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Compounds and methods for reducing app expression

Abstract

Provided are compounds, methods, and pharmaceutical compositions for reducing the amount or activity of APP RNA in a cell or animal, and in certain instances reducing the amount of APP protein in a cell or animal. Such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a neurodegenerative disease or disorder. Such symptoms and hallmarks include cognitive impairment, including a decline in memory and language skills, behavioral and psychological symptoms such as apathy and lack of motivation, gait disturbances and seizures, progressive dementia, and abnormal amyloid deposits.

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References Cited

U.S. PATENT DOCUMENTS

Patent No.	Issued Date	Patentee Name	U.S. Cl.	CPC
3687808	12/1971	Merigan et al.	N/A	N/A
4415732	12/1982	Caruthers et al.	N/A	N/A
4469863	12/1983	Ts'o et al.	N/A	N/A
4476301	12/1983	Imbach et al.	N/A	N/A
4500707	12/1984	Caruthers et al.	N/A	N/A
4725677	12/1987	Koster et al.	N/A	N/A
4845205	12/1988	Huynh Dinh et al.	N/A	N/A
4973679	12/1989	Caruthers et al.	N/A	N/A

4981957	12/1990	Lebleu et al.	N/A	N/A
5013830	12/1990	Ohutsuka et al.	N/A	N/A
5023243	12/1990	Tullis	N/A	N/A
5034506	12/1990	Summerton et al.	N/A	N/A
5118800	12/1991	Smith et al.	N/A	N/A
5130302	12/1991	Spielvogel et al.	N/A	N/A
5132418	12/1991	Caruthers et al.	N/A	N/A
5134066	12/1991	Rogers et al.	N/A	N/A
RE34036	12/1991	McGeehan	N/A	N/A
5149797	12/1991	Pederson et al.	N/A	N/A
5166315	12/1991	Summerton et al.	N/A	N/A
5175273	12/1991	Bischofberger et al.	N/A	N/A
5177196	12/1992	Meyer, Jr. et al.	N/A	N/A
5177198	12/1992	Spielvogel et al.	N/A	N/A
5188897	12/1992	Suhadolnik et al.	N/A	N/A
5194599	12/1992	Froehler et al.	N/A	N/A
5214134	12/1992	Weis et al.	N/A	N/A
5216141	12/1992	Benner	N/A	N/A
5220007	12/1992	Pederson et al.	N/A	N/A
5223618	12/1992	Cook et al.	N/A	N/A
5235033	12/1992	Summerton et al.	N/A	N/A
5256775	12/1992	Froehler	N/A	N/A
5264423	12/1992	Cohen et al.	N/A	N/A
5264562	12/1992	Matteucci	N/A	N/A
5264564	12/1992	Matteucci	N/A	N/A
5185444	12/1992	Summerton et al.	N/A	N/A
5276019	12/1993	Cohen et al.	N/A	N/A
5286717	12/1993	Cohen et al.	N/A	N/A
5319080	12/1993	Leumann	N/A	N/A
5321131	12/1993	Agrawal et al.	N/A	N/A
5359044	12/1993	Cook et al.	N/A	N/A
5366878	12/1993	Pederson et al.	N/A	N/A
5367066	12/1993	Urdea et al.	N/A	N/A
5378825	12/1994	Cook et al.	N/A	N/A
5386023	12/1994	Sanghvi et al.	N/A	N/A
5393878	12/1994	Leumann	N/A	N/A
5399676	12/1994	Froehler	N/A	N/A
5403711	12/1994	Walder et al.	N/A	N/A
5405938	12/1994	Sumerton et al.	N/A	N/A
5405939	12/1994	Suhadolnik et al.	N/A	N/A
5432272	12/1994	Benner	N/A	N/A
5434257	12/1994	Matteucci	N/A	N/A
5446137	12/1994	Maag et al.	N/A	N/A
5453496	12/1994	Caruthers et al.	N/A	N/A
5455233	12/1994	Spielvogel et al.	N/A	N/A
5457187	12/1994	Gmelner et al.	N/A	N/A
5457191	12/1994	Cook et al.	N/A	N/A
5459255	12/1994	Cook et al.	N/A	N/A
5466677	12/1994	Baxter et al.	N/A	N/A
5466786	12/1994	Burh et al.	N/A	N/A
5470967	12/1994	Huie et al.	N/A	N/A
5476925	12/1994	Letsinger et al.	N/A	N/A
5484908	12/1995	Froehler et al.	N/A	N/A
5489677	12/1995	Sanghvi et al.	N/A	N/A
5491133	12/1995	Walder et al.	N/A	N/A
5502177	12/1995	Matteucci et al.	N/A	N/A
5508270	12/1995	Baxter et al.	N/A	N/A
5514785	12/1995	Van Ness et al.	N/A	N/A
5519126	12/1995	Hecht	N/A	N/A
5519134	12/1995	Acevedo et al.	N/A	N/A
5525711	12/1995	Hawkins et al.	N/A	N/A
5527899	12/1995	Froehler	N/A	N/A
5536821	12/1995	Agrawal et al.	N/A	N/A
5541306	12/1995	Agrawal et al.	N/A	N/A
5541307	12/1995	Cook et al.	N/A	N/A
5550111	12/1995	Suhadolnik et al.	N/A	N/A
5552540	12/1995	Haralambidis	N/A	N/A
5561225	12/1995	Maddry et al.	N/A	N/A
5563253	12/1995	Agrawal et al.	N/A	N/A
5565350	12/1995	Kmiec	N/A	N/A
5565555	12/1995	Froehler et al.	N/A	N/A
5567811	12/1995	Mistura et al.	N/A	N/A
5571799	12/1995	Tkachuk et al.	N/A	N/A
5576427	12/1995	Cook et al.	N/A	N/A
5587361	12/1995	Cook et al.	N/A	N/A

5587469	12/1995	Cook et al.	N/A	N/A
5587470	12/1995	Cook et al.	N/A	N/A
5591722	12/1996	Montgomery et al.	N/A	N/A
5594121	12/1996	Froehler et al.	N/A	N/A
5596086	12/1996	Matteucci	N/A	N/A
5596091	12/1996	Switzer	N/A	N/A
5597909	12/1996	Urdea et al.	N/A	N/A
5602240	12/1996	De Mesmaeker et al.	N/A	N/A
5608046	12/1996	Cook et al.	N/A	N/A
5610289	12/1996	Cook et al.	N/A	N/A
5610300	12/1996	Altmann et al.	N/A	N/A
5614617	12/1996	Cook et al.	N/A	N/A
5618704	12/1996	Sanghvi et al.	N/A	N/A
5623065	12/1996	Cook et al.	N/A	N/A
5623070	12/1996	Cook et al.	N/A	N/A
5625050	12/1996	Beaton et al.	N/A	N/A
5627053	12/1996	Usman et al.	N/A	N/A
5633360	12/1996	Bishofberger et al.	N/A	N/A
5639873	12/1996	Barascut et al.	N/A	N/A
5645985	12/1996	Froehler et al.	N/A	N/A
5646265	12/1996	McGee	N/A	N/A
5646269	12/1996	Matteucci	N/A	N/A
5652355	12/1996	Metelev et al.	N/A	N/A
5652356	12/1996	Agrawal	N/A	N/A
5663312	12/1996	Chaturvedula	N/A	N/A
5670633	12/1996	Cook et al.	N/A	N/A
5670634	12/1996	Marotta et al.	N/A	N/A
5672697	12/1996	Buhr et al.	N/A	N/A
5677437	12/1996	Teng et al.	N/A	N/A
5677439	12/1996	Weis et al.	N/A	N/A
5681941	12/1996	Cook et al.	N/A	N/A
5698685	12/1996	Summerton et al.	N/A	N/A
5700920	12/1996	Altmann et al.	N/A	N/A
5700922	12/1996	Cook	N/A	N/A
5721218	12/1997	Froehler	N/A	N/A
5750692	12/1997	Cook et al.	N/A	N/A
5763588	12/1997	Matteucci et al.	N/A	N/A
5792608	12/1997	Swaminathan et al.	N/A	N/A
5792847	12/1997	Burh et al.	N/A	N/A
5801154	12/1997	Baracchini et al.	N/A	N/A
5808027	12/1997	Cook et al.	N/A	N/A
5830653	12/1997	Froehler et al.	N/A	N/A
5837449	12/1997	Monia et al.	N/A	N/A
5859221	12/1998	Cook et al.	N/A	N/A
5912410	12/1998	Cordell	N/A	N/A
5948903	12/1998	Cook et al.	N/A	N/A
5994517	12/1998	Ts'O	N/A	N/A
6005087	12/1998	Cook et al.	N/A	N/A
6005096	12/1998	Matteucci et al.	N/A	N/A
6166199	12/1999	Cook et al.	N/A	N/A
6177246	12/2000	Monia et al.	N/A	N/A
6300319	12/2000	Manoharan	N/A	N/A
6310048	12/2000	Kumar et al.	N/A	N/A
6426220	12/2001	Bennett et al.	N/A	N/A
6525191	12/2002	Ramasamy	N/A	N/A
6531584	12/2002	Cook et al.	N/A	N/A
6582908	12/2002	Fodor et al.	N/A	N/A
6600032	12/2002	Manoharan et al.	N/A	N/A
6660720	12/2002	Manoharan	N/A	N/A
6699671	12/2003	Gurney et al.	N/A	N/A
6770748	12/2003	Imanishi et al.	N/A	N/A
7015315	12/2005	Cook et al.	N/A	N/A
7053207	12/2005	Wengel et al.	N/A	N/A
7101993	12/2005	Cook et al.	N/A	N/A
7262177	12/2006	Ts'o et al.	N/A	N/A
7399845	12/2007	Seth et al.	N/A	N/A
7427672	12/2007	Imanishi et al.	N/A	N/A
7491805	12/2008	Vargeese et al.	N/A	N/A
7547684	12/2008	Seth et al.	N/A	N/A
7569686	12/2008	Bhat et al.	N/A	N/A
7635771	12/2008	Khvorova et al.	N/A	N/A
7666854	12/2009	Seth et al.	N/A	N/A
7696345	12/2009	Allerson et al.	N/A	N/A
7723509	12/2009	Manoharan et al.	N/A	N/A
7741457	12/2009	Swayze et al.	N/A	N/A

7750131	12/2009	Seth et al.	N/A	N/A
7829696	12/2009	Khvorova et al.	N/A	N/A
7875733	12/2010	Bhat et al.	N/A	N/A
7939677	12/2010	Bhat et al.	N/A	N/A
8022193	12/2010	Swayze et al.	N/A	N/A
8030467	12/2010	Seth et al.	N/A	N/A
8080644	12/2010	Wengel et al.	N/A	N/A
8088746	12/2011	Seth et al.	N/A	N/A
8088904	12/2011	Swayze et al.	N/A	N/A
8106022	12/2011	Manoharan et al.	N/A	N/A
8124745	12/2011	Allerson et al.	N/A	N/A
8153365	12/2011	Wengel et al.	N/A	N/A
8268980	12/2011	Seth et al.	N/A	N/A
8268985	12/2011	Khvorova et al.	N/A	N/A
8278283	12/2011	Seth et al.	N/A	N/A
8278425	12/2011	Prakash et al.	N/A	N/A
8278426	12/2011	Seth et al.	N/A	N/A
8283517	12/2011	Schilling et al.	N/A	N/A
8440803	12/2012	Swayze et al.	N/A	N/A
8501805	12/2012	Seth et al.	N/A	N/A
8530640	12/2012	Seth et al.	N/A	N/A
8546556	12/2012	Seth et al.	N/A	N/A
RE44779	12/2013	Imanishi et al.	N/A	N/A
8658784	12/2013	Khvorova et al.	N/A	N/A
8673560	12/2013	Leamon et al.	N/A	N/A
8828956	12/2013	Manoharan et al.	N/A	N/A
9005906	12/2014	Swayze et al.	N/A	N/A
9012421	12/2014	Migawa et al.	N/A	N/A
9127276	12/2014	Prakash et al.	N/A	N/A
9290760	12/2015	Rajeev et al.	N/A	N/A
10364432	12/2018	Van Roon-mom et al.	N/A	N/A
10900041	12/2020	De Vlaam et al.	N/A	N/A
11732260	12/2022	Rigo et al.	N/A	N/A
2001/0053519	12/2000	Fodor et al.	N/A	N/A
2003/0158403	12/2002	Manoharan et al.	N/A	N/A
2003/0175906	12/2002	Manoharan et al.	N/A	N/A
2003/0221204	12/2002	Golde et al.	N/A	N/A
2003/0228597	12/2002	Cowsert et al.	N/A	N/A
2003/0232435	12/2002	Dobie	N/A	N/A
2004/0171570	12/2003	Allerson et al.	N/A	N/A
2005/0043264	12/2004	Juang et al.	N/A	N/A
2005/0130923	12/2004	Bhat et al.	N/A	N/A
2005/0209179	12/2004	McSwiggen et al.	N/A	N/A
2006/0148740	12/2005	Platenburg	N/A	N/A
2006/0172964	12/2005	Tanzi et al.	N/A	N/A
2006/0247194	12/2005	McSwiggen et al.	N/A	N/A
2007/0031844	12/2006	Khvorova et al.	N/A	N/A
2007/0032443	12/2006	Kim et al.	N/A	N/A
2008/0039618	12/2007	Allerson et al.	N/A	N/A
2009/0023158	12/2008	Paul et al.	N/A	N/A
2010/0190807	12/2009	Porter et al.	N/A	N/A
2010/0190837	12/2009	Migawa et al.	N/A	N/A
2010/0197762	12/2009	Swayze et al.	N/A	N/A
2011/0166197	12/2010	Darling et al.	N/A	N/A
2013/0011887	12/2012	Dayton et al.	N/A	N/A
2013/0130378	12/2012	Manoharan et al.	N/A	N/A
2014/0107330	12/2013	Freier et al.	N/A	N/A
2015/0018540	12/2014	Prakash et al.	N/A	N/A
2015/0184153	12/2014	Freier et al.	N/A	N/A
2015/0191727	12/2014	Migawa et al.	N/A	N/A
2015/0267195	12/2014	Seth et al.	N/A	N/A
2015/0275212	12/2014	Albaek et al.	N/A	N/A
2016/0186175	12/2015	Seth et al.	N/A	N/A
2016/0238606	12/2015	McNeel et al.	N/A	N/A
2017/0044526	12/2016	Wan et al.	N/A	N/A
2017/0240888	12/2016	Tremblay et al.	N/A	N/A
2021/0040480	12/2020	Rigo et al.	N/A	N/A

FOREIGN PATENT DOCUMENTS

Patent No.	**Application Date**	**Country**	**CPC**
2601294	12/2017	EP	N/A
WO 1989/006693	12/1988	WO	N/A
WO 1993/013114	12/1992	WO	N/A
WO 1995/009236	12/1994	WO	N/A
WO 2001/042266	12/2000	WO	N/A

WO 2001/050829	12/2000	WO	N/A
WO 2004/045543	12/2003	WO	N/A
WO 2005/003350	12/2004	WO	N/A
WO 2005/042777	12/2004	WO	N/A
WO 2005/116204	12/2004	WO	N/A
WO 2009/105572	12/2008	WO	N/A
WO 2012/018257	12/2011	WO	N/A
WO 2013/173635	12/2012	WO	N/A
WO 2013/173637	12/2012	WO	N/A
WO 2014/144942	12/2013	WO	N/A
2014197826	12/2013	WO	N/A
2015023941	12/2014	WO	N/A
2015054676	12/2014	WO	N/A
WO 2017/064308	12/2016	WO	N/A
WO 2019/037133	12/2018	WO	N/A
WO 2019/143978	12/2018	WO	N/A
WO 2019/162692	12/2018	WO	N/A
WO 2019/169243	12/2018	WO	N/A
WO 2020/006267	12/2019	WO	N/A
WO 2020/124257	12/2019	WO	N/A
WO 2020/132227	12/2019	WO	N/A
WO 2020/160163	12/2019	WO	N/A
WO 2020/257194	12/2019	WO	N/A
WO 2022/026589	12/2021	WO	N/A

OTHER PUBLICATIONS

Nguyen, K V, beta-Amyloid precursor protein (APP) and the human diseases, Oct. 29, 2019, AIMS Neuroscience, 6: 273-281 (Year: 2019). cited by examiner

Stein, et al. Beta-amyloid deposition in chronic traumatic encephalpathy, 2015, Acta Neuropathol., 130, 21-34. (Year: 2015). cited by examiner

Grabowska-Pyrzewicz, W. et al, Antisense oligonucleotides for Alzheimer's disease therapy: from the mRNA to miRNA paradigm, 2021, EbioMedicine, 74, 1-10. (Year: 2021). cited by examiner

Zheng and Koo, The amyloid precursor protein: beyond amyloid, 2006, Molecular Neurodegeneration, 1, 5, p. 1-12 (Year: 2006). cited by examiner

Roberts et al., Advances in oligonucleotide drug delivery, 2020, Nature Reviews, 19, p. 673-694 (Year: 2020). cited by examiner

International Search Report for PCT/US21/043520 dated Jan. 5, 2022. cited by applicant

Ostergaard et al., "Understanding the effect of controlling phosphorothioate chirality in the DNA gap on the potency and safety of gapmer antisense oligonucleotides" Nucleic Acids Res (2020) 48: 1691-1700. cited by applicant

Allinquant et al., "Downregulation of amyloid precursor protein inhibits neurite outgrowth in vitro" J Cell Biol (1995) 128: 919-927. cited by applicant

Ali et al., "Nitric oxide activity and isoenzyme expression in the senescence-accelerated mouse p8 model of Alzheimer's disease: effects of anti-amyloid antibody and antisense treatments" J Gerontol A Biol Sci Med Sci (2009) 64: 1025-1030. cited by applicant

Armbrecht et al., "Antisense against Amyloid-β Protein Precursor Reverses Memory Deficits and Alters Gene Expression in Neurotropic and Insulin-Signaling Pathways in SAMP8 Mice" J Alzheimers Dis (2015) 46: 535-548. cited by applicant

Banks et al., "Delivery across the blood-brain barrier of antisense directed against amyloid beta: reversal of learning and memory deficits in mice overexpressing amyloid precursor protein" J Pharmacol Exp Ther (2001) 297: 1113-1121. cited by applicant

Bernstein et al., "Role for a bidentate ribonuclease in the initiation step of RNA interference" Nature (2001) 409: 363-366. cited by applicant

Branch et al., "A good antisense molecule is hard to find," TIBS (1998) 23:45-50. cited by applicant

Chang et al., "Targeting Amyloid-β Precursor Protein, APP, Splicing with Antisense Oligonucleotides Reduces Toxic Amyloid-β Production" Mol Ther (2018) 26: 1539-1551. cited by applicant

Chang et al., "Inhibition of the NGF and IL-1beta-induced expression of Alzheimer's amyloid precursor protein by antisense oligonucleotides" J Mol Neurosci (1999) 12: 69-74. cited by applicant

Chauhan et al., "Antisense inhibition at the beta-secretase-site of beta-amyloid precursor protein reduces cerebral amyloid and acetyl cholinesterase activity in Tg2576" Neuroscience (2007) 146: 143-151. cited by applicant

Chauhan "Trafficking of intracerebroventricularly injected antisense oligonucleotides in the mouse brain" Antisense Nucleic Acid Drug Dev (2002) 12: 353-357. cited by applicant

Chin "On the Preparation and Utilization of Isolated and Purified Oligonucleotides" Document purportedly located on a CD-ROM and contributed to the public collection of the Katherine R. Everett Law Library of the University of North Carolina on Mar. 14, 2002. cited by applicant

Coulson et al., "Down-regulation of the amyloid protein precursor of Alzheimer's disease by antisense oligonucleotides reduces neuronal adhesion to specific substrata" Brain Res (1997) 770: 72-80. cited by applicant

Crooke et al., "Basic Principles of Antisense Therapeutics" Antisense Research and Application (1998) Chapter 1:1-50. cited by applicant

Crooke, St., et al., "Antisense Drug Technology" Second Edition, CRC Press (2008) Chapters 1-28. cited by applicant

Currie et al., "Reduction of histone cytotoxicity by the Alzheimer beta-amyloid peptide precursor" Biochim Biophys Acta (1997) 1355: 248-258. cited by applicant

Dawson et al., "Age-related cognitive deficits, impaired long-term potentiation and reduction in synaptic marker density in mice lacking the beta-amyloid precursor protein" Neuroscience (1999) 90: 1-13. cited by applicant

Denman et al., "Facilitator oligonucleotides increase ribozyme RNA binding to full-length RNA substrates in vitro" FEBS Lett (1996) 382: 116-120. cited by applicant

Denman et al. "Hairpin ribozyme specificity in vivo: a case of promiscuous cleavage" Biochem Biophys Res Commun (1999) 257: 356-360. cited by applicant

Denman et al., "Differential activity of trans-acting hammerhead ribozymes targeted to beta amyloid peptide precursor mRNA by altering the symmetry of helices I and III" Arch Biochem Biophys (1995) 323: 71-78. cited by applicant

Denman et al. "Facilitated reduction of beta-amyloid peptide precursor by synthetic oligonucleotides in COS-7 cells expressing a hammerhead ribozyme" Arch Biochem Biophys (1997) 348: 82-90. cited by applicant

Dewachter et al., "Modeling Alzheimer's disease in transgenic mice: effect of age and of presenilin1 on amyloid biochemistry and pathology in APP/London mice" Exp Gerontol (2000) 35: 831-841. cited by applicant

Dingwall "Spotlight on BACE: the secretases as targets for treatment in Alzheimer disease" J Clin Invest (2001) 108: 1243-1246. cited by applicant

Dolzhanskaya et al., “In vivo ribozyme targeting of betaAPP+ mRNAs” Mol Cell Biol Res Commun (2000) 4: 239-247. cited by applicant
Dolzhanskaya et al., “Self-cleaving-ribozyme-mediated reduction of betaAPP in human rhabdomyosarcoma cells” Arch Biochem Biophys (2001) 387: 223-232. cited by applicant
Egli, et al., “Synthesis, improved antisense activity and structural rationale for the divergent RNA affinities of 3′-fluoro hexitol nucleic acid (FHNA and Ara-FHNA) modified oligonucleotides.” J Am Chem (2011) 133(41):16642-16649. cited by applicant
Elbashir et al., “RNA interference is mediated by 21- and 22-nucleotide RNAs” Genes Dev (2001) 15: 188-200. cited by applicant
Erickson et al., “Inflammation-induced dysfunction of the low-density lipoprotein receptor-related protein-1 at the blood-brain barrier: protection by the antioxidant N-acetylcysteine” Brain Behav Immun (2012) 26: 1085-1094. cited by applicant
Farr et al., “Central and peripheral administration of antisense oligonucleotide targeting amyloid-β protein precursor improves learning and memory and reduces neuroinflammatory cytokines in Tg2576 (AβPPswe) mice” J Alzheimers Dis (2014) 40: 1005-1016. cited by applicant
Feng et al., “Allele-specific silencing of Alzheimer's disease genes: the amyloid precursor protein genes with Swedish or London mutations” Gene (2006) 371: 68-74. cited by applicant
Gautschi et al., “Activity of a novel bcl-2/bcl-xLbispecific antisense oligonucleotide against tumors of diverse histologic origins” J. Natl. Cancer Inst. (2001) 93:463-471. cited by applicant
Harper et al., “Mouse cortical neurones lacking APP show normal neurite outgrowth and survival responses in vitro” Neuroreport (1998) 9: 3053-3058. cited by applicant
Hoffmann et al., “A possible role for the Alzheimer amyloid precursor protein in the regulation of epidermal basal cell proliferation” Eur J Cell Biol (2000) 79: 905-914. cited by applicant
International Search Report for PCT/US19/020246 dated May 10, 2019. cited by applicant
International Search Report for PCT/US20/015701 dated Jun. 23, 2020. cited by applicant
Kibbey et al., “beta-Amyloid precursor protein binds to the neurite-promoting IKVAV site of laminin” Proc Natl Acad Sci (1993) 90: 10150-10153. cited by applicant
Kienlen-Campard et al., “The processing and biological function of the human amyloid precursor protein (APP): lessons from different cellular models” Exp Gerontol (2000) 35: 843-850. cited by applicant
Konig et al., “Identification and differential expression of a novel alternative splice isoform of the beta A4 amyloid precursor protein (APP) mRNA in leukocytes and brain microglial cells” J Biol Chem (1992) 267: 1992. cited by applicant
Kumar et al., “Molecular cloning, expression, and regulation of hippocampal amyloid precursor protein of senescence accelerated mouse (SAMP8)” Biochem Cell Biol (2001) 79: 57-67. cited by applicant
Kumar et al., “Site-directed antisense oligonucleotide decreases the expression of amyloid precursor protein and reverses deficits in learning and memory in aged SAMP8 mice” Peptides (2000) 21: 1769-1775. cited by applicant
Le et al., “beta-Amyloid1-40 increases expression of beta-amyloid precursor protein in neuronal hybrid cells” J Neurochem (1995) 65: 2373-2376. cited by applicant
Le et al., “Beta-amyloid-induced neurotoxicity of a hybrid septal cell line associated with increased tau phosphorylation and expression of beta-amyloid precursor protein” J Neurochem (1997) 69: 978-985. cited by applicant
Leblanc et al., “Role of amyloid precursor protein (APP): study with antisense transfection of human neuroblastoma cells” J Neurosci Res (1992) 31: 635-645. cited by applicant
Li et al., “Polymorphic tetranucleotide repeat site within intron 7 of the beta-amyloid precursor protein gene and its lack of association with Alzheimer's disease” Hum Genet (1998) 103: 86-89. cited by applicant
Lima et al., “Single-stranded siRNAs activate RNAi in animals” Cell (2012) 150: 883-894. cited by applicant
Luo et al., “Characterization of the neurotrophic interaction between nerve growth factor and secreted alpha-amyloid precursor protein” J Neurosci Res (2001) 63: 410-420. cited by applicant
Luo et al., “Death of PC12 cells and hippocampal neurons induced by adenoviral-mediated FAD human amyloid precursor protein gene expression” J Neurosci Res (1999) 55: 629-642. cited by applicant
Magner et al., “Influence of mismatched and bulged nucleotides on SNP-preferential RNase H cleavage of RNA-antisense gapmer heteroduplexes” Sci Rep (2017) 7:12532 1-16. cited by applicant
Maher et al., “Comparative hybrid arrest by tandem antisense oligodeoxyribonucleotides or oligodeoxyribonucleoside methylphosphonates in a cell-free system” Nucl. Acid. Res. (1988) 16(8):3341-3358. cited by applicant
Majocha et al. “Modulation of the PC12 cell response to nerve growth factor by antisense oligonucleotide to amyloid precursor protein” Cell Mol NeuroBiol (1994) 14: 425-437. cited by applicant
Manczak et al., “RNA silencing of genes involved in Alzheimer's disease enhances mitochondrial function and synaptic activity” Biochim Biophys Acta (2013) 1832: 2368-2378. cited by applicant
Meng et al., “Amyloid beta protein precursor is involved in the growth of human colon carcinoma cell in vitro and in vivo” Int J Cancer (2001) 92: 31-39. cited by applicant
Miller et al., “Targeting Alzheimer's disease genes with RNA interference: an efficient strategy for silencing mutant alleles” Nucleic Acids Res (2004) 32: 661-668. cited by applicant
New England Biolabs 1998/1999 Catalog (cover page and pp. 121 and 284). cited by applicant
Nhan et al., “The multifaceted nature of amyloid precursor protein and its proteolytic fragments: friends and foes” Acta Neuropathol (2015) 129: 1-19. cited by applicant
Nykanen et al., “ATP requirements and small interfering RNA structure in the RNA interference pathway” Cell (2001) 107: 309-321. cited by applicant
Ohnishi et al., “Assessment of allele-specific gene silencing by RNA interference with mutant and wild-type reporter alleles” J RNAi Gene Silencing (2006) 2: 154-160. cited by applicant
Pietrzik et al., “From differentiation to proliferation: the secretory amyloid precursor protein as a local mediator of growth in thyroid epithelial cells” Proc Natl Acad Sci USA (1998) 95: 1770-1775. cited by applicant
Poon et al., “Antisense directed at the Abeta region of APP decreases brain oxidative markers in aged senescence accelerated mice” Brain Res. (2004) 1018: 86-96. cited by applicant
Poon et al., “Proteomic identification of less oxidized brain proteins in aged senescence-accelerated mice following administration of antisense oligonucleotide directed at the Abeta region of amyloid precursor protein” Brain Res Mol Brain Res (2005) 138: 8-16. cited by applicant
Reynolds et al., “Rational siRNA design for RNA interference” Nature Biotechnology (2004) 22(3):326-330. cited by applicant
Saitoh et al., “Secreted form of amyloid beta protein precursor is involved in the growth regulation of fibroblasts” Cell (1989) 58: 615-622. cited by applicant
Sandbrink et al., “APP gene family: unique age-associated changes in splicing of Alzheimer's betaA4-amyloid protein precursor” Neurobiol Dis (1994) 1: 13-24. cited by applicant
Sanghvi et al., “Heterocyclic Base Modifications in Nucleic Acids and Their Applications in Antisense Oligonucleotides” Antisense Research and Applications (1993) pp. 273-288. cited by applicant

Sawa et al., “APP-directed antisense oligonucleotides reduced APP gene expression in mouse models of Down Syndrome” Poster Presentation for Society of Neuroscience (2018) Nov. 3-7, 2018 San Diego, CA. cited by applicant
Sawa et al., “APP-directed antisense oligonucleotides reduced APP gene expression in mouse models of Down Syndrome” Abstract for Society of Neuroscience (2018) Nov. 3-7, 2018 San Diego, CA. cited by applicant
Seth et al., “Short Antisense Oligonucleotides with Novel 2′-4′ Conformationaly Restricted Nucleoside Analogues Show Improved Potency Without Increased Toxicity in Animals.” J Med Chem (2009) 52:10-13. cited by applicant
Sharp “RNA interference—2001” Genes Dev (2001) 15: 485-490. cited by applicant
Suh et al., “Molecular physiology, biochemistry, and pharmacology of Alzheimer's amyloid precursor protein (APP)” Ann NY Acad Sci (1996) 786: 169-183. cited by applicant
Woolf et al., “Specificity of antisense oligonucleotides in vivo” PNAS (1992) 89: 7305-7309. cited by applicant
Yoshikai et al., “Genomic organization of the human amyloid beta-protein precursor gene” Gene (1990) 87: 257-263. cited by applicant
Extended EP Search Report for 19760045.5 dated Feb. 28, 2022. cited by applicant
Nikiforov et al., “The use of phosphorothioate primers and exonuclease hydrolysis for the preparation of single-stranded PCR products and their detection by solid-phase hybridization” PCT Methods and Applications (1994) 3: 285-291. cited by applicant
Anderson et al., “Towards next generation antisense oligonucleotides: mesylphosphoramidate modification improves therapeutic index and duration of effect of gapmer antisense oligonucleotides” Nucl Acid Res (2021) 49: 9026-9041. cited by applicant
Monia et al., “Muclease Resistance and Antisense Activity of Modified Oligonucleotides Targeted to Ha-ras” J Biol Chem (1996) 271: 14533-14540. cited by applicant
Shyam et al., “Intraventricular Delivery of siRNA Nanoparticles to the Central Nervous System” Mol Ther Nucl Acids (2015) 4: e242. cited by applicant
Kurreck et al., “The Role of Backbone Modifications in Oligonucleotide-Based Strategies” Therapeutic Oligonucleotides, The Royal Society of Chemistry (2008) p. 1-22. cited by applicant
Chakravarthy et al., “Nucleic Acid-Based Theranostics for Tackling Alzheimer's Disease” Theranostics (2017) 7: 3933-3947. cited by applicant
Extended EP Search Report for 21849997.8 dated Jan. 27, 2025. cited by applicant
Partial EP Search Report for 21849997.8 dated Oct. 24, 2024. cited by applicant
International Search Report for PCT/US24/016102 dated Jul. 17, 2024. cited by applicant
Miroshnichenko et al., “Mesyl phosphoramidate antisense oligonucleotides as an alternative to phosphorothioates with improved biochemical and biological properties” PNAS (2019) 116: 1229-1234. cited by applicant

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Background/Summary

SEQUENCE LISTING

(1) The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0384USSEQ_ST25.txt, created on Jul. 14, 2021 which is 1007 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD

(2) Provided are compounds, methods, and pharmaceutical compositions for reducing the amount or activity of APP RNA in a cell or animal, and in certain instances reducing the amount of APP protein in a cell or animal. Certain such compounds, methods, and pharmaceutical compositions are useful to ameliorate at least one symptom or hallmark of a neurodegenerative disease or disorder. Such symptoms and hallmarks include cognitive impairment, including a decline in memory and language skills, behavioral and psychological symptoms such as apathy and lack of motivation, gait disturbances and seizures, progressive dementia, and abnormal amyloid deposits. Such neurodegenerative diseases and disorders include sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in Down Syndrome patients, and Cerebral Amyloid Angiopathy.

BACKGROUND

(3) Alzheimer's Disease (AD), including both sporadic Alzheimer's Disease and genetic/familial Alzheimer's Disease, is the most common cause of age-associated dementia, affecting an estimated 5.7 million Americans a year (Alzheimer's Association. 2018 Alzheimer's Disease Facts and Figures. *Alzheimer's Dement.* 2018; 14(3):367-429). AD is characterized by the accumulation of β-amyloid plaques in the brain prior to the onset of overt clinical symptoms. Such overt clinical symptoms include cognitive impairment, including a decline in memory and language skills, behavioral and psychological symptoms such as apathy and lack of motivation, gait disturbances and seizures, and progressive dementia.

(4) Patients with Down Syndrome (DS) can experience early-onset Alzheimer's disease (AD in DS), with amyloid plaque formation observed by age 40 in most DS patients, and Alzheimer's dementia observed by age 50 in more than 50% of Down Syndrome patients.

(5) Cerebral Amyloid Angiopathy (CAA) is a related disease that is characterized by the deposition of β-amyloid in blood vessels of the CNS. CAA is often observed in AD patients upon autopsy, but is also associated with aging in the absence of clinical signs of AD.

(6) AD, AD in DS, and CAA are all characterized by the abnormal accumulation of β-amyloid plaques. β-amyloid (Aβ) is derived from amyloid precursor protein (APP) upon processing of APP by α-, β-, and γ-secretases. In addition to the 42-amino acid fragment Aβ, a variety of other fragments of APP are also formed, several of which are proposed to contribute to the onset of dementia in AD (reviewed in Nhan, et al., “The multifaceted nature of amyloid precursor protein and its proteolytic fragments: friends and foes”, *Acta Neuropath.*, 2015, 129(1): 1-19). The increased incidence of AD in DS patients is thought to be directly related to the increased copy number of the APP gene, which resides on chromosome 21.

(7) Currently there is a lack of acceptable options for treating neurodegenerative diseases and disorders such as AD, AD in DS, and CAA. It is therefore an object herein to provide compounds, methods, and pharmaceutical compositions for the treatment of such diseases and disorders.

SUMMARY OF THE INVENTION

(8) Provided herein are compounds, methods and pharmaceutical compositions for reducing the amount or activity of APP RNA, and in certain embodiments reducing the amount of APP protein in a cell or animal. In certain embodiments, the animal has a neurodegenerative disease or disorder. In certain embodiments, the animal has Alzheimer's Disease (AD). In certain embodiments, the animal has Alzheimer's Disease in conjunction with Down Syndrome (AD in DS). In certain embodiments, the animal has Cerebral Amyloid Angiopathy (CAA). In certain embodiments, compounds useful for reducing expression of APP RNA are oligomeric compounds. In certain embodiments, compounds useful for reducing expression of APP RNA are modified oligonucleotides.

