGGCCCACATG ATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCTGAACCCCGACAACAGC GACGTGGACAAGCTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAG GAAAACCCCATCAACGCCAGCGGCGTGGACGCCAAGGCCATCCTGTCTGCCAGA CTGAGCAAGAGCAGACGGCTGGAAAATCTGATCGCCCAGCTGCCCGGCGAGAAG AAGAATGGCCTGTTCGGCAACCTGATTGCCCTGAGCCTGGGCCTGACCCCCAAC TTCAAGAGCAACTTCGACCTGGCCGAGGATGCCAAACTGCAGCTGAGCAAGGAC ACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTACGCC GACCTGTTTCTGGCCGCCAAGAACCTGTCCGACGCCATCCTGCTGAGCGACATC CTGAGAGTGAACACCGAGATCACCAAGGCCCCCCTGAGCGCCTCTATGATCAAG AGATACGACGAGCACCACCAGGACCTGACCCTGCTGAAAGCTCTCGTGCGGCAG CAGCTGCCTGAGAAGTACAAAGAGATTTTCTTCGACCAGAGCAAGAACGGCTAC GCCGGCTACATTGACGGCGGAGCCAGCCAGGAAGAGTTCTACAAGTTCATCAAG CCCATCCTGGAAAAGATGGACGGCACCGAGGAACTGCTCGTGAAGCTGAACAGA GAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAG ATCCACCTGGGAGAGCTGCACGCCATTCTGCGGCGGCAGGAAGATTTTTACCCA TTCCTGAAGGACAACCGGGAAAAGATCGAGAAGATCCTGACCTTCCGCATCCCC TACTACGTGGGCCCTCTGGCCAGGGGAAACAGCAGATTCGCCTGGATGACCAGA AAGAGCGAGGAAACCATCACCCCCTGGAACTTCGAGGAAGTGGTGGACAAGGGC GCTTCCGCCCAGAGCTTCATCGAGCGGATGACCAACTTCGATAAGAACCTGCCC AACGAGAAGGTGCTGCCCAAGCACAGCCTGCTGTACGAGTACTTCACCGTGTAT AACGAGCTGACCAAAGTGAAATACGTGACCGAGGGAATGAGAAAGCCCGCCTTC CTGAGCGGCGAGCAGAAAAAGGCCATCGTGGACCTGCTGTTCAAGACCAACCGG AAAGTGACCGTGAAGCAGCTGAAAGAGGACTACTTCAAGAAAATCGAGTGCTTC GACTCCGTGGAAATCTCCGGCGTGGAAGATCGGTTCAACGCCTCCCTGGGCACA TACCACGATCTGCTGAAAATTATCAAGGACAAGGACTTCCTGGACAATGAGGAA AACGAGGACATTCTGGAAGATATCGTGCTGACCCTGACACTGTTTGAGGACAGA GAGATGATCGAGGAACGGCTGAAAACCTATGCCCACCTGTTCGACGACAAAGTG ATGAAGCAGCTGAAGCGGCGGAGATACACCGGCTGGGGCAGGCTGAGCCGGAAG CTGATCAACGGCATCCGGGACAAGCAGTCCGGCAAGACAATCCTGGATTTCCTG AAGTCCGACGGCTTCGCCAACAGAAACTTCATGCAGCTGATCCACGACGACAGC CTGACCTTTAAAGAGGACATCCAGAAAGCCCAGGTGTCCGGCCAGGGCGATAGC CTGCACGAGCACATTGCCAATCTGGCCGGCAGCCCCGCCATTAAGAAGGGCATC CTGCAGACAGTGAAGGTGGTGGACGAGCTCGTGAAAGTGATGGGCCGGCACAAG CCCGAGAACATCGTGATCGAAATGGCCAGAGAGAACCAGACCACCCAGAAGGGA CAGAAGAACAGCCGCGAGAGAATGAAGCGGATCGAAGAGGGCATCAAAGAGCTG GGCAGCCAGATCCTGAAAGAACACCCCGTGGAAAACACCCAGCTGCAGAACGAG AAGCTGTACCTGTACTACCTGCAGAATGGGCGGGATATGTACGTGGACCAGGAA CTGGACATCAACCGGCTGTCCGACTACGATGTGGACGCCATCGTGCCTCAGAGC TTTCTGAAGGACGACTCCATCGACAACAAGGTGCTGACCAGAAGCGACAAGAAC CGGGGCAAGAGCGACAACGTGCCCTCCGAAGAGGTCGTGAAGAAGATGAAGAAC TACTGGCGGCAGCTGCTGAACGCCAAGCTGATTACCCAGAGAAAGTTCGACAAT CTGACCAAGGCCGAGAGAGGCGGCCTGAGCGAACTGGATAAGGCCGGCTTCATC AAGAGACAGCTGGTGGAAACCCGGCAGATCACAAAGCACGTGGCACAGATCCTG GACTCCCGGATGAACACTAAGTACGACGAGAATGACAAGCTGATCCGGGAAGTG AAAGTGATCACCCTGAAGTCCAAGCTGGTGTCCGATTTCCGGAAGGATTTCCAG TTTTACAAAGTGCGCGAGATCAACAACTACCACCACGCCCACGACGCCTACCTG AACGCCGTCGTGGGAACCGCCCTGATCAAAAAGTACCCTAAGCTGGAAAGCGAG TTCGTGTACGGCGACTACAAGGTGTACGACGTGCGGAAGATGATCGCCAAGAGC GAGCAGGAAATCGGCAAGGCTACCGCCAAGTACTTCTTCTACAGCAACATCATG AACTTTTTCAAGACCGAGATTACCCTGGCCAACGGCGAGATCCGGAAGCGGCCT CTGATCGAGACAAACGGCGAAACCGGGGAGATCGTGTGGGATAAGGGCCGGGAT TTTGCCACCGTGCGGAAAGTGCTGAGCATGCCCCAAGTGAATATCGTGAAAAAG ACCGAGGTGCAGACAGGCGGCTTCAGCAAAGAGTCTATCCTGCCCAAGAGGAAC AGCGATAAGCTGATCGCCAGAAAGAAGGACTGGGACCCTAAGAAGTACGGCGGC TTCGACAGCCCCACCGTGGCCTATTCTGTGCTGGTGGTGGCCAAAGTGGAAAAG GGCAAGTCCAAGAAACTGAAGAGTGTGAAAGAGCTGCTGGGGATCACCATCATG GAAAGAAGCAGCTTCGAGAAGAATCCCATCGACTTTCTGGAAGCCAAGGGCTAC AAAGAAGTGAAAAAGGACCTGATCATCAAGCTGCCTAAGTACTCCCTGTTCGAG CTGGAAAACGGCCGGAAGAGAATGCTGGCCTCTGCCGGCGAACTGCAGAAGGGA AACGAACTGGCCCTGCCCTCCAAATATGTGAACTTCCTGTACCTGGCCAGCCAC TATGAGAAGCTGAAGGGCTCCCCCGAGGATAATGAGCAGAAACAGCTGTTTGTG GAACAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGCGAGTTCTCC AAGAGAGTGATCCTGGCCGACGCTAATCTGGACAAAGTGCTGTCCGCCTACAAC AAGCACCGGGATAAGCCCATCAGAGAGCAGGCCGAGAATATCATCCACCTGTTT ACCCTGACCAATCTGGGAGCCCCTGCCGCCTTCAAGTACTTTGACACCACCATC GACCGGAAGAGGTACACCAGCACCAAAGAGGTGCTGGACGCCACCCTGATCCAC CAGAGCATCACCGGCCTGTACGAGACACGGATCGACCTGTCTCAGCTGGGAGGC GACAGCCCCAAGAAGAAGAGAAAGGTGGGAGTCGACGGATCCAGCGGCTCCGAG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		ACCCCAGGCACATCTGAGAGCGCCACCCCTGAGTCCACCGGTATGAACAATTCA CAGGGGAGAGTGACATTCGAAGACGTGACCGTGAACTTCACCCAGGGAGAATGG CAGCGCTTGAACCCAGAACAAAGGAACCTCTATCGGGACGTGATGCTGGAAAAC TACTCAAATTTGGTGAGCGTTGGGCAGGGTGAGACCACTAAGCCTGACGTGATC CTGAGATTGGAACAGGGCAAGGAGCCTTGGCTCGAGGAAGAGGAAGTCCTGGGC TCAGGGAGGGCCGAGAAAAACGGTGATATAGGAGGCCAGATATGGAAGCCTAAG GACGTCAAGGAGAGCCTGAGCGCTCCCAAGAAGAAAAGGAAGGTCCCAAAGAAA AAAAGAAAGGTGTGA
1248	CRISPR-Off fusion protein (aa)	MPKKKRKVPKKKRKVYNHDQEFDPPKVYPPVPAEKRKPIRVLSLEDGIATGLLV LKDLGIQVDRYIASEVCEDSITVGMVRHQGKIMYVGDVRSVTQKHIQEWGPEDL VIGGSPCNDLSIVNPARKGLYEGTGRLFFEFYRLLHDARPKEGDDRPFFWLFEN VVAMGVSDKRDISRFLESNPVMIDAKEVSAAHRARYFWGNLPGMNRPLASTVND KLELQECLEHGRIAKFSKVRTITTRSNSIKQGKDQHFPVEMNEKEDILWCTEME RVFGFPVHYTDVSNMSRLARQRLLGRSWSVPVIRHLFAPLKEYFACVSSGNSNA NSRGPSFSSGLVPLSLRGSHMAAIPALDPEAEPSMDVILVGSSELSSSVSPGTG RDLIAYEVKANQRNIEDICICCGSLQVHTQHPLFEGGICAPCKDKELDALFLYD DDGYQSYCSICCSGETLLICGNPDCTRCYCFECVDSLVGPGTSGKVHAMSNWVC YLCLPSSRSGLLQRRRKWRSQLKAFYDRESENPLEMFETVPVWRRQPVRVLSLF EDIKKELTSLGFLESGSDPGQLKHVVDVTDTVRKDVEEWGPEDLVYGATPPLGH TCDRPPSWYLFQFHRLLQYARPKPGSPRPFFWMFVDNLVLNKEDLDVASRELEM EPVTIPDVHGGSLQNAVRVWSNIPAIRSRHWALVSEEELSLLAQNKQSSKLAAK WPTKLVKNCFLPLREYFKYFSTELTSSLGGPSSGAPPPSGGSPAGSPTSTEEGT SESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSE LEDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLE DSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLV EEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHM IKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSAR LSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNEKSNEDLAEDAKLQLSKD TYDDDLDNLLAQIGDQYADLELAAKNLSDAILLSDILRVNTEITKAPLSASMIK RYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIK PILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYP FLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKG ASAQSFIERMTNEDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAF LSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGT YHDLLKIIKDKDELDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKV MKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDELKSDGFANRNFMQLIHDDS LTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHK PENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNE KLYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKN RGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFI KRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQ FYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKS EQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRD FATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGG FDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDELEAKGY KEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASH YEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYN KHRDKPIREQAENIIHLFTLTNLGAPAAFKYEDTTIDRKRYTSTKEVLDATLIH QSITGLYETRIDLSQLGGDSPKKKRKVGVDGSSGSETPGTSESATPESTGMNNS QGRVTFEDVTVNFTQGEWQRLNPEQRNLYRDVMLENYSNLVSVGQGETTKPDVI LRLEQGKEPWLEEEEVLGSGRAEKNGDIGGQIWKPKDVKESLSAPKKKRKVPKK KRKV
1249	gRNA #008 with updated modification pattern (m indicates a 2'-OMe modified nucleotide, * indicates a phosphorothioate bond)	mA*mG*mG*rArGrUrUrCrCrGrCrArGrUrArUrGrGrArUrGrUrUrUrUr ArGrArGmCmUmAmGmAmAmAmUmAmGmCrArArGrUrUrArArArArUrArAr GrGrCrUxArGrUrCrCrGrUrUxArUrCrAmAmCmUmUmGmAmAmAmAmGm UmGrGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