(9) Also provided are methods useful for ameliorating at least one symptom or hallmark of a neurodegenerative disease or disorder. In certain embodiments, the neurodegenerative disease is Alzheimer's Disease. In certain embodiments, the neurodegenerative disease is Alzheimer's Disease in Down Syndrome patients. In certain embodiments, the neurodegenerative disease is Cerebral Amyloid Angiopathy (CAA). In certain embodiments, the symptom or hallmark includes cognitive impairment, including a decline in memory and language skills, behavioral and psychological symptoms such as apathy and lack of motivation, gait disturbances and seizures, progressive dementia, or abnormal amyloid deposits.

Description

DETAILED DESCRIPTION OF THE INVENTION

(1) It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of “or” means “and/or” unless stated otherwise. Furthermore, the use of the term “including” as well as other forms, such as “includes” and “included”, is not limiting. Also, terms such as “element” or “component” encompass both elements and components comprising one unit and elements and components that comprise more than one subunit, unless specifically stated otherwise.

(2) The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including, but not limited to, patents, patent applications, articles, books, and treatises, are hereby expressly incorporated-by-reference for the portions of the document discussed herein, as well as in their entirety.

Definitions

(3) Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Where permitted, all patents, applications, published applications and other publications and other data referred to throughout in the disclosure are incorporated by reference herein in their entirety.

(4) Unless otherwise indicated, the following terms have the following meanings:

Definitions

(5) As used herein, “2′-deoxynucleoside” means a nucleoside comprising a 2′-H(H) deoxyribosyl sugar moiety. In certain embodiments, a 2′-deoxynucleoside is a 2′-β-D-deoxynucleoside and comprises a 2′-β-D-deoxyribosyl sugar moiety, which has the β-D configuration as found in naturally occurring deoxyribonucleic acids (DNA). In certain embodiments, a 2′-deoxynucleoside or a nucleoside comprising an unmodified 2′-deoxyribosyl sugar moiety may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).

(6) As used herein, “2′-substituted nucleoside” means a nucleoside comprising a 2′-substituted sugar moiety. As used herein, “2′-substituted” in reference to a sugar moiety means a sugar moiety comprising at least one 2′-substituent group other than H or OH.

(7) As used herein, “2′-MOE” means a 2′-OCH.sub.2CH.sub.2OCH.sub.3 group in place of the 2′-OH group of a ribosyl sugar moiety. A “2′-MOE sugar moiety” is a sugar moiety with a 2′-OCH.sub.2CH.sub.2OCH.sub.3 group in place of the 2′-OH group of a ribosyl sugar moiety. Unless otherwise indicated, a 2′-MOE sugar moiety is in the β-D configuration. “MOE” means O-methoxyethyl.

(8) As used herein, “2′-MOE nucleoside” means a nucleoside comprising a 2′-MOE sugar moiety.

(9) As used herein, “2′-OMe” or “2′-O-methyl sugar moiety” means a 2′-OCH.sub.3 group in place of the 2′-OH group of a ribosyl sugar moiety. Unless otherwise indicated, a 2′-OMe has the β-D stereochemical configuration.

(10) As used herein, “2′-OMe nucleoside” means a nucleoside comprising a 2′-OMe sugar moiety.

(11) As used herein, “3′ target site” refers to the 3′-most nucleotide of a target nucleic acid which is complementary to an antisense oligonucleotide, when the antisense oligonucleotide is hybridized to the target nucleic acid.

(12) As used herein, “5′ target site” refers to the 5′-most nucleotide of a target nucleic acid which is complementary to an antisense oligonucleotide, when the antisense oligonucleotide is hybridized to the target nucleic acid.

(13) As used herein, “5-methyl cytosine” means a cytosine modified with a methyl group attached to the 5 position. A 5-methyl cytosine is a modified nucleobase.

(14) As used herein, “abasic sugar moiety” means a sugar moiety of a nucleoside that is not attached to a nucleobase. Such abasic sugar moieties are sometimes referred to in the art as “abasic nucleosides.”

(15) As used herein, “administration” or “administering” means providing a pharmaceutical agent or composition to an animal.

(16) As used herein, “animal” means a human or non-human animal.

(17) As used herein, “antisense activity” means any detectable and/or measurable change attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease in the amount or expression of a target nucleic acid or protein encoded by such target nucleic acid compared to target nucleic acid levels or target protein levels in the absence of the antisense compound.

(18) As used herein, “antisense compound” means an oligomeric compound capable of achieving at least one antisense activity.

(19) As used herein, “antisense oligonucleotide” means an oligonucleotide, including the oligonucleotide portion of an oligomeric compound that is complementary to a target nucleic acid and is capable of achieving at least one antisense activity. Antisense oligonucleotides include but are not limited to antisense RNase H oligonucleotides.

(20) As used herein, “ameliorate” in reference to a treatment means improvement in at least one symptom relative to the same symptom in the absence of the treatment. In certain embodiments, amelioration is the reduction in the severity or frequency of a symptom or the delayed onset or slowing of progression in the severity or frequency of a symptom. In certain embodiments, the symptom or hallmark is cognitive impairment, including a decline in memory and language skills, behavioral and psychological symptoms such as apathy and lack of motivation, gait disturbances and seizures, progressive dementia, or abnormal amyloid deposits.

(21) As used herein, “bicyclic nucleoside” or “BNA” means a nucleoside comprising a bicyclic sugar moiety.

(22) As used herein, “bicyclic sugar” or “bicyclic sugar moiety” means a modified sugar moiety comprising two rings, wherein the second ring is formed via a bridge connecting two of the atoms in the first ring thereby forming a bicyclic structure. In certain embodiments, the first ring of the bicyclic sugar moiety is a furanosyl moiety. In certain embodiments, the bicyclic sugar moiety does not comprise a furanosyl moiety.

(23) As used herein, “cleavable moiety” means a bond or group of atoms that is cleaved under physiological conditions, for example, inside a cell, an animal, or a human.

(24) As used herein, “complementary” in reference to an oligonucleotide means that at least 70% of the nucleobases of the oligonucleotide or one or more regions thereof and the nucleobases of another nucleic acid or one or more regions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the other nucleic acid are aligned in opposing directions. Complementary nucleobases means nucleobases that are capable of forming hydrogen bonds with one another. Complementary nucleobase pairs include adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), 5-methyl cytosine (mC) and guanine (G). Certain modified nucleobases that pair with natural nucleobases or with other modified nucleobases are known in the art. For example, inosine can pair with adenosine, cytosine, or uracil. Complementary oligonucleotides and/or nucleic acids need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. As used herein, “fully complementary” or “100% complementary” in reference to oligonucleotides means that oligonucleotides are complementary to another oligonucleotide or nucleic acid at each nucleoside of the oligonucleotide.

(25) As used herein, “conjugate group” means a group of atoms that is directly attached to an oligonucleotide. Conjugate groups include a conjugate

moiety and a conjugate linker that attaches the conjugate moiety to the oligonucleotide.
(26) As used herein, “conjugate linker” means a single bond or a group of atoms comprising at least one bond that connects a conjugate moiety to an oligonucleotide.
(27) As used herein, “conjugate moiety” means a group of atoms that is attached to an oligonucleotide via a conjugate linker.
(28) As used herein, “contiguous” in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other. For example, “contiguous nucleobases” means nucleobases that are immediately adjacent to each other in a sequence.
(29) As used herein, “constrained ethyl” or “cEt” or “cEt modified sugar moiety” means a β-D ribosyl bicyclic sugar moiety wherein the second ring of the bicyclic sugar is formed via a bridge connecting the 4′-carbon and the 2′-carbon of the β-D ribosyl sugar moiety, wherein the bridge has the formula 4′-CH(CH.sub.3)—O-2′, and wherein the methyl group of the bridge is in the S configuration.
(30) As used herein, “cEt nucleoside” means a nucleoside comprising a cEt modified sugar moiety.
(31) As used herein, “chirally enriched population” means a plurality of molecules of identical molecular formula, wherein the number or percentage of molecules within the population that contain a particular stereochemical configuration at a particular chiral center is greater than the number or percentage of molecules expected to contain the same particular stereochemical configuration at the same particular chiral center within the population if the particular chiral center were stereorandom. Chirally enriched populations of molecules having multiple chiral centers within each molecule may contain one or more stereorandom chiral centers. In certain embodiments, the molecules are modified oligonucleotides. In certain embodiments, the molecules are oligomeric compounds comprising modified oligonucleotides.
(32) As used herein, “double-stranded” means a duplex formed by complementary strands of nucleic acids (including, but not limited to oligonucleotides) hybridized to one another. In certain embodiments, the two strands of a double-stranded region are separate molecules. In certain embodiments, the two strands are regions of the same molecule that has folded onto itself (e.g., a hairpin structure).
(33) As used herein, “duplex” or “duplex region” means the structure formed by two oligonucleotides or portions thereof that are hybridized to one another.
(34) As used herein, “gapmer” means a modified oligonucleotide comprising an internal region having a plurality of nucleosides that support RNase H cleavage positioned between external regions having one or more nucleosides, wherein at least one of the nucleosides comprising the internal region is chemically distinct from at least one nucleoside of each of the external regions. Specifically, the nucleosides that define the boundaries of the internal region and each external region must be chemically distinct. The internal region may be referred to as the “gap” and the external regions may be referred to as the “wings.” Unless otherwise indicated, “gapmer” refers to a sugar motif. In certain embodiments, the sugar moiety of each nucleoside of the gap is a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, the gap comprises one 2′-substituted nucleoside at position 1, 2, 3, 4, or 5 of the gap, and the remainder of the nucleosides of the gap are 2′-β-D-deoxynucleosides. Unless otherwise indicated, a gapmer may comprise one or more modified internucleoside linkages and/or modified nucleobases and such modifications do not necessarily follow the gapmer pattern of the sugar modifications.
(35) As used herein, “hotspot region” is a range of nucleobases on a target nucleic acid that is amenable to oligomeric compound-mediated reduction of the amount or activity of the target nucleic acid.
(36) As used herein, “hybridization” means the pairing or annealing of complementary oligonucleotides and/or nucleic acids. While not limited to a particular mechanism, the most common mechanism of hybridization involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases.
(37) As used herein, “internucleoside linkage” is the covalent linkage between adjacent nucleosides in an oligonucleotide. As used herein “modified internucleoside linkage” means any internucleoside linkage other than a phosphodiester internucleoside linkage. “Phosphorothioate internucleoside linkage” is a modified internucleoside linkage in which one of the non-bridging oxygen atoms of a phosphodiester internucleoside linkage is replaced with a sulfur atom.
(38) As used herein, “linker-nucleoside” means a nucleoside that links, either directly or indirectly, an oligonucleotide to a conjugate moiety. Linker-nucleosides are located within the conjugate linker of an oligomeric compound. Linker-nucleosides are not considered part of the oligonucleotide portion of an oligomeric compound even if they are contiguous with the oligonucleotide.
(39) As used herein, “non-bicyclic modified sugar moiety” means a modified sugar moiety that comprises a modification, such as a substituent, that does not form a bridge between two atoms of the sugar to form a second ring.
(40) As used herein, “mismatch” or “non-complementary” means a nucleobase of a first nucleic acid sequence that is not complementary with the corresponding nucleobase of a second nucleic acid sequence or target nucleic acid when the first and second nucleic acid sequences are aligned.
(41) As used herein, “motif” means the pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages, in an oligonucleotide.
(42) As used herein, “neurodegenerative disease” or “neurodegenerative disorder” means a condition marked by progressive loss of function or structure, including loss of neuronal function and death of neurons. In certain embodiments, the neurodegenerative disease is Alzheimer's Disease. In certain embodiments, the neurodegenerative disease is sporadic Alzheimer's Disease. In certain embodiments, the neurodegenerative disease is genetic/familial Alzheimer's Disease. In certain embodiments, the neurodegenerative disease is Alzheimer's Disease in Down Syndrome patients. In certain embodiments, the neurodegenerative disease is Cerebral Amyloid Angiopathy.
(43) As used herein, “nucleobase” means an unmodified nucleobase or a modified nucleobase. A nucleobase is a heterocyclic moiety. As used herein an “unmodified nucleobase” is adenine (A), thymine (T), cytosine (C), uracil (U), or guanine (G). As used herein, a “modified nucleobase” is a group of atoms other than unmodified A, T, C, U, or G capable of pairing with at least one other nucleobase. A “5-methyl cytosine” is a modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases.
(44) As used herein, “nucleobase sequence” means the order of contiguous nucleobases in a nucleic acid or oligonucleotide independent of any sugar or internucleoside linkage modification.
(45) As used herein, “nucleoside” means a compound or fragment of a compound comprising a nucleobase and a sugar moiety. The nucleobase and sugar moiety are each, independently, unmodified or modified.
(46) As used herein, “modified nucleoside” means a nucleoside comprising a modified nucleobase and/or a modified sugar moiety.
(47) As used herein, “linked nucleosides” are nucleosides that are connected in a contiguous sequence (i.e., no additional nucleosides are presented between those that are linked).
(48) As used herein, “oligomeric compound” means an oligonucleotide and optionally one or more additional features, such as a conjugate group or terminal group. An oligomeric compound may be paired with a second oligomeric compound that is complementary to the first oligomeric compound or may be unpaired. A “singled-stranded oligomeric compound” is an unpaired oligomeric compound. The term “oligomeric duplex” means a duplex formed by two oligomeric compounds having complementary nucleobase sequences. Each oligomeric compound of an oligomeric duplex may be referred to as a “duplexed oligomeric compound.”
(49) As used herein, “oligonucleotide” means a polymer or strand of linked nucleosides connected via internucleoside linkages, wherein each nucleoside and internucleoside linkage may be modified or unmodified. Unless otherwise indicated, oligonucleotides consist of 8-50 linked nucleosides. An oligonucleotide may be paired with a second oligonucleotide that is complementary to the oligonucleotide or it may be unpaired. A “single-stranded oligonucleotide” is an unpaired oligonucleotide. A “double-stranded oligonucleotide” is an oligonucleotide that is paired with a second oligonucleotide. An “oligonucleotide duplex” means a duplex formed by two paired oligonucleotides having complementary nucleobase

sequences. Each oligo of an oligonucleotide duplex is a “duplexed oligonucleotide” or a “double-stranded oligonucleotide”.
(50) As used herein, “modified oligonucleotide” means an oligonucleotide, wherein at least one nucleoside or internucleoside linkage is modified. As used herein, “unmodified oligonucleotide” means an oligonucleotide that does not comprise any nucleoside modifications or internucleoside modifications. Thus, each nucleoside of an unmodified oligonucleotide is a DNA or RNA nucleoside and each internucleoside linkage is a phosphodiester linkage.
(51) As used herein, “pharmaceutically acceptable carrier or diluent” means any substance suitable for use in administering to an animal. Certain such carriers enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, symps, slurries, suspension and lozenges for the oral ingestion by a subject. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile water, sterile saline, sterile buffer solution or sterile artificial cerebrospinal fluid.
(52) As used herein “pharmaceutically acceptable salts” means physiologically and pharmaceutically acceptable salts of compounds. Pharmaceutically acceptable salts retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.
(53) As used herein “pharmaceutical composition” means a mixture of substances suitable for administering to a subject. For example, a pharmaceutical composition may comprise an oligomeric compound and a sterile aqueous solution. In certain embodiments, a pharmaceutical composition shows activity in free uptake assay in certain cell lines.
(54) As used herein “prodrug” means a therapeutic agent in a first form outside the body that is converted to a second form within an animal or cells thereof. Typically, conversion of a prodrug within the animal is facilitated by the action of an enzymes (e.g., endogenous or viral enzyme) or chemicals present in cells or tissues and/or by physiologic conditions. In certain embodiments, the first form of the prodrug is less active than the second form.
(55) As used herein, “reducing or inhibiting the amount or activity” refers to a reduction or blockade of the transcriptional expression or activity relative to the transcriptional expression or activity in an untreated or control sample and does not necessarily indicate a total elimination of transcriptional expression or activity.
(56) As used herein, “RNase H compound” means an antisense compound that acts, at least in part, through RNase H to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. In certain embodiments, RNase H compounds are single-stranded. In certain embodiments, RNase H compounds are double-stranded. RNase H compounds may comprise conjugate groups and/or terminal groups. In certain embodiments, an RNase H compound modulates the amount or activity of a target nucleic acid. The term RNase H compound excludes antisense compounds that act principally through RISC/Ago2.
(57) As used herein, “antisense RNase H oligonucleotide” means an oligonucleotide comprising a region that is complementary to a target sequence, and which includes at least one chemical modification suitable for RNase H-mediated nucleic acid reduction.
(58) As used herein, “RNAi agent” means an antisense compound that acts, at least in part, through RISC or Ago2 to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. RNAi agents include, but are not limited to double-stranded siRNA, single-stranded RNA (ssRNA), and microRNA, including microRNA mimics. RNAi agents may comprise conjugate groups and/or terminal groups. In certain embodiments, an RNAi agent modulates the amount and/or activity of a target nucleic acid. The term RNAi agent excludes antisense compounds that act through RNase H.
(59) As used herein, “RNAi oligonucleotide” means an antisense RNAi oligonucleotide or a sense RNAi oligonucleotide.
(60) As used herein, “antisense RNAi oligonucleotide” means an oligonucleotide comprising a region that is complementary to a target sequence, and which includes at least one chemical modification suitable for RNAi.
(61) As used herein, “sense RNAi oligonucleotide” means an oligonucleotide comprising a region that is complementary to a region of an antisense RNAi oligonucleotide, and which is capable of forming a duplex with such antisense RNAi oligonucleotide. A duplex formed by an antisense RNAi oligonucleotide and a sense RNAi oligonucleotide is referred to as a double-stranded RNAi agent (dsRNAi) or a short interfering RNA (siRNA).
(62) As used herein, “self-complementary” in reference to an oligonucleotide means an oligonucleotide that at least partially hybridizes to itself.
(63) As used herein, “single-stranded” means a nucleic acid (including but not limited to an oligonucleotide) that is unpaired and is not part of a duplex. Single-stranded compounds are capable of hybridizing with complementary nucleic acids to form duplexes, at which point they are no longer single-stranded.
(64) As used herein, “stabilized phosphate group” means a 5′-phosphate analog that is metabolically more stable than a 5′-phosphate as naturally occurs on DNA or RNA.
(65) As used herein, “standard cell assay” means the assay described in Examples 1-3 or 5 and reasonable variations thereof.
(66) As used herein, “stereorandom chiral center” in the context of a population of molecules of identical molecular formula means a chiral center having a random stereochemical configuration. For example, in a population of molecules comprising a stereorandom chiral center, the number of molecules having the (S) configuration of the stereorandom chiral center may be but is not necessarily the same as the number of molecules having the (R) configuration of the stereorandom chiral center. The stereochemical configuration of a chiral center is considered random when it is the result of a synthetic method that is not designed to control the stereochemical configuration. In certain embodiments, a stereorandom chiral center is a stereorandom phosphorothioate internucleoside linkage.
(67) As used herein, “subject” means a human or non-human animal. The terms “subject” and “individual” are used interchangeably. In certain embodiments, the subject is human.
(68) As used herein, “sugar moiety” means an unmodified sugar moiety or a modified sugar moiety. As used herein, “unmodified sugar moiety” means a 2′-OH(H) ribosyl moiety, as found in RNA (an “unmodified RNA sugar moiety”), or a 2′-H(H) deoxyribosyl sugar moiety, as found in DNA (an “unmodified DNA sugar moiety”). Unmodified sugar moieties have one hydrogen at each of the 1′, 3′, and 4′ positions, an oxygen at the 3′ position, and two hydrogens at the 5′ position. As used herein, “modified sugar moiety” or “modified sugar” means a modified furanosyl sugar moiety or a sugar surrogate.
(69) As used herein, “sugar surrogate” means a modified sugar moiety having other than a furanosyl moiety that can link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide. Modified nucleosides comprising sugar surrogates can be incorporated into one or more positions within an oligonucleotide and such oligonucleotides are capable of hybridizing to complementary oligomeric compounds or target nucleic acids.
(70) As used herein, “symptom or hallmark” means any physical feature or test result that indicates the existence or extent of a disease or disorder. In certain embodiments, a symptom is apparent to a subject or to a medical professional examining or testing said subject. In certain embodiments, a hallmark is apparent upon invasive diagnostic testing, including, but not limited to, post-mortem tests.
(71) As used herein, “target nucleic acid” and “target RNA” mean a nucleic acid that an antisense compound is designed to affect. Target RNA means an RNA transcript and includes pre-mRNA and mRNA unless otherwise specified.
(72) As used herein, “target region” means a portion of a target nucleic acid to which an oligomeric compound is designed to hybridize.
(73) As used herein, “terminal group” means a chemical group or group of atoms that is covalently linked to a terminus of an oligonucleotide.
(74) As used herein, “therapeutically effective amount” means an amount of a pharmaceutical agent or composition that provides a therapeutic benefit to an animal. For example, a therapeutically effective amount improves a symptom of a disease or disorder.
(75) As used herein, “treating” means improving a subject's disease or disorder by administering an oligomeric agent or oligomeric compound described herein. In certain embodiments, treating a subject improves a symptom relative to the same symptom in the absence of the treatment. In

certain embodiments, treatment reduces in the severity or frequency of a symptom, or delays the onset of a symptom, slows the progression of a symptom, or slows the severity or frequency of a symptom.

Certain Embodiments

(76) The present disclosure provides the following non-limiting numbered embodiments: Embodiment 1. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion of an APP nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage. Embodiment 2. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, least 15, or 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOS: 2543-2572; wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage. Embodiment 3. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOS: 30-2542 or 2573-3057; wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage. Embodiment 4. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is complementary to at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of: an equal length portion of nucleobases 6193-6245 of SEQ ID NO: 2; an equal length portion of nucleobases 9656-9656 of SEQ ID NO: 2; an equal length portion of nucleobases 10203-10249 of SEQ ID NO: 2; an equal length portion of nucleobases 11246-11287 of SEQ ID NO: 2; an equal length portion of nucleobases 12566-12609 of SEQ ID NO: 2; an equal length portion of nucleobases 22914-22964 of SEQ ID NO: 2; an equal length portion of nucleobases 154394-154420 of SEQ ID NO: 2; an equal length portion of nucleobases 154736-154760 of SEQ ID NO: 2; an equal length portion of nucleobases 158598-158982 of SEQ ID NO: 2; an equal length portion of nucleobases 159558-159581 of SEQ ID NO: 2; an equal length portion of nucleobases 220028-220077 of SEQ ID NO: 2; an equal length portion of nucleobases 220237-220426 of SEQ ID NO: 2; an equal length portion of nucleobases 220710-220766 of SEQ ID NO: 2; an equal length portion of nucleobases 220893-220919 of SEQ ID NO: 2; an equal length portion of nucleobases 221002-221025 of SEQ ID NO: 2; an equal length portion of nucleobases 221138-221177 of SEQ ID NO: 2; an equal length portion of nucleobases 221315-221364 of SEQ ID NO: 2; an equal length portion of nucleobases 222414-222478 of SEQ ID NO: 2; an equal length portion of nucleobases 222548-222590 of SEQ ID NO: 2; an equal length portion of nucleobases 222663-222697 of SEQ ID NO: 2; an equal length portion of nucleobases 222764-222791 of SEQ ID NO: 2; an equal length portion of nucleobases 225366-225400 of SEQ ID NO: 2; an equal length portion of nucleobases 226497-226532 of SEQ ID NO: 2; an equal length portion of nucleobases 229282-229306 of SEQ ID NO: 2; an equal length portion of nucleobases 231282-231310 of SEQ ID NO: 2; an equal length portion of nucleobases 234328-234370 of SEQ ID NO: 2; an equal length portion of nucleobases 234802-234827 of SEQ ID NO: 2; an equal length portion of nucleobases 34556-34575 of SEQ ID NO: 2; an equal length portion of nucleobases 101718-101737 of SEQ ID NO: 2; an equal length portion of nucleobases 158795-158814 of SEQ ID NO: 2; or an equal length portion of nucleobases 292896-292922 of SEQ ID NO: 2; wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage. Embodiment 5. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of a sequence selected from: SEQ ID NOs: 140, 1240, 1279, 1402, 1437; SEQ ID NOs: 116, 202, 626; SEQ ID NOs: 830, 912, 962, 1049, 1164, 1236; SEQ ID NOs: 201, 1741, 1870; SEQ ID NOs: 273, 744, 824, 898, 1025; SEQ ID NOs: 296, 384, 1568, 1617, 1701, 1734, 1841; SEQ ID NOs: 1553, 1593, 1709, 1805, 1873; SEQ ID NOs: 340, 519, 590, 711, 795, 819; SEQ ID NOs: 178, 547, 577, 693, 769, 846, 2225, 2480, 3047-3050; SEQ ID NOs: 200, 1688, 1740, 1820, 1906; SEQ ID NOs: 2576, 2493, 2660, 2708, 2790, 2806, 2854, 2900, 2903, 2993, 3013; SEQ ID NOs: 2590, 2690, 2691, 2760, 2808, 2939, 3002; SEQ ID NOs: 2580, 2652, 2728, 2772, 2866, 2874, 2931, 3012; SEQ ID NOs: 2619, 2671, 2783, 2812, 2875, 2929; SEQ ID NOs: 2638, 2649, 2676, 2753, 2757, 2804, 2932, 2983; SEQ ID NOs: 2575, 2848, 2890, 2965; SEQ ID NOs: 2583, 2654, 2748, 2823, 2882; SEQ ID NOs: 1557, 1613, 1696, 2592, 2699, 2713, 2775, 2844, 2879, 2977, 2986; SEQ ID NOs: 338, 2574, 2642, 2666, 2689, 2740, 2754, 2847, 2859, 2899, 2950, 2987, 3014; SEQ ID NOs: 2641, 2675, 2799, 2856, 2933, 2974; SEQ ID NOs: 2610, 2780, 2851, 2943, 2956; SEQ ID NOs: 2766, 2855, 2925, 2988; SEQ ID NOs: 2645, 2715, 2727, 2787, 2842, 2843, 2938, 2940, 2967, 2978; SEQ ID NOs: 299, 2632, 3020; SEQ ID NOs: 2591, 2705, 2747, 2865, 2941, 3010; SEQ ID NOs: 2621, 2629, 2679, 2687, 2735, 2788, 2864, 2912, 2966; SEQ ID NOs: 2701, 2742, 2828, 2908; SEQ ID NOs: 2611, 2717, 2979; or SEQ ID NOs: 35,411,482, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage. Embodiment 6. The oligomeric compound of any of embodiments 1-5, wherein the modified oligonucleotide has a nucleobase sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to any of the nucleobase sequences of SEQ ID NO: 1-8 when measured across the entire nucleobase sequence of the modified oligonucleotide. Embodiment 7. The oligomeric compound of any of embodiments 1-6, wherein at least one nucleoside of the modified oligonucleotide is a modified nucleoside. Embodiment 8. The oligomeric compound of embodiment 7, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety. Embodiment 9. The oligomeric compound of embodiment 8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic modified sugar moiety. Embodiment 10. The oligomeric compound of embodiment 9, wherein the bicyclic modified sugar moiety comprises a 2′-4′ bridge, wherein the 2′-4′ bridge is selected from —O—CH.sub.2— and —O—CH(CH.sub.3)—. Embodiment 11. The oligomeric compound of any of embodiments 6-10, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety. Embodiment 12. The oligomeric compound of embodiment 8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic modified sugar moiety having a 2′-4′ bridge and at least one modified nucleoside comprising a non-bicyclic modified sugar moiety. Embodiment 13. The oligomeric compound of embodiment 11 or 12, wherein the non-bicyclic modified sugar moiety is a 2′-MOE sugar moiety or a 2′-OMe sugar moiety. Embodiment 14. The oligomeric compound of any of embodiments 1-13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate. Embodiment 15. The oligomeric compound of embodiment 14, wherein at least one modified nucleoside of the modified oligonucleotide comprises a sugar surrogate selected from morpholino and PNA. Embodiment 16. The oligomeric compound of any of embodiments 1-8, 11, or 13-15, wherein the modified oligonucleotide does not comprise a bicyclic sugar moiety. Embodiment 17. The oligomeric compound of any of embodiments 1-16, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage. Embodiment 18. The oligomeric compound of embodiment 17, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage. Embodiment 19. The oligomeric compound of embodiment 17 or embodiment 18, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage. Embodiment 20. The oligomeric compound of embodiment 16 or 17, wherein at least one internucleoside linkage is a mesyl phosphoramidate internucleoside linkage. Embodiment 21. The oligomeric compound of embodiment 17 or 19-20, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage. Embodiment 22. The oligomeric compound of any of embodiments 17, 19, or 21, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage. Embodiment 23. The oligomeric compound of any of embodiments 17, 19, or 20-21, wherein each internucleoside linkage is independently selected from a phosphodiester internucleoside linkage, a phosphorothioate internucleoside linkage, and a mesyl phosphoramidate internucleoside linkage. Embodiment 24. The oligomeric compound of any of embodiments 1-17 or 19-21, or 23, wherein at least 1, at least 2, at least 3, at least 4, or at least 5 internucleoside linkages of the modified oligonucleotide are mesyl phosphoramidate internucleoside linkages. Embodiment 25. The oligomeric compound of any of embodiments 1-24, wherein the modified oligonucleotide comprises a

modified nucleobase. Embodiment 26. The oligomeric compound of embodiment 25, wherein the modified nucleobase is a 5-methyl cytosine. Embodiment 27. The oligomeric compound of any of embodiments 1-26 wherein the modified oligonucleotide consists of 12-22, 12-20, 14-18, 14-20, 15-17, 15-25, 16-20, 16-18, or 18-20 linked nucleosides. Embodiment 28. The oligomeric compound of any of embodiments 1-27, wherein the modified oligonucleotide consists of 16 linked nucleosides. Embodiment 29. The oligomeric compound of any of embodiments 1-27, wherein the modified oligonucleotide consists of 20 linked nucleosides. Embodiment 30. The oligomeric compound of any of embodiments 1-29, wherein the modified oligonucleotide is a gapmer. Embodiment 31. The oligomeric compound of any of embodiments 1-29, wherein the modified oligonucleotide has a sugar motif comprising: a 5′-region consisting of 1-6 linked 5′-region nucleosides; a central region consisting of 6-10 linked central region nucleosides; and a 3′-region consisting of 1-6 linked 3′-region nucleosides; wherein the 3′-most nucleoside of the 5′-region and the 5′-most nucleoside of the 3′-region comprise modified sugar moieties, and each of the central region nucleosides is selected from a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety and a nucleoside comprising a 2′-substituted sugar moiety, wherein the central region comprises at least six nucleosides comprising a 2′-β-D-deoxyribosyl sugar moiety and no more than two nucleosides comprise a 2′-substituted sugar moiety. Embodiment 32. The oligomeric compound of embodiment 29, wherein each of the central region nucleosides is a 2′-β-D-deoxynucleoside. Embodiment 33. The oligomeric compound of embodiment 30 or embodiment 31, wherein the modified oligonucleotide has a sugar motif comprising: a 5′-region consisting of 6 linked 5′-region nucleosides; a central region consisting of 10 linked central region nucleosides; and a 3′-region consisting of 4 linked 3′-region nucleosides; wherein each of the 5′-region nucleosides and each of the 3′-region nucleosides is a 2′-MOE nucleoside, and each of the central region nucleosides is a 2′-β-D-deoxynucleoside. Embodiment 34. The oligomeric compound of embodiment 30 or embodiment 31, wherein the modified oligonucleotide has a sugar motif comprising: a 5′-region consisting of 5 linked 5′-region nucleosides; a central region consisting of 10 linked central region nucleosides; and a 3′-region consisting of 5 linked 3′-region nucleosides; wherein each of the 5′-region nucleosides and each of the 3′-region nucleosides is a 2′-MOE nucleoside, and each of the central region nucleosides is a 2′-β-D-deoxynucleoside. Embodiment 35. The oligomeric compound of embodiment 30 or embodiment 31, wherein the modified oligonucleotide has a sugar motif comprising: a 5′-region consisting of 3 linked 5′-region nucleosides; a central region consisting of 10 linked central region nucleosides; and a 3′-region consisting of 3 linked 3′-region nucleosides; wherein each of the 5′-region nucleosides and each of the 3′-region nucleosides is a cEt nucleoside, and each of the central region nucleosides is a 2′-β-D-deoxynucleoside. Embodiment 36. The oligomeric compound of embodiment 30, wherein the modified oligonucleotide has a sugar motif comprising: a 5′-region consisting of 3 linked 5′-region nucleosides; a central region consisting of 10 linked central region nucleosides; and a 3′-region consisting of 3 linked 3′-region nucleosides; wherein each of the 5′-region nucleosides and each of the 3′-region nucleosides is a cEt nucleoside, and the central region has the following formula: (Nd)(Nx)(Nd)n, wherein Nx is a 2′-OMe nucleoside and each Nd is a 2′-β-D-deoxynucleoside, and n is 8. Embodiment 37. The oligomeric compound of any of embodiments 1-36, wherein the modified oligonucleotide has an internucleoside linkage motif selected from: soosssssssssos, sooooossssssssssoss, sooossssssssssooss, soooossssssssssoss, sooossssssssssooos or ssoossssssssssooss, wherein s=a phosphorothioate internucleoside linkage and o=a phosphodiester internucleoside linkage. Embodiment 38. The oligomeric compound of any of embodiments 1-36, wherein the modified oligonucleotide has an internucleoside linkage motif selected from soozzsssssssos, soozzzsssssssos, soozzzzsssssos, soozzzzzssssos, zoozzzzsssssoz, soossssssszzsos, soossssssszzos, soossssssszzs, sooooozzsssssssoss, sooooozzzsssssssoss, sooooozzzzsssssoss, sooooozzzzzsssssoss, zooooozzzzsssssozz, sooooossssssszzsoss, sooooossssssszzoss, sooooossssssszzss, sooozzsssssssssooss, sooozzzsssssssooss, sooozzzzsssssooss, sooozzzzzsssssooss, zooozzzzsssssoozz, soooossssssszzsooss, soooossssssszzooss, and sooossssssssszzoss, wherein s=a phosphorothioate internucleoside linkage, o=a phosphodiester internucleoside linkage, and z=a mesyl phosphoramidate internucleoside linkage. Embodiment 39. The oligomeric compound of any of embodiments 1-38, consisting of the modified oligonucleotide. Embodiment 40. The oligomeric compound of any of embodiments 1-38, further comprising a conjugate group. Embodiment 41. The oligomeric compound of embodiment 40, wherein the conjugate group comprises a conjugate moiety and a conjugate linker. Embodiment 42. The oligomeric compound of embodiment 41, wherein the conjugate linker consists of a single bond. Embodiment 43. The oligomeric compound of embodiment 41 or embodiment 42, wherein the conjugate linker is cleavable. Embodiment 44. The oligomeric compound of embodiment 41, wherein the conjugate linker comprises 1-3 linker-nucleosides. Embodiment 45. The oligomeric compound of any of embodiments 40-44, wherein the conjugate group is attached to the modified oligonucleotide at the 5′-end of the modified oligonucleotide. Embodiment 46. The oligomeric compound of any of embodiments 40-44, wherein the conjugate group is attached to the modified oligonucleotide at the 3′-end of the modified oligonucleotide. Embodiment 47. The oligomeric compound of any of embodiments 1-38 or 40-45, comprising a terminal group. Embodiment 48. The oligomeric compound of any of embodiments 1-47 wherein the oligomeric compound is a singled-stranded oligomeric compound. Embodiment 49. The oligomeric compound of any of embodiments 1-43 or 45-48, wherein the oligomeric compound does not comprise linker-nucleosides. Embodiment 50. An oligomeric duplex comprising an oligomeric compound of any of embodiments 1-47 or 49. Embodiment 51. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or 23 nucleobases of any of SEQ ID NOS: 3058-3063; wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage. Embodiment 52. An oligomeric duplex, comprising a first oligomeric compound comprising a first modified oligonucleotide and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is an oligomeric compound of embodiment 51. Embodiment 53. The oligomeric duplex of embodiment 52, wherein at least one nucleoside of the first modified oligonucleotide comprises a modified sugar moiety selected from a 2′-OMe sugar moiety, a 2′-F sugar moiety, and a 2′-MOE sugar moiety. Embodiment 54. The oligomeric duplex of embodiment 53, wherein the first modified oligonucleotide consists of 23 linked nucleosides and has a sugar motif of efyyyyyyyyyyyfyfyyyyyyy, wherein each “e” represents a T-MOE sugar moiety, each “f” represents a 2′-F sugar moiety, and each “y” represents a 2′-OMe sugar moiety. Embodiment 55. The oligomeric duplex of embodiments 52-54 wherein the first modified oligonucleotide comprises a 5′-stabilized phosphate group. Embodiment 56. The oligomeric duplex of embodiment 55, wherein the 5′-stabilized phosphate group is 5′-vinylphosphonate. Embodiment 57. The oligomeric duplex of any of embodiments 52-56, wherein the first modified oligonucleotide consists of 23 linked nucleosides and has the internucleoside linkage motif of ssooooooooooooooooooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. Embodiment 58. The oligomeric duplex of any of embodiments 52-56, wherein the second modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a complementary region of at least 12 nucleosides that is at least 90% complementary to the nucleobase sequence of an equal length region of the first modified oligonucleotide. Embodiment 59. The oligomeric duplex of embodiment 58, wherein the complementary region is 21 nucleosides. Embodiment 60. The oligomeric duplex of embodiment 58 or embodiment 59, wherein the complementary region is at least 95% or is 100% complementary to an equal length portion of the first modified oligonucleotide. Embodiment 61. The oligomeric duplex of any of embodiments 58-60, wherein at least one nucleoside of the second modified oligonucleotide comprises a 2′-OMe sugar moiety, a 2′-F sugar moiety, or a 2′-MOE sugar moiety. Embodiment 62. The oligomeric duplex of any of embodiments 52-61, wherein the second modified oligonucleotide consists of 21 linked nucleosides and has a sugar motif of: yyyyyyfyfffyyyyyyyyyy, wherein each “f” represents a 2′-F sugar moiety and each “y” represents a 2′-OMe sugar moiety. Embodiment 63. The oligomeric duplex of any of embodiments 52-62, wherein the second oligomeric compound comprises a conjugate group. Embodiment 64. The oligomeric duplex of embodiment 63, wherein the second oligomeric compound comprises a conjugate group attached through a modified phosphoramidate internucleoside linkage. Embodiment 65. The oligomeric duplex of embodiment 63 or embodiment 64, wherein the conjugate group is C.sub.12-C.sub.20 alkyl. Embodiment 66. The oligomeric duplex of any of embodiments 63-65, wherein the conjugate group is C.sub.16 alkyl. Embodiment 67. The oligomeric duplex of any of embodiments 63-66, wherein the second modified oligonucleotide consists of 21 linked nucleosides and has the internucleoside linkage motif of ssooo[C16muP]ooooooooooooss, wherein each “o”

represents a phosphodiester internucleoside linkage, each “s” represents a phosphorothioate internucleoside linkage, and each “[C16muP]” represents a modified phosphoramidate internucleoside linkage, as shown below:
(77) ##STR00001## Embodiment 68. An antisense compound comprising or consisting of an oligomeric compound of any of embodiments 1-49 or 51 or an oligomeric duplex of any of embodiments 50 or 53-67. Embodiment 69. A chirally enriched population of oligomeric compounds of any of embodiments 1-49 or 51, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration. Embodiment 70. The chirally enriched population of embodiment 69, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Sp) configuration. Embodiment 71. The chirally enriched population of embodiment 69, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Rp) configuration. Embodiment 72. The chirally enriched population of embodiment 69, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage. Embodiment 73. The chirally enriched population of embodiment 72, wherein the population is enriched for modified oligonucleotides having the (Rp) configuration at one particular phosphorothioate internucleoside linkage and the (Sp) configuration at each of the remaining phosphorothioate internucleoside linkages. Embodiment 74. The chirally enriched population of embodiment 72, wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the Sp, Sp, and Rp configurations, in the 5′ to 3′ direction. Embodiment 75. A population of oligomeric compounds of any of embodiments 1-49 or 51, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom. Embodiment 76. A pharmaceutical composition comprising an oligomeric compound of any of embodiments 1-49 or 51, an oligomeric duplex of any of embodiments 50 or 52-67, an antisense compound of embodiment 68, or a population of any of embodiments 69-75 and a pharmaceutically acceptable carrier or diluent. Embodiment 77. The pharmaceutical composition of embodiment 76, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid, or phosphate-buffered saline (PBS). Embodiment 78. The pharmaceutical composition of embodiment 77, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the oligomeric duplex, the antisense compound, or the population and artificial cerebral spinal fluid. Embodiment 79. The pharmaceutical composition of embodiment 77, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the oligomeric duplex, the antisense compound, or the population and PBS. Embodiment 80. A method comprising administering to a subject the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79. Embodiment 81. A method of treating a disease or disorder associated with APP comprising administering to a subject having or at risk for developing a disease or disorder associated with APP a therapeutically effective amount of an oligomeric compound of any of embodiments 1-49 or 51, an oligomeric duplex of any of embodiments 50 or 52-67, an antisense compound of embodiment 68, a population of any of embodiments 69-75 or a pharmaceutical composition according to any of embodiments 76-79, thereby treating the disease or disorder associated with APP. Embodiment 82. The method of embodiment 81, wherein the APP-associated disease is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy. Embodiment 83. The method of any of embodiments 80-82 wherein administering the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79 ameliorates at least one symptom or hallmark of the APP-associated disease or disorder. Embodiment 84. The method of embodiment 83, wherein administering the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79 reduces or slows cognitive impairment, reduces or slows decline in memory and/or language skills, improves behavioral and psychological symptoms, reduces apathy, improves motivation, reduces gait disturbances, reduces seizures, reduces or slows progressive dementia, or reduces abnormal amyloid deposits. Embodiment 85. The method of any of embodiments 80-84, wherein APP protein levels in the subject are reduced. Embodiment 86. A method of reducing expression of APP in a cell comprising contacting the cell with the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79. Embodiment 87. The method of embodiment 86, wherein the cell is a cortical brain cell, or a hippocampal cell. Embodiment 88. Use of the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79 for treating a disease or disorder associated with APP. Embodiment 89. Use of the oligomeric compound of any of embodiments 1-49 or 51, the oligomeric duplex of any of embodiments 50 or 52-57, the antisense compound of embodiment 68, the population of any of embodiments 69-75, or the pharmaceutical composition of any of embodiments 76-79 in the manufacture of a medicament for treating a disease or disorder associated with APP. Embodiment 90. The use of embodiment 88 or 89, wherein the disease associated with APP is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy. Embodiment 91. The method of any of embodiments 80-85, wherein the subject is human. Embodiment 92. The method of embodiment 86 or embodiment 87, wherein the cell is a human. Embodiment 93. A modified oligonucleotide according to the following chemical structure:
(78) ##STR00002##
or a salt thereof. Embodiment 94. The modified oligonucleotide of embodiment 93, which is the sodium salt or the potassium ‘ ’ salt. Embodiment 95. A modified oligonucleotide according to the following chemical structure:
(79) ##STR00003## Embodiment 96. A modified oligonucleotide according to the following chemical structure:
(80) ##STR00004##
or a salt thereof. Embodiment 97. The modified oligonucleotide of embodiment 96, which is the sodium salt or the potassium salt. Embodiment 98. A modified oligonucleotide according to the following chemical structure:
(81) ##STR00005## Embodiment 99. A modified oligonucleotide according to the following chemical structure:
(82) ##STR00006##
or a salt thereof. Embodiment 100. The modified oligonucleotide of embodiment 99, which is the sodium salt or the potassium salt. Embodiment 101. A modified oligonucleotide according to the following chemical structure:
(83) ##STR00007## Embodiment 102. A modified oligonucleotide according to the following chemical structure:
(84) ##STR00008##
or a salt thereof. Embodiment 103. The modified oligonucleotide of embodiment 102, which is the sodium salt or the potassium salt. Embodiment 104. A modified oligonucleotide according to the following chemical structure:
(85) ##STR00009## Embodiment 105. A modified oligonucleotide according to the following chemical structure:
(86) ##STR00010##
or a salt thereof. Embodiment 106. The modified oligonucleotide of embodiment 105, which is the sodium salt or the potassium salt. Embodiment 107. A modified oligonucleotide according to the following chemical structure:
(87) ##STR00011## Embodiment 108. A modified oligonucleotide according to the following chemical structure:
(88) ##STR00012##
or a salt thereof. Embodiment 109. The modified oligonucleotide of embodiment 108, which is the sodium salt or the potassium salt. Embodiment 110. A modified oligonucleotide according to the following chemical structure:

(89) ##STR00013## Embodiment 111. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:
G.sub.es.sup.mC.sub.eoA.sub.eoT.sub.eoT.sub.es.sup.mC.sub.dsT.sub.ds.sup.mC.sub.dsT.sub.dsT.sub.dsA.sub.dsT.sub.dsA.sub.dsT.sub.dsT.sub.ds.sup.mC.su
(SEQ ID NO: 273), wherein: A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage. Embodiment 112. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:
G.sub.esT.sub.eoT.sub.eoT.sub.eoA.sub.es.sup.mC.sub.ds.sup.mC.sub.dsT.sub.dsT.sub.dsT.sub.dsA.sub.dsA.sub.ds.sup.mC.sub.dsA.sub.dsT.sub.dsT.sub.eo.su
(SEQ ID NO: 452), wherein: A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage. Embodiment 113. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:
G.sub.es.sup.mC.sub.eo.sup.mC.sub.eoA.sub.eoT.sub.esA.sub.dsT.sub.dsT.sub.dsG.sub.dsT.sub.ds.sup.mC.sub.dsA.sub.dsT.sub.dsT.sub.dsT.sub.dsT.sub.eoA
(SEQ ID NO: 462), wherein: A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage. Embodiment 114. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:
G.sub.esT.sub.eoA.sub.eoT.sub.eo.sup.mC.sub.es.sup.mC.sub.dsT.sub.ds.sup.mC.sub.dsT.sub.dsT.sub.dsA.sub.dsA.sub.dsT.sub.dsT.sub.ds.sup.mC.sub.ds.sup
ID NO: 482), wherein: A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage. Embodiment 115. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:
.sup.mC.sub.esT.sub.eo.sup.mC.sub.eo.sup.mC.sub.eoA.sub.esA.sub.dsT.sub.dsT.sub.dsT.sub.dsT.sub.dsA.sub.dsA.sub.ds.sup.mC.sub.dsT.sub.dsT.sub.dsG.su
(SEQ ID NO: 1064), wherein: A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage. Embodiment 116. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:
G.sub.esT.sub.eoT.sub.eo.sup.mC.sub.eoA.sub.es.sup.mC.sub.dsA.sub.dsG.sub.dsT.sub.dsT.sub.dsT.sub.dsA.sub.ds.sup.mC.sub.ds.sup.mC.sub.ds.sup.mC.sub
(SEQ ID NO: 2225), wherein: A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage. Embodiment 117. The oligomeric compound of any of embodiments 111-116, wherein the modified oligonucleotide is covalently linked to a conjugate group. Embodiment 118. A chirally enriched population of modified oligonucleotides of any of embodiments 93-110 or oligomeric compounds of any of embodiments 111-116, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration. Embodiment 119. The chirally enriched population of embodiment 118, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Sp) configuration. Embodiment 120. The chirally enriched population of embodiment 118, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the dip) configuration. Embodiment 121. The chirally enriched population of embodiment 118, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage. Embodiment 122. The chirally enriched population of embodiment 121, wherein the population is enriched for modified oligonucleotides having the dip) configuration at one particular phosphorothioate internucleoside linkage and the (Sp) configuration at each of the remaining phosphorothioate internucleoside linkages. Embodiment 123. The chirally enriched population of embodiment 121, wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the Sp, Sp, and lip configurations, in the 5′ to 3′ direction. Embodiment 124. A population of modified oligonucleotides of any of embodiments 93-110 or oligomeric compounds of any of embodiments 111-116, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom. Embodiment 125. A pharmaceutical composition comprising a modified oligonucleotide of any of embodiments 93-110, an oligomeric compound of any of embodiments 111-116, or a population of any of embodiments 118-124, and a pharmaceutically acceptable carrier or diluent. Embodiment 126. The pharmaceutical composition of embodiment 125, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid, or phosphate-buffered saline (PBS). Embodiment 127. The pharmaceutical composition of embodiment 126, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide, the oligomeric compound, or the population and artificial cereal spinal fluid. Embodiment 128. The pharmaceutical composition of embodiment 126, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide, the oligomeric compound, or the population and PBS. Embodiment 129. A method comprising administering to a subject the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128. Embodiment 130. A method of treating a disease or disorder associated with APP comprising administering to a subject having or at risk for developing a disease or disorder associated with APP a therapeutically effective amount of a modified oligonucleotide of any of embodiments 93-110, an oligomeric compound of any of embodiments 111-116, a population of any of embodiments 118-124, or a pharmaceutical composition of any of embodiments 125-128, thereby treating the disease or disorder associated with APP. Embodiment 131. The method of embodiment 130, wherein the APP-associated disease is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid Angiopathy. Embodiment 132. The method of any of embodiments 129-131 wherein administering the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128 ameliorates at least one symptom or hallmark of the APP-associated disease or disorder. Embodiment 133. The method of embodiment 132, wherein administering the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128 reduces or slows cognitive impairment, reduces or slows decline in memory and/or language skills, improves behavioral and psychological symptoms, reduces apathy, improves motivation, reduces gait disturbances, reduces seizures, reduces or slows progressive dementia, or reduces abnormal amyloid deposits. Embodiment 134. The method of any of embodiments 129-134, wherein APP protein levels in the subject are reduced. Embodiment 135. A method of reducing expression of APP in a cell comprising contacting the cell with the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128. Embodiment 136. The method of embodiment 135, wherein the cell is a cortical brain cell, or a hippocampal cell. Embodiment 137. Use of the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128 for treating a disease or disorder associated with APP. Embodiment 138. Use of the modified oligonucleotide of any of embodiments 93-110, the oligomeric compound of any of embodiments 111-116, the population of any of embodiments 118-124, or the pharmaceutical composition of any of embodiments 125-128 in the manufacture of a medicament for treating a disease or disorder associated with APP. Embodiment 139. The use of embodiment 137 or 138, wherein the disease associated with APP is sporadic Alzheimer's Disease, genetic/familial Alzheimer's Disease, Alzheimer's Disease in a Down Syndrome patient, or Cerebral Amyloid

Angiopathy. Embodiment 140. The method of any of embodiments 129-134, wherein the subject is human. Embodiment 141. The method of embodiment 135 or embodiment 136, wherein the cell is a human cell.

I. Certain Oligonucleotides

(90) In certain embodiments, provided herein are oligomeric compounds comprising oligonucleotides, which consist of linked nucleosides. Oligonucleotides may be unmodified oligonucleotides (RNA or DNA) or may be modified oligonucleotides. Modified oligonucleotides comprise at least one modification relative to unmodified RNA or DNA. That is, modified oligonucleotides comprise at least one modified nucleoside (comprising a modified sugar moiety and/or a modified nucleobase) and/or at least one modified internucleoside linkage. Certain modified nucleosides and modified internucleoside linkages suitable for use in modified oligonucleotides are described below.

(91) A. Certain Modified Nucleosides

(92) Modified nucleosides comprise a modified sugar moiety or a modified nucleobase or both a modified sugar moiety and a modified nucleobase. In certain embodiments, modified nucleosides comprising the following modified sugar moieties and/or the following modified nucleobases may be incorporated into antisense oligonucleotides.

(93) 1. Certain Sugar Moieties

(94) In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties. In certain embodiments, modified sugar moieties are bicyclic or tricyclic sugar moieties. In certain embodiments, modified sugar moieties are sugar surrogates. Such sugar surrogates may comprise one or more substitutions corresponding to those of other types of modified sugar moieties.

(95) In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties comprising a furanosyl ring with one or more substituent groups none of which bridges two atoms of the furanosyl ring to form a bicyclic structure. Such non bridging substituents may be at any position of the furanosyl, including but not limited to substituents at the 2′, 3′, 4′, and/or 5′ positions. In certain embodiments one or more non-bridging substituent of non-bicyclic modified sugar moieties is branched. Examples of 2′-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2′-F, 2′-OCH.sub.3 (“OMe” or “O-methyl”), and 2′-O(CH.sub.2).sub.2OCH.sub.3 (“MOE”). In certain embodiments, 2′-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF.sub.3, OCF.sub.3, O—C.sub.1-C.sub.10 alkoxy, O—C.sub.1-C.sub.10 substituted alkoxy, O—C.sub.1-C.sub.10 alkyl, O—C.sub.1-C.sub.10 substituted alkyl, S-alkyl, N(R.sub.m)-alkyl, O-alkenyl, S-alkenyl, N(R.sub.m)-alkenyl, O-alkynyl, S-alkynyl, N(R.sub.m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, O(CH.sub.2).sub.2SCH.sub.3, O(CH.sub.2).sub.2ON(R.sub.m)(R.sub.n) or OCH.sub.2C(═O)—N(R.sub.m)(R.sub.n), where each R.sub.m and R.sub.n is, independently, H, an amino protecting group, or substituted or unsubstituted C.sub.1-C.sub.10 alkyl, —O(CH.sub.2).sub.2ON(CH.sub.3).sub.2 (“DMAOE”), 2′-OCH.sub.2OCH.sub.2N(CH.sub.2).sub.2 (“DMAEOE”), and the 2′-substituent groups described in Cook et al., U.S. Pat. No. 6,531,584; Cook et al., U.S. Pat. No. 5,859,221; and Cook et al., U.S. Pat. No. 6,005,087. Certain embodiments of these 2′-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO.sub.2), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl. In certain embodiments, non-bicyclic modified sugar moieties comprise a substituent group at the 3′-position. Examples of substituent groups suitable for the 3′-position of modified sugar moieties include but are not limited to alkoxy (e.g., methoxy), alkyl (e.g., methyl, ethyl). In certain embodiments, non-bicyclic modified sugar moieties comprise a substituent group at the 4′-position. Examples of 4′-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to alkoxy (e.g., methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. Examples of 5′-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 5′-methyl (R or S), 5′-vinyl, ethyl, and 5′-methoxy. In certain embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2′-F-5′-methyl sugar moieties and the modified sugar moieties and modified nucleosides described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836).

(96) In certain embodiments, a 2′-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2′-substituent group selected from: F, NH.sub.2, N.sub.3, OCF.sub.3J OCH.sub.3, O(CH.sub.2).sub.3NH.sub.2, CH.sub.2CH═CH.sub.2, OCH.sub.2CH═CH.sub.2, OCH.sub.2CH.sub.2OCH.sub.3, O(CH.sub.2).sub.2SCH.sub.3, O(CH.sub.2).sub.2ON(R.sub.m)(R.sub.n), O(CH.sub.2).sub.2O(CH.sub.2).sub.2N(CH.sub.3).sub.2, and N-substituted acetamide (OCH.sub.2C(═O)—N(R.sub.m)(R.sub.n)), where each R.sub.m and R.sub.n is, independently, H, an amino protecting group, or substituted or unsubstituted C.sub.1-C.sub.10 alkyl.

(97) In certain embodiments, a 2′-substituted nucleoside non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2′-substituent group selected from: F, OCF.sub.3J OCH.sub.3, OCH.sub.2CH.sub.2OCH.sub.3, O(CH.sub.2).sub.2SCH.sub.3, O(CH.sub.2).sub.2ON(CH.sub.3).sub.2, O(CH.sub.2).sub.2O(CH.sub.2).sub.2N(CH.sub.3).sub.2, O(CH.sub.2).sub.2ON(CH.sub.3).sub.2 (“DMAOE”), OCH.sub.2OCH.sub.2N(CH.sub.2).sub.2 (“DMAEOE”) and OCH.sub.2C(═O)—N(H)CH.sub.3 (“NMA”).

(98) In certain embodiments, a 2′-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2′-substituent group selected from: F, OCH.sub.3, and OCH.sub.2CH.sub.2OCH.sub.3.

(99) In naturally occurring nucleic acids, sugars are linked to one another 3′ to 5′. In certain embodiments, oligonucleotides include one or more nucleoside or sugar moiety linked at an alternative position, for example at the 2′ or inverted 5′ to 3′. For example, where the linkage is at the 2′ position, the 2′-substituent groups may instead be at the 3′-position.

(100) Certain modified sugar moieties comprise a substituent that bridges two atoms of the furanosyl ring to form a second ring, resulting in a bicyclic sugar moiety. Nucleosides comprising such bicyclic sugar moieties have been referred to as bicyclic nucleosides (BNAs), locked nucleosides, or conformationally restricted nucleotides (CRN). Certain such compounds are described in US Patent Publication No. 2013/0190383; and PCT publication WO 2013/036868. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4′ and the 2′ furanose ring atoms, n certain such embodiments, the furanose ring is a ribose ring. Examples of such 4′ to 2′ bridging sugar substituents include but are not limited to: 4′-CH.sub.2-2′, 4′-(CH.sub.2).sub.2-2′, 4′-(CH.sub.2).sub.3-2′, 4′-CH.sub.2—O-2′ (“LNA”), 4′-CH.sub.2—S-2′, 4′-(CH.sub.2).sub.2—O-2′ (“ENA”), 4′-CH(CH.sub.3)—O-2′ (referred to as “constrained ethyl” or “cEt” when in the S configuration), 4′-CH.sub.2—O—CH.sub.2-2′, 4′-CH.sub.2—N(R)-2′, 4′-CH(CH.sub.2OCH.sub.3)—O-2′ (“constrained MOE” or “cMOE”) and analogs thereof (see, e.g., Seth et al., U.S. Pat. No. 7,399,845, Bhat et al., U.S. Pat. No. 7,569,686, Swayze et al., U.S. Pat. No. 7,741,457, and Swayze et al., U.S. Pat. No. 8,022,193), 4′-C(CH.sub.3)(CH.sub.3)—O-2′ and analogs thereof (see, e.g, Seth et al., U.S. Pat. No. 8,278,283), 4′-CH.sub.2—N(OCH.sub.3)-2′ and analogs thereof (see, e.g., Prakash et al., U.S. Pat. No. 8,278,425), 4′-CH.sub.2—O—N(CH.sub.3)-2′ (see, e.g., Allerson et al., U.S. Pat. No. 7,696,345 and Allerson et al., U.S. Pat. No. 8,124,745), 4′-CH.sub.2—C(H)(CH.sub.3)-2′ (see, e.g, Zhou, el at, J. Org. Chem., 2009, 74, 118-134), 4′-CH.sub.2—C(═CH.sub.2)-2′ and analogs thereof (see e.g., Seth et al., U.S. Pat. No. 8,278,426), 4′-C(R.sub.aR.sub.b)—N(R)—O-2′, 4′—C(R.sub.aR.sub.b)—O—N(R)-2′, 4′-CH.sub.2—O—N(R)-2′, and 4′-CH.sub.2—N(R)—O-2′, wherein each R, R.sub.a, and R.sub.b is, independently, H, a protecting group, or C.sub.1-C.sub.12 alkyl (see, e.g. Imanishi et al., U.S. Pat. No. 7,427,672).

(101) In certain embodiments, such 4′ to 2′ bridges independently comprise from 1 to 4 linked groups independently selected from: —[C(Ra)(Rb)]n-, —[C(Ra)(Rb)]n-O—, C(Ra)═C(Rb)—, C(Ra)═N—, C(═NRa)—, —C(═O)—, —C(═S)—, —O—, —Si(Ra)2-, —S(═O)x-, and N(Ra)—; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each Ra and Rb is, independently, H, a protecting group, hydroxyl, C1-C12 alkyl, substituted C1-C12 alkyl, C2-C12 alkenyl, substituted C2-C12 alkenyl, C2-C12 alkynyl, substituted C2-C12 alkynyl, C5-C20 aryl, substituted C5-C20 aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C5-C7 alicyclic radical, substituted C5-C7 alicyclic radical, halogen, OJ1, NJ1J2, SJ1, N3, COOJ1, acyl (C(═O)—H), substituted acyl, CN, sulfonyl (S(═O)2-J1), or sulfoxyl (S(═O)-J1); and each J1 and J2 is, independently, H, C1-C12 alkyl, substituted C1-C12 alkyl, C2-C12 alkenyl, substituted C2-C12 alkenyl, C2-C12 alkynyl, substituted C2-C12 alkynyl, C5-C20 aryl, substituted C5-C20 aryl, acyl (C(═O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C1-C12 aminoalkyl, substituted

C1-C12 aminoalkyl, or a protecting group.
(102) Additional bicyclic sugar moieties are known in the art, see, for example: Freier et al., Nucleic Acids Research, 1997, 25(22), 4429-4443, Albaek et al., J. Org. Chem., 2006, 71, 7731-7740, Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron, 1998, 54, 3607-3630; Wahlestedt et al., Proc. Natl. Acad. Sci. U.S.A, 2000, 97, 5633-5638; Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; Singh et al., J. Org. Chem., 1998, 63, 10035-10039; Srivastava et al., J. Am. Chem. Soc., 2007, 129, 8362-8379; Elayadi et al., Curr. Opinion Invens. Drugs, 2001, 2, 558-561; Braasch et al., Chem. Biol., 2001, 8, 1-7; Omm et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; Wengel et al., U.S. Pat. No. 7,053,207, Imanishi et al., U.S. Pat. No. 6,268,490, Imanishi et al. U.S. Pat. No. 6,770,748, Imanishi et al., U.S. RE44,779; Wengel et al., U.S. Pat. No. 6,794,499, Wengel et al., U.S. Pat. No. 6,670,461; Wengel et al., U.S. Pat. No. 7,034,133, Wengel et al., U.S. Pat. No. 8,080,644; Wengel et al., U.S. Pat. No. 8,034,909; Wengel et al., U.S. Pat. No. 8,153,365; Wengel et al., U.S. Pat. No. 7,572,582; and Ramasamy et al., U.S. Pat. No. 6,525,191, Torsten et al., WO 2004/106356, Wengel et al., WO 1999/014226; Seth et al., WO 2007/134181; Seth et al., U.S. Pat. No. 7,547,684; Seth et al., U.S. Pat. No. 7,666,854; Seth et al., U.S. Pat. No. 8,088,746; Seth et al., U.S. Pat. No. 7,750,131; Seth et al., U.S. Pat. No. 8,030,467; Seth et al., U.S. Pat. No. 8,268,980; Seth et al., U.S. Pat. No. 8,546,556; Seth et al., U.S. Pat. No. 8,530,640; Migawa et al., U.S. Pat. No. 9,012,421; Seth et al., U.S. Pat. No. 8,501,805; Allerson et al., US2008/0039618; and Migawa et al., US2015/0191727. In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, an LNA nucleoside (described herein) may be in the α-L configuration or in the β-D configuration.
(103) ##STR00014##
α-L-methyleneoxy (4′-CH.sub.2—O-2′) or α-L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research*, 2003, 21, 6365-6372). The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. et al., (2005) Nucleic Acids Research 33(1): 439-447; Mook, O R. et al., (2007) Mai Cane Ther 6(3):833-843; Grunweller, A. et al., (2003) Nucleic Acids Research 31(12):3185-3193). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When the positions of specific bicyclic nucleosides (e.g., LNA or cEt) are identified in exemplified embodiments herein, they are in the β-D configuration, unless otherwise specified.
(104) In certain embodiments, modified sugar moieties comprise one or more non-bridging sugar substituent and one or more bridging sugar substituent (e.g., 5′-substituted and 4′-2′ bridged sugars).
(105) In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, e.g., with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents as described herein. For example, certain sugar surrogates comprise a 4′-sulfur atom and a substitution at the 2′-position (see. e.g., Bhat et al., U.S. 7,875,733 and Bhat et al., U.S. Pat. No. 7,939,677) and/or the 5′ position.
(106) In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran (“THP”). Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include but are not limited to hexitol nucleic acid (“HNA”), anitol nucleic acid (“ANA”), manitol nucleic acid (“MNA”) (see, e.g., Leumann, C J. *Bioorg*. & *Med. Chem.* 2002, 10, 841-854), fluoro HNA:
(107) ##STR00015##
(“F-HNA”, see e.g. Swayze et al., U.S. Pat. No. 8,088,904; Swayze et al., U.S. Pat. No. 8,440,803; Swayze et al., U.S. Pat. No. 8,796,437; and Swayze et al., U.S. Pat. No. 9,005,906; F-HNA can also be referred to as a F-THP or 3′-fluoro tetrahydropyran), and nucleosides comprising additional modified THP compounds having the formula:
(108) ##STR00016##
wherein, independently, for each of said modified THP nucleoside: Bx is a nucleobase moiety; T.sub.3 and T.sub.4 are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T.sub.3 and T.sub.4 is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T.sub.3 and T.sub.4 is H, a hydroxyl protecting group, a linked conjugate group, or a 5′ or 3′-terminal group;
q.sub.1, q.sub.2, q.sub.3, q.sub.4, q.sub.5, q.sub.6 and q.sub.7 are each, independently, H, C.sub.1-C.sub.6 alkyl, substituted C.sub.1-C.sub.6 alkyl, C.sub.2-C.sub.6 alkenyl, substituted C.sub.2-C.sub.6 alkenyl, C.sub.2-C.sub.6 alkynyl, or substituted C.sub.2-C.sub.6 alkynyl; and each of R.sub.1 and R.sub.2 is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NTT. ST, N.sub.3, OC(═X)J.sub.1, OC(═X)NJ.sub.1J.sub.2, NJ.sub.3C(═X)NJ.sub.1J.sub.2, and CN, wherein X is O, S or NJ.sub.1, and each J.sub.1, J.sub.2, and J.sub.3 is, independently, H or C.sub.1-C.sub.6 alkyl.
(109) In certain embodiments, modified THP nucleosides are provided wherein q.sub.1, q.sub.2, q.sub.3, q.sub.4, q.sub.5, q.sub.6 and q.sub.7 are each H.
(110) In certain embodiments, at least one of q.sub.1, q.sub.2, q.sub.3, q.sub.4, q.sub.5, q.sub.6 and q.sub.7 is other than H. In certain embodiments, at least one of q.sub.1, q.sub.2, q.sub.3, q.sub.4, q.sub.5, q.sub.6 and q.sub.7 is methyl. In certain embodiments, modified THP nucleosides are provided wherein one of R.sub.1 and R.sub.2 is F. In certain embodiments, R.sub.1 is F and R.sub.2 is H, in certain embodiments, R.sub.1 is methoxy and R.sub.2 is H, and in certain embodiments, R.sub.1 is methoxyethoxy and R.sub.2 is H.
(111) In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example, nucleosides comprising morpholino sugar moieties and their use in oligonucleotides have been reported (see, e.g., Braasch et al., Biochemistry, 2002, 47, 4503-4510 and Summerton et al., U.S. Pat. No. 5,698,685; Summerton et al., U.S. Pat. No. 5,166,315; Summerton et al., U.S. Pat. No. 5,185,444; and Summerton et al., U.S. Pat. No. 5,034,506). As used here, the term “morpholino” means a sugar surrogate having the following structure:
(112) ##STR00017##
In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are referred to herein as “modified morpholinos.”
(113) In certain embodiments, sugar surrogates comprise acyclic moieties. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to: peptide nucleic acid (“PNA”), acyclic butyl nucleic acid (see, e.g., Kumar et al., Org. Biomol. Chem., 2013, 11, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., WO2011/133876. In certain embodiments, sugar surrogates comprise acyclic moieties. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include, but are not limited to: peptide nucleic acid (“PNA”), acyclic butyl nucleic acid (see, e.g., Kumar et al., *Org. Biomol. Chem.*, 2013, 11, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., US2013/130378. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262. Additional PNA compounds suitable for use in the oligonucleotides of the invention are described in, for example, in Nielsen et al., *Science*, 1991, 254, 1497-1500.
(114) In certain embodiments, sugar surrogates are the “unlocked” sugar structure of UNA (unlocked nucleic acid) nucleosides. UNA is an unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked sugar surrogate. Representative U.S. publications that teach the preparation of UNA include, but are not limited to, U.S. Pat. No. 8,314,227; and US Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.
(115) In certain embodiments, sugar surrogates are the glycerol as found in GNA (glycol nucleic acid) nucleosides as depicted below:
(116) ##STR00018##
(117) where Bx represents any nucleobase.
(118) Many other bicyclic and tricyclic sugar and sugar surrogats are known in the art that can be used in modified nucleosides.