1250	CRISPR-Off variant 1 plasmid sequence	AGGGGCGCTCGAGCAGGTTCAGAAGGAGATCAAAAACCCCCAAGGATCAAACAT GAAGAGACCTGCTGCCACCAAGAAGGCCGGCCAGGCCAAGAAAAAGTACAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACAGTCCCCTTGAGATGTATAAAACTGTGCCTGTGTGGAAGAGAGAGCC AGTGCGGGTGCTGTCCCTTTTTGGTGACATCAAGAAAGAGCTGACGACTTTGGG CTTTCTGGAAAACGGCTCTGACCCGGGCCGACTGAAACATTTGGACGATGTCAC CAATACGGTGAGGAGGGACGTGGAAGAATGGGGCCCGTTCGACCTCGTGTACGG CTCCACGCCGCCCCTCGGCCACGCCTGTGACCATCCTCCCGGGTGGTACCTGTT CCAGTTCCACCGTGTGCTTCAGTACGCGAGGCCCAGGCCGGGCAGCCCGCAGGC CTTCTTCTGGATGTTTGTGGACAACCTGGTGCTGACCGAGGATGACCGGGCTGT AGCCACTCGCTTCCTGGAGACTGACCCGGTGACCATCCAGGACGTCTGTGGCAG AGCTGTCCGGAACGCCGTGCACGTGTGGAGCAACATCCCGGCCGTGAAAAGCAG GCACTCGGCCCTGTTTTCCCAGGAGGAATCATTCCTGCGGGCTCAGGACAGGCA GAGAGCAAAGCCCCCCGCCCGGGGGCCAGCCAAGCTGGTGAAGAATTGTTTTCT CCCCCTGAGAGAATATTTCAAGTATTTTTCAACAGAATTCACTTCCTCTTTGGG AGGACCCTCCTCTGGCGCCCCACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCC AACCAGCACAGAGGAGGGCACCAGCGAGTCCGCCACACCAGAGTCTGGACCTGG CACCAGCACAGAGCCATCCGAGGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCC TACCTCCACCGAAGAGGGCACCAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGG CACCTCTACAGAGCCAAGCGAGCTCGAGGACAAGAAGTACAGCATCGGCCTGGC CATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACCGACGAGTACAAGGTGCC CAGCAAGAAATTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCAAGAAGAA CCTGATCGGAGCCCTGCTGTTCGACAGCGGCGAAACAGCCGAGGCCACCCGGCT GAAGAGAACCGCCAGAAGAAGATACACCAGACGGAAGAACCGGATCTGCTATCT GCAAGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACAG ACTGGAAGAGTCCTTCCTGGTGGAAGAGGATAAGAAGCACGAGCGGCACCCCAT CTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAGAAGTACCCCACCATCTA CCACCTGAGAAAGAAACTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGAT CTATCTGGCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGG CGACCTGAACCCCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCA GACCTACAACCAGCTGTTCGAGGAAAACCCCATCAACGCCAGCGGCGTGGACGC CAAGGCCATCCTGTCTGCCAGACTGAGCAAGAGCAGACGGCTGGAAAATCTGAT CGCCCAGCTGCCCGGCGAGAAGAAGAATGGCCTGTTCGGCAACCTGATTGCCCT GAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAGGATGC CAAACTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGC CCAGATCGGCGACCAGTACGCCGACCTGTTTCTGGCCGCCAAGAACCTGTCCGA CGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAGATCACCAAGGCCCC CCTGAGCGCCTCTATGATCAAGAGATACGACGAGCACCACCAGGACCTGACCCT GCTGAAAGCTCTCGTGCGGCAGCAGCTGCCTGAGAAGTACAAAGAGATTTTCTT CGACCAGAGCAAGAACGGCTACGCCGGCTACATTGACGGCGGAGCCAGCCAGGA AGAGTTCTACAAGTTCATCAAGCCCATCCTGGAAAAGATGGACGGCACCGAGGA ACTGCTCGTGAAGCTGAACAGAGAGGACCTGCTGCGGAAGCAGCGGACCTTCGA CAACGGCAGCATCCCCCACCAGATCCACCTGGGAGAGCTGCACGCCATTCTGCG GCGGCAGGAAGATTTTTACCCATTCCTGAAGGACAACCGGGAAAAGATCGAGAA GATCCTGACCTTCCGCATCCCCTACTACGTGGGCCCTCTGGCCAGGGGAAACAG CAGATTCGCCTGGATGACCAGAAAGAGCGAGGAAACCATCACCCCCTGGAACTT CGAGGAAGTGGTGGACAAGGGCGCTTCCGCCCAGAGCTTCATCGAGCGGATGAC CAACTTCGATAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCT GTACGAGTACTTCACCGTGTATAACGAGCTGACCAAAGTGAAATACGTGACCGA GGGAATGAGAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTGGA CCTGCTGTTCAAGACCAACCGGAAAGTGACCGTGAAGCAGCTGAAAGAGGACTA CTTCAAGAAAATCGAGTGCTTCGACTCCGTGGAAATCTCCGGCGTGGAAGATCG GTTCAACGCCTCCCTGGGCACATACCACGATCTGCTGAAAATTATCAAGGACAA GGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAAGATATCGTGCTGAC CCTGACACTGTTTGAGGACAGAGAGATGATCGAGGAACGGCTGAAAACCTATGC CCACCTGTTCGACGACAAAGTGATGAAGCAGCTGAAGCGGCGGAGATACACCGG CTGGGGCAGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGG CAAGACAATCCTGGATTTCCTGAAGTCCGACGGCTTCGCCAACAGAAACTTCAT GCAGCTGATCCACGACGACAGCCTGACCTTTAAAGAGGACATCCAGAAAGCCCA GGTGTCCGGCCAGGGCGATAGCCTGCACGAGCACATTGCCAATCTGGCCGGCAG CCCCGCCATTAAGAAGGGCATCCTGCAGACAGTGAAGGTGGTGGACGAGCTCGT GAAAGTGATGGGCCGGCACAAGCCCGAGAACATCGTGATCGAAATGGCCAGAGA GAACCAGACCACCCAGAAGGGACAGAAGAACAGCCGCGAGAGAATGAAGCGGAT CGAAGAGGGCATCAAAGAGCTGGGCAGCCAGATCCTGAAAGAACACCCCGTGGA AAACACCCAGCTGCAGAACGAGAAGCTGTACCTGTACTACCTGCAGAATGGGCG GGATATGTACGTGGACCAGGAACTGGACATCAACCGGCTGTCCGACTACGATGT GGACGCCATCGTGCCTCAGAGCTTTCTGAAGGACGACTCCATCGACAACAAGGT GCTGACCAGAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCTCCGAAGA GGTCGTGAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAACGCCAAGCTGAT TACCCAGAGAAAGTTCGACAATCTGACCAAGGCCGAGAGAGGCGGCCTGAGCGA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		ACTGGATAAGGCCGGCTTCATCAAGAGACAGCTGGTGGAAACCCGGCAGATCAC AAAGCACGTGGCACAGATCCTGGACTCCCGGATGAACACTAAGTACGACGAGAA TGACAAGCTGATCCGGGAAGTGAAAGTGATCACCCTGAAGTCCAAGCTGGTGTC CGATTTCCGGAAGGATTTCCAGTTTTACAAAGTGCGCGAGATCAACAACTACCA CCACGCCCACGACGCCTACCTGAACGCCGTCGTGGGAACCGCCCTGATCAAAAA GTACCCTAAGCTGGAAAGCGAGTTCGTGTACGGCGACTACAAGGTGTACGACGT GCGGAAGATGATCGCCAAGAGCGAGCAGGAAATCGGCAAGGCTACCGCCAAGTA CTTCTTCTACAGCAACATCATGAACTTTTTCAAGACCGAGATTACCCTGGCCAA CGGCGAGATCCGGAAGCGGCCTCTGATCGAGACAAACGGCGAAACCGGGGAGAT CGTGTGGGATAAGGGCCGGGATTTTGCCACCGTGCGGAAAGTGCTGAGCATGCC CCAAGTGAATATCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCAGCAAAGA GTCTATCCTGCCCAAGAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTG GGACCCTAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTATTCTGTGCT GGTGGTGGCCAAAGTGGAAAAGGGCAAGTCCAAGAAACTGAAGAGTGTGAAAGA GCTGCTGGGGATCACCATCATGGAAAGAAGCAGCTTCGAGAAGAATCCCATCGA CTTTCTGGAAGCCAAGGGCTACAAAGAAGTGAAAAAGGACCTGATCATCAAGCT GCCTAAGTACTCCCTGTTCGAGCTGGAAAACGGCCGGAAGAGAATGCTGGCCTC TGCCGGCGAACTGCAGAAGGGAAACGAACTGGCCCTGCCCTCCAAATATGTGAA CTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAGGGCTCCCCCGAGGATAA TGAGCAGAAACAGCTGTTTGTGGAACAGCACAAGCACTACCTGGACGAGATCAT CGAGCAGATCAGCGAGTTCTCCAAGAGAGTGATCCTGGCCGACGCTAATCTGGA CAAAGTGCTGTCCGCCTACAACAAGCACCGGGATAAGCCCATCAGAGAGCAGGC CGAGAATATCATCCACCTGTTTACCCTGACCAATCTGGGAGCCCCTGCCGCCTT CAAGTACTTTGACACCACCATCGACCGGAAGAGGTACACCAGCACCAAAGAGGT GCTGGACGCCACCCTGATCCACCAGAGCATCACCGGCCTGTACGAGACACGGAT CGACCTGTCTCAGCTGGGAGGCGACAGCCCCAAGAAGAAGAGAAAGGTGGGAGT CGACGGATCCAGCGGCTCCGAGACCCCAGGCACATCTGAGAGCGCCACCCCTGA GTCCACCGGTATGAACAATTCACAGGGGAGAGTGACATTCGAAGACGTGACCGT GAACTTCACCCAGGGAGAATGGCAGCGCTTGAACCCAGAACAAAGGAACCTCTA TCGGGACGTGATGCTGGAAAACTACTCAAATTTGGTGAGCGTTGGGCAGGGTGA GACCACTAAGCCTGACGTGATCCTGAGATTGGAACAGGGCAAGGAGCCTTGGCT CGAGGAAGAGGAAGTCCTGGGCTCAGGGAGGGCCGAGAAAAACGGTGATATAGG AGGCCAGATATGGAAGCCTAAGGACGTCAAGGAGAGCCTGAGCGCTAAACGTCC GGCAGCAACCAAAAAAGCAGGTCAGGCCAAGAAAAAATGAGGATCCTGAGTCTA GAAAAGATATATATAGGATTGAAGATCTCTCAGTTAAGTCTACAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAGAAGAGCCTCCTGCAGGAAGCTTGGCGTAATCATGGTCATAGCTGTTTCCTG TGTGAAATTGTTATCCGCTCACAATTCCACACAACATACGAGCCGGAAGCATAA AGTGTAAAGCCTGGGGTGCCTAATGAGTGAGCTAACTCACATTAATTGCGTTGC GCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGCCAGCTGCATTAATGAA TCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCCGCTTCCTCGCTCAC TGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACTCAAA GGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATGTG AGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTT TTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCA GAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAG CTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGC CTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATCT CAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGCACGAACCCCCCGT TCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTCCAACCCGGT AAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGAGC GAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTA CACTAGAAGAACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGG AAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGG TTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGA TCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAAACTCACGTTA AGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAA TTAAAAATGAAGTTTTAAATCAAGCCCAATCTGAATAATGTTACAACCAATTAA CCAATTCTGATTAGAAAAACTCATCGAGCATCAAATGAAACTGCAATTTATTCA TATCAGGATTATCAATACCATATTTTTGAAAAAGCCGTTTCTGTAATGAAGGAG AAAACTCACCGAGGCAGTTCCATAGGATGGCAAGATCCTGGTATCGGTCTGCGA TTCCGACTCGTCCAACATCAATACAACCTATTAATTTCCCCTCGTCAAAAATAA GGTTATCAAGTGAGAAATCACCATGAGTGACGACTGAATCCGGTGAGAATGGCA AAAGTTTATGCATTTCTTTCCAGACTTGTTCAACAGGCCAGCCATTACGCTCGT CATCAAAATCACTCGCATCAACCAAACCGTTATTCATTCGTGATTGCGCCTGAG CGAGACGAAATACGCGATCGCTGTTAAAAGGACAATTACAAACAGGAATCGAAT GCAACCGGCGCAGGAACACTGCCAGCGCATCAACAATATTTTCACCTGAATCAG GATATTCTTCTAATACCTGGAATGCTGTTTTTCCGGGGATCGCAGTGGTGAGTA ACCATGCATCATCAGGAGTACGGATAAAATGCTTGATGGTCGGAAGAGGCATAA ATTCCGTCAGCCAGTTTAGTCTGACCATCTCATCTGTAACATCATTGGCAACGC TACCTTTGCCATGTTTCAGAAACAACTCTGGCGCATCGGGCTTCCCATACAAGC GATAGATTGTCGCACCTGATTGCCCGACATTATCGCGAGCCCATTTATACCCAT ATAAATCAGCATCCATGTTGGAATTTAATCGCGGCCTCGACGTTTCCCGTTGAA TATGGCTCATAACACCCCTTGTATTACTGTTTATGTAAGCAGACAGTTTTATTG TTCATGATGATATATTTTTATCTTGTGCAATGTAACATCAGAGATTTTGAGACA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		CGGGCCAGAGCTGCATCGCGCGTTTCGGTGATGACGGTGAAAACCTCTGACACA TGCAGCTCCCGGAGACGGTCACAGCTTGTCTGTAAGCGGATGCCGGGAGCAGAC AAGCCCGTCAGGGCGCGTCAGCGGGTGTTGGCGGGTGTCGGGGCTGGCTTAACT ATGCGGCATCAGAGCAGATTGTACTGAGAGTGCACCATATGCGGTGTGAAATAC CGCACAGATGCGTAAGGAGAAAATACCGCATCAGGCGCCATTCGCCATTCAGGC TGCGCAACTGTTGGGAAGGGCGATCGGTGCGGGCCTCTTCGCTATTACGCCAGC TGGCGAAAGGGGGATGTGCTGCAAGGCGATTAAGTTGGGTAACGCCAGGGTTTT CCCAGTCACGACGTTGTAAAACGACGGCCAGTGAATTGTAATACGACTCACTAT A