(119) 2. Certain Modified Nucleobases
(120) In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising an unmodified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleoside that does not comprise a nucleobase, referred to as an abasic nucleoside. In certain embodiments, modified oligonucleotides comprise one or more inosine nucleosides (i.e., nucleosides comprising a hypoxanthine nucleobase).
(121) In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and 0-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 5-methylcytosine, 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (—C≡C—CH.sub.3) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. Pat. No. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J. I., Ed., John Wiley & Sons, 1990, 858-859; Englisch et al., *Angewandte Chemie*, International Edition, 1991, 30, 613; Sanghvi, Y. S., Chapter 15, *Antisense Research and Applications*, Crooke, S. T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; and those disclosed in Chapters 6 and 15, *Antisense Drug Technology*, Crooke S. T., Ed., CRC Press, 2008, 163-166 and 442-443.
(122) Publications that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include without limitation, Manoharan et al., US2003/0158403; Manoharan et al., US2003/0175906; Dinh et al., U.S. Pat. No. 4,845,205; Spielvogel et al., U.S. Pat. No. 5,130,302; Rogers et al., U.S. Pat. No. 5,134,066; Bischofberger et al., U.S. Pat. No. 5,175,273; Urdea et al., U.S. Pat. No. 5,367,066; Benner et al., U.S. Pat. No. 5,432,272; Matteucci et al., U.S. Pat. No. 5,434,257; Gmeiner et al., U.S. Pat. No. 5,457,187; Cook et al., U.S. Pat. No. 5,459,255; Froehler et al., U.S. Pat. No. 5,484,908; Matteucci et al., U.S. Pat. No. 5,502,177; Hawkins et al., U.S. Pat. No. 5,525,711; Haralambidis et al., U.S. Pat. No. 5,552,540; Cook et al., U.S. Pat. No. 5,587,469; Froehler et al., U.S. Pat. No. 5,594,121; Switzer et al., U.S. Pat. No. 5,596,091; Cook et al., U.S. Pat. No. 5,614,617; Froehler et al., U.S. Pat. No. 5,645,985; Cook et al., U.S. Pat. No. 5,681,941; Cook et al., U.S. Pat. No. 5,811,534; Cook et al., U.S. Pat. No. 5,750,692; Cook et al., U.S. Pat. No. 5,948,903; Cook et al., U.S. Pat. No. 5,587,470; Cook et al., U.S. Pat. No. 5,457,191; Matteucci et al., U.S. Pat. No. 5,763,588; Froehler et al., U.S. Pat. No. 5,830,653; Cook et al., U.S. Pat. No. 5,808,027; Cook et al., U.S. Pat. No. 6,166,199; and Matteucci et al., U.S. Pat. No. 6,005,096.
(123) 3. Certain Modified Internucleoside Linkages
(124) The naturally occurring internucleoside linkage of RNA and DNA is a 3′ to 5′ phosphodiester linkage. In certain embodiments, nucleosides of modified oligonucleotides may be linked together using one or more modified internucleoside linkages. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphates, which contain a phosphodiester bond (“P═O”) (also referred to as unmodified or naturally occurring linkages), phosphotriesters, methylphosphonates, phosphoramidates, and phosphorothioates (“P═S”), and phosphorodithioates (“HS—P═S”). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino (—CH.sub.2—N(CH.sub.3)—O—CH.sub.2—), thiodiester, thionocarbamate (—O—C(═O)(NH)—S—); siloxane (—O—SiH.sub.2—O—); and N,N′-dimethylhydrazine (—CH.sub.2—N(CH.sub.3)—N(CH.sub.3)—). Modified internucleoside linkages, compared to naturally occurring phosphate linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.
(125) Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having a chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside linkages, or as populations of modified oligonucleotides comprising phosphorothioate linkages in particular stereochemical configurations. In certain embodiments, populations of modified oligonucleotides comprise phosphorothioate internucleoside linkages wherein all of the phosphorothioate internucleoside linkages are stereorandom. Such modified oligonucleotides can be generated using synthetic methods that result in random selection of the stereochemical configuration of each phosphorothioate linkage. Nonetheless, each individual phosphorothioate of each individual oligonucleotide molecule has a defined stereoconfiguration. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising one or more particular phosphorothioate internucleoside linkages in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 80% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 90% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate linkage is present in at least 99% of the molecules in the population. Such chirally enriched populations of modified oligonucleotides can be generated using synthetic methods known in the art, e.g., methods described in Oka et al., *JACS* 125, 8307 (2003), Wan et al. *Nuc. Acid. Res.* 42, 13456 (2014), and WO 2017/015555. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one indicated phosphorothioate in the (Sp) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate in the (Rp) configuration. In certain embodiments, modified oligonucleotides comprising (Rp) and/or (S′p) phosphorothioates comprise one or more of the following formulas, respectively, wherein “B” indicates a nucleobase:
(126) ##STR00019##
Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.
(127) Neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3′-CH.sub.2—N(CH.sub.3)—O-5′), amide-3 (3′-CH.sub.2—C(═O)—N(H)-5′), amide-4 (3′-CH.sub.2—N(H)—C(═O)-5′), formacetal (3′-O—CH.sub.2—O-5′), methoxypropyl (MOP), and thioformacetal (3′-S—CH.sub.2—O-5′). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: *Carbohydrate Modifications in Antisense Research*; Y. S. Sanghvi and P. D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH.sub.2 component parts.
(128) In certain embodiments, modified oligonucleotides comprise one or more inverted nucleoside, as shown below:
(129) ##STR00020##
wherein each Bx independently represents any nucleobase.
(130) In certain embodiments, an inverted nucleoside is terminal (i.e., the last nucleoside on one end of an oligonucleotide) and so only one

internucleoside linkage depicted above will be present. In certain such embodiments, additional features (such as a conjugate group) may be attached to the inverted nucleoside. Such terminal inverted nucleosides can be attached to either or both ends of an oligonucleotide.
(131) In certain embodiments, such groups lack a nucleobase and are referred to herein as inverted sugar moieties. In certain embodiments, an inverted sugar moiety is terminal (i.e., attached to the last nucleoside on one end of an oligonucleotide) and so only one internucleoside linkage above will be present. In certain such embodiments, additional features (such as a conjugate group) may be attached to the inverted sugar moiety. Such terminal inverted sugar moieties can be attached to either or both ends of an oligonucleotide.
(132) In certain embodiments, nucleic acids can be linked 2′ to 5′ rather than the standard 3′ to 5′ linkage. Such a linkage is illustrated below.
(133) ##STR00021##
wherein each Bx represents any nucleobase.
B. Certain Motifs
(134) In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more modified internucleoside linkage. In such embodiments, the modified, unmodified, and differently modified sugar moieties, nucleobases, and/or internucleoside linkages of a modified oligonucleotide define a pattern or motif. In certain embodiments, the patterns of sugar moieties, nucleobases, and internucleoside linkages are each independent of one another. Thus, a modified oligonucleotide may be described by its sugar motif, nucleobase motif and/or internucleoside linkage motif (as used herein, nucleobase motif describes the modifications to the nucleobases independent of the sequence of nucleobases).
(135) 1. Certain Sugar Motifs
(136) In certain embodiments, oligonucleotides comprise one or more type of modified sugar and/or unmodified sugar moiety arranged along the oligonucleotide or region thereof in a defined pattern or sugar motif. In certain instances, such sugar motifs include but are not limited to any of the sugar modifications discussed herein.
(137) Uniformly Modified Oligonucleotides
(138) In certain embodiments, modified oligonucleotides comprise or consist of a region having a fully modified sugar motif. In such embodiments, each nucleoside of the fully modified region of the modified oligonucleotide comprises a modified sugar moiety. In certain embodiments, each nucleoside of the entire modified oligonucleotide comprises a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise or consist of a region having a fully modified sugar motif, wherein each nucleoside within the fully modified region comprises the same modified sugar moiety, referred to herein as a uniformly modified sugar motif. In certain embodiments, a fully modified oligonucleotide is a uniformly modified oligonucleotide. In certain embodiments, each nucleoside of a uniformly modified nucleotide comprises the same 2′-modification.
(139) Gapmer Oligonucleotides
(140) In certain embodiments, modified oligonucleotides comprise or consist of a region having a gapmer motif, which is defined by two external regions or “wings” and a central or internal region or “gap.” The three regions of a gapmer motif (the 5′-wing, the gap, and the 3′-wing) form a contiguous sequence of nucleosides wherein at least some of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3′-most nucleoside of the 5′-wing and the 5′-most nucleoside of the 3′-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap (i.e., the wing/gap junction). In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar motifs of the two wings are the same as one another (symmetric gapmer). In certain embodiments, the sugar motif of the 5′-wing differs from the sugar motif of the 3′-wing (asymmetric gapmer).
(141) In certain embodiments, the wings of a gapmer comprise 1-6 nucleosides. In certain embodiments, each nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least one nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least two nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least three nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least four nucleosides of each wing of a gapmer comprises a modified sugar moiety.
(142) In certain embodiments, the gap of a gapmer comprises 7-12 nucleosides. In certain embodiments, each nucleoside of the gap of a gapmer comprises a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a modified sugar moiety.
(143) In certain embodiments, the gapmer is a deoxy gapmer. In certain embodiments, the nucleosides on the gap side of each wing/gap junction comprise 2′-deoxyribosyl sugar moieties and the nucleosides on the wing sides of each wing/gap junction comprise modified sugar moieties. In certain embodiments, each nucleoside of the gap comprises a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, each nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a modified sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a 2′-OMe sugar moiety.
(144) Herein, the lengths (number of nucleosides) of the three regions of a gapmer may be provided using the notation [# of nucleosides in the 5′-wing]-[# of nucleosides in the gap]-[# of nucleosides in the 3′-wing]. Thus, a 3-10-3 gapmer consists of 3 linked nucleosides in each wing and 10 linked nucleosides in the gap. Where such nomenclature is followed by a specific modification, that modification is the modification in each sugar moiety of each wing and the gap nucleosides comprise 2′-β-D-deoxyribosyl sugar moieties. Thus, a 5-10-5 MOE gapmer consists of 5 linked 2′-MOE nucleosides in the 5′-wing, 10 linked 2′-β-D-deoxynucleosides in the gap, and 5 linked 2′-MOE nucleosides in the 3′-wing. A 3-10-3 cEt gapmer consists of 3 linked cEt nucleosides in the 5′-wing, 10 linked 2′-β-D-deoxynucleosides in the gap, and 3 linked cEt nucleosides in the 3′-wing. A 5-8-5 gapmer consists of 5 linked nucleosides comprising a modified sugar moiety in the 5′-wing, 8 linked 2′-β-D-deoxynucleosides in the gap, and 5 linked nucleosides comprising a modified sugar moiety in the 3′-wing. A 5-8-5 mixed gapmer has at least two different modified sugar moieties in the 5′- and/or the 3′-wing.
(145) In certain embodiments, modified oligonucleotides are 5-10-5 MOE gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 BNA gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 cEt gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 LNA gapmers.
(146) In certain embodiments, modified oligonucleotides are 5-8-5 mixed gapmers that consist of 5 linked 2′-MOE nucleosides in the 5′-wing, 8 linked 2′-β-D-deoxynucleosides in the gap, and a mixture of cEt and 2′-MOE nucleosides in the 3′-wing. In certain embodiments, modified nucleosides have a sugar motif of eeeeeddddddddkkeee, where each “e” represents a nucleoside comprising a 2′-MOE modified sugar moiety, each “d” represents a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety, and each “k” represents a nucleoside comprising a cEt modified sugar moiety. In certain embodiments, modified nucleosides have a sugar motif of eeeeeddddddddkeeee, where each “e” represents a nucleoside comprising a 2′-MOE modified sugar moiety, each “d” represents a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety, and each “k” represents a nucleoside comprising a cEt modified sugar moiety.
(147) 2. Certain Nucleobase Motifs
(148) In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In

certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-methyl cytosines. In certain embodiments, all of the cytosine nucleobases are 5-methyl cytosines and all of the other nucleobases of the modified oligonucleotide are unmodified nucleobases.

(149) In certain embodiments, modified oligonucleotides comprise a block of modified nucleobases. In certain such embodiments, the block is at the 3′-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 3′-end of the oligonucleotide. In certain embodiments, the block is at the 5′-end of the oligonucleotide. In certain embodiments the block is within 3 nucleosides of the 5′-end of the oligonucleotide.

(150) In certain embodiments, oligonucleotides having a gapmer motif comprise a nucleoside comprising a modified nucleobase. In certain such embodiments, one nucleoside comprising a modified nucleobase is in the central gap of an oligonucleotide having a gapmer motif. In certain such embodiments, the sugar moiety of said nucleoside is a 2′-deoxyribosyl sugar moiety. In certain embodiments, the modified nucleobase is selected from: a 2-thiopyrimidine and a 5-propynepyrimidine.

(151) 3. Certain Internucleoside Linkage Motifs

(152) In certain embodiments, oligonucleotides comprise modified and/or unmodified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each internucleoside linking group is a phosphodiester internucleoside linkage (P═O). In certain embodiments, each internucleoside linking group of a modified oligonucleotide is a phosphorothioate internucleoside linkage (P═S). In certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a phosphorothioate internucleoside linkage and phosphodiester internucleoside linkage. In certain embodiments, each phosphorothioate internucleoside linkage is independently selected from a stereorandom phosphorothioate a (Sp) phosphorothioate, and a (Rp) phosphorothioate.

(153) In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer and the internucleoside linkages within the gap are all modified. In certain such embodiments, some or all of the internucleoside linkages in the wings are unmodified phosphodiester internucleoside linkages. In certain embodiments, the terminal internucleoside linkages are modified. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer, and the internucleoside linkage motif comprises at least one phosphodiester internucleoside linkage in at least one wing, wherein the at least one phosphodiester linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate linkages are stereorandom. In certain embodiments, all of the phosphorothioate linkages in the wings are (Sp) phosphorothioates, and the gap comprises at least one Sp, Sp, Rp motif. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising such internucleoside linkage motifs.

(154) In certain embodiments, modified nucleotides have an internucleoside linkage motif of soosssssssssos, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphate internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of sooooosssssssssssoss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphate internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of sooosssssssssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphate internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of soooosssssssssssoss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphate internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of ssoosssssssssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphate internucleoside linkage. In certain embodiments, modified nucleotides have an internucleoside linkage motif of sooosssssssssssooos, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphate internucleoside linkage.

(155) C. Certain Lengths

(156) It is possible to increase or decrease the length of an oligonucleotide without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the oligonucleotides were able to direct specific cleavage of the target RNA, albeit to a lesser extent than the oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase oligonucleotides, including those with 1 or 3 mismatches.

(157) In certain embodiments, oligonucleotides (including modified oligonucleotides) can have any of a variety of ranges of lengths. In certain embodiments, oligonucleotides consist of X to Y linked nucleosides, where X represents the fewest number of nucleosides in the range and Y represents the largest number nucleosides in the range. In certain such embodiments, X and Y are each independently selected from 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, and 50; provided that X≤Y. For example, in certain embodiments, oligonucleotides consist of 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 29, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to 30, or 29 to 30 linked nucleosides.

(158) D. Certain Modified Oligonucleotides

(159) In certain embodiments, the above modifications (sugar, nucleobase, internucleoside linkage) are incorporated into a modified oligonucleotide. In certain embodiments, modified oligonucleotides are characterized by their modification motifs and overall lengths. In certain embodiments, such parameters are each independent of one another. Thus, unless otherwise indicated, each internucleoside linkage of an oligonucleotide having a gapmer sugar motif may be modified or unmodified and may or may not follow the gapmer modification pattern of the sugar modifications. For example, the internucleoside linkages within the wing regions of a sugar gapmer may be the same or different from one another and may be the same or different from the internucleoside linkages of the gap region of the sugar motif. Likewise, such sugar gapmer oligonucleotides may comprise one or more modified nucleobase independent of the gapmer pattern of the sugar modifications. Unless otherwise indicated, all modifications are independent of nucleobase sequence.

(160) E. Certain Populations of Modified Oligonucleotides

(161) Populations of modified oligonucleotides in which all of the modified oligonucleotides of the population have the same molecular formula can be stereorandom populations or chirally enriched populations. All of the chiral centers of all of the modified oligonucleotides are stereorandom in a stereorandom population. In a chirally enriched population, at least one particular chiral center is not stereorandom in the modified oligonucleotides of the population. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for β-D ribosyl sugar moieties, and all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for both β-D ribosyl sugar moieties and at least one, particular phosphorothioate internucleoside linkage in

a particular stereochemical configuration.
(162) F. Nucleobase Sequence
(163) In certain embodiments, oligonucleotides (unmodified or modified oligonucleotides) are further described by their nucleobase sequence. In certain embodiments oligonucleotides have a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain such embodiments, a region of an oligonucleotide has a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain embodiments, the nucleobase sequence of a region or entire length of an oligonucleotide is at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the second oligonucleotide or nucleic acid, such as a target nucleic acid.
(164) II. Certain Oligomeric Compounds
(165) In certain embodiments, provided herein are oligomeric compounds, which consist of an oligonucleotide (modified or unmodified) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups consist of one or more conjugate moiety and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2′-position of a nucleoside of a modified oligonucleotide. In certain embodiments, conjugate groups that are attached to either or both ends of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups or terminal groups are attached at the 3′ and/or 5′-end of oligonucleotides. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3′-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3′-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at the 5′-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5′-end of oligonucleotides.
(166) Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.
(167) A. Certain Conjugate Groups
(168) In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance.
(169) In certain embodiments, conjugation of one or more carbohydrate moieties to a modified oligonucleotide can optimize one or more properties of the modified oligonucleotide. In certain embodiments, the carbohydrate moiety is attached to a modified subunit of the modified oligonucleotide. For example, the ribose sugar of one or more ribonucleotide subunits of a modified oligonucleotide can be replaced with another moiety, e.g. a non-carbohydrate (preferably cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS), which is a modified sugar moiety. A cyclic carrier may be a carbocyclic ring system, i.e., one or more ring atoms may be a heteroatom, e.g., nitrogen, oxygen, sulphur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, e.g. fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds. In certain embodiments, the modified oligonucleotide is a gapmer.
(170) In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, e.g., fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, 660, 306-309; Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, 20, 533-538), an aliphatic chain, e.g., do-decan-diol or undecyl residues (Saison-Behmoaras et al., *EMBO J*, 1991, 10, 1111-1118: Kabanov et al., *FEBS Lett.*, 1990, 259, 327-330; Svinarchuk et al., *Biochimie*, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., *Tetrahedron Lett.*, 1995, 36, 3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, 14, 969-973), or adamantane acetic acid a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, 1264, 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.*, 1996, 277, 923-937), a tocopherol group (Nishina et al., *Molecular Therapy Nucleic Acids*, 2015, 4, e220; and Nishina et al., *Molecular Therapy*, 2008, 16, 734-740), or a GalNAc cluster (e.g., WO2014/179620).
(171) In certain embodiments, conjugate groups may be selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl.
(172) In certain embodiments, conjugate groups may be selected from any of C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, and C5 alkyl, where the alkyl chain has one or more unsaturated bonds.
(173) 1. Conjugate Moieties
(174) Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates (e.g., GalNAc), vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes.
(175) In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fen-bufen, ketoprofen, (S)-(+)-pranoprofcn, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indo-methicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.
(176) 2. Conjugate Linkers
(177) Conjugate moieties are attached to oligonucleotides through conjugate linkers. In certain oligomeric compounds, the conjugate linker is a single chemical bond (i.e., the conjugate moiety is attached directly to an oligonucleotide through a single bond). In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbyl chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.
(178) In certain embodiments, a conjugate linker comprises pyrrolidine.
(179) In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain such embodiments, the conjugate linker comprises groups selected from alkyl, amino, oxo, amide and ether groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain embodiments, the conjugate linker includes at least one neutral linking group.
(180) In certain embodiments, conjugate linkers, including the conjugate linkers described above, are bifunctional linking moieties, e.g., those known in the art to be useful for attaching conjugate groups to compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to bind to a particular site on a compound and the other is selected to bind to a conjugate group. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles

for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.
(181) Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C.sub.1-C.sub.10 alkyl, substituted or unsubstituted C.sub.2-C.sub.10 alkenyl or substituted or unsubstituted C.sub.2-C.sub.10 alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.
(182) In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise exactly 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise the TCA motif. In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methyl cytosine, 4-N-benzoyl-5-methyl cytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.
(183) Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid. For example, an oligomeric compound may comprise (1) a modified oligonucleotide consisting of 8-30 nucleosides and (2) a conjugate group comprising 1-10 linker-nucleosides that are contiguous with the nucleosides of the modified oligonucleotide. The total number of contiguous linked nucleosides in such an oligomeric compound is more than 30. Alternatively, an oligomeric compound may comprise a modified oligonucleotide consisting of 8-30 nucleosides and no conjugate group. The total number of contiguous linked nucleosides in such an oligomeric compound is no more than 30. Unless otherwise indicated conjugate linkers comprise no more than 10 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 5 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 2 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 1 linker-nucleoside.
(184) In certain embodiments, it is desirable for a conjugate group to be cleaved from the oligonucleotide. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated or parent oligonucleotide. Thus, certain conjugate linkers may comprise one or more cleavable moieties. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.
(185) In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphate linkage between an oligonucleotide and a conjugate moiety or conjugate group.
(186) In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, the one or more linker-nucleosides are linked to one another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain embodiments, a cleavable moiety is 2′-deoxynucleoside that is attached to either the 3′ or 5′-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2′-deoxyadenosine.
(187) 3. Cell-Targeting Moieties
(188) In certain embodiments, a conjugate group comprises a cell-targeting moiety. In certain embodiments, a conjugate group has the general formula:
(189) ##STR00022##
(190) wherein n is from 1 to about 3, m is 0 when n is 1, m is 1 when n is 2 or greater, j is 1 or 0, and k is 1 or 0.
(191) In certain embodiments, n is 1, j is 1 and k is 0. In certain embodiments, n is 1, j is 0 and k is 1. In certain embodiments, n is 1, j is 1 and k is 1. In certain embodiments, n is 2, j is 1 and k is 0. In certain embodiments, n is 2, j is 0 and k is 1. In certain embodiments, n is 2, j is 1 and k is 1. In certain embodiments, n is 3, j is 1 and k is 0. In certain embodiments, n is 3, j is 0 and k is 1. In certain embodiments, n is 3, j is 1 and k is 1.
(192) In certain embodiments, conjugate groups comprise cell-targeting moieties that have at least one tethered ligand. In certain embodiments, cell-targeting moieties comprise two tethered ligands covalently attached to a branching group. In certain embodiments, cell-targeting moieties comprise three tethered ligands covalently attached to a branching group.
(193) In certain embodiments, each ligand of a cell-targeting moiety has an affinity for at least one type of receptor on a target cell. In certain embodiments, each ligand has an affinity for at least one type of receptor on the surface of a mammalian liver cell. In certain embodiments, each ligand has an affinity for the hepatic asialoglycoprotein receptor (ASGP-R). In certain embodiments, each ligand is a carbohydrate.
(194) In certain embodiments, the cell-targeting moiety targets neurons. In certain embodiments, the cell-targeting moiety targets a neurotransmitter receptor. In certain embodiments, the cell targeting moiety targets a neurotransmitter transporter. In certain embodiments, the cell targeting moiety targets a GABA transporter. See e.g., WO 2011/131693, WO 2014/064257.
(195) B. Certain Terminal Groups
(196) In certain embodiments, oligomeric compounds comprise one or more terminal groups. In certain such embodiments, oligomeric compounds comprise a stabilized 5′-phosphate. Stabilized 5′-phosphates include, but are not limited to 5′-phosphonates, including, but not limited to 5′-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic sugar moieties and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2′-linked nucleosides or sugar moieties. In certain such embodiments, the 2′-linked group is an abasic sugar moiety.
(197) III. Antisense Activity
(198) In certain embodiments, oligomeric compounds and oligomeric duplexes are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity; such oligomeric compounds and oligomeric duplexes are antisense compounds. In certain embodiments, antisense compounds have antisense activity when they reduce or inhibit the amount or activity of a target nucleic acid by 25% or more in the standard cell assay. In certain embodiments, antisense compounds selectively affect one or more target nucleic acid. Such antisense compounds comprise a nucleobase sequence that hybridizes to one or more target nucleic acid, resulting in one or more desired antisense activity and does not hybridize to one or more non-target

nucleic acid or does not hybridize to one or more non-target nucleic acid in such a way that results in significant undesired antisense activity.
(199) In certain antisense activities, hybridization of an antisense compound to a target nucleic acid results in recruitment of a protein that cleaves the target nucleic acid. For example, certain antisense compounds result in RNase H mediated cleavage of the target nucleic acid. RNase H is a cellular endonuclease that cleaves the RNA strand of an RNA:DNA duplex. The DNA in such an RNA:DNA duplex need not be unmodified DNA. In certain embodiments, described herein are antisense compounds that are sufficiently "DNA-like" to elicit RNase H activity. In certain embodiments, one or more non-DNA-like nucleoside in the gap of a gapmer is tolerated.
(200) In certain antisense activities, an antisense compound or a portion of an antisense compound is loaded into an RNA-induced silencing complex (RISC), ultimately resulting in cleavage of the target nucleic acid. For example, certain antisense compounds result in cleavage of the target nucleic acid by Argonaute. Antisense compounds that are loaded into RISC are RNAi compounds. RNAi compounds may be double-stranded (siRNA or dsRNAi) or single-stranded (ssRNA).
(201) In certain embodiments, hybridization of an antisense compound to a target nucleic acid does not result in recruitment of a protein that cleaves that target nucleic acid. In certain embodiments, hybridization of the antisense compound to the target nucleic acid results in alteration of splicing of the target nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in inhibition of a binding interaction between the target nucleic acid and a protein or other nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in alteration of translation of the target nucleic acid.
(202) Antisense activities may be observed directly or indirectly. In certain embodiments, observation or detection of an antisense activity involves observation or detection of a change in an amount of a target nucleic acid or protein encoded by such target nucleic acid, a change in the ratio of splice variants of a nucleic acid or protein and/or a phenotypic change in a cell or animal.
(203) IV. Certain Target Nucleic Acids
(204) In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain such embodiments, the target nucleic acid is selected from: a mature mRNA and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target RNA is a mature mRNA. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain embodiments, the target region is entirely within an intron. In certain embodiments, the target region spans an intron/exon junction. In certain embodiments, the target region is at least 50% within an intron. In certain embodiments, the target nucleic acid is the RNA transcriptional product of a retrogene. In certain embodiments, the target nucleic acid is a non-coding RNA. In certain embodiments, the target non-coding RNA is selected from: a long non-coding RNA, a short non-coding RNA, an intronic RNA molecule.
(205) A. Complementarity/Mismatches to the Target Nucleic Acid and Duplex Complementarity
(206) In certain embodiments, oligonucleotides are complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain embodiments, oligonucleotides are 99%, 95%, 90%, 85%, or 80% complementary to the target nucleic acid. In certain embodiments, oligonucleotides are at least 80% complementary to the target nucleic acid over the entire length of the oligonucleotide and comprise a region that is 100% or fully complementary to a target nucleic acid. In certain embodiments, the region of full complementarity is from 6 to 20, 10 to 18, or 18 to 20 nucleobases in length.
(207) It is possible to introduce mismatch bases without eliminating activity. For example, Gautschi et al (J. Natl. Cancer Inst. 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL in vitro and in vivo. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity in vivo. Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358, 1988) tested a series of tandem 14 nucleobase oligonucleotides, and 28 and 42 nucleobase oligonucleotides comprised of the sequence of two or three of the tandem oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase oligonucleotides.
(208) In certain embodiments, oligonucleotides comprise one or more mismatched nucleobases relative to the target nucleic acid. In certain embodiments, antisense activity against the target is reduced by such mismatch, but activity against a non-target is reduced by a greater amount. Thus, in certain embodiments selectivity of the oligonucleotide is improved. In certain embodiments, the mismatch is specifically positioned within an oligonucleotide having a gapmer motif. In certain embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, or 8 from the 5′-end of the gap region. In certain embodiments, the mismatch is at position 9, 8, 7, 6, 5, 4, 3, 2, 1 from the 3′-end of the gap region. In certain embodiments, the mismatch is at position 1, 2, 3, or 4 from the 5′-end of the wing region. In certain embodiments, the mismatch is at position 4, 3, 2, or 1 from the 3′-end of the wing region.
(209) B. APP
(210) In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid, wherein the target nucleic acid is APP. In certain embodiments, APP nucleic acid has the sequence set forth SEQ ID NO: 1 (the cDNA of Ensembl transcript ENST00000346798.7 from version 94: October 2018) or the complement of SEQ ID NO: 2 (GENB ANK Accession No. NC_000021.9 truncated from nucleotides 25878001 to 26174000). In certain embodiments, APP nucleic acid has the sequence set forth in any of known splice variants of APP, including but not limited to SEQ ID NO: 3 (the cDNA of Ensembl transcript ENST00000357903.7 from version 94: October 2018), SEQ ID NO: 4 (the cDNA of Ensembl transcript ENST00000348990.9 from version 94: October 2018), SEQ ID NO: 5 (the cDNA of Ensembl transcript ENST00000440126.7 from version 94: October 2018), SEQ ID NO: 6 (the cDNA of Ensembl transcript ENST00000354192.7 from version 94: October 2018), SEQ ID NO: 7 (the cDNA of Ensembl transcript ENST00000358918.7 from version 94: October 2018), and/or SEQ ID NO: 8 (GENBANK Accession No. NM_201414.2). In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or SEQ ID NO: 8 reduces the amount of APP RNA, and in certain embodiments reduces the amount of APP protein. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or SEQ ID NO: 8 results in reduced aggregation of β-amyloid. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide and a conjugate group.
(211) C. Certain Target Nucleic Acids in Certain Tissues
(212) In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid, wherein the target nucleic acid is expressed in a pharmacologically relevant tissue. In certain embodiments, the pharmacologically relevant tissues are the cells and tissues that comprise the central nervous system. Such tissues include the cortex, and the hippocampus. Such cells include cortical brain cells, hippocampal cells. In certain embodiments, such cells include cells within the limbic system, for example, cells within the hippocampus, the amygdala, and/or parahippocampal gyrus.
(213) V. Certain Pharmaceutical Compositions
(214) In certain embodiments, described herein are pharmaceutical compositions comprising one or more oligomeric compounds. In certain embodiments, the one or more oligomeric compounds each consists of a modified oligonucleotide. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises or consists of a sterile saline solution and one or more oligomeric compound. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and sterile water. In certain embodiments,

the sterile water is pharmaceutical grade water. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and phosphate-buffered saline (PBS). In certain embodiments, the sterile PBS is pharmaceutical grade PBS. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and artificial cerebrospinal fluid. In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

(215) In certain embodiments, a pharmaceutical composition comprises a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, a pharmaceutical composition consists of a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, a pharmaceutical composition consists essentially of a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

(216) In certain embodiments, pharmaceutical compositions comprise one or more oligomeric compound and one or more excipients. In certain embodiments, excipients are selected from water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose and polyvinylpyrrolidone.

(217) In certain embodiments, oligomeric compounds may be admixed with pharmaceutically acceptable active and/or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions depend on a number of criteria, including, but not limited to, route of administration, extent of disease or disorder, or dose to be administered.

(218) In certain embodiments, pharmaceutical compositions comprising an oligomeric compound encompass any pharmaceutically acceptable salts of the oligomeric compound, esters of the oligomeric compound, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising oligomeric compounds comprising one or more oligonucleotide, upon administration to an animal, including a human, are capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of oligomeric compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts. In certain embodiments, prodrugs comprise one or more conjugate group attached to an oligonucleotide, wherein the conjugate group is cleaved by endogenous nucleases within the body.

(219) Lipid moieties have been used in nucleic acid therapies in a variety of methods. In certain such methods, the nucleic acid, such as an oligomeric compound, is introduced into preformed liposomes or lipoplexes made of mixtures of cationic lipids and neutral lipids. In certain methods, DNA complexes with mono- or poly-cationic lipids are formed without the presence of a neutral lipid. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to a particular cell or tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to fat tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to muscle tissue.

(220) In certain embodiments, pharmaceutical compositions comprise a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical compositions including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

(221) In certain embodiments, pharmaceutical compositions comprise one or more tissue-specific delivery molecules designed to deliver the one or more pharmaceutical agents of the present invention to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

(222) In certain embodiments, pharmaceutical compositions comprise a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™ and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

(223) In certain embodiments, pharmaceutical compositions are prepared for oral administration. In certain embodiments, pharmaceutical compositions are prepared for buccal administration. In certain embodiments, a pharmaceutical composition is prepared for administration by injection (e.g., intravenous, subcutaneous, intramuscular, intrathecal (IT), intracerebroventricular (ICV), etc.). In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (e.g., ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, e.g., in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes.

(224) VI. Certain Compositions

(225) 1. Compound No, 1353686

(226) In certain embodiments, Compound No. 1353686 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5′ to 3′) GCATTCTCTTATATTCCTTA (SEQ ID NO: 273), wherein each of nucleosides 1-5 and 16-20 (from 5′ to 3′) are 2′-MOE nucleosides and each of nucleosides 6-15 are 2′-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

(227) In certain embodiments, Compound No. 1353686 is represented by the following chemical notation (5′ to 3′): G.sub.es.sup.mC.sub.eoA.sub.eoT.sub.eoT.sub.es.sup.mC.sub.dsT.sub.ds.sup.mC.sub.dsT.sub.dsT.sub.dsA.sub.dsT.sub.dsA.sub.dsT.sub.dsT.sub.ds.sup.mC.su (SEQ ID NO: 273), wherein, A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage.

(228) In certain embodiments, Compound No. 1353686 is represented by the following chemical structure:

(229) ##STR00023##

(230) In certain embodiments, the sodium salt of Compound No. 1353686 is represented by the following chemical structure:

(231) ##STR00024##

2. Compound No, 1353884

(232) In certain embodiments, Compound No. 1353884 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5′ to 3′) GTTTACCTTTAACATTCCTC (SEQ ID NO: 452), wherein each of nucleosides 1-5 and 16-20 (from 5′ to 3′) are 2′-MOE nucleosides and each of nucleosides 6-15 are 2′-β-D-deoxynucleosides. wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is

a 5-methyl cytosine.
(233) In certain embodiments, Compound No. 1353884 is represented by the following chemical notation (5′ to 3′):
G.sub.esT.sub.eoT.sub.eoT.sub.eoA.sub.es.sup.mC.sub.ds.sup.mC.sub.dsT.sub.dsT.sub.dsT.sub.dsA.sub.dsA.sub.ds.sup.mC.sub.dsA.sub.dsT.sub.dsT.sub.eo.su
(SEQ ID NO: 452), wherein, A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage.
(234) In certain embodiments, Compound No. 1353884 is represented by the following chemical structure:
(235) ##STR00025##
(236) In certain embodiments, the sodium salt of Compound No. 1353884 is represented by the following chemical structure:
(237) ##STR00026##
3. Compound No, 1353931
(238) In certain embodiments, Compound No. 1353931 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5′ to 3′) GCCATATTGTCATTTTACAC (SEQ ID NO: 462), wherein each of nucleosides 1-5 and 16-20 (from 5′ to 3′) are 2′-MOE nucleosides and each of nucleosides 6-15 are 2′-(t-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.
(239) In certain embodiments, Compound No. 1353931 is represented by the following chemical notation (5′ to 3′):
G.sub.es.sup.mC.sub.eo.sup.mC.sub.eoA.sub.dsT.sub.dsA.sub.dsT.sub.dsT.sub.dsG.sub.dsT.sub.ds.sup.mC.sub.dsA.sub.dsT.sub.dsT.sub.dsT.sub.dsT.sub.eoA
(SEQ ID NO: 462), wherein, A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage.
(240) In certain embodiments, Compound No. 1353931 is represented by the following chemical structure:
(241) ##STR00027##
(242) In certain embodiments, the sodium salt of Compound No. 1353931 is represented by the following chemical structure:
(243) ##STR00028##
4. Compound No, 1354035
(244) In certain embodiments, Compound No. 1354035 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5′ to 3′) GTATCCTCTTAATTCCTATA (SEQ ID NO: 482), wherein each of nucleosides 1-5 and 16-20 (from 5′ to 3′) are 2′-MOE nucleosides and each of nucleosides 6-15 are 2′-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.
(245) In certain embodiments, Compound No. 1354035 is represented by the following chemical notation (5′ to 3′):
G.sub.esT.sub.eoA.sub.eoT.sub.eo.sup.mC.sub.es.sup.mC.sub.dsT.sub.ds.sup.mC.sub.dsT.sub.dsT.sub.dsA.sub.dsA.sub.dsT.sub.dsT.sub.ds.sup.mC.sub.ds.sup
(SEQ ID NO: 482), wherein, A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage.
(246) In certain embodiments, Compound No. 1354035 is represented by the following chemical structure:
(247) ##STR00029##
(248) In certain embodiments, the sodium salt of Compound No. 1354035 is represented by the following chemical structure:
(249) ##STR00030##
5. Compound No, 1398227
(250) In certain embodiments, Compound No. 1398227 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5′ to 3′) CTCCAATTTTAACTTGCACC (SEQ ID NO: 1064), wherein each of nucleosides 1-5 and 16-20 (from 5′ to 3′) are 2′-MOE nucleosides and each of nucleosides 6-15 are 2′-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.
(251) In certain embodiments, Compound No. 1398227 is represented by the following chemical notation (5′ to 3′):
.sup.mC.sub.esT.sub.eo.sup.mC.sub.eo.sup.mC.sub.eoA.sub.esA.sub.dsT.sub.dsT.sub.dsT.sub.dsT.sub.dsA.sub.dsA.sub.ds.sup.mC.sub.dsT.sub.dsT.sub.dsG.su
(SEQ ID NO: 1064), wherein, A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage.
(252) In certain embodiments, Compound No. 1398227 is represented by the following chemical structure:
(253) ##STR00031##
(254) In certain embodiments, the sodium salt of Compound No. 1398227 is represented by the following chemical structure:
(255) ##STR00032##
6. Compound No, 1398456
(256) In certain embodiments, Compound No. 1398456 is characterized as a 5-10-5 MOE gapmer having a sequence of (from 5′ to 3′) GTTCACAGTTTACCCCAAGC (SEQ ID NO: 2225), wherein each of nucleosides 1-5 and 16-20 (from 5′ to 3′) are 2′-MOE nucleosides and each of nucleosides 6-15 are 2′-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages and the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.
(257) In certain embodiments, Compound No. 1398456 is represented by the following chemical notation (5′ to 3′):
G.sub.esT.sub.eoT.sub.eo.sup.mC.sub.eoA.sub.es.sup.mC.sub.dsA.sub.dsG.sub.dsT.sub.dsT.sub.dsT.sub.dsA.sub.dsA.sub.ds.sup.mC.sub.ds.sup.mC.sub.ds.sup.mC.sub.ds.sup.mC.sub.ds.sup.mC.sub.sub
(SEQ ID NO: 2225), wherein, A=an adenine nucleobase, .sup.mC=a 5-methyl cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′ MOE sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage.
(258) In certain embodiments, Compound No. 1398456 is represented by the following chemical structure:
(259) ##STR00033##
(260) In certain embodiments, the sodium salt of Compound No. 1398456 is represented by the following chemical structure:
(261) ##STR00034##
(262) Under certain conditions, certain compounds disclosed herein act as acids. Although such compounds may be drawn or described in protonated

(free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of such compounds exist in equilibrium among such forms. For example, a phosphate linkage of an oligonucleotide in aqueous solution exists in equilibrium among free acid, anion and salt forms. Unless otherwise indicated, compounds described herein are intended to include all such forms. Moreover, certain oligonucleotides have several such linkages, each of which is in equilibrium. Thus, oligonucleotides in solution exist in an ensemble of forms at multiple positions all at equilibrium. The term “oligonucleotide” is intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise intended to include corresponding forms. Herein, a structure depicting the free acid of a compound followed by the term “or a salt thereof” expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation. In certain instances, one or more specific cation is identified.