1251	CRISPR-Off variant 1 alternative plasmid sequence	AGGGGCGCTCGAGCAGGTTCAGAAGGAGATCAAAAACCCCCAAGGATCAAACAT GAAGAGACCTGCTGCCACCAAGAAGGCCGGCCAGGCCAAGAAAAAGTACAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACAGTCCCCTTGAGATGTATAAAACTGTGCCTGTGTGGAAGAGAGAGCC AGTGCGGGTGCTGTCCCTTTTTGGTGACATCAAGAAAGAGCTGACGACTTTGGG CTTTCTGGAAAACGGCTCTGACCCGGGCCGACTGAAACATTTGGACGATGTCAC CAATACGGTGAGGAGGGACGTGGAAGAATGGGGCCCGTTCGACCTCGTGTACGG CTCCACGCCGCCCCTCGGCCACGCCTGTGACCATCCTCCCGGGTGGTACCTGTT CCAGTTCCACCGTGTGCTTCAGTACGCGAGGCCCAGGCCGGGCAGCCCGCAGGC CTTCTTCTGGATGTTTGTGGACAACCTGGTGCTGACCGAGGATGACCGGGCTGT AGCCACTCGCTTCCTGGAGACTGACCCGGTGACCATCCAGGACGTCTGTGGCAG AGCTGTCCGGAACGCCGTGCACGTGTGGAGCAACATCCCGGCCGTGAAAAGCAG GCACTCGGCCCTGTTTTCCCAGGAGGAATCATTCCTGCGGGCTCAGGACAGGCA GAGAGCAAAGCCCCCCGCCCGGGGGCCAGCCAAGCTGGTGAAGAATTGTTTTCT CCCCCTGAGAGAATATTTCAAGTATTTTTCAACAGAATTCACTTCCTCTTTGGG AGGACCCTCCTCTGGCGCCCCACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCC AACCAGCACAGAGGAGGGCACCAGCGAGTCCGCCACACCAGAGTCTGGACCTGG CACCAGCACAGAGCCATCCGAGGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCC TACCTCCACCGAAGAGGGCACCAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGG CACCTCTACAGAGCCAAGCGAGCTCGAGGACAAGAAGTACAGCATCGGCCTGGC CATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACCGACGAGTACAAGGTGCC CAGCAAGAAATTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCAAGAAGAA CCTGATCGGAGCCCTGCTGTTCGACAGCGGCGAAACAGCCGAGGCCACCCGGCT GAAGAGAACCGCCAGAAGAAGATACACCAGACGGAAGAACCGGATCTGCTATCT GCAAGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACAG ACTGGAAGAGTCCTTCCTGGTGGAAGAGGATAAGAAGCACGAGCGGCACCCCAT CTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAGAAGTACCCCACCATCTA CCACCTGAGAAAGAAACTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGAT CTATCTGGCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGG CGACCTGAACCCCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCA GACCTACAACCAGCTGTTCGAGGAAAACCCCATCAACGCCAGCGGCGTGGACGC CAAGGCCATCCTGTCTGCCAGACTGAGCAAGAGCAGACGGCTGGAAAATCTGAT CGCCCAGCTGCCCGGCGAGAAGAAGAATGGCCTGTTCGGCAACCTGATTGCCCT GAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAGGATGC CAAACTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGC CCAGATCGGCGACCAGTACGCCGACCTGTTTCTGGCCGCCAAGAACCTGTCCGA CGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAGATCACCAAGGCCCC CCTGAGCGCCTCTATGATCAAGAGATACGACGAGCACCACCAGGACCTGACCCT GCTGAAAGCTCTCGTGCGGCAGCAGCTGCCTGAGAAGTACAAAGAGATTTTCTT CGACCAGAGCAAGAACGGCTACGCCGGCTACATTGACGGCGGAGCCAGCCAGGA AGAGTTCTACAAGTTCATCAAGCCCATCCTGGAAAAGATGGACGGCACCGAGGA ACTGCTCGTGAAGCTGAACAGAGAGGACCTGCTGCGGAAGCAGCGGACCTTCGA CAACGGCAGCATCCCCCACCAGATCCACCTGGGAGAGCTGCACGCCATTCTGCG GCGGCAGGAAGATTTTTACCCATTCCTGAAGGACAACCGGGAAAAGATCGAGAA GATCCTGACCTTCCGCATCCCCTACTACGTGGGCCCTCTGGCCAGGGGAAACAG CAGATTCGCCTGGATGACCAGAAAGAGCGAGGAAACCATCACCCCCTGGAACTT CGAGGAAGTGGTGGACAAGGGCGCTTCCGCCCAGAGCTTCATCGAGCGGATGAC CAACTTCGATAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCT GTACGAGTACTTCACCGTGTATAACGAGCTGACCAAAGTGAAATACGTGACCGA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		GGGAATGAGAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTGGA CCTGCTGTTCAAGACCAACCGGAAAGTGACCGTGAAGCAGCTGAAAGAGGACTA CTTCAAGAAAATCGAGTGCTTCGACTCCGTGGAAATCTCCGGCGTGGAAGATCG GTTCAACGCCTCCCTGGGCACATACCACGATCTGCTGAAAATTATCAAGGACAA GGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAAGATATCGTGCTGAC CCTGACACTGTTTGAGGACAGAGAGATGATCGAGGAACGGCTGAAAACCTATGC CCACCTGTTCGACGACAAAGTGATGAAGCAGCTGAAGCGGCGGAGATACACCGG CTGGGGCAGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGG CAAGACAATCCTGGATTTCCTGAAGTCCGACGGCTTCGCCAACAGAAACTTCAT GCAGCTGATCCACGACGACAGCCTGACCTTTAAAGAGGACATCCAGAAAGCCCA GGTGTCCGGCCAGGGCGATAGCCTGCACGAGCACATTGCCAATCTGGCCGGCAG CCCCGCCATTAAGAAGGGCATCCTGCAGACAGTGAAGGTGGTGGACGAGCTCGT GAAAGTGATGGGCCGGCACAAGCCCGAGAACATCGTGATCGAAATGGCCAGAGA GAACCAGACCACCCAGAAGGGACAGAAGAACAGCCGCGAGAGAATGAAGCGGAT CGAAGAGGGCATCAAAGAGCTGGGCAGCCAGATCCTGAAAGAACACCCCGTGGA AAACACCCAGCTGCAGAACGAGAAGCTGTACCTGTACTACCTGCAGAATGGGCG GGATATGTACGTGGACCAGGAACTGGACATCAACCGGCTGTCCGACTACGATGT GGACGCCATCGTGCCTCAGAGCTTTCTGAAGGACGACTCCATCGACAACAAGGT GCTGACCAGAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCTCCGAAGA GGTCGTGAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAACGCCAAGCTGAT TACCCAGAGAAAGTTCGACAATCTGACCAAGGCCGAGAGAGGCGGCCTGAGCGA ACTGGATAAGGCCGGCTTCATCAAGAGACAGCTGGTGGAAACCCGGCAGATCAC AAAGCACGTGGCACAGATCCTGGACTCCCGGATGAACACTAAGTACGACGAGAA TGACAAGCTGATCCGGGAAGTGAAAGTGATCACCCTGAAGTCCAAGCTGGTGTC CGATTTCCGGAAGGATTTCCAGTTTTACAAAGTGCGCGAGATCAACAACTACCA CCACGCCCACGACGCCTACCTGAACGCCGTCGTGGGAACCGCCCTGATCAAAAA GTACCCTAAGCTGGAAAGCGAGTTCGTGTACGGCGACTACAAGGTGTACGACGT GCGGAAGATGATCGCCAAGAGCGAGCAGGAAATCGGCAAGGCTACCGCCAAGTA CTTCTTCTACAGCAACATCATGAACTTTTTCAAGACCGAGATTACCCTGGCCAA CGGCGAGATCCGGAAGCGGCCTCTGATCGAGACAAACGGCGAAACCGGGGAGAT CGTGTGGGATAAGGGCCGGGATTTTGCCACCGTGCGGAAAGTGCTGAGCATGCC CCAAGTGAATATCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCAGCAAAGA GTCTATCCTGCCCAAGAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTG GGACCCTAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTATTCTGTGCT GGTGGTGGCCAAAGTGGAAAAGGGCAAGTCCAAGAAACTGAAGAGTGTGAAAGA GCTGCTGGGGATCACCATCATGGAAAGAAGCAGCTTCGAGAAGAATCCCATCGA CTTTCTGGAAGCCAAGGGCTACAAAGAAGTGAAAAAGGACCTGATCATCAAGCT GCCTAAGTACTCCCTGTTCGAGCTGGAAAACGGCCGGAAGAGAATGCTGGCCTC TGCCGGCGAACTGCAGAAGGGAAACGAACTGGCCCTGCCCTCCAAATATGTGAA CTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAGGGCTCCCCCGAGGATAA TGAGCAGAAACAGCTGTTTGTGGAACAGCACAAGCACTACCTGGACGAGATCAT CGAGCAGATCAGCGAGTTCTCCAAGAGAGTGATCCTGGCCGACGCTAATCTGGA CAAAGTGCTGTCCGCCTACAACAAGCACCGGGATAAGCCCATCAGAGAGCAGGC CGAGAATATCATCCACCTGTTTACCCTGACCAATCTGGGAGCCCCTGCCGCCTT CAAGTACTTTGACACCACCATCGACCGGAAGAGGTACACCAGCACCAAAGAGGT GCTGGACGCCACCCTGATCCACCAGAGCATCACCGGCCTGTACGAGACACGGAT CGACCTGTCTCAGCTGGGAGGCGACAGCCCCAAGAAGAAGAGAAAGGTGGGAGT CGACGGATCCAGCGGCTCCGAGACCCCAGGCACATCTGAGAGCGCCACCCCTGA GTCCACCGGTATGAACAATTCACAGGGGAGAGTGACATTCGAAGACGTGACCGT GAACTTCACCCAGGGAGAATGGCAGCGCTTGAACCCAGAACAAAGGAACCTCTA TCGGGACGTGATGCTGGAAAACTACTCAAATTTGGTGAGCGTTGGGCAGGGTGA GACCACTAAGCCTGACGTGATCCTGAGATTGGAACAGGGCAAGGAGCCTTGGCT CGAGGAAGAGGAAGTCCTGGGCTCAGGGAGGGCCGAGAAAAACGGTGATATAGG AGGCCAGATATGGAAGCCTAAGGACGTCAAGGAGAGCCTGAGCGCTAAACGTCC GGCAGCAACCAAAAAAGCAGGTCAGGCCAAGAAAAAATGAGGATCCTGAGTCTA GAAAAGATATATATAGGATTGAAGATCTCTCAGTTAAGTCTACAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAGAAGAGCGAATTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCC TGGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCG TAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAA TGGCGAATGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTC ACACCGCATATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAG CCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCT CCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCA GAGGTTTTCACCGTCATCACCGAAACGCGCGATGCAGCTCTGGCCCGTGTCTCA AAATCTCTGATGTTACATTGCACAAGATAAAAATATATCATCATGAACAATAAA ACTGTCTGCTTACATAAACAGTAATACAAGGGGTGTTATGAGCCATATTCAACG GGAAACGTCGAGGCCGCGATTAAATTCCAACATGGATGCTGATTTATATGGGTA TAAATGGGCTCGCGATAATGTCGGGCAATCAGGTGCGACAATCTATCGCTTGTA TGGGAAGCCCGATGCGCCAGAGTTGTTTCTGAAACATGGCAAAGGTAGCGTTGC CAATGATGTTACAGATGAGATGGTCAGACTAAACTGGCTGACGGAATTTATGCC TCTTCCGACCATCAAGCATTTTATCCGTACTCCTGATGATGCATGGTTACTCAC CACTGCGATCCCCGGAAAAACAGCATTCCAGGTATTAGAAGAATATCCTGATTC AGGTGAAAATATTGTTGATGCGCTGGCAGTGTTCCTGCGCCGGTTGCATTCGAT TCCTGTTTGTAATTGTCCTTTTAACAGCGATCGCGTATTTCGTCTCGCTCAGGC