(263) In certain embodiments, modified oligonucleotides or oligomeric compounds are in aqueous solution with sodium. In certain embodiments, modified oligonucleotides or oligomeric compounds are in aqueous solution with potassium. In certain embodiments, modified oligonucleotides or oligomeric compounds are in PBS. In certain embodiments, modified oligonucleotides or oligomeric compounds are in water. In certain such embodiments, the pH of the solution is adjusted with NaOH and/or HCl to achieve a desired pH.

(264) Herein, certain specific doses are described. A dose may be in the form of a dosage unit. For clarity, a dose (or dosage unit) of a modified oligonucleotide or an oligomeric compound in milligrams indicates the mass of the free acid form of the modified oligonucleotide or oligomeric compound. As described above, in aqueous solution, the free acid is in equilibrium with anionic and salt forms. However, for the purpose of calculating dose, it is assumed that the modified oligonucleotide or oligomeric compound exists as a solvent-free, sodium-acetate free, anhydrous, free acid. For example, where a modified oligonucleotide or an oligomeric compound is in solution comprising sodium (e.g., saline), the modified oligonucleotide or oligomeric compound may be partially or fully de-protonated and in association with Na+ ions. However, the mass of the protons are nevertheless counted toward the weight of the dose, and the mass of the Na+ ions are not counted toward the weight of the dose. Thus, for example, a dose, or dosage unit, of 10 mg of a number of fully protonated molecules that weighs 10 mg. This would be equivalent to 10.59 mg of solvent-free, sodium acetate-free, anhydrous sodiated Compound No. 1353686, 1353884, 1353931, 1354035, 1398227, or 1398456. When an oligomeric compound comprises a conjugate group, the mass of the conjugate group is included in calculating the dose of such oligomeric compound. If the conjugate group also has an acid, the conjugate group is likewise assumed to be fully protonated for the purpose of calculating dose.

(265) VII. Certain Comparator Compositions

(266) In certain embodiments, Compound No. 1369631, disclosed as APP2585 in WO/2005/042777 (incorporated herein by reference) is a comparator compound. Compound No. 1369631 is a 5-8-5 ENA-modified oligonucleotide, having a nucleobase sequence (from 5′ to 3′) TCATGTGCATGTTCAGTC (incorporated herein as SEQ ID NO: 3070). Compound No. 1369631 has a sugar motif (from 5′ to 3′) aaaaaddddddddaaaaa; wherein each “a” represents an ENA sugar moiety, and each “d” represents a 2′-β-D-deoxyribosyl sugar moiety. Compound No. 1369631 has an internucleoside linkage motif (from 5′ to 3′): sssssssssssssssss; wherein each “s” represents a phosphorothioate internucleoside linkage. Each cytosine residue in Compound No. 1369631 is a 5-methyl cytosine.

(267) In certain embodiments, Compound No. 1369632, disclosed as “APP2-666” in WO/2005/042777 is a comparator compound. Compound No. 1369632 is a 6-6-6 ENA-modified oligonucleotide, having a nucleobase sequence (from 5′ to 3′) TCATGTGCATGTTCAGTC (SEQ ID NO: 3070). Compound No. 1369632 has a sugar motif (from 5′ to 3′) aaaaaaddddddaaaaaa; wherein each “a” represents an ENA sugar moiety, and each “d” represents a 2′-β-D-deoxyribosyl sugar moiety. Compound No. 1369632 has an internucleoside linkage motif (from 5′ to 3′): sssssssssssssssss; wherein each “s” represents a phosphorothioate internucleoside linkage. Each cytosine residue in Compound No. 1369632 is a 5-methyl cytosine.

(268) In certain embodiments, Compound No. 156352, described in US 2003/0232435 (incorporated herein by reference) is a comparator compound. Compound No. 156352 is a 5-10-5 MOE gapmer, having the nucleobase sequence (from 5′ to 3′) TGTCACTTTCTTCAGCCAGT (incorporated herein as SEQ ID NO: 3071). Compound No. 156352 has a sugar motif (from 5′ to 3′) eeeeeddddddddddeeeee; wherein each “d” represents a 2′-β-D-deoxyribosyl sugar moiety, and each “e” represents a 2′-MOE sugar moiety. Compound No. 156352 has an internucleoside linkage motif (from 5′ to 3′): sssssssssssssssss; wherein each “s” represents a phosphorothioate internucleoside linkage. Each cytosine residue in Compound No. 156352 is a 5-methyl cytosine.

(269) In certain embodiments, compounds described herein are superior relative to compounds described in WO/2005/042777 and US 2003/0232435 because they demonstrate one or more improved properties.

(270) For example, as provided in Examples 7, 17, and 28, Compound Nos. 1353686, 1353884, 1353931, and 1354035 demonstrate 3 hour functional observational battery (FOB) scores in mice of 0, 0, 1.33, and 0, respectively, while Comparator Compounds 1369631, 1369632, and 156352 demonstrated FOB scores of 6, 2.5, and 6, respectively. Compound Nos. 1353686, 1353884, 1353931, and 1354035 are demonstrably more tolerable than each of Comparator Compound Nos. 1369631, 1369632, and 156352 in this assay.

(271) For example, as provided in Example 27, Compound No. 1398227 demonstrated an 81% reduction and Compound No. 1398456 demonstrated an 84% reduction of APP RNA, while Comparator Compound No. 1369632 demonstrated a 15% reduction of APP RNA in vitro in the standard cell assay in SH-SY5Y cells. Compound Nos. 1398227 and 1398456 are demonstrably more active than Comparator Compound No. 1369632 in this assay.

(272) VIII. Certain Hotspot Regions

(273) a. Nucleobases 12566-12609 of SEP ID NO: 2

(274) In certain embodiments, nucleobases 12566-12609 of SEQ ID NO: 2 comprise a hotspot region (hotspot ID No. 5). In certain embodiments, modified oligonucleotides are complementary within nucleobases 12566-12609 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, modified oligonucleotides are 5-10-5 or 6-10-4 gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeddddddddddeeeee, wherein each “e” is nucleoside comprising a 2′-MOE sugar moiety and each “d” is a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeddddddddddeeeee, wherein each “e” is nucleoside comprising a 2′-MOE sugar moiety, and each “d” is a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in order from 5′ to 3′: sooossssssssssooss or sooooossssssssssoss.

(275) The nucleobase sequences of SEQ ID Nos: 273, 744, 824, 898 and 1025 are complementary within nucleobases 12566-12609 of SEQ ID NO: 2.

(276) Compounds 1353686, 1397821, 1397908, 1398005, 1399362, and 1539870 are complementary within nucleobases 12566-12609 of SEQ ID NO: 2.

(277) In certain embodiments, modified oligonucleotides complementary within nucleobases 12566-12609 of SEQ ID NO: 2. achieve at least 49% reduction of APP RNA in vitro in the standard cell assay in SH-SY5Y cells. In certain embodiments, modified oligonucleotides complementary within nucleobases 12566-12609 of SEQ ID NO: 2 achieve an average of 69% reduction of APP RNA in vitro in the standard cell assay in SH-SY5Y cells.

(278) b. Nucleobases 158596-158982 of SEP ID NO: 2

(279) In certain embodiments, nucleobases 158596-158982 of SEQ ID NO: 2 comprise a hotspot region (hotspot ID no. 9). In certain embodiments, modified oligonucleotides are complementary within nucleobases 158596-158982 of SEQ ID NO: 2. In certain embodiments, modified

oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, modified oligonucleotides are 5-10-5 or 6-10-4 gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeddddddddddeeeee, wherein each “e” is nucleoside comprising a 2′-MOE sugar moiety and each “d” is a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeeddddddddddeeee, wherein each “e” is nucleoside comprising a 2′-MOE sugar moiety, and each “d” is a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in order from 5′ to 3′: sooossssssssssooss or sooooossssssssssoss.

(280) The nucleobase sequences of SEQ ID Nos: 178, 547, 577, 693, 769, 846, 2225, 2480, and 3047-30505 are complementary within nucleobases 158596-158982 of SEQ ID NO: 2.

(281) Compounds 1354057, 1397573, 1398456, 1398549, 1398604, 1398618, 1398913, 1399136, 1539237-1539240, and 1539867 are complementary within nucleobases 158596-158982 of SEQ ID NO: 2.

(282) In certain embodiments, modified oligonucleotides complementary within nucleobases 158596-158982 of SEQ ID NO: 2. achieve at least 60% reduction of APP RNA in vitro in the standard cell assay in SH-SY5Y cells. In certain embodiments, modified oligonucleotides complementary within nucleobases 12566-12609 of SEQ ID NO: 2 achieve an average of 73% reduction of APP RNA in vitro in the standard cell assay in SH-SY5Y cells.

(283) c. Nucleobases 292896-292922 of SEP ID NO: 2

(284) In certain embodiments, nucleobases 292896-292922 of SEQ ID NO: 2 comprise a hotspot region (hotspot ID No. 32). In certain embodiments, modified oligonucleotides are complementary within nucleobases 292896-292922 of SEQ ID NO: 2. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, modified oligonucleotides are 5-10-5 gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeddddddddddeeeee, wherein each “e” is nucleoside comprising a 2′-MOE sugar moiety and each “d” is a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in order from 5′ to 3′: sooossssssssssooss.

(285) The nucleobase sequences of SEQ ID Nos: 35, 411, and 482 are complementary within nucleobases 292896-292922 of SEQ ID NO: 2.

(286) Compounds 1354044, 1354035, and 1353677 are complementary within nucleobases 292896-292922 of SEQ ID NO: 2.

(287) In certain embodiments, modified oligonucleotides complementary within nucleobases 292896-292922 of SEQ ID NO: 2. achieve at least 65% reduction of APP RNA in vitro in the standard cell assay in SH-SY5Y cells. In certain embodiments, modified oligonucleotides complementary within nucleobases 292896-292922 of SEQ ID NO: 2 achieve an average of 71% reduction of APP RNA in vitro in the standard cell assay in SH-SY5Y cells.

(288) d. Additional Hotspot Regions

(289) In certain embodiments, the ranges described in the Table below comprise hotspot regions, including those described above. Each hotspot region begins with the nucleobase of SEQ ID NO: 2 identified in the “Start Site SEQ ID NO: 2” column and ends with the nucleobase of SEQ ID NO: 2 identified in the “Stop Site SEQ ID NO: 2” column. In certain embodiments, oligomeric compounds comprise modified oligonucleotides that are complementary within any of the hotspot regions 1-32, as defined in the table below. In certain embodiments, modified oligonucleotides are 16 nucleobases in length. In certain embodiments, modified oligonucleotides are 20 nucleobases in length.

(290) In certain embodiments, oligomeric compounds comprise modified oligonucleotides that are gapmers. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeddddddddddeeeee, wherein each “e” is nucleoside comprising a 2′-MOE sugar moiety and each “d” is a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, modified oligonucleotides have the sugar motif eeeeeddddddddddeeee, wherein each “e” is nucleoside comprising a 2′-MOE sugar moiety, and each “d” is a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, modified oligonucleotides have the sugar motif kkkddddddddddkkk, wherein each “k” is a nucleoside comprising a cEt sugar moiety, and each “d” is a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, modified oligonucleotides have the sugar motif kkkdyddddddddkkk, wherein each “y” is nucleoside comprising a 2′-OMe sugar moiety, each “k” is a nucleoside comprising a cEt sugar moiety, and each “d” is a nucleoside comprising a 2′-β-D-deoxyribosyl sugar moiety. In certain embodiments, modified oligonucleotides are 5-10-5 or 6-10-4 MOE gapmers. In certain embodiments, modified oligonucleotides are 3-10-3 cEt gapmers. In certain embodiments, the gapmers comprise a 2′-substituted nucleoside in the gap. In certain embodiments, the 2′-substituted nucleoside comprises a 2′-OMe sugar moiety. In certain embodiments, the 2′-substituted nucleoside is at position 2 of the gap (5′ to 3′).

(291) In certain embodiments, the internucleoside linkages of the modified oligonucleotides are phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages. In certain embodiments, the phosphodiester (“o”) and phosphorothioate (“s”) internucleoside linkages are arranged in order from 5′ to 3′: In certain embodiments, modified nucleotides have an internucleoside linkage motif of soossssssssssos, sooooossssssssssoss, soooossssssssssooss, soooossssssssssoss, soooossssssssssooos, or ssoossssssssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

(292) In certain embodiments, modified oligonucleotides complementary to nucleobases within an in vitro hotspot region achieve at least “Min.% Red. in vitro” in SH-SY5Y and/or A431 cells (minimum % reduction, relative to untreated control cells) of APP RNA in vitro in the standard cell assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve an average of “Avg.% Red. in vitro” in SH-SY5Y and/or A431 cells (average % reduction, relative to untreated control cells) of APP RNA in vitro in the standard cell assay, as indicated in the table below. In certain embodiments, modified oligonucleotides complementary to nucleobases within the hotspot region achieve a maximum of “Max. % Red. in vitro” in SH-SY5Y and/or A431 cells (maximum % reduction, relative to untreated control cells) of APP RNA in vitro in the standard cell assay, as indicated in the table below.

(293) TABLE-US-00001 TABLE A APP in vitro Hotspot Regions SEQ ID SEQ ID SH-SY5Y Cells A431 Cells NO: 2 NO: 2 Min. % Max. % Avg. % Min. % Max. % Avg. % Start Stop Red. in Red. in Red. in Red. in Red. in Red. in Compound No. in SEQ ID NO in ID Site Site vitro vitro vitro vitro vitro vitro range range 1 6193 6245 57 83 77 n.d. n.d. n.d. 1353833, 1397770, 140, 1240, 1398054, 1398752, 1279, 1402, 1399103 1437 2 9622 9656 72 87 80 n.d. n.d. n.d. 1353668, 1353736, 116, 202, 626 1398653 3 10203 10249 57 72 64 n.d. n.d. n.d. 1397525, 1397713, 830, 912, 962, 1398045, 1398267, 1049, 1164, 1398674, 1398782 1236 4 11246 11287 74 84 78 n.d. n.d. n.d. 1353733, 1397711, 201, 1741, 1399201 1870 5 12566 12609 49 81 69 n.d. n.d. n.d. 1353686, 1397821, 273, 744, 824, 1397908, 1398005, 898, 1025 1399362, 1539870 6 22914 22964 60 95 75 n.d. n.d. n.d. 1353832, 1353861, 296, 384, 1397580, 1398429, 1568, 1617, 1398671, 1398737, 1701, 1734, 1399267 1841 7 154394 154420 74 84 78 n.d. n.d. n.d. 1398034, 1398895, 1553, 1593, 1399087, 1399234, 1709, 1805, 1399503 1873 8 154736 154760 52 81 70 n.d. n.d. n.d. 1354072, 1397866, 340, 519, 590, 1397905, 1398238, 711, 795, 819 1399015, 1399275 9 158596 158982 60 91 73 n.d. n.d. n.d. 1354057, 1397573, 178, 547, 577, 1398456, 1398549, 693, 769, 846, 1398604, 1398618, 2225, 2480, 1398913, 1399136, 3047-3050 1539237-1539240, 1539867 10 159558 159581 64 89 77 n.d. n.d. n.d. 1353731, 1397655, 200, 1688, 1397959, 1398047, 1740, 1820, 1398505 1906 11 220028 220077 n.d. n.d. n.d. 47 95 78 1463194, 1463199, 2576, 2493, 1463229, 1463297, 2660, 2708, 1463307, 1463320, 2790, 2806, 1463404, 1463479, 2854, 2900, 1463511, 1463521, 2903, 2993, 1463543 3013 12 220237 220281 n.d. n.d. n.d. 74 96 89 1463386, 1463394, 2590, 2690, 1463203, 1463553, 2691, 2760, 1463464, 1463286, 2808, 2939, 1463389 3002 13 220368 220426 n.d. n.d. n.d. 61 81 79 1463445, 1463600, 2580, 2652, 1463482, 1463516, 2728, 2772, 1463226, 1463185, 2866, 2874, 1463204, 1463555 2931, 3012 14 220710 220766 n.d. n.d. n.d. 77 95 87 1463195, 1463223, 2619, 2671, 1463276,

1463472, 2783, 2812, 1463483, 1463497 2875, 2929 15 220892 220919 n.d. n.d. n.d. 84 96 92 1463172, 1463192, 2638, 2649, 1463294, 1463361, 2676, 2753, 1463374, 1463388, 2757, 2804, 1463498, 1463578 2932, 2983 16 221002 221025 n.d. n.d. n.d. 86 92 88 1463181, 1463225, 2575, 2848, 1463248, 1463446 2890, 2965 17 221138 221177 n.d. n.d. n.d. 78 89 85 1463188, 1463190, 2583, 2654, 1463252, 1463277, 2748, 2823, 1463349 2882 18 221315 221364 79 83 81 88 95 91 1398485, 1398644, 1557, 1613, 1399147, 1399147, 1696, 2592, 1463176, 1463289, 2699, 2713, 1463324, 1463380, 2775, 2844, 1463425, 1463454, 2879, 2977, 1463455, 1463542 2986 19 222414 222478 59 59 59 73 94 86 1354064, 1463179, 338, 2574, 1463261, 1463268, 2642, 2666, 1463304, 1463376, 2689, 2740, 1463379, 1463381, 2754, 2847, 1463433, 1463510, 2859, 2899, 1463522, 1463595, 2950, 2987, 1463612 3014 20 222548 222590 n.d. n.d. n.d. 72 93 86 1463589, 1463290, 2641, 2675, 1463599, 1463485, 2799, 2856, 1463499, 1463305 2933, 2974 21 222663 222697 n.d. n.d. n.d. 63 90 76 1463484, 1463459, 2610, 2780, 1463584, 1463182, 2851, 2943, 1463409, 1463527 2956 22 222764 222791 n.d. n.d. n.d. 91 87 85 1463424, 1463481, 2766, 2855, 1463440, 1463384, 2925, 2988 23 225366 225400 n.d. n.d. n.d. 69 91 78 1463178, 1463264, 2645, 2715, 1463336, 1463417, 2727, 2787, 1463422, 1463525, 2842, 2843, 1463547, 1463552, 2938, 2940, 1463560, 1463608 2967, 2978 24 226497 226532 68 68 68 86 92 89 1353844, 1463546, 299, 2632, 1463577 3020 25 229282 229306 n.d. n.d. n.d. 70 91 83 1463288, 1463344, 2591, 2705, 1463494, 1463512, 2747, 2865, 1463550, 1463562 2941, 3010 26 231282 231310 n.d. n.d. n.d. 71 91 82 1463228, 1463244, 2621, 2629, 1463308, 1463353, 2679, 2687, 1463356, 1463489, 2735, 2788, 1463533, 1463535, 2864, 2912, 1463537 2966 27 234328 234370 n.d. n.d. n.d. 78 91 86 1463292, 1463313, 2701, 2742, 1463339, 1463460 2828, 2908 28 234802 234827 n.d. n.d. n.d. 78 90 85 1363337, 1463426, 2611, 2717, 1463575 2979 29 34556 34575 91 91 91 n.d. n.d. n.d. 1398227 1064 30 101718 101737 84 84 84 n.d. n.d. n.d. 1353931 462 31 158795 158814 82 82 82 n.d. n.d. n.d. 1353884 452 32 292896 292922 64 75 71 n.d. n.d. n.d. 1354044, 1354035, 35, 411, 482 1353677

IX. Certain RNAi Compositions

(294) In certain embodiments, oligomeric duplexes comprise a first oligomeric compound comprising a first modified oligonucleotide and a second oligomeric compound comprising a second modified oligonucleotide. In certain embodiments, the first modified oligonucleotide is an antisense RNAi oligonucleotide and the second modified oligonucleotide is a sense RNAi oligonucleotide. In certain embodiments, oligomeric duplexes comprise an antisense RNAi oligonucleotide complementary to a human APP nucleic acid and a sense oligonucleotide complementary to the antisense RNAi oligonucleotides.

(295) In certain embodiments, Compound No. 1581405 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551732 and a second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1579196. In certain embodiments, Compound No. 1581406 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551735 and second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1551736. In certain embodiments, Compound No. 1581407 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551737 and a second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1551741. In certain embodiments, Compound No. 1581408 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551739 and a second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1551740. In certain embodiments, Compound No. 1581409 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551742 and a second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1551743. In certain embodiments, Compound No. 1581410 is an oligomeric duplex comprising a first oligomeric compound comprising an antisense RNAi oligonucleotide Compound No. 1551744 and a second oligomeric compound comprising a sense RNAi oligonucleotide Compound No. 1551745.

(296) Certain oligomeric duplexes comprise a first oligomeric compound comprising a first modified oligonucleotide and a second oligomeric compound comprising a second modified oligonucleotide according to chemical notations as provided in Table B below. As set forth in Table B: A=an adenine nucleobase, C=a cytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, U=a uracil nucleobase, e=a 2′ MOE sugar moiety, y=a 2′-O-methylribosyl sugar moiety, f=a 2′-fluororibosyl sugar moiety, s=a phosphorothioate internucleoside linkage, o=a phosphodiester internucleoside linkage, C16muP=a hexadecane sulfonyl phosphoramidate internucleoside linkage, and VP=a 5′-vinylphosphonate.

(297) TABLE-US-00002 Antisense Sense RNAi RNAi Oligo- Chemical Notation oligo- Chemical Notation of Com- nucleotide of Antisense RNAi SEQ nucleotide Sense RNAi SEQ pound Compound Oligonucleotide ID Compound Oligonucleotide ID Number Number (5′ to 3′) NO Number (5′ to 3′) NO 1581405 1551732 [VP]T.sub.esG.sub.fsA.sub.yoA.sub.yoC.sub.yoU.sub.yo 3058 1579196 A.sub.ysA.sub.ysA.sub.yoA.sub.yoU.sub.yoC.sub.y[C16muP] 3064 U.sub.yoG.sub.yoU.sub.yoA.sub.yoG.sub.yoG.sub.yoU.sub.yoU.sub.fo C.sub.foA.sub.yoA.sub.foC.sub.foC.sub.foU.sub.yoA.sub.yo G.sub.yoG.sub.foA.sub.yoU.sub.yoU.sub.yoU.sub.yoU.sub.ys C.sub.yoA.sub.yoA.sub.yoG.sub.yoU.sub.yoU.sub.ysC.sub.ysA.sub.y C.sub.ysG.sub.y 1581406 1551735 [VP]T.sub.esA.sub.fsA.sub.yoU.sub.yoU.sub.yoU.sub.yo 3059 1551736 C.sub.ysU.sub.ysG.sub.yoU.sub.yoA.sub.yoU.sub.y[C16muP] 3065 A.sub.yoU.sub.yoU.sub.yoU.sub.yoA.sub.yoU.sub.yoG.sub.yoU.sub.fo U.sub.foA.sub.yoC.sub.foA.sub.foU.sub.foA.sub.yoA.sub.yo A.sub.yoA.sub.foU.sub.yoA.sub.yoC.sub.yoA.sub.yoG.sub.ys A.sub.yoU.sub.yoA.sub.yoA.sub.yoA.sub.yoU.sub.ysU.sub.ys U.sub.ysG.sub.y A.sub.y 1581407 1551737 [VP]T.sub.esA.sub.fsA.sub.yoG.sub.yoA.sub.yoA.sub.yo 3060 1551741 G.sub.ysA.sub.ysU.sub.yoA.sub.yoC.sub.yoA.sub.y[C16muP] 3066 A.sub.yoC.sub.yoA.sub.yoA.sub.yoA.sub.yoC.sub.yoG.sub.yoU.sub.fo C.sub.foA.sub.yoC.sub.foG.sub.foU.sub.foU.sub.yoU.sub.yo G.sub.yoU.sub.foG.sub.yoU.sub.yoA.sub.yoU.sub.yoC.sub.ys G.sub.yoU.sub.yoU.sub.yoU.sub.yoC.sub.yoU.sub.ysU.sub.ysA.sub.y C.sub.ysU.sub.y 1581408 1551739 [VP]T.sub.esG.sub.fsA.sub.yoG.sub.yoA.sub.yoC.sub.yo 3061 1551740 U.sub.ysG.sub.ysA.sub.yoG.sub.yoC.sub.yoG.sub.y[C16muP] 3067 U.sub.yoG.sub.yoA.sub.yoU.sub.yoU.sub.yoC.sub.yoA.sub.yoU.sub.fo C.sub.foA.sub.yoU.sub.foG.sub.foA.sub.foA.sub.yoU.sub.yo G.sub.yoC.sub.foG.sub.yoC.sub.yoU.sub.yoC.sub.yoA.sub.ys C.sub.yoA.sub.yoG.sub.yoU.sub.yoC.sub.yoU.sub.ysC.sub.ysA.sub.y U.sub.ysA.sub.y 1581409 1551742 [VP]T.sub.esU.sub.fsC.sub.yoU.sub.yoG.sub.yoA.sub.yo 3062 1551743 A.sub.ysC.sub.ysA.sub.yoU.sub.yoU.sub.yoU.sub.y[C16muP] 3068 A.sub.yoA.sub.yoU.sub.yoA.sub.yoC.sub.yoU.sub.yoU.sub.yoA.sub.fo U.sub.foU.sub.yoA.sub.foA.sub.foG.sub.foU.sub.yoA.sub.yo A.sub.yoA.sub.foA.sub.yoA.sub.yoU.sub.yoG.sub.yoU.sub.ys U.sub.yoU.sub.yoU.sub.yoC.sub.yoA.sub.yoG.sub.ysA.sub.ysA.sub.y U.sub.ysU.sub.y 1581410 1551744 [VP]T.sub.esG.sub.fsG.sub.yoG.sub.yoC.sub.yoA.sub.yo 3063 1551745 U.sub.ysG.sub.ysA.sub.yoG.sub.yoU.sub.yoU.sub.y[C16muP] 3069 U.sub.yoC.sub.yoA.sub.yoC.sub.yoU.sub.yoU.sub.yoA.sub.yoC.sub.fo U.sub.foG.sub.yoU.sub.foA.sub.foA.sub.foG.sub.yo A.sub.yoA.sub.foA.sub.yoC.sub.yoU.sub.yoC.sub.yoA.sub.ys U.sub.yoG.sub.yoA.sub.yoU.sub.yoG.sub.yoC.sub.yoC.sub.ysC.sub.ys C.sub.ysC.sub.y A.sub.y

Nonlimiting Disclosure and Incorporation by Reference

(298) Each of the literature and patent publications listed herein is incorporated by reference in its entirety. While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references, GenBank accession numbers, ENSEMBL identifiers, and the like recited in the present application is incorporated herein by reference in its entirety.

(299) Although the sequence listing accompanying this filing identifies each sequence as either “RNA” or “DNA” as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as “RNA” or “DNA” to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2′-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2′-OH in place of one 2′-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) in place of an uracil of RNA). Accordingly, nucleic acid sequences provided herein,

including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligomeric compound having the nucleobase sequence “ATCGATCG” encompasses any oligomeric compounds having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence “AUCGAUCG” and those having some DNA bases and some RNA bases such as “AUCGATCG” and oligomeric compounds having other modified nucleobases, such as “AT.sup.mCGAUCG,” wherein .sup.mC indicates a cytosine base comprising a methyl group at the 5-position.

(300) Certain compounds described herein (e.g., modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), as a or (3 such as for sugar anomers, or as (D) or (L), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that are drawn or described with undefined stereochemistry include all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, tautomeric forms of the compounds herein are also included unless otherwise indicated. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

(301) The compounds described herein include variations in which one or more atoms are replaced with a non-radioactive isotope or radioactive isotope of the indicated element. For example, compounds herein that comprise hydrogen atoms encompass all possible deuterium substitutions for each of the .sup.1H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: .sup.2H or .sup.3H in place of .sup.1H, .sup.13C or .sup.14C in place of .sup.12C, .sup.15N in place of .sup.14N, .sup.17O or .sup.18O in place of .sup.16O, and .sup.33S, .sup.34S, .sup.35S, or .sup.36S in place of .sup.32S. In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the oligomeric compound that are beneficial for use as a therapeutic or research tool. In certain embodiments, radioactive isotopic substitutions may make the compound suitable for research or diagnostic purposes such as imaging.

EXAMPLES

(302) The following examples illustrate certain embodiments of the present disclosure and are not limiting. Moreover, where specific embodiments are provided, the inventors have contemplated generic application of those specific embodiments. For example, disclosure of an oligonucleotide having a particular motif provides reasonable support for additional oligonucleotides having the same or similar motif. And, for example, where a particular high-affinity modification appears at a particular position, other high-affinity modifications at the same position are considered suitable, unless otherwise indicated.

Example 1: Effect of Mixed Backbone 5-10-5 MOE Gapmers on Human APP In Vitro, Single Dose

(303) Modified oligonucleotides complementary to human APP nucleic acid were synthesized and tested for their effect on APP RNA levels in vitro. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each separate experiment are presented in separate tables below.

(304) The modified oligonucleotides in the tables below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length. The sugar motif of the gapmers is (from 5′ to 3′): eeeeeddddddddddeeeee; wherein each ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and each ‘e’ represents a 2′-MOE sugar moiety. The internucleoside linkage motif for the gapmers is (from 5′ to 3′): sooosssssssssssooss; wherein each ‘o’ represents a phosphodiester internucleoside linkage and each ‘s’ represents a phosphorothioate internucleoside linkage. All cytosine nucleobases are 5-methylcytosines.

(305) “Start site” indicates the 5′-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. “Stop site” indicates the 3′-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are complementary to SEQ ID NO: 1 (ENSEMBL Accession No. ENST00000346798.7 from version 94: October 2018), and/or SEQ ID NO: 2 (the complement of GENBANK Accession No. NC_000021.9, truncated from nucleotides 25878001 to 26174000). ‘N/A’ indicates that the modified oligonucleotide is not 100% complementary to that particular target sequence.

(306) Cultured SH-SY5Y cells at a density of 20,000 cells per well were treated with 4,000 nM of modified oligonucleotide by electroporation. After a treatment period of approximately 24 hours, RNA was isolated from the cells and APP RNA levels were measured by quantitative real-time RTPCR. Human APP primer probe set RTS35572 (forward sequence CGGAGCAGACACAGACTATG, designated herein as SEQ ID NO: 11; reverse sequence CCTCTACCTCATCACCATCCT, designated herein as SEQ ID NO: 12; probe sequence AGTAGAAGTAGCAGAGGAGGAAGAAGTGG, designated herein as SEQ ID NO: 13) was used to measure APP RNA levels. APP RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented as percent of APP RNA, relative to untreated control cells (% UTC). The values marked by the symbol “f” indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the activity of the modified oligonucleotides complementary to the amplicon region.

(307) TABLE-US-00003 TABLE 1 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ SEQ ID SEQ No: 1 ID No: No: 2 ID No: SEQ Compound Start 1 Stop Start 2 Stop APP (% ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1353644 N/A N/A 273926 273945 GGTTAAGTTTCAACTCATTC 24 30 1353648 N/A N/A 76445 76464 CCTTTCAATATTGTTCTTCC 26 31 1353653 N/A N/A 96474 96493 GCCTCATTTTCTATGCATCC 15 32 1353666 N/A N/A 233346 233365 TGCATCAATTCCTTTGGGTT 25 33 1353674 N/A N/A 107660 107679 ACACTCTTTGCTTACCCACT 35 34 1353677 2919 2938 292903 292922 CGTGTGTATCCTCTTAATTC 25 35 1353685 N/A N/A 282274 282293 TCAAGTTTACCTACCTCCAC 98 36 1353688 N/A N/A 219303 219322 TGTGTCATAACCTGCATCAA 61† 37 1353689 N/A N/A 219394 219413 ACCAACTTCATCCTGAATCT 57 38 1353692 N/A N/A 27291 27310 AGCGCACTATTCTCTCTTGT 26 39 1353694 N/A N/A 153323 153342 AGTACATATTCATTCAATCT 32 40 1353696 N/A N/A 91426 91445 TACTACTCTTATCATGACCA 26 41 1353708 N/A N/A 4669 4688 AATTCGATCCTTTTATCTGC 48 42 1353721 N/A N/A 199217 199236 CCATCAATTGTCACCACCTC 31 43 1353722 N/A N/A 176809 176828 CCCAACATCTCAAGCTGTCT 32 44 1353727 N/A N/A 184663 184682 GAGCACTCCATTTCATATTC 32 45 1353732 N/A N/A 163515 163534 TGGTTATCTACAATGTGCAA 39 46 1353737 N/A N/A 238508 238527 GTCACACTATACTTTGTTAT 24 47 1353739 N/A N/A 152153 152172 TGGTGGATTACCTCGAACCA 75 48 1353741 N/A N/A 105867 105886 TTTCACATACCATACTCAGA 51 49 1353745 N/A N/A 84230 84249 GAACTCAAAAATACTGCTCC 49 50 1353754 N/A N/A 224770 224789 GACACTTGAAAATTCACACT 23 51 1353788 967 986 173886 173905 GGGCACACTTCCCTTCAGTC 36 52 1353789 N/A N/A 53100 53119 TGCAAATTTCATCACCAAAC 66 53 1353793 N/A N/A 219398 219417 ACTTACCAACTTCATCCTGA 81 54 1353802 N/A N/A 208597 208616 TTTGCATATTCATACTTGGA 26 55 1353803 N/A N/A 33641 33660 ATGTCAACACTAACCCAACT 59 56 1353807 N/A N/A 33840 33859 TACTCACTTACATAGTTGAT 38 57 1353834 N/A N/A 276227 276246 CCAAAACTTCTTTCTAGGCC 33 58 1353837 N/A N/A 158880 158899 GTTCTCTCTAAATATCAGCT 28 59 1353838 388 407 120651 120670 CACTTACAAACTCACCAACT 44 60 1353843 N/A N/A 62013 62032 CAGGACTTACTTCTTGGCAA 70 61 1353846 1179 1198 191578 191597 ATGTTCATTCTCATCCCCAG 37 62 1353855 N/A N/A 56176 56195 GCCACTATTTGCTACACAAT 44 63 1353858 N/A N/A 84581 84600 TCAGACTGTTTCCTCCAGTT 33 64 1353867 N/A N/A 228779 228798 GCATGCTAAATCAGTTCTCT 22 65 1353869 N/A N/A 281988 282007 GTTTCAGTATATTCTCTGCC 40 66 1353871 N/A N/A 164097 164116 GCCAGAATGTACTTCCTTAT 37 67 1353874 N/A N/A 195929 195948 TCCATTTTACCTCATACACT 50 68 1353878 N/A N/A 288816 288835 GGATCTTTAATCTCCAGCCC 37 69 1353879 N/A N/A 281184 281203 ACCACAACTTTTATCATCTT 38 70 1353888 N/A N/A 132424 132443 CCTACAGTATTTCTCATTCA 51 71 1353889 N/A N/A 93552 93571 GCTCATTTTTTTTACATGAC 8 72 1353891 N/A N/A 19936 19955 AAGCTTTCCACATTTGCTTA 66 73 1353897 N/A N/A

105713 105732 CAACAATCTGCAACTCTTCT 62 74 1353899 N/A N/A 167731 167750 GTTGAATTTCTTACACTTTC 8 75
1353901 N/A N/A 123282 123301 CGCCATTATTATTTCAACTC 17 76 1353910 633 652 122938 122957
CGAGTCATCCTCCTCCGCAT 17 77 1353923 N/A N/A 260567 260586 CCCTCATTAGATTTCCTCCA 47 78 1353943 N/A N/A
216405 216424 CCATGATGTTCCTTCCTGGC 34 79 1353947 N/A N/A 266304 266323 TGAGTCTGTTACTTCTGGTA 28 80 1353949
N/A N/A 33701 33720 GCAGTGACCACAACTTGACC 63 81 1353951 1861 1880 262178 262197 CCAGGCTGAACTCTCCATTC
51 82 1353952 577 596 122882 122901 GGCAACACACAAACTCTACC 35 83 1353969 N/A N/A 10486 10505
TGTCCTATTTATTCCTCATC 23 84 1353978 N/A N/A 88026 88045 TTGTAATTCCTTTTTTGGAT 18 85 1353989 N/A N/A
4688 4707 TCCGTCTTAATCTTCACTCA 20 86 1353993 N/A N/A 25097 25116 TACATCATTTTCTTGCAGTC 30 87
1353996 N/A N/A 8728 8747 TCATCACCATACATAGCAGC 37 88 1354004 N/A N/A 219408 219427
AGAACAGCTTACTTACCAAC 111 89 1354005 N/A N/A 141474 141493 ATGAACATGTCACTTAGGCT 48 90 1354007 N/A N/A
104230 104249 TGGTCTATATATTTCAGGCA 11 91 1354019 N/A N/A 68525 68544 GTATTCTTTTCCTTGCCGTT 35 92
1354022 N/A N/A 41389 41408 TCTGCTTTATTACTTGGATA 32 93 1354025 449 468 120712 120731 TCGCAAACATCCATCCTCTC
27 94 1354029 N/A N/A 180345 180364 GCTGACATTCTAACATTTCA 24 95 1354032 2156 2175 282190 282209
GTCGCTATGACAACACCGCC 42 96 1354051 N/A N/A 105744 105763 CTTTCCAACCTATTACCATC 50 97 1354055 N/A N/A
15616 15635 ACTGTATTTCTTCTACATCC 21 98 1354070 N/A N/A 130151 130170 GCTGATATTCTCACTTTATC 102 99 1354078
2592 2611 292576 292595 ACAGCTAAATTCTTTACAGT 34 100 1354080 N/A N/A 120580 120599 ACCGCAGAAGACATCAAGGA 66
101 1354086 N/A N/A 116604 116623 TCATCAATATACAGTATGCA 38 102 1354089 N/A N/A 33628 33647
CCCAACTTCTACCACGCACA 56 103 1354091 3246 3265 293230 293249 ACTTCGATTATTTAATGTCT 57 104 1354097 N/A N/A
49650 49669 TTCAACTTGTCCACGGACTT 40 105 1354099 N/A N/A 35914 35933 ATGTACTAATATCCAGTGGC 33 106 1354101
2033 2052 276363 276382 GCATCCATCTTCACTTCAGA 48 107

(308) TABLE-US-00004 TABLE 2 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ Com- No: 1 No: 1 No: 2 ID No: APP SEQ pound Start Stop Start 2 Stop (% ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1353637 N/A N/A 244555 244574 CGTCTCTTTATCACTTTACT 23 108 1353639 N/A N/A 54257 54276 GCTCAATTTGCACAAATCTC 29 109 1353643 N/A N/A 98612 98631
GCACAATTATTGTTTCCTCT 16 110 1353645 N/A N/A 25100 25119 GCTTACATCATTTTCTTGCA 15 111 1353646 N/A N/A 171484
171503 GTGTACATATTCATGTCACA 39 112 1353649 N/A N/A 124113 124132 TGGTACTATTTCTAAGGAAT 41 113 1353656 N/A N/A
107667 107686 TTGTAAGACACTCTTTGCTT 46 114 1353658 N/A N/A 85021 85040 AGGACATTCATTTTTGACCA 27 115 1353668
N/A N/A 9636 9655 GTGAACATAACTTCAAGCTT 28 116 1353672 N/A N/A 33633 33652 ACTAACCCAACTTCTACCAC
65 117 1353676 N/A N/A 33719 33738 ATCAACAAACTGTTAACTGC 62 118 1353680 2621 2640 292605 292624
GAGAGAATCTATTCATGCAC 50 119 1353684 N/A N/A 165830 165849 GCCAATACATCTGTCATTCT 48 120 1353691 N/A N/A 211612
211631 ATGTATTTCTACCTCTAGGC 38 121 1353700 N/A N/A 105772 105791 ACTGTCACTCTCACGCCCCT 65 122 1353702 N/A N/A
164083 164102 CCTTATACCACTTCTCTGTA 58 123 1353719 453 472 120716 120735 AGTTTCGCAAACATCCATCC 76 124
1353724 N/A N/A 105679 105698 CAACAAATGCCATCAGTCTC 72 125 1353726 N/A N/A 152368 152387 GCAGCATATACAAGGTACAA
34 126 1353735 2157 2176 282191 282210 TGTCGCTATGACAACACCGC 51 127 1353768 N/A N/A 120603 120622
TCCATCTGTATCACAGTGTT 74 128 1353769 N/A N/A 219401 219420 CTTACTTACCAACTTCATCC 91 129 1353770 N/A N/A 267413
267432 TCTAGTATTTCACTAGTGCA 33 130 1353772 N/A N/A 116757 116776 TTGCTTTGATCTTTCAGGTA 41 131 1353775 N/A N/A
281221 281240 TTCAACTTTATCTACTTGAA 64 132 1353782 N/A N/A 15618 15637 GTACTGTATTTCTTCTACAT 40 133 1353784
N/A N/A 181088 181107 ACTAACATTTGCTACTGCAC 48 134 1353787 N/A N/A 94504 94523 GTTCACATTTCAGACCACCA 58
135 1353795 N/A N/A 189342 189361 ACTTGCATTTCAAGTTCCCA 56 136 1353812 N/A N/A 178219 178238
GCAGCAGTACAAACCACATC 47 137 1353823 N/A N/A 62014 62033 ACAGGACTTACTTCTTGGCA 85 138 1353826 N/A N/A
84268 84287 TTCAATATACACCCTGGGTA 33 139 1353833 N/A N/A 6224 6243 GACCAGTATTATTCCATCTA 17 140
1353849 N/A N/A 28032 28051 GCTCTCATAATATCCTCATC 19 141 1353852 N/A N/A 228352 228371 CCCATATTATCTATGGACAA
30 142 1353854 2064 2083 276394 276413 AACTTCATATCCTGAGTCAT 72 143 1353857 N/A N/A 289147 289166
GTCAACAATCATTTGCATGC 61 144 1353872 N/A N/A 174425 174444 TACACCTTATCAATGCAACT 62 145 1353880 N/A N/A 72154
72173 TCTACCTTTGCAATTTTCTA 91 146 1353882 N/A N/A 274063 274082 GGACAGTTTCCCTTTCTCAT 39 147 1353886 N/A N/A
44381 44400 GCACAAATTTTATCACATCC 23 148 1353893 N/A N/A 134374 134393 GCCTACTATATGCTCAACAT 60 149 1353896
N/A N/A 50552 50571 AGATTACTTCTTTTCCTGCA 61 150 1353908 579 598 122884 122903 TGGGCAACACACAAACTCTA
34 151 1353917 N/A N/A 262696 262715 CCACACATTTTCCTTGTGAA 21 152 1353926 3247 3266 293231 293250
TACTTCGATTATTTAATGTC 85 153 1353928 N/A N/A 141829 141848 GTGAGCTAACATTTTTCCTC 40 154 1353934 N/A N/A 57149
57168 TGGTACTTTTTAATCAGTTC 31 155 1353945 N/A N/A 92733 92752 AGTTACTGTCACAACAAGGC 36 156 1353950 1181
1200 191580 191599 GCATGTTCATTCTCATCCCC 27 157 1353954 N/A N/A 105868 105887 TTTTCACATACCATACTCAG 60 158
1353955 N/A N/A 203618 203637 CCATCAATGTCCATTTAGCA 53 159 1353958 3127 3146 293111 293130 GTACAATCATCCTGCAGAAA
44 160 1353961 N/A N/A 276228 276247 CCCAAAACTTCTTTCTAGGC 38 161 1353974 N/A N/A 130297 130316
CCAAGTATTTTCCTGCATCA 31 162 1353986 N/A N/A 38386 38405 GCCTTATTATCTCAAACTCA 38 163 1353991 N/A N/A
260987 261006 GTCTCATTTTCCAATCATAG 35 164 1353995 N/A N/A 33841 33860 GTACTCACTTACATAGTTGA 58 165 1354001
N/A N/A 154231 154250 CTGTAATTTGTATTCACACT 23 166 1354006 1697 1716 219387 219406 TCATCCTGAATCTCCTCGGC 70 167
1354008 N/A N/A 216780 216799 GCAACTTATTACAACTCTCA 43 168 1354013 N/A N/A 4672 4691
CTCAATTCGATCCTTTTATC 64 169 1354018 N/A N/A 33644 33663 AGCATGTCAACACTAACCCA 42 170 1354020 N/A N/A
225511 225530 CCATATCTTTCAATCCTGCC 37 171 1354023 389 408 120652 120671 TCACTTACAAACTCACCAAC 62 172
1354030 N/A N/A 220662 220681 GCCAAATATTTCACAGCAAT 10 173 1354037 635 654 122940 122959
TCCGAGTCATCCTCCTCCGC 22 174 1354041 N/A N/A 10520 10539 AGGCTTATTCATCTTTTCCC 26 175 1354042 N/A N/A
84113 84132 ACAGGAGCATCCTCTTTTTC 69 176 1354056 N/A N/A 282275 282294 GTCAAGTTTACCTACCTCCA 115 177 1354057
N/A N/A 158958 158977 GCAGATATTTCAATATACAG 14 178 1354061 N/A N/A 105719 105738 TTGCTCCAACAATCTGCAAC 64 179
1354069 N/A N/A 282128 282147 TTCTGCAAAGAACACCTTGA 68 180 1354075 N/A N/A 229318 229337 TTGGATTCATCTCCATACTC
34 181 1354092 N/A N/A 88105 88124 TGGTCATTACTACTTACACA 46 182 1354093 N/A N/A 197708 197727
TTGGTCTTTTTTTACCCCGA 31 183 1354094 N/A N/A 233418 233437 AACTAATTATCAGATATGCA 52 184 1354098 N/A N/A 19938
19957 GTAAGCTTTCCACATTTGCT 58 185

(309) TABLE-US-00005 TABLE 3 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1353636 3338 3357 293322 293341 GCCACTTCCATTTTCATCTT 53 186
1353640 2199 2218 282233 282252 GTACTGTTTCTTCTTCAGCA 29 187 1353642 N/A N/A 230836 230855 GCATCATATATATACTTCTT 29
188 1353647 N/A N/A 22819 22838 TTTGACTTGTTTTTCACCAC 16 189 1353651 N/A N/A 175225 175244 GTAGTTCATACTTCCTACTC 26
190 1353675 2106 2125 282140 282159 TGAACCCACATCTTCTGCAA 54 191 1353682 N/A N/A 282318 282337
GCCTAATTCTCTCATAGTCT 20 192 1353683 N/A N/A 212180 212199 TGTCACAATATTCATACTTA 22 193 1353699 N/A N/A 225514
225533 CCGCCATATCTTTCAATCCT 31 194 1353703 N/A N/A 33757 33776 TTGTCAATTACATCAGCAAC 26 195 1353705 3129 3148

293113 293132 CTGTACAATCATCCTGCAGA 30 196 1353706 N/A N/A 95358 95377 CTACAATTATCCACATGGCA 24 197 1353717 N/A N/A 38467 38486 AGTCACTCAAACTTTGATTT 39 198 1353718 N/A N/A 72172 72191 TCCAATTTGCAACCTCATTC 36 199 1353731 N/A N/A 159559 159578 GCATTCATTCTATTTGGTGC 11 200 1353733 N/A N/A 11253 11272 GCAACAGATCTCTTATTCTC 16 201 1353736 N/A N/A 9637 9656 GGTGAACATAACTTCAAGCT 13 202 1353740 N/A N/A 172804 172823 CACATCTTACCTGTCAACAT 55 203 1353760 N/A N/A 146928 146947 CGGACTTTTTTCTTCTTGCT 39 204 1353763 N/A N/A 131534 131553 CACCATCTATAATACCATCT 25 205 1353773 N/A N/A 105776 105795 GTAGACTGTCACTCTCACGC 32 206 1353774 2066 2085 276396 276415 TGAACTTCATATCCTGAGTC 53 207 1353777 N/A N/A 15647 15666 GTCTACCCATTTTCCTCTAT 44 208 1353778 N/A N/A 105680 105699 ACAACAAATGCCATCAGTCT 50 209 1353779 N/A N/A 246007 246026 TGCTGATCTGATTTCCAACT 27 210 1353794 N/A N/A 85151 85170 GTTTTCTACACTCTCTTCAT 42 211 1353796 N/A N/A 126055 126074 GTCACATGATATTTCAGATA 21 212 1353797 N/A N/A 153108 153127 TTCACAATATTTGCAACACA 23 213 1353798 N/A N/A 181220 181239 CCATCACATCTTTTAATGCT 53 214 1353800 638 657 122943 122962 ACATCCGAGTCATCCTCCTC 29 215 1353801 N/A N/A 228353 228372 ACCCATATTATCTATGGACA 21 216 1353804 N/A N/A 191874 191893 GACATCATTTAATTTGTGCT 24 217 1353811 N/A N/A 268185 268204 ACAGCATGATATTCCTCACC 33 218 1353817 N/A N/A 154489 154508 GTTCACATTTCTTACAACAC 25 219 1353819 N/A N/A 33843 33862 CAGTACTCACTTACATAGTT 41 220 1353820 1701 1720 219391 219410 AACTTCATCCTGAATCTCCT 32 221 1353822 N/A N/A 204992 205011 GTGATCTTTTTCAGACAACC 22 222 1353827 N/A N/A 33634 33653 CACTAACCCAACTTCTACCA 67 223 1353831 N/A N/A 6792 6811 GTACATTCCACTTTGTTTTA 24 224 1353841 N/A N/A 54387 54406 GTTGACATATACCTACCTAT 64 225 1353842 N/A N/A 165834 165853 GCTAGCCAATACATCTGTCA 54 226 1353847 N/A N/A 222140 222159 GTTTCAACTATATTCCTACT 25 227 1353850 2487 2506 292471 292490 TCAGGCATCTACTTGTGTTA 26 228 1353864 N/A N/A 164084 164103 TCCTTATACCACTTCTCTGT 38 229 1353866 N/A N/A 29351 29370 TGGTCAATTCTCTTGAACAA 30 230 1353875 N/A N/A 45571 45590 TGGTTCATTTCTTTAGCCAC 14 231 1353883 N/A N/A 105738 105757 AACCTATTACCATCTGGCCT 54 232 1353887 N/A N/A 121258 121277 AGCTACTTCACTGTTCTACC 52 233 1353898 N/A N/A 117352 117371 CTGAACTTTCTAACTTGCAA 58 234 1353900 600 619 122905 122924 ATTGTCACTTTCTTCAGCCA 27 235 1353905 N/A N/A 63454 63473 GTTCATACTCCTTTCAAGAT 33 236 1353907 N/A N/A 33646 33665 ACAGCATGTCAACACTAACC 60 237 1353913 N/A N/A 178598 178617 ATGTGATTTCACTAACCGGC 13 238 1353914 N/A N/A 134530 134549 GCTTGAATTACTATTGATCT 23 239 1353932 1313 1332 198027 198046 TGGATAACTGCCTTCTTATC 38 240 1353933 N/A N/A 274949 274968 GCACCATTTCCTCATCCAAT 27 241 1353935 N/A N/A 50739 50758 GTGCTTATAACTCTCATACT 26 242 1353946 N/A N/A 219402 219421 GCTTACTTACCAACTTCATC 75 243 1353959 N/A N/A 92773 92792 GTTTCTTTACCCACATCTTC 18 244 1353967 N/A N/A 217227 217246 GTTGTGTTATCCATATCCTA 24 245 1353977 N/A N/A 25101 25120 AGCTTACATCATTTTCTTGC 27 246 1353980 N/A N/A 108206 108225 ACTGCACTATTAGTCATATC 37 247 1353981 N/A N/A 281265 281284 GCACTACATTGCTTCATACT 50 248 1353982 N/A N/A 263016 263035 TCCTTATTTCACTATCTATC 51 249 1353983 N/A N/A 105869 105888 GTTTTCACATACCATACTCA 45 250 1353984 N/A N/A 261096 261115 GTCTTCTCTTATGTCACCAA 28 251 1353985 390 409 120653 120672 ATCACTTACAAACTCACCAA 39 252 1353990 N/A N/A 233550 233569 AGTTCCTTTTCACCTATCCT 34 253 1353992 N/A N/A 84177 84196 GTCCAAAACACAGTACAACA 17 254 1354015 N/A N/A 98830 98849 GGCTACATCCTCAATTCATT 32 255 1354045 N/A N/A 276282 276301 CAGGACAACCAATTAGTTTT 78 256 1354048 N/A N/A 88860 88879 CCGGACATGTTTTCTTTTAC 18 257 1354052 N/A N/A 84273 84292 GTAATTTCAATATACACCCT 17 258 1354076 2671 2690 292655 292674 CCACAAGAATAATATACAAC 50 259 1354087 N/A N/A 120611 120630 CCCGTCATTCCATCTGTATC 84 260 1354095 N/A N/A 4674 4693 CACTCAATTCGATCCTTTTA 44 261 1354102 N/A N/A 189857 189876 GCTTAATACATCCTGTTCAA 46 262 1354103 N/A N/A 59208 59227 ACAGCTATTTTAATGTCATC 57 263

(310) TABLE-US-00006 TABLE 4 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1353650 645 664 122950 122969 CCACCAGACATCCGAGTCAT 59 264 1353652 N/A N/A 246441 246460 GCTACACTATCAATCTTGAA 64 265 1353659 3341 3360 293325 293344 ATTGCCACTTCCATTTTCAT 54 266 1353662 N/A N/A 179244 179263 GCTTGCTTACCTTCTAGTTC 39 267 1353667 N/A N/A 33648 33667 CAACAGCATGTCAACACTAA 65 268 1353669 N/A N/A 230837 230856 AGCATCATATATATACTTCT 33 269 1353670 N/A N/A 219393 219412 CCAACTTCATCCTGAATCTC 69 270 1353678 N/A N/A 276283 276302 GCAGGACAACCAATTAGTTT 50 271 1353681 N/A N/A 153293 153312 GCATCTTTTACTATCTGCCA 21 272 1353686 N/A N/A 12586 12605 GCATTCTCTTATATTCCTTA 19 273 1353693 602 621 122907 122926 ACATTGTCACTTTCTTCAGC 43 274 1353698 N/A N/A 282270 282289 GTTTACCTACCTCCACCACA 93 275 1353716 396 415 120659 120678 AAGGGCATCACTTACAAACT 38 276 1353720 N/A N/A 164092 164111 AATGTACTTCCTTATACCAC 31 277 1353742 N/A N/A 128791 128810 GGCTATATTCTCTCTTCAAT 23 278 1353746 N/A N/A 219403 219422 AGCTTACTTACCAACTTCAT 95 279 1353748 N/A N/A 281269 281288 TACTGCACTACATTGCTTCA 70 280 1353750 N/A N/A 101643 101662 CCGGATTATTTCACATTCTC 13 281 1353752 N/A N/A 284992 285011 GGATTCTTTTTCCTTAGGTC 21 282 1353766 N/A N/A 206318 206337 CAGGACATATCATCATCTTC 40 283 1353767 N/A N/A 193342 193361 ATTGTTATTCATCTTAAGGC 28 284 1353771 N/A N/A 263075 263094 GTCAAATCTGCATCTCTGCA 41 285 1353781 N/A N/A 112542 112561 ATGTGCTCATTATATGCTAT 44 286 1353785 2721 2740 292705 292724 CCCATCGATTCTTAAAGCAT 29 287 1353786 N/A N/A 84275 84294 TTGTAATTTCAATATACACC 34 288 1353790 N/A N/A 33844 33863 ACAGTACTCACTTACATAGT 48 289 1353806 N/A N/A 160206 160225 GTCTCATCACATTTTAAGCA 32 290 1353808 N/A N/A 271068 271087 ACATCATATTCTTACTGTTA 30 291 1353818 N/A N/A 146929 146948 ACGGACTTTTTTCTTCTTGC 57 292 1353824 N/A N/A 105858 105877 CCATACTCAGAAAGCCATGT 64 293 1353825 N/A N/A 262031 262050 GAAGCAGCTCATCTAAACCA 74 294 1353830 N/A N/A 17037 17056 AACAACTATTTGAGACATGC 15 295 1353832 N/A N/A 22918 22937 AGCAGCATTTCATCACAATT 23 296 1353835 N/A N/A 38724 38743 GCACCAGACCTTCTCACTTC 42 297 1353840 N/A N/A 276076 276095 GCCTTTAAATACATGCTATA 62 298 1353844 N/A N/A 226497 226516 CCGTACTTTGCCATTCATTT 32 299 1353859 N/A N/A 228354 228373 AACCCATATTATCTATGGAC 34 300 1353863 2589 2608 292573 292592 GCTAAATTCTTTACAGTACA 38 301 1353865 N/A N/A 84222 84241 AAATACTGCTCCTATAGGGT 59 302 1353873 N/A N/A 4679 4698 ATCTTCACTCAATTCGATCC 56 303 1353885 N/A N/A 33637 33656 CAACACTAACCCAACTTCTA 90 304 1353890 N/A N/A 33764 33783 CCAATCATTGTCAATTACAT 30 305 1353902 N/A N/A 198341 198360 TTCTCATAATTTTTGCTGGA 60 306 1353903 N/A N/A 234566 234585 TCCCACTTAATTTTTCATCC 21 307 1353906 N/A N/A 105872 105891 GCTGTTTTCACATACCATAC 29 308 1353909 N/A N/A 166805 166824 TTGAACTCTTTTTCTCCAAT 35 309 1353920 N/A N/A 105739 105758 CAACCTATTACCATCTGGCC 90 310 1353922 N/A N/A 190594 190613 AGGTTATTCAAATATCACCA 27 311 1353936 N/A N/A 105681 105700 AACAACAAATGCCATCAGTC 49 312 1353937 N/A N/A 6794 6813 TAGTACATTCCACTTTGTTT 22 313 1353938 N/A N/A 120616 120635 CACTTCCCGTCATTCCATCT 85 314 1353940 N/A N/A 121799 121818 GCTAGATCAGATTTCTCAAC 54 315 1353942 N/A N/A 30248 30267 CCCTTCTACTCTTGTTTCCA 41 316 1353948 N/A N/A 175488 175507 GGAGCTTTTCCATTACATTC 31 317 1353957 N/A N/A 51568 51587 TCATATTGTCTTCAATGTGC 23 318 1353963 N/A N/A 54402 54421 TCTAGTTTTTCAACAGTTGA 59 319 1353968 1509 1528 218262 218281 GACATACTTCTTTAGCATAT 38 320 1353972 N/A N/A 10233 10252 CGTTCATCATCATTTAACCA 23 321 1353979 2067 2086 276397 276416 ATGAACTTCATATCCTGAGT 64 322 1354003 2107 2126 282141 282160 TTGAACCCACATCTTCTGCA 56 323 1354011 N/A N/A 59242 59261 TTTCACTTTGTCATCCTCCC 52 324 1354016 N/A N/A 46440 46459 TCCATCACTGTCTATATCTC 49 325 1354021 N/A N/A 92842 92861 CACCATATTACTTATGCACC 17 326 1354026 3134 3153 293118 293137 TGATTCTGTACAATCATCCT 39 327 1354034 N/A N/A 117357 117376 GGTTACTGAACTTTCTAACT 45 328 1354036 N/A N/A 26673 26692 TCAGAATTCACTTGACATGC 56 329 1354038 N/A N/A 86229 86248 AGGTCATTAACTTTACTATC 28 330 1354043 N/A N/A 212832 212851 TGCAACTGTTCATCTCACCT 59 331 1354046 N/A N/A 95359 95378 GCTACAATTATCCACATGGC 32 332 1354049 N/A N/A 89149 89168 GTGTATTTTCCCATACTGTA 16 333 1354050 N/A N/A 172859 172878 GCAGTCAATCAACTCCAACT 22 334 1354053 N/A N/A 73586 73605 TTGCCAATTTTCAGCCTACA 38 335 1354060 N/A

N/A 131535 131554 GCACCATCTATAATACCATC 17 336 1354063 N/A N/A 181233 181252 GTAGTTTAATTCACCATCAC 15 337 1354064 N/A N/A 222419 222438 TTGTACTGAACTGACTCCAA 41 338 1354071 N/A N/A 63463 63482 CACATCATGGTTCATACTCC 24 339 1354072 N/A N/A 154738 154757 AGGTCTCTATATTTTGGTCC 19 340 1354081 N/A N/A 136250 136269 GCTTCATTACCACTTCTGAT 19 341

(311) TABLE-US-00007 TABLE 5 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1353641 N/A N/A 179401 179420 AAGAGCTTTTTCTATCTCCT 60 342 1353655 N/A N/A 101644 101663 TCCGGATTATTTCACATTCT 18 343 1353657 N/A N/A 86554 86573 GTGCTCATTTCACATCAGAC 26 344 1353660 2590 2609 292574 292593 AGCTAAATTCTTTACAGTAC 31 345 1353661 N/A N/A 7782 7801 GTCTGCTTTTCTTCTTATAC 23 346 1353663 1780 1799 262097 262116 CGTAACTGATCCTTGGTTCA 48 347 1353665 N/A N/A 276318 276337 AACCCAGAACCTGTATTACA 88 348 1353679 N/A N/A 276079 276098 GCTGCCTTTAAATACATGCT 40 349 1353687 N/A N/A 167609 167628 ATGCCATTTACTACACTGAA 39 350 1353690 N/A N/A 153294 153313 AGCATCTTTTACTATCTGCC 28 351 1353697 N/A N/A 118930 118949 CTGTATCTTGTCATTCCTTA 27 352 1353709 N/A N/A 183237 183256 TGGTTATTTACCTCTACGGC 113 353 1353710 N/A N/A 161596 161615 GCATCATTTTTATATGAGAT 16 354 1353713 N/A N/A 19228 19247 TCCAGATATTACTTTCTTCA 24 355 1353723 N/A N/A 51896 51915 GAAGCATATTCCTCTATCCT 19 356 1353729 N/A N/A 46766 46785 GTGGTAACTATTTCTGGGCA 50 357 1353730 N/A N/A 219395 219414 TACCAACTTCATCCTGAATC 71 358 1353738 N/A N/A 194605 194624 TTGGATTTATCAATCTTCAA 33 359 1353747 698 717 151960 151979 ACTTCTACTACTTTGTCTTC 39† 360 1353753 N/A N/A 12614 12633 GCATTCACAACACACATCCT 21 361 1353755 N/A N/A 105705 105724 TGCAACTCTTCTTTCAAGGT 39 362 1353757 N/A N/A 198583 198602 CACTTTCTTGCACTCTCCAA 79 363 1353758 N/A N/A 33695 33714 ACCACAACTTGACCCAGGCC 57 364 1353762 N/A N/A 173247 173266 GTGACTTATACTCAATGACA 23 365 1353765 N/A N/A 33846 33865 TCACAGTACTCACTTACATA 52 366 1353776 N/A N/A 285840 285859 GTACTCATTTTTGTTCTTAC 68 367 1353791 N/A N/A 281406 281425 AGTCACTCATAACTCATGCT 54 368 1353792 N/A N/A 223647 223666 TGCAACTTTTCAAGCAAGGA 20 369 1353805 N/A N/A 54772 54791 GCTTTTTTAATTCTTCAATC 55 370 1353809 2114 2133 282148 282167 CCTTTGTTTGAACCCACATC 70 371 1353810 N/A N/A 33638 33657 TCAACACTAACCCAACTTCT 72 372 1353813 N/A N/A 122991 123010 CCACCTTACCTCCCATCTGC 102† 373 1353814 N/A N/A 219406 219425 AACAGCTTACTTACCAACTT 95 374 1353815 N/A N/A 26969 26988 GCACAACTTTATTTCTAGAC 12 375 1353816 N/A N/A 206339 206358 GTCTAATTTCTCTTCAACAG 55 376 1353821 N/A N/A 191271 191290 GTCCATTTTGCAATTATAGC 35 377 1353828 N/A N/A 263976 263995 TAGTCTATATATTTTCTGCA 24 378 1353829 447 466 120710 120729 GCAAACATCCATCCTCTCCT 35 379 1353836 N/A N/A 105740 105759 CCAACCTATTACCATCTGGC 50 380 1353845 N/A N/A 40654 40673 ACACACTTGCCAATATCCTC 50 381 1353848 N/A N/A 4684 4703 TCTTAATCTTCACTCAATTC 110 382 1353856 N/A N/A 271256 271275 CAGAACATTCTTGTTAGCAC 35 383 1353861 N/A N/A 22919 22938 CAGCAGCATTTCATCACAAT 27 384 1353862 N/A N/A 131601 131620 GTGCATAATTTATTACATGA 34 385 1353870 606 625 122911 122930 ATCCACATTGTCACTTTCTT 34 386 1353876 N/A N/A 230838 230857 AAGCATCATATATATACTTC 65 387 1353877 1512 1531 218265 218284 GCGGACATACTTCTTTAGCA 35 388 1353881 N/A N/A 59977 59996 CAGTACTTTATTCTGTTCAC 79 389 1353894 N/A N/A 234610 234629 GCATTAGTTTCTTTAATGGT 35 390 1353904 N/A N/A 113619 113638 CAACTCTTTCAACTCTTGCA 56 391 1353915 N/A N/A 282272 282291 AAGTTTACCTACCTCCACCA 97 392 1353919 N/A N/A 128792 128811 TGGCTATATTCTCTCTTCAA 29 393 1353921 N/A N/A 105862 105881 CATACCATACTCAGAAAGCC 62 394 1353929 N/A N/A 95932 95951 TTTCTTATATCCATGATGCT 62 395 1353941 N/A N/A 120617 120636 CCACTTCCCGTCATTCCATC 81 396 1353944 N/A N/A 246486 246505 CCAGTTTTTATCTTGACCTC 40 397 1353965 N/A N/A 226558 226577 GGAGACATTTCAACATGGCA 25 398 1353970 2072 2091 276402 276421 TGATGATGAACTTCATATCC 85 399 1353971 N/A N/A 84227 84246 CTCAAAAATACTGCTCCTAT 74 400 1353987 N/A N/A 30591 30610 TGGTTAGGTCACTTCTTTTA 40 401 1353988 3226 3245 293210 293229 GTAGTCATCCTTCAAAGAAA 78 402 1353997 N/A N/A 105874 105893 ATGCTGTTTTCACATACCAT 52 403 1354000 N/A N/A 10349 10368 GTGAACCCACTTCTTGTCTT 33 404 1354002 3347 3366 293331 293350 CCTTATATTGCCACTTCCAT 71 405 1354009 N/A N/A 136343 136362 CACTGCACTTAGTTCCACCA 64 406 1354010 N/A N/A 176271 176290 CGATGCATTTTTTCACAAAA 32 407 1354024 N/A N/A 214164 214183 GTGCTAAATTCATCCTTATC 47 408 1354033 N/A N/A 90338 90357 CCTTGCTATTCATTTTTCAA 27 409 1354040 N/A N/A 33767 33786 GCTCCAATCATTGTCAATTA 52 410 1354044 2912 2931 292896 292915 ATCCTCTTAATTCCTATATC 36 411 1354054 555 574 122860 122879 TCGGAACTTGTCAATTCCGC 92 412 1354058 N/A N/A 228472 228491 ACGGACTCACACTTGCTGAT 43 413 1354062 N/A N/A 164093 164112 GAATGTACTTCCTTATACCA 44 414 1354065 N/A N/A 74023 74042 ATCCACACTTTCATACTCAG 103 415 1354077 N/A N/A 65593 65612 TAGCACACATCAGTTTCCAC 37 416 1354079 N/A N/A 92844 92863 TACACCATATTACTTATGCA 37 417 1354085 N/A N/A 84370 84389 ATGAGAATCATCTATGCGAT 48 418 1354100 N/A N/A 158755 158774 TGCTAATGTTTCAAATGCAA 39 419

(312) TABLE-US-00008 TABLE 6 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1353638 N/A N/A 19930 19949 TCCACATTTGCTTACATTCT 29 420 1353654 N/A N/A 228475 228494 ATAACGGACTCACACTTGCT 46 421 1353664 N/A N/A 27002 27021 GACACTTTTATCTTGCACTA 18 422 1353671 N/A N/A 95933 95952 GTTTCTTATATCCATGATGC 12 423 1353673 N/A N/A 87912 87931 GTGCCAATTTCAACAGTGGA 18 424 1353695 1860 1879 262177 262196 CAGGCTGAACTCTCCATTCA 75 425 1353701 N/A N/A 226834 226853 AGGTCATTATCAATGACTTC 50 426 1353704 N/A N/A 120232 120251 TTGGACATTTTAATCTGCTT 43 427 1353707 2000 2019 276330 276349 TTGATATTTGTCAACCCAGA 41 428 1353711 N/A N/A 33818 33837 ACAGAACCAACAAGTCCTCT 47 429 1353712 N/A N/A 194644 194663 AGCAATTTTCCACTGCAGGC 55 430 1353714 N/A N/A 33639 33658 GTCAACACTAACCCAACTTC 45 431 1353715 N/A N/A 219397 219416 CTTACCAACTTCATCCTGAA 81 432 1353725 N/A N/A 8660 8679 ACTCACACACTGTTTCAAGC 18 433 1353728 N/A N/A 198591 198610 GCTTACTTCACTTTCTTGCA 33 434 1353734 N/A N/A 167693 167712 TCTGATATTCACTTATCTGA 26 435 1353743 N/A N/A 282273 282292 CAAGTTTACCTACCTCCACC 88 436 1353744 2153 2172 282187 282206 GCTATGACAACACCGCCCAC 48 437 1353749 N/A N/A 92931 92950 GTGAATCTTCTTTTACCACA 13 438 1353751 448 467 120711 120730 CGCAAACATCCATCCTCTCC 40 439 1353756 N/A N/A 55920 55939 CCAAGCTTTTTTACTACTCA 71 440 1353759 2591 2610 292575 292594 CAGCTAAATTCTTTACAGTA 43 441 1353761 N/A N/A 180027 180046 GTTGTTTGTACCACATGTCA 49 442 1353764 N/A N/A 286488 286507 AAGTCAATATTTCCTGCTTA 42 443 1353780 N/A N/A 259747 259766 GCTTGCTTTTCCACACCACC 53 444 1353783 N/A N/A 162208 162227 GCAAGACTTTTCTTTGCTCC 19 445 1353799 N/A N/A 49548 49567 TCCTAATTCTTTGATAACAC 47 446 1353839 N/A N/A 32280 32299 GTATTATTTCTTTTACGCCT 18 447 1353851 576 595 122881 122900 GCAACACACAAACTCTACCC 34 448 1353853 N/A N/A 105708 105727 ATCTGCAACTCTTCTTTCAA 108 449 1353860 3228 3247 293212 293231 CTGTAGTCATCCTTCAAAGA 66 450 1353868 N/A N/A 219407 219426 GAACAGCTTACTTACCAACT 80 451 1353884 N/A N/A 158795 158814 GTTTACCTTTAACATTCCTC 18 452 1353892 1175 1194 191574 191593 TCATTCTCATCCCCAGGTGT 40 453 1353895 N/A N/A 139767 139786 GTCTAATTATACCATTCCTC 51 454 1353911 N/A N/A 41356 41375 CACAACATATATGTATCTCC 18 455 1353912 N/A N/A 120620 120639 AAACCACTTCCCGTCATTCC 129 456 1353918 614 633 122919 122938 TCAGCAGAATCCACATTGTC 51 457 1353924 N/A N/A 75269 75288 GCCTACTTTTCTACTTAGTC 44 458 1353925 N/A N/A 234725 234744 GCCAGCTTTTCCTTTCACAT 39 459 1353927 N/A N/A 271490 271509 CACTTCATATCTGAGCATTC 43 460 1353930 N/A N/A 281694 281713 GTCAGCATTTTCCTAGTCAT 75 461 1353931 N/A N/A 101718 101737 GCCATATTGTCATTTTACAC 16 462 1353939 N/A N/A 219072 219091 GTTCTCCTATTTCTGTTCTC 79 463 1353953 N/A N/A 84435 84454 GCAGCTTCACATTAGATTCT 24 464 1353956 N/A N/A 184659 184678 ACTCCATTTCATATTCATAC 21 465 1353960 N/A N/A 176674 176693 CAAGCAGCATCCTCCTCCCC 77 466 1353962 N/A N/A 10485 10504 GTCCTATTTATTCCTCATCC 40 467 1353964 N/A N/A 132421 132440 ACAGTATTTCTCATTCAGCA 26 468 1353966 N/A N/A 53082 53101 ACATTCATGCTACTGCAATC 112 469 1353973 N/A N/A 24844 24863