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		GCAATCACGAATGAATAACGGTTTGGTTGATGCGAGTGATTTTGATGACGAGCG TAATGGCTGGCCTGTTGAACAAGTCTGGAAAGAAATGCATAAACTTTTGCCATT CTCACCGGATTCAGTCGTCACTCATGGTGATTTCTCACTTGATAACCTTATTTT TGACGAGGGGAAATTAATAGGTTGTATTGATGTTGGACGAGTCGGAATCGCAGA CCGATACCAGGATCTTGCCATCCTATGGAACTGCCTCGGTGAGTTTTCTCCTTC ATTACAGAAACGGCTTTTTCAAAAATATGGTATTGATAATCCTGATATGAATAA ATTGCAGTTTCATTTGATGCTCGATGAGTTTTTCTAATCAGAATTGGTTAATTG GTTGTAACATTATTCAGATTGGGCTTGATTTAAAACTTCATTTTTAATTTAAAA GGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTG AGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTT GAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGC TACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGG TAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTTCTAGTGTAGCCGT AGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGC TAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGT TGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGG GTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACC TACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACA GGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAG GGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTG AGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCA GCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT TCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGT GAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCG AGGAAGCGGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTA ATGCAGCTGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGC AATTAATGTGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCT TCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAA CAGCTATGACCATGATTACGCCAAGCTTTAATACGACTCACTATA
1252	CRISPR-Off variant 1 amino acid sequence	MKRPAATKKAGQAKKKYNHDQEFDPPKVYPPVPAEKRKPIRVLSLEDGIATGLL VLKDLGIQVDRYIASEVCEDSITVGMVRHQGKIMYVGDVRSVTQKHIQEWGPED LVIGGSPCNDLSIVNPARKGLYEGTGRLFFEFYRLLHDARPKEGDDRPFFWLFE NVVAMGVSDKRDISRFLESNPVMIDAKEVSAAHRARYFWGNLPGMNRPLASTVN DKLELQECLEHGRIAKFSKVRTITTRSNSIKQGKDQHFPVEMNEKEDILWCTEM ERVFGFPVHYTDVSNMSRLARQRLLGRSWSVPVIRHLFAPLKEYFACVSSGNSN ANSRGPSFSSGLVPLSLRGSHSPLEMYKTVPVWKREPVRVLSLFGDIKKELTTL GFLENGSDPGRLKHLDDVTNTVRRDVEEWGPFDLVYGSTPPLGHACDHPPGWYL FQFHRVLQYARPRPGSPQAFFWMFVDNLVLTEDDRAVATRFLETDPVTIQDVCG RAVRNAVHVWSNIPAVKSRHSALESQEESFLRAQDRQRAKPPARGPAKLVKNCF LPLREYFKYESTEFTSSLGGPSSGAPPPSGGSPAGSPTSTEEGTSESATPESGP GTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSELEDKKYSIGL AIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLEDSGETAEATR LKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELVEEDKKHERHP IFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKERGHFLIE GDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENL IAQLPGEKKNGLFGNLIALSLGLTPNEKSNEDLAEDAKLQLSKDTYDDDLDNLL AQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLT LLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTE ELLVKLNREDLLRKQRTEDNGSIPHQIHLGELHAILRRQEDFYPELKDNREKIE KILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERM TNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIV DLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTYHDLLKIIKD KDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYT GWGRLSRKLINGIRDKQSGKTILDELKSDGFANRNEMQLIHDDSLTFKEDIQKA QVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMAR ENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNG RDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSE EVVKKMKNYWRQLLNAKLITQRKEDNLTKAERGGLSELDKAGFIKRQLVETRQI TKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQFYKVREINNY HHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAK YFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSM PQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGEDSPTVAYSV LVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIK LPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPED NEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQ AENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETR IDLSQLGGDSPKKKRKVGVDGSSGSETPGTSESATPESTGMNNSQGRVTFEDVT VNFTQGEWQRLNPEQRNLYRDVMLENYSNLVSVGQGETTKPDVILRLEQGKEPW LEEEEVLGSGRAEKNGDIGGQIWKPKDVKESLSAKRPAATKKAGQAKKK
1253	CRISPR-Off variant 2 plasmid sequence	AGAAACTAGCGTAAATTCAAATATAGGTCAGGCTTCAACGTCAACAAATATGAT GAAGAGACCTGCTGCCACCAAGAAGGCCGGCCAGGCCAAGAAAAAGTACAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG
		CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT
		GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA
		GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA
		CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA
		TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC
		TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA
		TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA
		CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA
		GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA
		CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA
		GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT
		GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT
		GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC
		CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG
		CTCCCACAGCCCTATGGAGATATACAAGACAGTGTCTGCATGGAAGAGACAGCC
		AGTGAGGGTGCTGAGCCTTTTTGGGAATATTGATAAAGAACTAAAGAGTTTGGG
		CTTTTTGGAAATCGGTTCTGATTCTGAGGGAGGAACACTGAAGTACGTGGAAGA
		TGTCACGAATGTCGTGAGGAGAGACGTGGAGAAATGGGGCCCCTTTGACCTGGT
		GTATGGCTCGACGAATCCCCTAGGCAACTCTTGTGACCGCTGTCCTGGCTGGTA
		CATGTTCCAATTCCACCGGATCCTGCAGTATGCGCGGCCTCGCCAAGACAGTCA
		GAAGCCCTTCTTCTGGATATTTATGGACAATCTGCTGCTGACTGAGGATGATCA
		AGTGACAACTGTCCGCTTCCTTCAGACAGAGGCTGTGACCCTCCAGGATGTCCG
		TGGCAGAGTCCTCCAGAATGCTGTGAGGGTATGGAGCAACATTCCAGGACTGAA
		GAGTAAGCACTCAGTCCTGACGCCAAAGGAAGAACAGTCTCTGCAAGCCCAAGT
		CAGAACCAGAAGCAAGCTGCCCACCCAGGTTAACCCCCTGGTGAAGACCTGCCT
		TCTCCCCCTGAGAGAGTACTTCAAGTGTTTTTCTCAGAATTCACTTCCTCTTGG
		AGGACCCTCCTCTGGCGCCCCACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCC
		AACCAGCACAGAGGAGGGCACCAGCGAGTCCGCCACACCAGAGTCTGGACCTGG
		CACCAGCACAGAGCCATCCGAGGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCC
		TACCTCCACCGAAGAGGGCACCAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGG
		CACCTCTACAGAGCCAAGCGAGCTCGAGGACAAGAAGTACAGCATCGGCCTGGC
		CATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACCGACGAGTACAAGGTGCC
		CAGCAAGAAATTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCAAGAAGAA
		CCTGATCGGAGCCCTGCTGTTCGACAGCGGCGAAACAGCCGAGGCCACCCGGCT
		GAAGAGAACCGCCAGAAGAAGATACACCAGACGGAAGAACCGGATCTGCTATCT
		GCAAGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACAG
		ACTGGAAGAGTCCTTCCTGGTGGAAGAGGATAAGAAGCACGAGCGGCACCCCAT
		CTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAGAAGTACCCCACCATCTA
		CCACCTGAGAAAGAAACTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGAT
		CTATCTGGCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGG
		CGACCTGAACCCCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCA
		GACCTACAACCAGCTGTTCGAGGAAAACCCCATCAACGCCAGCGGCGTGGACGC
		CAAGGCCATCCTGTCTGCCAGACTGAGCAAGAGCAGACGGCTGGAAAATCTGAT
		CGCCCAGCTGCCCGGCGAGAAGAAGAATGGCCTGTTCGGCAACCTGATTGCCCT
		GAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAGGATGC
		CAAACTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGC
		CCAGATCGGCGACCAGTACGCCGACCTGTTTCTGGCCGCCAAGAACCTGTCCGA
		CGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAGATCACCAAGGCCCC
		CCTGAGCGCCTCTATGATCAAGAGATACGACGAGCACCACCAGGACCTGACCCT
		GCTGAAAGCTCTCGTGCGGCAGCAGCTGCCTGAGAAGTACAAAGAGATTTTCTT
		CGACCAGAGCAAGAACGGCTACGCCGGCTACATTGACGGCGGAGCCAGCCAGGA
		AGAGTTCTACAAGTTCATCAAGCCCATCCTGGAAAAGATGGACGGCACCGAGGA
		ACTGCTCGTGAAGCTGAACAGAGAGGACCTGCTGCGGAAGCAGCGGACCTTCGA
		CAACGGCAGCATCCCCCACCAGATCCACCTGGGAGAGCTGCACGCCATTCTGCG
		GCGGCAGGAAGATTTTTACCCATTCCTGAAGGACAACCGGGAAAAGATCGAGAA
		GATCCTGACCTTCCGCATCCCCTACTACGTGGGCCCTCTGGCCAGGGGAAACAG
		CAGATTCGCCTGGATGACCAGAAAGAGCGAGGAAACCATCACCCCCTGGAACTT
		CGAGGAAGTGGTGGACAAGGGCGCTTCCGCCCAGAGCTTCATCGAGCGGATGAC
		CAACTTCGATAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCT
		GTACGAGTACTTCACCGTGTATAACGAGCTGACCAAAGTGAAATACGTGACCGA
		GGGAATGAGAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTGGA
		CCTGCTGTTCAAGACCAACCGGAAAGTGACCGTGAAGCAGCTGAAAGAGGACTA
		CTTCAAGAAAATCGAGTGCTTCGACTCCGTGGAAATCTCCGGCGTGGAAGATCG
		GTTCAACGCCTCCCTGGGCACATACCACGATCTGCTGAAAATTATCAAGGACAA
		GGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAAGATATCGTGCTGAC
		CCTGACACTGTTTGAGGACAGAGAGATGATCGAGGAACGGCTGAAAACCTATGC
		CCACCTGTTCGACGACAAAGTGATGAAGCAGCTGAAGCGGCGGAGATACACCGG
		CTGGGGCAGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGG
		CAAGACAATCCTGGATTTCCTGAAGTCCGACGGCTTCGCCAACAGAAACTTCAT
		GCAGCTGATCCACGACGACAGCCTGACCTTTAAAGAGGACATCCAGAAAGCCCA
		GGTGTCCGGCCAGGGCGATAGCCTGCACGAGCACATTGCCAATCTGGCCGGCAG
		CCCCGCCATTAAGAAGGGCATCCTGCAGACAGTGAAGGTGGTGGACGAGCTCGT
		GAAAGTGATGGGCCGGCACAAGCCCGAGAACATCGTGATCGAAATGGCCAGAGA
		GAACCAGACCACCCAGAAGGGACAGAAGAACAGCCGCGAGAGAATGAAGCGGAT
		CGAAGAGGGCATCAAAGAGCTGGGCAGCCAGATCCTGAAAGAACACCCCGTGGA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		AAACACCCAGCTGCAGAACGAGAAGCTGTACCTGTACTACCTGCAGAATGGGCG GGATATGTACGTGGACCAGGAACTGGACATCAACCGGCTGTCCGACTACGATGT GGACGCCATCGTGCCTCAGAGCTTTCTGAAGGACGACTCCATCGACAACAAGGT GCTGACCAGAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCTCCGAAGA GGTCGTGAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAACGCCAAGCTGAT TACCCAGAGAAAGTTCGACAATCTGACCAAGGCCGAGAGAGGCGGCCTGAGCGA ACTGGATAAGGCCGGCTTCATCAAGAGACAGCTGGTGGAAACCCGGCAGATCAC AAAGCACGTGGCACAGATCCTGGACTCCCGGATGAACACTAAGTACGACGAGAA TGACAAGCTGATCCGGGAAGTGAAAGTGATCACCCTGAAGTCCAAGCTGGTGTC CGATTTCCGGAAGGATTTCCAGTTTTACAAAGTGCGCGAGATCAACAACTACCA CCACGCCCACGACGCCTACCTGAACGCCGTCGTGGGAACCGCCCTGATCAAAAA GTACCCTAAGCTGGAAAGCGAGTTCGTGTACGGCGACTACAAGGTGTACGACGT GCGGAAGATGATCGCCAAGAGCGAGCAGGAAATCGGCAAGGCTACCGCCAAGTA CTTCTTCTACAGCAACATCATGAACTTTTTCAAGACCGAGATTACCCTGGCCAA CGGCGAGATCCGGAAGCGGCCTCTGATCGAGACAAACGGCGAAACCGGGGAGAT CGTGTGGGATAAGGGCCGGGATTTTGCCACCGTGCGGAAAGTGCTGAGCATGCC CCAAGTGAATATCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCAGCAAAGA GTCTATCCTGCCCAAGAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTG GGACCCTAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTATTCTGTGCT GGTGGTGGCCAAAGTGGAAAAGGGCAAGTCCAAGAAACTGAAGAGTGTGAAAGA GCTGCTGGGGATCACCATCATGGAAAGAAGCAGCTTCGAGAAGAATCCCATCGA CTTTCTGGAAGCCAAGGGCTACAAAGAAGTGAAAAAGGACCTGATCATCAAGCT GCCTAAGTACTCCCTGTTCGAGCTGGAAAACGGCCGGAAGAGAATGCTGGCCTC TGCCGGCGAACTGCAGAAGGGAAACGAACTGGCCCTGCCCTCCAAATATGTGAA CTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAGGGCTCCCCCGAGGATAA TGAGCAGAAACAGCTGTTTGTGGAACAGCACAAGCACTACCTGGACGAGATCAT CGAGCAGATCAGCGAGTTCTCCAAGAGAGTGATCCTGGCCGACGCTAATCTGGA CAAAGTGCTGTCCGCCTACAACAAGCACCGGGATAAGCCCATCAGAGAGCAGGC CGAGAATATCATCCACCTGTTTACCCTGACCAATCTGGGAGCCCCTGCCGCCTT CAAGTACTTTGACACCACCATCGACCGGAAGAGGTACACCAGCACCAAAGAGGT GCTGGACGCCACCCTGATCCACCAGAGCATCACCGGCCTGTACGAGACACGGAT CGACCTGTCTCAGCTGGGAGGCGACAGCCCCAAGAAGAAGAGAAAGGTGGGAGT CGACGGATCCAGCGGCTCCGAGACCCCAGGCACATCTGAGAGCGCCACCCCTGA GTCCACCGGTATGAACAATTCACAGGGGAGAGTGACATTCGAAGACGTGACCGT GAACTTCACCCAGGGAGAATGGCAGCGCTTGAACCCAGAACAAAGGAACCTCTA TCGGGACGTGATGCTGGAAAACTACTCAAATTTGGTGAGCGTTGGGCAGGGTGA GACCACTAAGCCTGACGTGATCCTGAGATTGGAACAGGGCAAGGAGCCTTGGCT CGAGGAAGAGGAAGTCCTGGGCTCAGGGAGGGCCGAGAAAAACGGTGATATAGG AGGCCAGATATGGAAGCCTAAGGACGTCAAGGAGAGCCTGAGCGCTGCTAAACG TCCGGCAGCAACCAAAAAAGCAGGTCAGGCCAAGAAAAAATGAGGATCCTGAGT CTAGAAAGAGCCTTCTGAGCCCAGCGACTTCTGAAGGGCCCCTTGCAAAGTAAT AGGGCTTCTGCCTAAGCCTCTCCCTCCAGCCAATAGGCAGCTTTCTTAACTATC CTAACAAGCCTTGGACCAAATGGAAATAAAGCTTTTTGATGCAGTGTTAATTAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAGAAGAGCGAATTCACTGGCCGTCGTTTTACAACGTCGTGACTG GGAAAACCCTGGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGC CAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCG CAGCCTGAATGGCGAATGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTG CGGTATTTCACACCGCATATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGC ATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGC TTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTG CATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGATGCAGCTCTGGCC CGTGTCTCAAAATCTCTGATGTTACATTGCACAAGATAAAAATATATCATCATG AACAATAAAACTGTCTGCTTACATAAACAGTAATACAAGGGGTGTTATGAGCCA TATTCAACGGGAAACGTCGAGGCCGCGATTAAATTCCAACATGGATGCTGATTT ATATGGGTATAAATGGGCTCGCGATAATGTCGGGCAATCAGGTGCGACAATCTA TCGCTTGTATGGGAAGCCCGATGCGCCAGAGTTGTTTCTGAAACATGGCAAAGG TAGCGTTGCCAATGATGTTACAGATGAGATGGTCAGACTAAACTGGCTGACGGA ATTTATGCCTCTTCCGACCATCAAGCATTTTATCCGTACTCCTGATGATGCATG GTTACTCACCACTGCGATCCCCGGAAAAACAGCATTCCAGGTATTAGAAGAATA TCCTGATTCAGGTGAAAATATTGTTGATGCGCTGGCAGTGTTCCTGCGCCGGTT GCATTCGATTCCTGTTTGTAATTGTCCTTTTAACAGCGATCGCGTATTTCGTCT CGCTCAGGCGCAATCACGAATGAATAACGGTTTGGTTGATGCGAGTGATTTTGA TGACGAGCGTAATGGCTGGCCTGTTGAACAAGTCTGGAAAGAAATGCATAAACT TTTGCCATTCTCACCGGATTCAGTCGTCACTCATGGTGATTTCTCACTTGATAA CCTTATTTTTGACGAGGGGAAATTAATAGGTTGTATTGATGTTGGACGAGTCGG AATCGCAGACCGATACCAGGATCTTGCCATCCTATGGAACTGCCTCGGTGAGTT TTCTCCTTCATTACAGAAACGGCTTTTTCAAAAATATGGTATTGATAATCCTGA TATGAATAAATTGCAGTTTCATTTGATGCTCGATGAGTTTTTCTAATCAGAATT GGTTAATTGGTTGTAACATTATTCAGATTGGGCTTGATTTAAAACTTCATTTTT AATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCC CTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAG GATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAA AACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTT TTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTTCTAG

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		TGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACC TCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTC TTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCT GAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAAC TGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAA AGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGG AGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACC TCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGA AAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTG CTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCG CCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGT CAGTGAGCGAGGAAGCGGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCC GATTCATTAATGCAGCTGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGA GCGCAACGCAATTAATGTGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACA CTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCA CACAGGAAACAGCTATGACCATGATTACGCCAAGCTTTAATACGACTCACTATA
1254	CRISPR-Off variant 2 amino acid sequence	MKRPAATKKAGQAKKKYNHDQEFDPPKVYPPVPAEKRKPIRVLSLEDGIATGLL VLKDLGIQVDRYIASEVCEDSITVGMVRHQGKIMYVGDVRSVTQKHIQEWGPFD LVIGGSPCNDLSIVNPARKGLYEGTGRLFFEFYRLLHDARPKEGDDRPFFWLFE NVVAMGVSDKRDISRFLESNPVMIDAKEVSAAHRARYFWGNLPGMNRPLASTVN DKLELQECLEHGRIAKFSKVRTITTRSNSIKQGKDQHFPVFMNEKEDILWCTEM ERVFGFPVHYTDVSNMSRLARQRLLGRSWSVPVIRHLFAPLKEYFACVSSGNSN ANSRGPSFSSGLVPLSLRGSHSPMEIYKTVSAWKRQPVRVLSLFGNIDKELKSL GFLEIGSDSEGGTLKYVEDVTNVVRRDVEKWGPFDLVYGSTNPLGNSCDRCPGW YMFQFHRILQYARPRQDSQKPFFWIFMDNLLLTEDDQVTTVRFLQTEAVTLQDV RGRVLQNAVRVWSNIPGLKSKHSVLTPKEEQSLQAQVRTRSKLPTQVNPLVKTC LLPLREYFKCFSQNSLPLGGPSSGAPPPSGGSPAGSPTSTEEGTSESATPESGP GTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSELEDKKYSIGL AIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLEDSGETAEATR LKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHP IFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKERGHFLIE GDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENL IAQLPGEKKNGLFGNLIALSLGLTPNEKSNFDLAEDAKLQLSKDTYDDDLDNLL AQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLT LLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTE ELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPELKDNREKIE KILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERM TNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIV DLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTYHDLLKIIKD KDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYT GWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKA QVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMAR ENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNG RDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSE EVVKKMKNYWRQLLNAKLITQRKEDNLTKAERGGLSELDKAGFIKRQLVETRQI TKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNY HHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAK YFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSM PQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSV LVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIK LPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPED NEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQ AENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETR IDLSQLGGDSPKKKRKVGVDGSSGSETPGTSESATPESTGMNNSQGRVTFEDVT VNFTQGEWQRLNPEQRNLYRDVMLENYSNLVSVGQGETTKPDVILRLEQGKEPW LEEEEVLGSGRAEKNGDIGGQIWKPKDVKESLSAAKRPAATKKAGQAKKK
1255	CRISPR-Off variant 3 plasmid sequence	AGAAACTAGCGTAAATTCAAATATAGGTCAGGCTTCAACGTCAACAAATATGAT GAAGAGACCTGCTGCCACCAAGAAGGCCGGCCAGGCCAAGAAAAAGTACAATCA CGATCAGGAGTTCGACCCCCCTAAGGTGTACCCACCAGTGCCTGCAGAGAAGAG GAAGCCAATCCGGGTGCTGAGCCTGTTTGATGGCATCGCCACCGGCCTGCTGGT GCTGAAGGATCTGGGCATCCAGGTGGACCGGTACATCGCCTCCGAGGTGTGCGA GGATTCTATCACCGTGGGCATGGTGCGCCACCAGGGCAAGATCATGTATGTGGG CGACGTGCGGTCCGTGACACAGAAGCACATCCAGGAGTGGGGCCCATTCGATCT GGTGATCGGCGGCAGCCCCTGTAATGACCTGTCCATCGTGAACCCTGCAAGGAA GGGACTGTACGAGGGAACCGGCCGGCTGTTCTTTGAGTTTTATAGACTGCTGCA CGACGCCAGGCCTAAGGAGGGCGACGATAGACCATTCTTTTGGCTGTTCGAGAA TGTGGTGGCTATGGGCGTGAGCGATAAGAGGGACATCTCCAGGTTTCTGGAGTC TAACCCCGTGATGATCGATGCAAAGGAGGTGTCCGCCGCACACAGAGCCAGGTA TTTCTGGGGCAATCTGCCAGGAATGAACAGGCCACTGGCAAGCACCGTGAATGA CAAGCTGGAGCTGCAGGAGTGCCTGGAGCACGGAAGGATCGCCAAGTTTTCCAA GGTGCGCACAATCACCACACGGAGCAATTCCATCAAGCAGGGCAAGGATCAGCA CTTCCCCGTGTTCATGAACGAGAAGGAGGACATCCTGTGGTGTACCGAGATGGA GAGAGTGTTCGGCTTTCCAGTGCACTACACAGACGTGTCTAACATGAGCAGGCT GGCAAGGCAGCGGCTGCTGGGCAGATCTTGGAGCGTGCCCGTGATCAGGCACCT