AATCAATTGCATTCCAAGGC 20 470 1353975 N/A N/A 164096 164115 CCAGAATGTACTTCCTTATA 52 471 1353976 N/A N/A 35655 35674 AGATCATATACTATACACAA 16 472 1353994 N/A N/A 106120 106139 TAGGTATTCTCACTGGTTGC 44 473 1353998 N/A N/A 276226 276245 CAAAACTTCTTTCTAGGCCT 48 474 1353999 N/A N/A 4687 4706 CCGTCTTAATCTTCACTCAA 32 475 1354012 N/A N/A 153322 153341 GTACATATTCATTCAATCTA 24 476 1354014 N/A N/A 230840 230859 GCAAGCATCATATATATACT 40 477 1354017 N/A N/A 122999 123018 CACAAAGGCCACCTTACCTC 67† 478 1354027 N/A N/A 224097 224116 CATCACTTTACTATCTGGGC 27 479 1354028 N/A N/A 66492 66511 GCACTCTTATCTTTCCCCTC 43 480 1354031 N/A N/A 90387 90406 GCACACATTTGCAATTCTTA 9 481 1354035 2914 2933 292898 292917 GTATCCTCTTAATTCCTATA 26 482 1354039 N/A N/A 214339 214358 GTTCCATTATTCCTTAGCTA 26 483 1354047 N/A N/A 115871 115890 CTGTACTGCCATCCTGAGCA 64 484 1354059 3350 3369 293334 293353 TCCCCTTATATTGCCACTTC 52 485 1354066 N/A N/A 264370 264389 CGCAGATTTTCTCCTAAGGC 34 486 1354067 N/A N/A 173443 173462 GTCAACTTTCATGTAAGGAA 14 487 1354068 N/A N/A 12940 12959 GCTGTTCGAATCTTCAATCT 25 488 1354073 N/A N/A 105865 105884 TCACATACCATACTCAGAAA 57 489 1354074 N/A N/A 33700 33719 CAGTGACCACAACTTGACCC 45 490 1354082 N/A N/A 278101 278120 TTGTAATATTCATTGCACTA 48 491 1354083 N/A N/A 105743 105762 TTTCCAACCTATTACCATCT 93 492 1354084 N/A N/A 128965 128984 GCAACACATTTATTTGATAC 21 493 1354088 N/A N/A 207518 207537 GCAGTCTTTCAACTTTTAAT 30 494 1354090 879 898 152141 152160 TCGAACCACCTCTTCCACAG 89 495 1354096 N/A N/A 84229 84248 AACTCAAAAATACTGCTCCT 58 496 1354104 177 196 61940 61959 TGAATCCCACTTCCCATTCT 43 497

(313) TABLE-US-00009 TABLE 7 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 28 178 1397536 N/A N/A 20330 20349 CTCTAAGCATTGTCCCAGAC 97 498 1397546 N/A N/A 51886 51905 CCTCTATCCTTTGTCAGCCC 88 499 1397549 N/A N/A 180977 180996 GCTCCTGTCTTTACAACGAC 43 500 1397553 N/A N/A 218532 218551 GCCAAACCACATATTGCTCT 54 501 1397597 N/A N/A 16201 16220 TGCATAGATCTTCCCATTCT 50 502 1397629 N/A N/A 36133 36152 TTGTTCCTTCATTTAGTGGA 63 503 1397707 N/A N/A 177940 177959 TGGCATATATCATCCCTAAC 31 504 1397760 N/A N/A 222733 222752 CAGCATGACTCCATTCTTCC 43 505 1397819 N/A N/A 19452 19471 AGTTTTGTCCAAATCAGGCC 34 506 1397865 N/A N/A 83559 83578 GCCTGCTCTACCTCTGACCA 85 507 1397871 N/A N/A 12325 12344 TAGTCTGCATATTTTCACAT 129 508 1397915 N/A N/A 277176 277195 CTCCATGATCTTACTCTTGC 70 509 1397972 N/A N/A 9591 9610 CTGGCATTTGAAATCTTCCA 23 510 1398022 N/A N/A 41110 41129 AGTGCATCATATTCTACACT 45 511 1398029 N/A N/A 247486 247505 TCATGGCCTTTTCATACCCA 63 512 1398111 N/A N/A 66405 66424 CCACTGCTCATCTCCCTCAT 76 513 1398159 N/A N/A 186569 186588 TAGCAGCAATACCAACATCA 49 514 1398180 N/A N/A 283786 283805 TTCCTCACACTGCTCATCCA 107 515 1398205 N/A N/A 22544 22563 AGCCTTTCCTTATTTTTGCT 42 516 1398208 N/A N/A 130875 130894 TAGCCATCCCTCTTCTGCCC 78 517 1398237 N/A N/A 59235 59254 TTGTCATCCTCCCTGCTTCT 143 518 1398238 N/A N/A 154736 154755 GTCTCTATATTTTGGTCCCA 20 519 1398239 N/A N/A 85262 85281 ACTGCACTTTTTGATGAACC 57 520 1398245 N/A N/A 10438 10457 CTGGAACCATCTTAATCACT 62 521 1398271 N/A N/A 153179 153198 TTGGTCATTTAATATCAACT 27 522 1398328 N/A N/A 98898 98917 TGCTCCACATCTTCTGTCTT 66 523 1398340 N/A N/A 262025 262044 GCTCATCTAAACCAAACAAA 92 524 1398388 N/A N/A 28247 28266 CTGCTACTGACATAATACAC 87 525 1398391 N/A N/A 104334 104353 AAGAGCTTATTAACTGCCTC 56 526 1398402 N/A N/A 8054 8073 TGTGAATTTATTCCTAGAGC 42 527 1398418 N/A N/A 50161 50180 GAGGCAATCTGATATTGACA 62 528 1398437 N/A N/A 32628 32647 GGCACAGTCTTATTATGACA 47 529 1398439 N/A N/A 53337 53356 TGAGCTTCTTTTCTCCTACA 51 530 1398448 N/A N/A 235762 235781 GCATCTGAACTTCTTGAGGT 34 531 1398477 N/A N/A 211022 211041 GTGCACCCTCACACCGACCT 54 532 1398503 N/A N/A 96479 96498 AATTTGCCTCATTTTCTATG 64 533 1398514 N/A N/A 274850 274869 GTGAAGCTATCTTCTCTCCT 41 534 1398538 N/A N/A 88573 88592 TAGGTCCCACACATGCATCT 71 535 1398596 N/A N/A 159977 159996 AAGCATGCTACAACCCGGGC 48 536 1398600 N/A N/A 290099 290118 GTTCCATCCATTATGTGCCC 86 537 1398677 N/A N/A 172780 172799 TGCCACCCTCCCCAAGATCA 93 538 1398693 N/A N/A 196724 196743 CAGCTGCCTTTTCAAGTGTA 79 539 1398775 N/A N/A 13727 13746 CCACAATTCAACTAGCAGCA 62 540 1398791 N/A N/A 271277 271296 GTACTCCATCTCCTCCCATC 69 541 1398797 N/A N/A 25026 25045 CTCCAACATCCACACTCAGA 66 542 1398808 N/A N/A 92208 92227 ATATCAGTTTTTCTCTAGGT 43 543 1398826 N/A N/A 4666 4685 TCGATCCTTTTATCTGCACC 33 544 1398871 N/A N/A 104721 104740 CTCCACTCAAACTCTCCATA 112 545 1398877 N/A N/A 207866 207885 CTCTTGTTACATACTTCCCA 67 546 1398913 N/A N/A 158957 158976 CAGATATTTCAATATACAGT 25 547 1398915 N/A N/A 122623 122642 GCATGGGTTACACTTTGGTA 57 548 1398931 N/A N/A 31689 31708 CCACCACACAGCCCTCACTC 96 549 1398942 N/A N/A 27081 27100 CCACCTTCCTTCTATGTACA 57 550 1398963 N/A N/A 43440 43459 CAGCACTGAGAATCAAGTTC 48 551 1398996 N/A N/A 38482 38501 GACCTCTTTTATTTTAGTCA 70 552 1399019 N/A N/A 101646 101665 TTTCCGGATTATTTCACATT 67 553 1399030 N/A N/A 7225 7244 GCTACTGAAGCTCTCTGGTC 44 554 1399037 N/A N/A 90276 90295 GCTGGGTTTCTTTTTCTCAC 36 555 1399048 670 689 122975 122994 CTGCATAGTCTGTGTCTGCT 26† 556 1399049 N/A N/A 33961 33980 TGCAAACTTCATCCCTACTT 46 557 1399075 N/A N/A 136253 136272 AGTGCTTCATTACCACTTCT 32 558 1399084 N/A N/A 95341 95360 GCATAAACCATAGAGCTCTC 45 559 1399130 N/A N/A 46665 46684 AAGACTTTCAAATTCTAGCC 51 560 1399138 N/A N/A 15399 15418 AACCATGAATATCAATGCCT 30 561 1399167 N/A N/A 105775 105794 TAGACTGTCACTCTCACGCC 96 562 1399180 N/A N/A 24049 24068 GTATTGTTCTCTCCAGGTTT 45 563 1399241 N/A N/A 48042 48061 GCTAATGCATTCCTTACCCC 48 564 1399242 N/A N/A 74672 74691 AGCTTTTCCATACCAGTCCC 74 565 1399278 N/A N/A 30241 30260 ACTCTTGTTTCCATGAGTTT 77 566 1399288 N/A N/A 191322 191341 GATGTCTTTCACCACTCCCA 53 567 1399306 N/A N/A 103107 103126 ACAAGGCTACTCTTCAACTT 109 568 1399336 N/A N/A 87088 87107 GCTGACTCTCCCATTTATTT 31 569 1399357 N/A N/A 228777 228796 ATGCTAAATCAGTTCTCTTG 37 570 1399366 N/A N/A 286108 286127 CGCCCCATGCCACATTTCTC 76 571 1399387 N/A N/A 266250 266269 GCCTTGTACAAACTCTCTAC 75 572 1399413 N/A N/A 115996 116015 CCACATGTCAAACCGTGGCT 91 573 1399414 N/A N/A 167484 167503 ACGCTACATTCCATTTTCTA 76 574

(314) TABLE-US-00010 TABLE 8 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 9 178 1397547 N/A N/A 41113 41132 CCTAGTGCATCATATTCTAC 122 575 1397552 N/A N/A 167698 167717 GCTTTTCTGATATTCACTTA 31 576 1397573 N/A N/A 158959 158978 TGCAGATATTTCAATATACA 16 577 1397586 N/A N/A 186616 186635 GTTCAATATCCTTAGCTCTA 48 578 1397618 N/A N/A 228778 228797 CATGCTAAATCAGTTCTCTT 39 579 1397632 N/A N/A 160222 160241 ATGGCTCTATTCCCTAGTCT 26 580 1397660 N/A N/A 32629 32648 GGGCACAGTCTTATTATGAC 40 581 1397668 N/A N/A 274919 274938 GCTTCCACTTGATAACCTAT 47 582 1397832 N/A N/A 92225 92244 GCTCATTACCCATCCTTATA 31 583 1397850 N/A N/A 277181 277200 GCTCACTCCATGATCTTACT 62 584 1397859 N/A N/A 191323 191342 GGATGTCTTTCACCACTCCC 49 585 1397869 N/A N/A 36146 36165 GCAGGTCCTATTTTTGTTCC 53 586 1397872 N/A N/A 248516 248535 CCTCAGGTCCCACCCAGATC 97 587 1397879 N/A N/A 290135 290154 GTAGATATACAGCTCCCTCA 74 588 1397889 N/A N/A 222749 222768 TAGCATTCCTTCTTCTCAGC 29 589 1397905 N/A N/A 154737 154756 GGTCTCTATATTTTGGTCCC 24 590 1397910 N/A N/A 262028 262047 GCAGCTCATCTAAACCAAAC 93 591 1397937 N/A N/A 104737 104756 TGGGACTATAACTCTACTCC 35 592 1398012 N/A N/A 181001 181020 AGGCATTCAGACTTCTGTCT 19 593 1398018 N/A N/A 283789 283808 TCCTTCCTCACACTGCTCAT 84 594 1398058 671 690 122976 122995 TCTGCATAGTCTGTGTCTGC 14† 595 1398065 N/A N/A 22545 22564 CAGCCTTTCCTTATTTTTGC 20 596 1398066 N/A N/A 51895 51914 AAGCATATTCCTCTATCCTT 84 597 1398068 N/A N/A 20335 20354 GAATCCTCTAAGCATTGTCC 32 598 1398110 N/A N/A 104346 104365 ACTGTGCTCTTCAAGAGCTT 112 599 1398112 N/A N/A 76738 76757 GCTACCTCCTATTCTGCTGA 76 600 1398121 N/A N/A 95363 95382 TCTGGCTACAATTATCCACA 27 601 1398131

N/A N/A 106105 106124 GTTGCTTTCTCCTAACACTT 24 602 1398133 N/A N/A 53483 53502 TGGCTTATGATCTATACACT 23 603 1398143 N/A N/A 16217 16236 GATCAATGTTCCTTTTTGCA 28 604 1398192 N/A N/A 43475 43494 GCAACTCACAACTAATGTCT 43 605 1398215 N/A N/A 211438 211457 TGGCCTTCCCAATTTTCACC 44 606 1398222 N/A N/A 130876 130895 GTAGCCATCCCTCTTCTGCC 68 607 1398235 N/A N/A 87089 87108 TGCTGACTCTCCCATTTATT 52 608 1398289 N/A N/A 28249 28268 ATCTGCTACTGACATAATAC 87 609 1398304 N/A N/A 98899 98918 CTGCTCCACATCTTCTGTCT 78 610 1398316 N/A N/A 25030 25049 ATGACTCCAACATCCACACT 63 611 1398344 N/A N/A 13728 13747 TCCACAATTCAACTAGCAGC 64 612 1398382 N/A N/A 19453 19472 AAGTTTTGTCCAAATCAGGC 30 613 1398457 N/A N/A 30250 30269 CACCCTTCTACTCTTGTTTC 66 614 1398494 N/A N/A 12458 12477 TGGTTGTACCCCTAAGAATC 23 615 1398501 N/A N/A 88705 88724 TGGTCATTCCTTATGAGACC 91 616 1398506 N/A N/A 33962 33981 TTGCAAACTTCATCCCTACT 56 617 1398524 N/A N/A 207867 207886 TCTCTTGTTACATACTTCCC 78 618 1398528 N/A N/A 90300 90319 TTGGGACAATATCATGCCAA 27 619 1398559 N/A N/A 66406 66425 GCCACTGCTCATCTCCCTCA 36 620 1398560 N/A N/A 15499 15518 GCACATTTACATGCTCCCTT 52 621 1398569 N/A N/A 96508 96527 TCTACAGTTAATATTTGCCC 19 622 1398578 N/A N/A 10442 10461 GCTTCTGGAACCATCTTAAT 47 623 1398603 N/A N/A 38617 38636 AGCCAAGTTCATATCAAACT 24 624 1398617 N/A N/A 196847 196866 GCTCTCAACTTTGATGTTCA 60 625 1398653 N/A N/A 9622 9641 AAGCTTCCATATTAGGACCA 20 626 1398673 N/A N/A 116378 116397 TCTGCAGGCCTCAATCTGCT 79 627 1398702 N/A N/A 177973 177992 TGTGCCTCTTCTTCCAGCAA 40 628 1398787 N/A N/A 218615 218634 TCATTGGTTTTAATCAGTTC 40 629 1398879 N/A N/A 286122 286141 CACAGCGATCAAACCGCCCC 82 630 1398896 N/A N/A 173494 173513 GCACATCACAACAATTCTCC 28 631 1398916 N/A N/A 8087 8106 TGATGCACATATCCAGGCTT 19 632 1398953 N/A N/A 50175 50194 GTGACACAACATCAGAGGCA 51 633 1398982 N/A N/A 101647 101666 GTTTCCGGATTATTTCACAT 49 634 1399000 N/A N/A 59436 59455 GCATCACAATTCTTCATTGC 75 635 1399028 N/A N/A 103109 103128 GAACAAGGCTACTCTTCAAC 57 636 1399045 N/A N/A 24060 24079 GCCTTTACACTGTATTGTTC 21 637 1399050 N/A N/A 27082 27101 CCCACCTTCCTTCTATGTAC 36 638 1399057 N/A N/A 122706 122725 GCAGACCCAATATATTAGGA 63 639 1399058 N/A N/A 271278 271297 AGTACTCCATCTCCTCCCAT 78 640 1399139 N/A N/A 31690 31709 ACCACCACACAGCCCTCACT 75 641 1399181 N/A N/A 153192 153211 GTTTCTGTAACATTTGGTCA 16 642 1399216 N/A N/A 85285 85304 GCTGCTTATTTTCATCTAAT 14 643 1399248 N/A N/A 83591 83610 CTCAACCTATACCACTATCC 94 644 1399291 N/A N/A 236468 236487 TGTCAATTTTCCCTTTCATC 21 645 1399331 N/A N/A 48068 48087 CACCATGCAGATTATCAGCT 32 646 1399354 N/A N/A 7248 7267 TCTCATACTCTGCCCATCAA 58 647 1399431 N/A N/A 46666 46685 AAAGACTTTCAAATTCTAGC 55 648 1399449 N/A N/A 4739 4758 CTGCAGCCTCCACACAGCTT 57 649 1399490 N/A N/A 266251 266270 TGCCTTGTACAAACTCTCTA 50 650 1399515 N/A N/A 136339 136358 GCACTTAGTTCCACCATCAT 46 651

(315) TABLE-US-00011 TABLE 9 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 19 178 1397582 N/A N/A 173495 173514 TGCACATCACAACAATTCTC 41 652 1397664 487 506 N/A N/A ATGTCTCTTTGGCGACGGTG 38 653 1397672 N/A N/A 7253 7272 GTTCATCTCATACTCTGCCC 31 654 1397684 N/A N/A 266253 266272 GCTGCCTTGTACAAACTCTC 69 655 1397697 N/A N/A 277244 277263 GCTGCTGTCTTCTTTGCACA 40 656 1397699 N/A N/A 46722 46741 GCACTCATAACTAGGGTTCC 51 657 1397705 N/A N/A 12535 12554 CCTCCTTTTTATTCTGTCTA 40 658 1397716 N/A N/A 76749 76768 CCTGACCACTTGCTACCTCC 77 659 1397733 N/A N/A 283790 283809 TTCCTTCCTCACACTGCTCA 70 660 1397734 N/A N/A 236609 236628 GCACATGTTTTCTTTGTAAC 34 661 1397783 N/A N/A 27083 27102 ACCCACCTTCCTTCTATGTA 73 662 1397786 N/A N/A 8088 8107 TTGATGCACATATCCAGGCT 12 663 1397928 N/A N/A 153231 153250 ATGCATACTCTTTAAGGAAC 35 664 1397933 N/A N/A 54055 54074 GCTAGGACAGATTAGCACCC 25 665 1397950 672 691 122977 122996 ATCTGCATAGTCTGTGTCTG 33† 666 1397955 N/A N/A 5176 5195 AACCTGTCTTAACTAGCCCT 44 667 1398059 N/A N/A 103466 103485 GGTATCTGTCTACACCTGCT 42 668 1398076 N/A N/A 25053 25072 TGTGACTCAGATCCAAGGTC 30 669 1398092 N/A N/A 228780 228799 AGCATGCTAAATCAGTTCTC 41 670 1398162 N/A N/A 59439 59458 AGGGCATCACAATTCTTCAT 54 671 1398177 N/A N/A 50216 50235 CTGCAGTCTTACTCTTGGAT 50 672 1398185 N/A N/A 96751 96770 TGTCTCTTCTGCAACTTACT 37 673 1398202 N/A N/A 271283 271302 GGGTTAGTACTCCATCTCCT 43 674 1398229 N/A N/A 248590 248609 CCCTTCGCTTTGAATCCTTT 70 675 1398243 N/A N/A 38643 38662 ATGCACGACTTCTATAACTT 36 676 1398262 N/A N/A 101648 101667 GGTTTCCGGATTATTTCACA 16 677 1398291 N/A N/A 51927 51946 AGTTGCTGATATACTTGGAC 38 678 1398296 N/A N/A 32657 32676 ACAGTTTCTTGATTTTTCCC 41 679 1398310 N/A N/A 181219 181238 CATCACATCTTTTAATGCTT 76 680 1398331 N/A N/A 92226 92245 TGCTCATTACCCATCCTTAT 50 681 1398409 N/A N/A 36412 36431 GAGCTCTTTCCTCACTGGGA 48 682 1398441 N/A N/A 28296 28315 TCCAATGTTCTCATTGCCCA 35 683 1398444 N/A N/A 30251 30270 CCACCCTTCTACTCTTGTTT 58 684 1398463 N/A N/A 66424 66443 TCCTATCCTATCTCTCTGGC 63 685 1398468 N/A N/A 167726 167745 ATTTCTTACACTTTCAAGAT 69 686 1398472 N/A N/A 219500 219519 GCTGTTCTATTAACTTCCAT 27 687 1398481 N/A N/A 34438 34457 ATCTGATTTTGAAACCAGTC 31 688 1398487 N/A N/A 16323 16342 GTATCTTCATTTAATCACTT 30 689 1398515 N/A N/A 15501 15520 GAGCACATTTACATGCTCCC 85 690 1398517 N/A N/A 48077 48096 CTGGACTCTCACCATGCAGA 46 691 1398545 N/A N/A 13730 13749 CCTCCACAATTCAACTAGCA 59 692 1398549 N/A N/A 158960 158979 GTGCAGATATTTCAATATAC 26 693 1398607 N/A N/A 95375 95394 TCATATTCTTCATCTGGCTA 66 694 1398620 N/A N/A 19474 19493 ACTCTATTCATCCTACCCCA 40 695 1398631 N/A N/A 24067 24086 CCTCACAGCCTTTACACTGT 57 696 1398656 N/A N/A 131385 131404 TTGTTATCAAGATTTCACCC 34 697 1398665 N/A N/A 41114 41133 TCCTAGTGCATCATATTCTA 64 698 1398712 N/A N/A 22560 22579 TTTGAACTACTAGATCAGCC 33 699 1398726 N/A N/A 286123 286142 GCACAGCGATCAAACCGCCC 56 700 1398740 N/A N/A 85286 85305 TGCTGCTTATTTTCATCTAA 34 701 1398744 N/A N/A 207876 207895 CCACTAGTATCTCTTGTTAC 37 702 1398827 N/A N/A 197165 197184 GGTGATTCAGTCTCTGTCCT 66 703 1398847 N/A N/A 10186 10205 GCTTTCAAATATCCTTGGCC 30 704 1398880 N/A N/A 20339 20358 CCATGAATCCTCTAAGCATT 45 705 1398889 N/A N/A 104397 104416 CCAGCCTATTTCTCTCCTAA 49 706 1398900 N/A N/A 177974 177993 TTGTGCCTCTTCTTCCAGCA 35 707 1398901 N/A N/A 211495 211514 GCAGAATATCCTTCATAGTC 39 708 1398951 N/A N/A 83772 83791 GTCTCTGACTTTTTCCGATT 64 709 1398979 N/A N/A 136341 136360 CTGCACTTAGTTCCACCATC 37 710 1399015 N/A N/A 154739 154758 AAGGTCTCTATATTTTGGTC 29 711 1399054 N/A N/A 10452 10471 CTCCACTCCTGCTTCTGGAA 71 712 1399055 1147 1166 191546 191565 ACTTGTCAACGGCATCAGGG 52 713 1399086 N/A N/A 88706 88725 CTGGTCATTCCTTATGAGAC 76 714 1399090 N/A N/A 98900 98919 GCTGCTCCACATCTTCTGTC 39 715 1399100 N/A N/A 223642 223661 CTTTTCAAGCAAGGAAAAAC 75 716 1399144 N/A N/A 104785 104804 TCTCAATAGATACTTATCGC 51 717 1399155 N/A N/A 186702 186721 GCTCACTCATGCCTTCTGCA 59 718 1399158 N/A N/A 31692 31711 GCACCACCACACAGCCCTCA 90 719 1399222 N/A N/A 161363 161382 CACAGCTTTGTAACCTGCTC 29 720 1399280 N/A N/A 43544 43563 CAGCAAGGCCACTCTCCATA 73 721 1399315 N/A N/A 274952 274971 CTAGCACCATTTCCTCATCC 57 722 1399337 N/A N/A 90302 90321 CCTTGGGACAATATCATGCC 41 723 1399339 N/A N/A 106107 106126 TGGTTGCTTTCTCCTAACAC 69 724 1399382 N/A N/A 87095 87114 CTGTAGTGCTGACTCTCCCA 60 725 1399415 N/A N/A 116885 116904 GCTGTGAACTTCCACTGCTT 60 726 1399419 N/A N/A 262030 262049 AAGCAGCTCATCTAAACCAA 69 727 1399499 N/A N/A 291487 291506 GTTGCTTTACCTCTAAGGTC 38 728

(316) TABLE-US-00012 TABLE 10 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 22 178 1396900 N/A N/A 96766 96785 GCCATCTCATTTAGTTGTCT 34 729 1397542 N/A N/A 5589 5608 CCCTTCTACCAACACTTCGC 43 730 1397603 674 693 122979 122998 CCATCTGCATAGTCTGTGTC 8† 731 1397611 N/A N/A 10202 10221 GTTTCATACACTCAAGGCTT 55 732 1397679 N/A N/A 223644 223663 AACTTTTCAAGCAAGGAAAA 98 733 1397688 N/A N/A 286281 286300

ACGCAAATCCCTGCCAGTGT 55 734 1397712 N/A N/A 87234 87253 GTCTCCTCTGTCAACACAAC 33 735 1397730 N/A N/A 90345 90364 CCATTAGCCTTGCTATTCAT 55 736 1397755 N/A N/A 46765 46784 TGGTAACTATTTCTGGGCAA 41 737 1397780 N/A N/A 136363 136382 GTGGTCTCAGCATCCTGTTC 61 738 1397794 N/A N/A 186707 186726 AGCCTGCTCACTCATGCCTT 62 739 1397810 1148 1167 191547 191566 TACTTGTCAACGGCATCAGG 54 740 1397827 N/A N/A 104398 104417 TCCAGCCTATTTCTCTCCTA 62 741 1397875 N/A N/A 59746 59765 GCACTTGATTCCATTTCCTC 60 742 1397903 N/A N/A 54223 54242 TGCTAAGATCTCATTCTAGA 60 743 1397908 N/A N/A 12566 12585 CCCAACTTAATTTTTTCCAA 29 744 1397921 N/A N/A 88810 88829 GTTGACCATTCAAAGGTCCC 26 745 1397961 N/A N/A 36626 36645 TCCCATCTAAATTTTGCTTT 62 746 1397984 N/A N/A 178256 178275 ATGCTTTTTTCACAACAGCA 35 747 1398100 N/A N/A 16368 16387 ACAGGTTTTCCCCACATCTT 43 748 1398101 N/A N/A 41191 41210 ACACCATCACAACAGAACCC 51 749 1398116 N/A N/A 103557 103576 TCACCAACTCTTCTTTAGCA 41 750 1398120 N/A N/A 7255 7274 CTGTTCATCTCATACTCTGC 49 751 1398124 N/A N/A 66434 66453 GCCTCCTACTTCCTATCCTA 69 752 1398155 N/A N/A 22565 22584 GCTTGTTTGAACTACTAGAT 56 753 1398182 N/A N/A 98901 98920 TGCTGCTCCACATCTTCTGT 49 754 1398260 N/A N/A 161377 161396 TCTCCATTCAAATCCACAGC 47 755 1398280 N/A N/A 27096 27115 TGGGTAAATAATTACCCACC 80 756 1398298 N/A N/A 213022 213041 GGTAGTTATCTCTATCCCTC 42 757 1398300 N/A N/A 10457 10476 GAACCCTCCACTCCTGCTTC 67 758 1398313 N/A N/A 291771 291790 GGTGACACTCAAATCTGTGT 52 759 1398334 N/A N/A 283828 283847 CCGTTCCTTTCCACCCTGCT 58 760 1398343 N/A N/A 50217 50236 ACTGCAGTCTTACTCTTGGA 70 761 1398360 N/A N/A 28297 28316 TTCCAATGTTCTCATTGCCC 26 762 1398425 N/A N/A 104812 104831 GAGGTCATAAAAATCATGCT 57 763 1398451 N/A N/A 271286 271305 CCTGGGTTAGTACTCCATCT 47 764 1398589 N/A N/A 281185 281204 CACCACAACTTTTATCATCT 27 765 1398591 N/A N/A 219603 219622 GGCGACATTCCTCCAGTCTT 30 766 1398598 1765 1784 262082 262101 GTTCACTAATCATGTTGGCC 62 767 1398602 N/A N/A 38722 38741 ACCAGACCTTCTCACTTCGA 64 768 1398618 N/A N/A 158961 158980 AGTGCAGATATTTCAATATA 40 769 1398621 N/A N/A 15502 15521 AGAGCACATTTACATGCTCC 92 770 1398640 N/A N/A 85287 85306 GTGCTGCTTATTTTCATCTA 40 771 1398690 N/A N/A 8089 8108 ATTGATGCACATATCCAGGC 26 772 1398692 N/A N/A 48079 48098 ATCTGGACTCTCACCATGCA 53 773 1398770 N/A N/A 30253 30272 CACCACCCTTCTACTCTTGT 61 774 1398804 N/A N/A 95377 95396 TTTCATATTCTTCATCTGGC 35 775 1398851 N/A N/A 153295 153314 AAGCATCTTTTACTATCTGC 65 776 1398860 N/A N/A 83789 83808 CCAGAAGTGCTTTCAAGGTC 82 777 1398866 N/A N/A 208224 208243 GCAGGTGAATAACTACTGGA 31 778 1398867 N/A N/A 34538 34557 CCAGACTCTACTCAAGGTTT 45 779 1398905 N/A N/A 275135 275154 GCTCTTGGCCTAATCACTCT 82 780 1398952 N/A N/A 167728 167747 GAATTTCTTACACTTTCAAG 50 781 1398962 N/A N/A 117302 117321 TTAGCTTCTTATATTGCACA 73 782 1399016 N/A N/A 248595 248614 GCAGTCCCTTCGCTTTGAAT 50 783 1399021 N/A N/A 20340 20359 GCCATGAATCCTCTAAGCAT 34 784 1399121 N/A N/A 131437 131456 GCCACCTACAAATTGAGCCT 42 785 1399125 N/A N/A 25099 25118 CTTACATCATTTTCTTGCAG 71 786 1399137 N/A N/A 106309 106328 TTGCAGTTCTCATATCATAA 21 787 1399156 N/A N/A 174177 174196 TGGCCATGCTTTATCAGGGA 57 788 1399173 N/A N/A 101704 101723 TTACACTCATTTTTAGTAGC 49 789 1399197 N/A N/A 92227 92246 ATGCTCATTACCCATCCTTA 41 790 1399227 N/A N/A 31693 31712 TGCACCACCACACAGCCCTC 79 791 1399232 N/A N/A 228781 228800 TAGCATGCTAAATCAGTTCT 37 792 1399237 489 508 N/A N/A GCATGTCTCTTTGGCGACGG 43 793 1399238 N/A N/A 32729 32748 GTACAAGCACAGATTAACTC 40 794 1399275 N/A N/A 154740 154759 GAAGGTCTCTATATTTTGGT 48 795 1399279 N/A N/A 78498 78517 CGTAGTGTCATAATTGCTCT 59 796 1399282 N/A N/A 197970 197989 TCCCATTCTCTCATGACCTA 48 797 1399297 N/A N/A 13861 13880 CTACTCTATCATCACCTGGA 67 798 1399303 N/A N/A 51952 51971 CCATACTGATAAATCTGCAT 71 799 1399318 N/A N/A 266509 266528 ACTTCATCAATGAAGTGCTA 45 800 1399334 N/A N/A 24084 24103 ACCCCAGCATGCTCCCACCT 91 801 1399348 N/A N/A 19476 19495 TAACTCTATTCATCCTACCC 101 802 1399391 N/A N/A 236644 236663 TGCTTCTCAGGATTCGCACC 41 803 1399420 N/A N/A 43883 43902 GCATCACACAACAGCTGACA 41 804 1399447 N/A N/A 181234 181253 GGTAGTTTAATTCACCATCA 47 805