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		GTTCGCCCCTCTGAAGGAGTATTTTGCCTGCGTGAGCAGCGGCAACTCCAATGC CAACAGCCGGGGCCCCTCTTTCAGCTCCGGATTGGTGCCTCTGAGCCTGAGGGG CTCCCACAGTCCCCTTGAGATGTATAAAACTGTGCCTGTGTGGAAGAGAGAGCC AGTGCGGGTGCTGTCCCTTTTTGGTGACATCAAGAAAGAGCTGACGACTTTGGG CTTTCTGGAAAACGGCTCTGACCCGGGCCGACTGAAACATTTGGACGATGTCAC CAATACGGTGAGGAGGGACGTGGAAGAATGGGGCCCGTTCGACCTCGTGTACGG CTCCACGCCGCCCCTCGGCCACGCCTGTGACCATCCTCCCGGGTGGTACCTGTT CCAGTTCCACCGTGTGCTTCAGTACGCGAGGCCCAGGCCGGGCAGCCCGCAGGC CTTCTTCTGGATGTTTGTGGACAACCTGGTGCTGACCGAGGATGACCGGGCTGT AGCCACTCGCTTCCTGGAGACTGACCCGGTGACCATCCAGGACGTCTGTGGCAG AGCTGTCCGGAACGCCGTGCACGTGTGGAGCAACATCCCGGCCGTGAAAAGCAG GCACTCGGCCCTGTTTTCCCAGGAGGAATCATTCCTGCGGGCTCAGGACAGGCA GAGAGCAAAGCCCCCCGCCCGGGGGCCAGCCAAGCTGGTGAAGAATTGTTTTCT CCCCCTGAGAGAATATTTCAAGTATTTTTCAACAGAATTCACTTCCTCTTTGGG AGGACCCTCCTCTGGCGCCCCACCACCTAGCGGCGGCTCCCCTGCCGGCTCTCC AACCAGCACAGAGGAGGGCACCAGCGAGTCCGCCACACCAGAGTCTGGACCTGG CACCAGCACAGAGCCATCCGAGGGCTCTGCCCCAGGCTCTCCTGCAGGCAGCCC TACCTCCACCGAAGAGGGCACCAGCACAGAGCCTTCTGAGGGCAGCGCCCCAGG CACCTCTACAGAGCCAAGCGAGCTCGAGGACAAGAAGTACAGCATCGGCCTGGC CATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACCGACGAGTACAAGGTGCC CAGCAAGAAATTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCAAGAAGAA CCTGATCGGAGCCCTGCTGTTCGACAGCGGCGAAACAGCCGAGGCCACCCGGCT GAAGAGAACCGCCAGAAGAAGATACACCAGACGGAAGAACCGGATCTGCTATCT GCAAGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACAG ACTGGAAGAGTCCTTCCTGGTGGAAGAGGATAAGAAGCACGAGCGGCACCCCAT CTTCGGCAACATCGTGGACGAGGTGGCCTACCACGAGAAGTACCCCACCATCTA CCACCTGAGAAAGAAACTGGTGGACAGCACCGACAAGGCCGACCTGCGGCTGAT CTATCTGGCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGG CGACCTGAACCCCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCA GACCTACAACCAGCTGTTCGAGGAAAACCCCATCAACGCCAGCGGCGTGGACGC CAAGGCCATCCTGTCTGCCAGACTGAGCAAGAGCAGACGGCTGGAAAATCTGAT CGCCCAGCTGCCCGGCGAGAAGAAGAATGGCCTGTTCGGCAACCTGATTGCCCT GAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAGGATGC CAAACTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGC CCAGATCGGCGACCAGTACGCCGACCTGTTTCTGGCCGCCAAGAACCTGTCCGA CGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAGATCACCAAGGCCCC CCTGAGCGCCTCTATGATCAAGAGATACGACGAGCACCACCAGGACCTGACCCT GCTGAAAGCTCTCGTGCGGCAGCAGCTGCCTGAGAAGTACAAAGAGATTTTCTT CGACCAGAGCAAGAACGGCTACGCCGGCTACATTGACGGCGGAGCCAGCCAGGA AGAGTTCTACAAGTTCATCAAGCCCATCCTGGAAAAGATGGACGGCACCGAGGA ACTGCTCGTGAAGCTGAACAGAGAGGACCTGCTGCGGAAGCAGCGGACCTTCGA CAACGGCAGCATCCCCCACCAGATCCACCTGGGAGAGCTGCACGCCATTCTGCG GCGGCAGGAAGATTTTTACCCATTCCTGAAGGACAACCGGGAAAAGATCGAGAA GATCCTGACCTTCCGCATCCCCTACTACGTGGGCCCTCTGGCCAGGGGAAACAG CAGATTCGCCTGGATGACCAGAAAGAGCGAGGAAACCATCACCCCCTGGAACTT CGAGGAAGTGGTGGACAAGGGCGCTTCCGCCCAGAGCTTCATCGAGCGGATGAC CAACTTCGATAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAGCACAGCCTGCT GTACGAGTACTTCACCGTGTATAACGAGCTGACCAAAGTGAAATACGTGACCGA GGGAATGAGAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTGGA CCTGCTGTTCAAGACCAACCGGAAAGTGACCGTGAAGCAGCTGAAAGAGGACTA CTTCAAGAAAATCGAGTGCTTCGACTCCGTGGAAATCTCCGGCGTGGAAGATCG GTTCAACGCCTCCCTGGGCACATACCACGATCTGCTGAAAATTATCAAGGACAA GGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAAGATATCGTGCTGAC CCTGACACTGTTTGAGGACAGAGAGATGATCGAGGAACGGCTGAAAACCTATGC CCACCTGTTCGACGACAAAGTGATGAAGCAGCTGAAGCGGCGGAGATACACCGG CTGGGGCAGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGG CAAGACAATCCTGGATTTCCTGAAGTCCGACGGCTTCGCCAACAGAAACTTCAT GCAGCTGATCCACGACGACAGCCTGACCTTTAAAGAGGACATCCAGAAAGCCCA GGTGTCCGGCCAGGGCGATAGCCTGCACGAGCACATTGCCAATCTGGCCGGCAG CCCCGCCATTAAGAAGGGCATCCTGCAGACAGTGAAGGTGGTGGACGAGCTCGT GAAAGTGATGGGCCGGCACAAGCCCGAGAACATCGTGATCGAAATGGCCAGAGA GAACCAGACCACCCAGAAGGGACAGAAGAACAGCCGCGAGAGAATGAAGCGGAT CGAAGAGGGCATCAAAGAGCTGGGCAGCCAGATCCTGAAAGAACACCCCGTGGA AAACACCCAGCTGCAGAACGAGAAGCTGTACCTGTACTACCTGCAGAATGGGCG GGATATGTACGTGGACCAGGAACTGGACATCAACCGGCTGTCCGACTACGATGT GGACGCCATCGTGCCTCAGAGCTTTCTGAAGGACGACTCCATCGACAACAAGGT GCTGACCAGAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCTCCGAAGA GGTCGTGAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAACGCCAAGCTGAT TACCCAGAGAAAGTTCGACAATCTGACCAAGGCCGAGAGAGGCGGCCTGAGCGA ACTGGATAAGGCCGGCTTCATCAAGAGACAGCTGGTGGAAACCCGGCAGATCAC AAAGCACGTGGCACAGATCCTGGACTCCCGGATGAACACTAAGTACGACGAGAA TGACAAGCTGATCCGGGAAGTGAAAGTGATCACCCTGAAGTCCAAGCTGGTGTC CGATTTCCGGAAGGATTTCCAGTTTTACAAAGTGCGCGAGATCAACAACTACCA CCACGCCCACGACGCCTACCTGAACGCCGTCGTGGGAACCGCCCTGATCAAAAA GTACCCTAAGCTGGAAAGCGAGTTCGTGTACGGCGACTACAAGGTGTACGACGT GCGGAAGATGATCGCCAAGAGCGAGCAGGAAATCGGCAAGGCTACCGCCAAGTA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		CTTCTTCTACAGCAACATCATGAACTTTTTCAAGACCGAGATTACCCTGGCCAA CGGCGAGATCCGGAAGCGGCCTCTGATCGAGACAAACGGCGAAACCGGGGAGAT CGTGTGGGATAAGGGCCGGGATTTTGCCACCGTGCGGAAAGTGCTGAGCATGCC CCAAGTGAATATCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCAGCAAAGA GTCTATCCTGCCCAAGAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTG GGACCCTAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTATTCTGTGCT GGTGGTGGCCAAAGTGGAAAAGGGCAAGTCCAAGAAACTGAAGAGTGTGAAAGA GCTGCTGGGGATCACCATCATGGAAAGAAGCAGCTTCGAGAAGAATCCCATCGA CTTTCTGGAAGCCAAGGGCTACAAAGAAGTGAAAAAGGACCTGATCATCAAGCT GCCTAAGTACTCCCTGTTCGAGCTGGAAAACGGCCGGAAGAGAATGCTGGCCTC TGCCGGCGAACTGCAGAAGGGAAACGAACTGGCCCTGCCCTCCAAATATGTGAA CTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAGGGCTCCCCCGAGGATAA TGAGCAGAAACAGCTGTTTGTGGAACAGCACAAGCACTACCTGGACGAGATCAT CGAGCAGATCAGCGAGTTCTCCAAGAGAGTGATCCTGGCCGACGCTAATCTGGA CAAAGTGCTGTCCGCCTACAACAAGCACCGGGATAAGCCCATCAGAGAGCAGGC CGAGAATATCATCCACCTGTTTACCCTGACCAATCTGGGAGCCCCTGCCGCCTT CAAGTACTTTGACACCACCATCGACCGGAAGAGGTACACCAGCACCAAAGAGGT GCTGGACGCCACCCTGATCCACCAGAGCATCACCGGCCTGTACGAGACACGGAT CGACCTGTCTCAGCTGGGAGGCGACAGCCCCAAGAAGAAGAGAAAGGTGGGAGT CGACGGATCCAGCGGCTCCGAGACCCCAGGCACATCTGAGAGCGCCACCCCTGA GTCCACCGGTATGAACAATTCACAGGGGAGAGTGACATTCGAAGACGTGACCGT GAACTTCACCCAGGGAGAATGGCAGCGCTTGAACCCAGAACAAAGGAACCTCTA TCGGGACGTGATGCTGGAAAACTACTCAAATTTGGTGAGCGTTGGGCAGGGTGA GACCACTAAGCCTGACGTGATCCTGAGATTGGAACAGGGCAAGGAGCCTTGGCT CGAGGAAGAGGAAGTCCTGGGCTCAGGGAGGGCCGAGAAAAACGGTGATATAGG AGGCCAGATATGGAAGCCTAAGGACGTCAAGGAGAGCCTGAGCGCTAAACGTCC GGCAGCAACCAAAAAAGCAGGTCAGGCCAAGAAAAAATGAGGATCCTGAGTCTA GAAAAGATATATATAGGATTGAAGATCTCTCAGTTAAGTCTACAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAGAAGAGCGAATTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCC TGGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCG TAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAA TGGCGAATGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTC ACACCGCATATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAG CCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCT CCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCA GAGGTTTTCACCGTCATCACCGAAACGCGCGATGCAGCTCTGGCCCGTGTCTCA AAATCTCTGATGTTACATTGCACAAGATAAAAATATATCATCATGAACAATAAA ACTGTCTGCTTACATAAACAGTAATACAAGGGGTGTTATGAGCCATATTCAACG GGAAACGTCGAGGCCGCGATTAAATTCCAACATGGATGCTGATTTATATGGGTA TAAATGGGCTCGCGATAATGTCGGGCAATCAGGTGCGACAATCTATCGCTTGTA TGGGAAGCCCGATGCGCCAGAGTTGTTTCTGAAACATGGCAAAGGTAGCGTTGC CAATGATGTTACAGATGAGATGGTCAGACTAAACTGGCTGACGGAATTTATGCC TCTTCCGACCATCAAGCATTTTATCCGTACTCCTGATGATGCATGGTTACTCAC CACTGCGATCCCCGGAAAAACAGCATTCCAGGTATTAGAAGAATATCCTGATTC AGGTGAAAATATTGTTGATGCGCTGGCAGTGTTCCTGCGCCGGTTGCATTCGAT TCCTGTTTGTAATTGTCCTTTTAACAGCGATCGCGTATTTCGTCTCGCTCAGGC GCAATCACGAATGAATAACGGTTTGGTTGATGCGAGTGATTTTGATGACGAGCG TAATGGCTGGCCTGTTGAACAAGTCTGGAAAGAAATGCATAAACTTTTGCCATT CTCACCGGATTCAGTCGTCACTCATGGTGATTTCTCACTTGATAACCTTATTTT TGACGAGGGGAAATTAATAGGTTGTATTGATGTTGGACGAGTCGGAATCGCAGA CCGATACCAGGATCTTGCCATCCTATGGAACTGCCTCGGTGAGTTTTCTCCTTC ATTACAGAAACGGCTTTTTCAAAAATATGGTATTGATAATCCTGATATGAATAA ATTGCAGTTTCATTTGATGCTCGATGAGTTTTTCTAATCAGAATTGGTTAATTG GTTGTAACATTATTCAGATTGGGCTTGATTTAAAACTTCATTTTTAATTTAAAA GGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTG AGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTT GAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGC TACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGG TAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTTCTAGTGTAGCCGT AGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGC TAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGT TGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGG GTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACC TACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACA GGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAG GGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTG AGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCA GCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT TCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGT GAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCG AGGAAGCGGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTA ATGCAGCTGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGC AATTAATGTGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCT TCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAA

TABLE 18-continued

Sequence listing.

SEQ	Description	Sequence
		CAGCTATGACCATGATTACGCCAAGCTTTAATACGACTCACTATA
1256	CRISPR-Off variant 3 amino acid sequence	MKRPAATKKAGQAKKKYNHDQEFDPPKVYPPVPAEKRKPIRVLSLEDGIATGLL VLKDLGIQVDRYIASEVCEDSITVGMVRHQGKIMYVGDVRSVTQKHIQEWGPED LVIGGSPCNDLSIVNPARKGLYEGTGRLFFEFYRLLHDARPKEGDDRPFFWLFE NVVAMGVSDKRDISRFLESNPVMIDAKEVSAAHRARYFWGNLPGMNRPLASTVN DKLELQECLEHGRIAKFSKVRTITTRSNSIKQGKDQHFPVEMNEKEDILWCTEM ERVFGFPVHYTDVSNMSRLARQRLLGRSWSVPVIRHLFAPLKEYFACVSSGNSN ANSRGPSFSSGLVPLSLRGSHSPLEMYKTVPVWKREPVRVLSLFGDIKKELTTL GFLENGSDPGRLKHLDDVTNTVRRDVEEWGPFDLVYGSTPPLGHACDHPPGWYL FQFHRVLQYARPRPGSPQAFFWMFVDNLVLTEDDRAVATRFLETDPVTIQDVCG RAVRNAVHVWSNIPAVKSRHSALESQEESFLRAQDRQRAKPPARGPAKLVKNCF LPLREYFKYFSTEFTSSLGGPSSGAPPPSGGSPAGSPTSTEEGTSESATPESGP GTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSELEDKKYSIGL AIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLEDSGETAEATR LKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESELVEEDKKHERHP IFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKERGHFLIE GDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENL IAQLPGEKKNGLFGNLIALSLGLTPNEKSNEDLAEDAKLQLSKDTYDDDLDNLL AQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLT LLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTE ELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIE KILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERM TNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIV DLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTYHDLLKIIKD KDELDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYT GWGRLSRKLINGIRDKQSGKTILDELKSDGFANRNEMQLIHDDSLTFKEDIQKA QVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMAR ENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNG RDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSE EVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQI TKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDERKDFQFYKVREINNY HHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAK YFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSM PQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGEDSPTVAYSV LVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIK LPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPED NEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQ AENIIHLFTLTNLGAPAAFKYEDTTIDRKRYTSTKEVLDATLIHQSITGLYETR IDLSQLGGDSPKKKRKVGVDGSSGSETPGTSESATPESTGMNNSQGRVTFEDVT VNFTQGEWQRLNPEQRNLYRDVMLENYSNLVSVGQGETTKPDVILRLEQGKEPW LEEEEVLGSGRAEKNGDIGGQIWKPKDVKESLSAKRPAATKKAGQAKKK

TABLE 19

Annotation of PLA003 amino acid sequence

Name	Type	Minimum	Maximum	Length
SV40 NLS	CDS	2	8	7
SV40 NLS	CDS	9	15	7
DNMT3A	CDS	17	317	301
Linker	CDS	318	344	27
DNMT3L full-length	CDS	345	730	386
XTEN80	CDS	731	810	80
dCas9	CDS	811	2180	1370
NLS	CDS	2181	2187	7
XTEN16	CDS	2188	2208	21
ZIM3	CDS	2211	2310	100
SV40 NLS	CDS	2313	2319	7
SV40 NLS	CDS	2320	2326	7

TABLE 20

Annotation of PLA003 polynucleotide sequence

Name	Type	Minimum	Maximum	Length
SV40 NLS	CDS	4	24	21
SV40 NLS	CDS	25	45	21
DNMT3A	CDS	49	951	903
Linker	CDS	952	1032	81
DNMT3L full-length	CDS	1033	2190	1158
XTEN80	CDS	2191	2430	240
dCas9	CDS	2431	6540	4110
NLS	CDS	6541	6561	21
XTEN16	CDS	6562	6624	63
ZIM3	CDS	6631	6930	300
SV40 NLS	CDS	6937	6957	21
SV40 NLS	CDS	6958	6978	21
stop	terminator	6979	6981	3

SEQUENCE LISTING

The patent contains a lengthy sequence listing. A copy of the sequence listing is available in electronic form from the USPTO web site (https://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US12390538B2). An electronic copy of the sequence listing will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

The invention claimed is:

1. A method, comprising administering an epigenetic editing system to a subject, wherein the subject comprises detectable levels of HBV DNA, HBsAg, and/or HBeAg in plasma of the subject, wherein the epigenetic editing system comprises

a) a fusion protein comprising

i) a dCas9 protein domain,

ii) a DNMT3A domain and

iii) a human KRAB domain

or one or more nucleic acid molecules encoding the fusion protein,

and b) a guide RNA (gRNA) comprising a nucleic acid base sequence selected from the group consisting of SEQ ID NOs: 1093-1110, 1130-1164, 1166-1173, 1175-1199, 1201-1235, and 1249, wherein the nucleic acid base sequence comprises a region complementary to a strand of a target region wherein the target region comprises a sequence selected from the group consisting of SEQ ID NOs: 333-350, 370-404, 406-413, 415-439, and 441-475.

2. The method of claim **1**, wherein the fusion protein further comprises a DNMT3L domain.

3. The method of claim **1**, wherein the dCas9 protein domain is from *Streptococcus pyogenes* or *Staphylococcus aureus*.

4. The method of claim **3**, wherein the dCas9 protein domain comprises a sequence selected from the group consisting of SEQ ID NOs: 12, 13, 27, 28 and 29.

5. The method of claim **3**, wherein the dCas9 protein domain is from *Streptococcus pyogenes*.

6. The method of claim **4**, wherein the dCas9 protein domain comprises the sequence of SEQ ID NO: 12.

7. The method of claim **1**, wherein the DNMT3A domain comprises a sequence selected from the group consisting of SEQ ID NOs: 1028 and 1029.

8. The method of claim **1**, wherein the DNMT3A domain comprises a sequence of SEQ ID NO: 1029.

9. The method of claim **1**, wherein the human KRAB domain comprises a sequence selected from the group consisting of SEQ ID NOs: 495, 551, 536, 537, 707, and 717.

10. The method of claim **1**, wherein the human KRAB domain is a ZIM3 KRAB domain.

11. The method of claim **10**, wherein the ZIM3 KRAB domain comprises the sequence of SEQ ID NO: 495.

12. The method of claim **1**, wherein the target region comprises the sequence of SEQ ID NO: 391.

13. The method of claim **1**, wherein the target region comprises the sequence of SEQ ID NO: 392.

14. The method of claim **1**, wherein the gRNA comprises the nucleic acid base sequence of SEQ ID NO: 1151 or 1249.

15. The method of claim **2**, wherein the DNMT3L domain is a human DNMT3L domain.

16. The method of claim **2**, wherein the DNMT3L domain comprises a sequence selected from the group consisting of SEQ ID NOs: 1032-1035.

17. The method of claim **16**, wherein the DNMT3L domain comprises the sequence of SEQ ID NO: 1033.

18. The method of claim **1**, wherein the dCas9 protein domain comprises a sequence of SEQ ID NO: 12, the DNMT3A domain comprises a sequence of SEQ ID NO: 1029, and the human KRAB domain comprises a sequence of SEQ ID NO: 495.

19. The method of claim **1**, wherein the dCas9 protein domain comprises a sequence with at least 99% sequence identity to the sequence of SEQ ID NO: 12, the DNMT3A domain comprises a sequence with at least 99% sequence identity to the sequence of SEQ ID NO: 1029, and the human KRAB domain comprises a sequence with at least 99% sequence identity to the sequence of SEQ ID NO: 495.

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