(317) TABLE-US-00013 TABLE 11 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 21 178 1397526 675 694 122980 122999 CCCATCTGCATAGTCTGTGT 6† 806 1397589 N/A N/A 25214 25233 CCAGGGCCTACTCCTGGCCA 92 807 1397630 N/A N/A 83865 83884 GCTGGCATTTACAAGCATCT 93 808 1397644 N/A N/A 92228 92247 AATGCTCATTACCCATCCTT 63 809 1397696 N/A N/A 178301 178320 AGTCTGTCAACCCACTTGCT 78 810 1397720 N/A N/A 267011 267030 TGCTAATGTCACCACTTACT 63 811 1397728 N/A N/A 99000 99019 TTGTTACATAAAACCTGCTC 84 812 1397744 N/A N/A 101944 101963 GTTGACTATTTATATAAGTC 46 813 1397787 N/A N/A 117540 117559 ACTCTTACTTTCATCTGGCA 74 814 1397790 1769 1788 262086 262105 CTTGGTTCACTAATCATGTT 84 815 1397835 N/A N/A 30257 30276 GTAACACCACCCTTCTACTC 78 816 1397847 N/A N/A 38726 38745 CAGCACCAGACCTTCTCACT 30 817 1397852 N/A N/A 59748 59767 ATGCACTTGATTCCATTTCC 58 818 1397866 N/A N/A 154741 154760 TGAAGGTCTCTATATTTTGG 34 819 1397890 490 509 N/A N/A TGCATGTCTCTTTGGCGACG 65 820 1397976 N/A N/A 199218 199237 GCCATCAATTGTCACCACCT 54 821 1397986 N/A N/A 286286 286305 TAGATACGCAAATCCCTGCC 88 822 1398001 N/A N/A 85440 85459 AGACTCATGATCTACTTCCT 42 823 1398005 N/A N/A 12584 12603 ATTCTCTTATATTCCTTACC 51 824 1398011 N/A N/A 213023 213042 TGGTAGTTATCTCTATCCCT 43 825 1398015 N/A N/A 48250 48269 ATCCCATTCTGTCTAGCCCC 68 826 1398019 N/A N/A 13864 13883 TGGCTACTCTATCATCACCT 65 827 1398023 N/A N/A 7259 7278 GCCACTGTTCATCTCATACT 32 828 1398032 N/A N/A 219852 219871 GTGCTACTTATAATGCATGT 50 829 1398045 N/A N/A 10203 10222 AGTTTCATACACTCAAGGCT 38 830 1398108 1149 1168 191548 191567 ATACTTGTCAACGGCATCAG 62 831 1398211 N/A N/A 88811 88830 CGTTGACCATTCAAAGGTCC 75 832 1398284 N/A N/A 162414 162433 CCGCAACAATTATCTGGCCC 31 833 1398323 N/A N/A 50423 50442 GCTCTCCCTTTGTAGAGCCC 85 834 1398354 N/A N/A 41284 41303 CTTGATTACTTCAACTTAGT 66 835 1398390 N/A N/A 16369 16388 TACAGGTTTTCCCCACATCT 42 836 1398417 N/A N/A 238484 238503 TCCAGCAGTATCCACCTGCT 101 837 1398432 N/A N/A 275150 275169 GGGAATTCACTTCCTGCTCT 70 838 1398453 N/A N/A 104399 104418 GTCCAGCCTATTTCTCTCCT 15 839 1398460 N/A N/A 19477 19496 GTAACTCTATTCATCCTACC 51 840 1398484 N/A N/A 167730 167749 TTGAATTTCTTACACTTTCA 66 841 1398498 N/A N/A 8112 8131 ATCCCTGTTTCATAAAGCTA 42 842 1398525 N/A N/A 51953 51972 GCCATACTGATAAATCTGCA 46 843 1398554 N/A N/A 283831 283850 AGTCCGTTCCTTTCCACCCT 69 844 1398576 N/A N/A 31694 31713 CTGCACCACCACACAGCCCT 92 845 1398604 N/A N/A 158963 158982 TAAGTGCAGATATTTCAATA 40 846 1398619 N/A N/A 95409 95428 GCTGTCTGTACCACTCTAAA 39 847 1398638 N/A N/A 182231 182250 CTTTCATGCTACCACTGCAT 54 848 1398648 N/A N/A 131438 131457 TGCCACCTACAAATTGAGCC 61 849 1398660 N/A N/A 66435 66454 CGCCTCCTACTTCCTATCCT 72 850 1398675 N/A N/A 174406 174425 TCAAGCTGCATCAGCCAGGC 49 851 1398682 N/A N/A 153965 153984 TCCATCTTGCACTCTGTTCT 38 852 1398779 N/A N/A 20341 20360 AGCCATGAATCCTCTAAGCA 25 853 1398801 N/A N/A 248601 248620 GTTCTTGCAGTCCCTTCGCT 41 854 1398813 N/A N/A 47184 47203 GAGTCATGTCTTACTGTTCT 44 855 1398833 N/A N/A 22636 22655 GTCAAATGCAACAACTTACA 49 856 1398836 N/A N/A 106310 106329 GTTGCAGTTCTCATATCATA 29 857 1398863 N/A N/A 24092 24111 CTTCCAACACCCCAGCATGC 75 858 1398912 N/A N/A 104841 104860 CCCGTTGATCGATTTCCCCA 87 859 1398957 N/A N/A 90350 90369 GATGTCCATTAGCCTTGCTA 44 860 1398971 N/A N/A 15580 15599 ACTCAATATCCTACCTCTCC 72 861 1398978 N/A N/A 87240 87259 ATGGTTGTCTCCTCTGTCAA 42 862 1398988 N/A N/A 28304 28323 TCCTCCATTCCAATGTTCTC 54 863 1399031 N/A N/A 136850 136869 ACCACATGCTCTCATATGCA 63 864 1399117 N/A N/A 78587 78606 GCCATTGATCACTTCATCAC 79 865 1399118 N/A N/A 5704 5723 GCAGACCTATTTTCTAAGCT 25 866 1399165 N/A N/A 103651 103670 GCAGGACTTATCACTCCACA 40 867 1399191 N/A N/A 97296 97315 GCTCAATTAAACCACAGTTT 33 868 1399194 N/A N/A 223645 223664 CAACTTTTCAAGCAAGGAAA 45 869 1399208 N/A N/A 10463 10482 GCTCATGAACCCTCCACTCC 78 870 1399215 N/A N/A 291914 291933 ATGGTATTTTTTCCTCCCCT 44 871 1399235 N/A N/A 36627 36646 ATCCCATCTAAATTTTGCTT 78 872 1399283 N/A N/A 34543 34562 TTGCACCAGACTCTACTCAA 61 873 1399320 N/A N/A 281267 281286 CTGCACTACATTGCTTCATA

62 874 1399321 N/A N/A 271407 271426 GCTTAGGCCACCCTCTCTTC 95 875 1399365 N/A N/A 27132 27151 CTGGGTACATAATACTAGGT 23 876 1399368 N/A N/A 186890 186909 TGGCAAAACAACCATATGCT 62 877 1399377 N/A N/A 32758 32777 TTGGTTCATTATTTAAGCTT 29 878 1399399 N/A N/A 228782 228801 ATAGCATGCTAAATCAGTTC 42 879 1399448 N/A N/A 54343 54362 CTGCTATACAGCTACTTGTA 82 880 1399485 N/A N/A 208241 208260 TCTATCAGTCATACCAGGCA 45 881 1399507 N/A N/A 44380 44399 CACAAATTTTATCACATCCC 89 882

(318) TABLE-US-00014 TABLE 12 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 16 178 1397565 N/A N/A 54943 54962 GCTCATTATCTCATTTGACT 54 883 1397590 N/A N/A 27146 27165 GCTGACAAACTGTACTGGGT 31 884 1397602 N/A N/A 15582 15601 CCACTCAATATCCTACCTCT 56 885 1397638 N/A N/A 16370 16389 CTACAGGTTTTCCCCACATC 47 886 1397646 N/A N/A 85572 85591 GCCCATCCAAAGCCCTACCT 51 887 1397648 N/A N/A 88961 88980 GCTACTCATTTATTATACAA 29 888 1397671 N/A N/A 131531 131550 CATCTATAATACCATCTGGT 43 889 1397694 N/A N/A 154031 154050 TAGCACATTTACTTATGTGC 91 890 1397702 N/A N/A 30260 30279 CTGGTAACACCACCCTTCTA 99 891 1397704 1150 1169 191549 191568 GATACTTGTCAACGGCATCA 41 892 1397710 N/A N/A 223646 223665 GCAACTTTTCAAGCAAGGAA 21 893 1397721 N/A N/A 59835 59854 GCCTCAAACTCTCTCTGTAC 89 894 1397745 N/A N/A 22653 22672 TCCAGCTACATTTGCCTGTC 43 895 1397753 N/A N/A 34544 34563 CTTGCACCAGACTCTACTCA 49 896 1397782 N/A N/A 199233 199252 TCGAACTTGAACTATGCCAT 37 897 1397821 N/A N/A 12589 12608 GTAGCATTCTCTTATATTCC 24 898 1397854 1770 1789 262087 262106 CCTTGGTTCACTAATCATGT 51 899 1397860 N/A N/A 50509 50528 CCAGGTTTAAATTCCAGGTT 19 900 1397873 N/A N/A 281352 281371 ATGTTGCTTTATTCTTGCTC 45 901 1397882 N/A N/A 44382 44401 TGCACAAATTTTATCACATC 45 902 1397936 N/A N/A 286566 286585 GCACAGTTACCTCCTTGGGA 33 903 1397949 N/A N/A 20342 20361 AAGCCATGAATCCTCTAAGC 43 904 1397989 N/A N/A 10464 10483 TGCTCATGAACCCTCCACTC 84 905 1398009 N/A N/A 106333 106352 GCTCATCTCCCCCCATTTCT 85 906 1398073 N/A N/A 178316 178335 CTAGAGCTTTTTCCTAGTCT 44 907 1398225 N/A N/A 183299 183318 GATTTCATTTTACCCCAGCC 39 908 1398241 N/A N/A 275456 275475 AGTCATCTTCTCTACCGTGT 60 909 1398251 N/A N/A 208257 208276 TGCTACCCATCTGTTCTCTA 44 910 1398259 N/A N/A 8147 8166 CCTCTCTGAATACTCAGCTA 43 911 1398267 N/A N/A 10204 10223 CAGTTTCATACACTCAAGGC 29 912 1398326 N/A N/A 213471 213490 GCTGGCTTTTTTTTAGCTTT 63 913 1398335 N/A N/A 87241 87260 CATGGTTGTCTCCTCTGTCA 23 914 1398368 N/A N/A 48252 48271 ACATCCCATTCTGTCTAGCC 57 915 1398370 N/A N/A 33011 33030 GCATAGGTTTAAATTCTAAC 33 916 1398398 N/A N/A 187170 187189 CCTCTTTTCATCAGAGCCCA 66 917 1398405 N/A N/A 95443 95462 AAGCTACTCTTCTACCCCAA 45 918 1398442 N/A N/A 256336 256355 ACAGCTTCTTCCATCCACTG 72 919 1398450 N/A N/A 47214 47233 CTCCAACCTAAGCCTTTACT 88 920 1398478 N/A N/A 31695 31714 GCTGCACCACCACACAGCCC 74 921 1398483 N/A N/A 228784 228803 TGATAGCATGCTAAATCAGT 42 922 1398527 N/A N/A 104869 104888 TTGGTTGTAGAACCCAACCA 116 923 1398536 N/A N/A 97312 97331 GCATACAACAAACTCAGCTC 37 924 1398548 N/A N/A 103653 103672 TGGCAGGACTTATCACTCCA 22 925 1398553 N/A N/A 92231 92250 CTTAATGCTCATTACCCATC 66 926 1398558 N/A N/A 24095 24114 CTTCTTCCAACACCCCAGCA 75 927 1398564 279 298 83948 83967 GGCTTCTACCACATTGGTGA 32 928 1398608 N/A N/A 283832 283851 CAGTCCGTTCCTTTCCACCC 55 929 1398615 N/A N/A 104400 104419 GGTCCAGCCTATTTCTCTCC 33 930 1398639 N/A N/A 122796 122815 CTGCATGTCTACAAAGTGTA 76 931 1398662 N/A N/A 162429 162448 GCACAGGACAATCATCCGCA 27 932 1398664 N/A N/A 219948 219967 ACTCATGGCTTCCCTGCTCA 60 933 1398689 N/A N/A 137243 137262 GCTCTGTTCTAGTACAACCA 42 934 1398697 N/A N/A 41313 41332 GATGGTCTCACCCAAAGAAC 69 935 1398802 N/A N/A 13865 13884 ATGGCTACTCTATCATCACC 72 936 1398830 N/A N/A 38852 38871 CCTTCTTACAATTATGCTCT 74 937 1398840 N/A N/A 7260 7279 TGCCACTGTTCATCTCATAC 32 938 1398878 N/A N/A 174492 174511 TCACATTCCCTCATCAGCAC 72 939 1398914 N/A N/A 167732 167751 TGTTGAATTTCTTACACTTT 50 940 1398919 N/A N/A 90363 90382 GTACTACAAATCAGATGTCC 40 941 1398990 N/A N/A 28306 28325 TCTCCTCCATTCCAATGTTC 37 942 1399072 N/A N/A 291954 291973 TGGTTCCCCAACTCCACAGT 58 943 1399079 N/A N/A 154743 154762 ATTGAAGGTCTCTATATTTT 48 944 1399151 N/A N/A 52321 52340 ATGCAATATCATATTCATCA 28 945 1399157 N/A N/A 238498 238517 ACTTTGTTATACTATCCAGC 34 946 1399196 N/A N/A 36991 37010 AAGAGATCCATCTCTGCTCA 47 947 1399206 N/A N/A 25225 25244 CCCTCATTCATCCAGGGCCT 28 948 1399246 N/A N/A 5730 5749 TCATTTCTTTTCTACAGCCA 30 949 1399256 N/A N/A 66493 66512 TGCACTCTTATCTTTCCCCT 40 950 1399268 N/A N/A 102007 102026 GGTTTATGTTCAAACTGTCT 32 951 1399272 N/A N/A 99137 99156 ATGCCTCTGATACACTGACT 37 952 1399312 N/A N/A 78589 78608 CTGCCATTGATCACTTCATC 68 953 1399345 N/A N/A 19478 19497 GGTAACTCTATTCATCCTAC 31 954 1399396 N/A N/A 267016 267035 GCCACTGCTAATGTCACCAC 72 955 1399430 N/A N/A 117541 117560 TACTCTTACTTTCATCTGGC 21 956 1399452 676 695 122981 123000 TCCCATCTGCATAGTCTGTG 3† 957 1399482 N/A N/A 271736 271755 ACGGCATGACAATCTTGGGA 37 958 1399483 N/A N/A 159315 159334 CAGCAACCAATGCCATGTCT 41 959

(319) TABLE-US-00015 TABLE 13 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 16 178 1394454 1151 1170 191550 191569 AGATACTTGTCAACGGCATC 40 960 1394557 677 696 122982 123001 CTCCCATCTGCATAGTCTGT 3T 961 1397525 N/A N/A 10208 10227 TCACCAGTTTCATACACTCA 28 962 1397548 N/A N/A 19479 19498 TGGTAACTCTATTCATCCTA 41 963 1397550 N/A N/A 80223 80242 GCTTCTCTCTCTATAACACC 72 964 1397596 N/A N/A 228920 228939 GAGGTGCCCACACATGCACA 53 965 1397616 N/A N/A 139947 139966 GCACTGCTTTTCTATTTCCA 92 966 1397627 N/A N/A 88962 88981 AGCTACTCATTTATTATACA 46 967 1397661 N/A N/A 33210 33229 TGTTAATTCATAGACTCTCC 40 968 1397673 N/A N/A 283833 283852 TCAGTCCGTTCCTTTCCACC 93 969 1397674 N/A N/A 7461 7480 TCGGAACATTTATACTATTT 28 970 1397675 N/A N/A 187172 187191 AGCCTCTTTTCATCAGAGCC 51 971 1397676 N/A N/A 54944 54963 TGCTCATTATCTCATTTGAC 37 972 1397756 N/A N/A 22716 22735 ATGCTCCCACTGAATGGCTC 19 973 1397824 N/A N/A 154041 154060 GCGCATTTACTAGCACATTT 14 974 1397883 N/A N/A 5996 6015 GCAGCAGGTTTCCATAAACT 24 975 1397907 N/A N/A 41368 41387 CTGTTTAGTATTCACAACAT 37 976 1397914 N/A N/A 52343 52362 GCCTTACAGATCCTCATCTT 82 977 1397929 N/A N/A 45391 45410 TCATATCTAATTCAGTGTTC 52 978 1397931 N/A N/A 267020 267039 ACGGGCCACTGCTAATGTCA 45 979 1397940 N/A N/A 104401 104420 TGGTCCAGCCTATTTCTCTC 19 980 1397970 N/A N/A 95445 95464 GTAAGCTACTCTTCTACCCC 46 981 1398053 N/A N/A 38853 38872 CCCTTCTTACAATTATGCTC 64 982 1398079 N/A N/A 178317 178336 GCTAGAGCTTTTTCCTAGTC 40 983 1398132 N/A N/A 50555 50574 CCAAGATTACTTCTTTTCCT 42 984 1398153 N/A N/A 281405 281424 GTCACTCATAACTCATGCTT 76 985 1398246 2362 2381 292346 292365 GCTGTCCAACTTCAGAGGCT 43 986 1398293 N/A N/A 106425 106444 GCTATGCTATCTTAACGCAT 48 987 1398325 N/A N/A 87264 87283 TGGAGATTTATCCTATACTA 34 988 1398339 N/A N/A 8253 8272 GCATGTTTCTTCAACATGTA 49 989 1398362 1772 1791 262089 262108 ATCCTTGGTTCACTAATCAT 82 990 1398375 491 510 N/A N/A CTGCATGTCTCTTTGGCGAC 33 991 1398376 N/A N/A 131537 131556 ATGCACCATCTATAATACCA 41 992 1398399 N/A N/A 97654 97673 GCTCACAACAACCCCTCATA 52 993 1398416 N/A N/A 208267 208286 GAGGATTCTTTGCTACCCAT 51 994 1398424 N/A N/A 271750 271769 ATGCCATCACTTGAACGGCA 122 995 1398535 N/A N/A 27288 27307 GCACTATTCTCTCTTGTGTA 44 996 1398626 N/A N/A 102167 102186 GGATCTTCATTCTCTAAGCT 45 997 1398635 N/A N/A 258189 258208 GCTGTAGTACCCTTTTCTCT 46 998 1398681 N/A N/A 183302 183321 GCTGATTTCATTTTACCCCA 27 999 1398687 N/A N/A 219992 220011 GCCCACTATCTTTTAAGTTT 28 1000 1398707 N/A N/A 92232 92251 CCTTAATGCTCATTACCCAT 68 1001 1398738 N/A N/A 103654 103673 TTGGCAGGACTTATCACTCC 40 1002

1398748 N/A N/A 16371 16390 ACTACAGGTTTTCCCCACAT 56 1003 1398768 N/A N/A 223648 223667 GTGCAACTTTTCAAGCAAGG 17 1004 1398780 N/A N/A 167733 167752 ATGTTGAATTTCTTACACTT 47 1005 1398814 N/A N/A 99771 99790 CCCCCAAATTTTTCATGGCA 63 1006 1398829 N/A N/A 163587 163606 GTGTATTTATCATATTTGCT 20 1007 1398869 N/A N/A 66494 66513 TTGCACTCTTATCTTTCCCC 36 1008 1398897 N/A N/A 34545 34564 ACTTGCACCAGACTCTACTC 57 1009 1398922 N/A N/A 275946 275965 TGTGTCTTTTTCCATGTGCA 11 1010 1398966 N/A N/A 118307 118326 GCTCAGTCATATTTGCAAAT 37 1011 1398974 N/A N/A 287613 287632 GTTCAGGAACTCCTTTGCTA 61 1012 1399006 N/A N/A 159402 159421 GCCTGAGAGACTCATCCCTC 49 1013 1399038 281 300 83950 83969 TTGGCTTCTACCACATTGGT 23 1014 1399044 N/A N/A 30262 30281 CCCTGGTAACACCACCCTTC 69 1015 1399056 N/A N/A 24096 24115 GCTTCTTCCAACACCCCAGC 42 1016 1399081 N/A N/A 241296 241315 GTTAGCCTTTCCTTATCTGT 41 1017 1399116 N/A N/A 31797 31816 TATCCACTGGACCTTCCCTA 77 1018 1399177 N/A N/A 10465 10484 CTGCTCATGAACCCTCCACT 67 1019 1399189 N/A N/A 48384 48403 CTAGAGTGCTTTCATGGCCA 53 1020 1399270 N/A N/A 174503 174522 GCTCAATTCAATCACATTCC 31 1021 1399293 N/A N/A 25226 25245 TCCCTCATTCATCCAGGGCC 47 1022 1399314 N/A N/A 90450 90469 GTATTTTCTCAACTTTGTAC 29 1023 1399344 N/A N/A 59981 60000 CCCACAGTACTTTATTCTGT 61 1024 1399362 N/A N/A 12590 12609 CGTAGCATTCTCTTATATTC 30 1025 1399376 N/A N/A 213987 214006 GCTACTATACCTCACAGCCC 76 1026 1399394 N/A N/A 85706 85725 GTGGATTTCATCTTTCCATC 27 1027 1399404 N/A N/A 15583 15602 GCCACTCAATATCCTACCTC 18 1028 1399406 N/A N/A 47285 47304 GCTGTAGGCCCTCCCCCACC 59 1029 1399417 N/A N/A 13867 13886 ACATGGCTACTCTATCATCA 54 1030 1399423 N/A N/A 36993 37012 TCAAGAGATCCATCTCTGCT 65 1031 1399444 N/A N/A 199259 199278 GGAAGACATCCTTCCAGCTT 94 1032 1399454 N/A N/A 20347 20366 CCTACAAGCCATGAATCCTC 63 1033 1399463 N/A N/A 104991 105010 GGACAATGACTAATTCCTCA 55 1034 1399472 N/A N/A 154890 154909 CCTTGTTCACCTGTTACCTC 47 1035 1399493 N/A N/A 28312 28331 CTACCTTCTCCTCCATTCCA 66 1036

(320) TABLE-US-00016 TABLE 14 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 16 178 1394455 1152 1171 191551 191570 GAGATACTTGTCAACGGCAT 53 1037 1394558 492 511 N/A N/A ACTGCATGTCTCTTTGGCGA 32 1038 1397531 N/A N/A 50556 50575 GCCAAGATTACTTCTTTTCC 31 1039 1397535 N/A N/A 52344 52363 GGCCTTACAGATCCTCATCT 65 1040 1397538 N/A N/A 80447 80466 TCTTCAGATTCCTATGGTAA 82 1041 1397556 N/A N/A 97658 97677 CTATGCTCACAACAACCCCT 76 1042 1397562 N/A N/A 15584 15603 TGCCACTCAATATCCTACCT 28 1043 1397583 N/A N/A 187840 187859 GTCCTCACCCATCAAGGTAC 49 1044 1397584 N/A N/A 183303 183322 AGCTGATTTCATTTTACCCC 26 1045 1397595 N/A N/A 220506 220525 GGTACATCCATCTACAACAT 38 1046 1397641 N/A N/A 163735 163754 GCAGTTTACCTCCATATCTC 28 1047 1397682 285 304 83954 83973 TTGGTTGGCTTCTACCACAT 23 1048 1397713 N/A N/A 10209 10228 ATCACCAGTTTCATACACTC 41 1049 1397729 N/A N/A 267126 267145 GAGCACATACATCAATAGTT 80 1050 1397751 N/A N/A 283850 283869 ACACTCTGATCTATGGGTCA 51 1051 1397761 N/A N/A 38854 38873 TCCCTTCTTACAATTATGCT 75 1052 1397768 N/A N/A 104415 104434 TGCCCAGGCTCATTTGGTCC 65 1053 1397836 N/A N/A 28315 28334 GTACTACCTTCTCCTCCATT 68 1054 1397843 N/A N/A 7476 7495 CCTCTGTTCAACTCATCGGA 37 1055 1397849 N/A N/A 118328 118347 CCCACCTCATCTGTCAGCTC 72 1056 1397888 N/A N/A 16382 16401 GCCTACTCAGAACTACAGGT 38 1057 1398002 N/A N/A 41607 41626 ACCCATTAGACATTTCAGCA 25 1058 1398025 N/A N/A 45401 45420 ATGCCTCATTTCATATCTAA 62 1059 1398078 N/A N/A 140359 140378 TGGACCATCATCTAGATGCA 78 1060 1398081 N/A N/A 287634 287653 ATCAAGCAATTCTTCAGGCA 45 1061 1398157 N/A N/A 281614 281633 GCAGATGTCCTAATTTCCTT 49 1062 1398209 N/A N/A 131575 131594 GACAAGTTTTCACTAACTAC 43 1063 1398227 N/A N/A 34556 34575 CTCCAATTTTAACTTGCACC 9 1064 1398254 N/A N/A 47429 47448 TGAGCCCTATGAACTGTTTC 49 1065 1398290 N/A N/A 66495 66514 CTTGCACTCTTATCTTTCCC 42 1066 1398324 N/A N/A 55029 55048 TTGCCATATCTCATCAGCCT 70 1067 1398363 N/A N/A 25504 25523 TGAGGCTCATTTCAAACTCT 46 1068 1398421 N/A N/A 59991 60010 CGCCATTGTTCCCACAGTAC 60 1069 1398440 N/A N/A 90844 90863 GCATATATTTTATTACACCA 14 1070 1398465 N/A N/A 223649 223668 GGTGCAACTTTTCAAGCAAG 30 1071 1398493 N/A N/A 229317 229336 TGGATTCATCTCCATACTCA 33 1072 1398534 N/A N/A 175045 175064 ACTTCATATTTTTATCCCCC 50 1073 1398609 N/A N/A 159445 159464 GCACTTTCTCTTCTCCATGC 29 1074 1398629 N/A N/A 276309 276328 CCTGTATTACATCATAATTA 67 1075 1398703 N/A N/A 13878 13897 GCCAAATACTCACATGGCTA 56 1076 1398716 N/A N/A 107302 107321 CTGCATCTCATCCTATAGAT 91 1077 1398733 N/A N/A 37132 37151 CTAGAATGTCATTCTCCGCT 82 1078 1398735 N/A N/A 8269 8288 AAGCTAAATCTCTATTGCAT 51 1079 1398776 N/A N/A 271935 271954 CCACTGTTATTACAATGGTC 64 1080 1398825 N/A N/A 19482 19501 GCCTGGTAACTCTATTCATC 39 1081 1398849 N/A N/A 154893 154912 ACTCCTTGTTCACCTGTTAC 45 1082 1398920 2436 2455 292420 292439 AATCATAAAACGGGTTTGTT 66 1083 1398921 N/A N/A 10471 10490 TCATCCCTGCTCATGAACCC 77 1084 1398956 N/A N/A 85707 85726 TGTGGATTTCATCTTTCCAT 33 1085 1398961 N/A N/A 178593 178612 ATTTCACTAACCGGCAAAAC 81 1086 1398968 N/A N/A 102173 102192 GCTGTAGGATCTTCATTCTC 31 1087 1399007 N/A N/A 33400 33419 TCCCTTCTCTAAATCAGGCC 67 1088 1399023 N/A N/A 99957 99976 AGCTGATAAAGATACCATCC 34 1089 1399026 N/A N/A 105023 105042 ACTGATTATCAAATTCCGGA 21 1090 1399070 N/A N/A 87501 87520 GCATTTTTCTCTCTTCAAGC 15 1091 1399111 N/A N/A 27294 27313 TTCAGCGCACTATTCTCTCT 68 1092 1399119 N/A N/A 258531 258550 GCTTCATAACACCAGCCTTC 81 1093 1399185 N/A N/A 122983 123002 CCTCCCATCTGCATAGTCTG 8† 1094 1399190 N/A N/A 92233 92252 TCCTTAATGCTCATTACCCA 51 1095 1399193 N/A N/A 208564 208583 GCTTCATACATCCTCTAACT 56 1096 1399195 N/A N/A 24098 24117 GTGCTTCTTCCAACACCCCA 45 1097 1399255 N/A N/A 88991 89010 TTCATAGTCTATCTTTTGCT 37 1098 1399295 N/A N/A 154158 154177 GCATCAGGCTAACAAGTTCA 19 1099 1399301 N/A N/A 241408 241427 GCACAAGACCTCATCCAGGC 28 1100 1399325 N/A N/A 103737 103756 CTCTCTGTTACCACGCCTCT 66 1101 1399349 N/A N/A 20363 20382 GTACTTTTAACTCATTCCTA 43 1102 1399371 N/A N/A 31804 31823 TGGTAAATATCCACTGGACC 42 1103 1399372 N/A N/A 48520 48539 GCACAGCCAAGACTACGGTC 64 1104 1399385 N/A N/A 95446 95465 TGTAAGCTACTCTTCTACCC 69 1105 1399397 N/A N/A 213989 214008 GGGCTACTATACCTCACAGC 80 1106 1399398 N/A N/A 199260 199279 TGGAAGACATCCTTCCAGCT 72 1107 1399427 N/A N/A 6030 6049 TCGGCTTCTACCTTTAGCGA 12 1108 1399470 N/A N/A 167734 167753 GATGTTGAATTTCTTACACT 35 1109 1399479 N/A N/A 22721 22740 ACTTCATGCTCCCACTGAAT 91 1110 1399495 N/A N/A 30275 30294 CCCCACATCCAAACCCTGGT 85 1111 1399505 1781 1800 262098 262117 CCGTAACTGATCCTTGGTTC 47 1112 1399514 N/A N/A 12616 12635 TTGCATTCACAACACACATC 44 1113

(321) TABLE-US-00017 TABLE 15 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 27 178 1397529 N/A N/A 183422 183441 GCTCAACACTCAATAGATGA 62 1114 1397567 N/A N/A 19538 19557 GACCCTACATCATCTCATAT 61 1115 1397625 N/A N/A 103738 103757 TCTCTCTGTTACCACGCCTC 69 1116 1397665 N/A N/A 89001 89020 ATGTACTGATTTCATAGTCT 26 1117 1397670 N/A N/A 27295 27314 ATTCAGCGCACTATTCTCTC 67 1118 1397714 N/A N/A 140679 140698 TTCCCACTCTGCTCCTCGCT 80 1119 1397741 N/A N/A 15586 15605 GTTGCCACTCAATATCCTAC 49 1120 1397754 N/A N/A 163836 163855 GCACAGATGCTAATCACCAT 42 1121 1397765 N/A N/A 220523 220542 TCGGACTTACTGTAATGGGT 24 1122 1397781 N/A N/A 241566 241585 TGGACTATTTCCCACCCGGC 67 1123 1397791 N/A N/A 13879 13898 AGCCAAATACTCACATGGCT 84 1124 1397828 N/A N/A 199261 199280 CTGGAAGACATCCTTCCAGC 102 1125 1397842 N/A N/A 86228 86247 GGTCATTAACTTTACTATCA 18 1126 1397892 N/A N/A 105087 105106 GCTGCATGCTTCCAATTGCA 73 1127 1397895 N/A N/A 97661 97680 CTCCTATGCTCACAACAACC 93 1128 1397904 1153 1172 191552 191571 CGAGATACTTGTCAACGGCA 41 1129 1397934 N/A N/A 276312 276331 GAACCTGTATTACATCATAA 107 1130 1397967 N/A N/A 122984 123003 ACCTCCCATCTGCATAGTCT 25† 1131

1397985 N/A N/A 87515 87534 GCCACACATAACAAGCATTT 44 1132 1397998 N/A N/A 25571 25590 AGTGTTTTTTCTTCAGGGTT 32 1133 1398024 N/A N/A 223650 223669 AGGTGCAACTTTTCAAGCAA 51 1134 1398042 N/A N/A 61088 61107 GCAGGCAATAGACCACTTCA 71 1135 1398080 N/A N/A 47467 47486 GCTTGTTAACTACATGGGTC 66 1136 1398085 N/A N/A 52612 52631 TGGCAGTTATACACAGATCC 60 1137 1398098 N/A N/A 10488 10507 TTTGTCCTATTTATTCCTCA 55 1138 1398115 N/A N/A 118329 118348 GCCCACCTCATCTGTCAGCT 72 1139 1398140 N/A N/A 84110 84129 GGAGCATCCTCTTTTTCTTC 61 1140 1398146 N/A N/A 92291 92310 TGTGGAATACTATATTATCA 36 1141 1398150 N/A N/A 7555 7574 TCTGAGCTCTCACTATGAAA 59 1142 1398168 N/A N/A 100458 100477 AGGAACTTCTGACTACCATA 80 1143 1398299 N/A N/A 33411 33430 CAGTGGTTTAATCCCTTCTC 71 1144 1398307 N/A N/A 213992 214011 GTTGGGCTACTATACCTCAC 65 1145 1398318 N/A N/A 50557 50576 AGCCAAGATTACTTCTTTTC 54 1146 1398322 N/A N/A 28316 28335 TGTACTACCTTCTCCTCCAT 87 1147 1398330 1857 1876 262174 262193 GCTGAACTCTCCATTCACGG 40 1148 1398350 N/A N/A 66496 66515 GCTTGCACTCTTATCTTTCC 43 1149 1398358 N/A N/A 131576 131595 TGACAAGTTTTCACTAACTA 71 1150 1398365 N/A N/A 12645 12664 AGAGAACTTTGACAATACTA 45 1151 1398380 N/A N/A 6108 6127 TCATGGTTTCTCATCGATTA 41 1152 1398476 N/A N/A 22725 22744 ACCCACTTCATGCTCCCACT 55 1153 1398509 N/A N/A 281695 281714 GGTCAGCATTTTCCTAGTCA 53 1154 1398555 N/A N/A 8273 8292 GTTCAAGCTAAATCTCTATT 70 1155 1398561 N/A N/A 55716 55735 GTGGCATCTACTGCTAGGAC 49 1156 1398567 N/A N/A 20368 20387 TCCTTGTACTTTTAACTCAT 43 1157 1398601 N/A N/A 159493 159512 GCCAACTTCTCTGCAACATA 28 1158 1398652 N/A N/A 30290 30309 ACATCGCCTCACTTCCCCCA 57 1159 1398658 N/A N/A 80455 80474 GCATACCATCTTCAGATTCC 63 1160 1398751 N/A N/A 229661 229680 GCACACCAAGTCAACATTCC 33 1161 1398764 N/A N/A 41790 41809 ACTCCAGCCTCACATAGGGA 68 1162 1398777 N/A N/A 267335 267354 GTTTGGTTTTTCTATACTTC 34 1163 1398782 N/A N/A 10211 10230 GTATCACCAGTTTCATACAC 43 1164 1398838 N/A N/A 37290 37309 GAGCAACTTACAAGGCAGAC 52 1165 1398839 N/A N/A 283851 283870 CACACTCTGATCTATGGGTC 47 1166 1398852 N/A N/A 188099 188118 CAGCAAGCCAGATTACTGTC 64 1167 1398862 N/A N/A 24099 24118 TGTGCTTCTTCCAACACCCC 55 1168 1398888 N/A N/A 258534 258553 TGGGCTTCATAACACCAGCC 64 1169 1398903 N/A N/A 104451 104470 TGCACATATCACCAACGACC 79 1170 1398983 N/A N/A 175126 175145 ATGGAAGTCTCACATCTGGT 46 1171 1399017 N/A N/A 154923 154942 ATCCTCTCATTGTACTGCAT 34 1172 1399033 N/A N/A 34557 34576 TCTCCAATTTTAACTTGCAC 40 1173 1399060 N/A N/A 102231 102250 GTGATTTACCATTTTCAGGC 31 1174 1399062 N/A N/A 31805 31824 TTGGTAAATATCCACTGGAC 64 1175 1399082 2438 2457 292422 292441 TAAATCATAAAACGGGTTTG 74 1176 1399106 N/A N/A 208565 208584 TGCTTCATACATCCTCTAAC 61 1177 1399176 N/A N/A 90845 90864 CGCATATATTTTATTACACC 27 1178 1399209 N/A N/A 154175 154194 GTCCTTCCCTGCTACAGGCA 36 1179 1399229 N/A N/A 272135 272154 GGTTTCCCTTTATTTGGACT 50 1180 1399252 N/A N/A 178595 178614 TGATTTCACTAACCGGCAAA 84 1181 1399316 N/A N/A 167736 167755 TTGATGTTGAATTTCTTACA 46 1182 1399373 493 512 N/A N/A CACTGCATGTCTCTTTGGCG 35 1183 1399405 N/A N/A 48756 48775 GCAGCATCCCACCAGTGTAT 88 1184 1399424 N/A N/A 287691 287710 GCCATCTCTCTATAGTTATA 48 1185 1399440 N/A N/A 108219 108238 TTGCCTCTTTTTGACTGCAC 53 1186 1399450 N/A N/A 95447 95466 ATGTAAGCTACTCTTCTACC 67 1187 1399458 N/A N/A 38855 38874 TTCCCTTCTTACAATTATGC 65 1188 1399484 N/A N/A 16618 16637 CCGGCCTTTTTGATTACTCT 76 1189 1399509 N/A N/A 45498 45517 GCATGCTTATACCACTAAGT 47 1190

(322) TABLE-US-00018 TABLE 16 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 11 178 1396905 N/A N/A 66497 66516 TGCTTGCACTCTTATCTTTC 43 1191 1397650 N/A N/A 103991 104010 GCTATGAGTTCACAAAGCTC 40 1192 1397698 N/A N/A 50716 50735 GTGGTTTTATTACTAGGATT 31 1193 1397717 N/A N/A 80456 80475 TGCATACCATCTTCAGATTC 68 1194 1397731 N/A N/A 33440 33459 TGCTGGCCCAAATTCCATCC 33 1195 1397752 N/A N/A 100904 100923 CAGGAATCATCAATGCAGGC 51 1196 1397773 N/A N/A 159495 159514 ACGCCAACTTCTCTGCAACA 41 1197 1397820 N/A N/A 22807 22826 TTCACCACATAACATCAGGA 54 1198 1397864 N/A N/A 7573 7592 CCACTCCATACATTTGCATC 67 1199 1397878 N/A N/A 154927 154946 TGGCATCCTCTCATTGTACT 18 1200 1397898 N/A N/A 34559 34578 GTTCTCCAATTTTAACTTGC 39 1201 1397947 N/A N/A 84221 84240 AATACTGCTCCTATAGGGTC 48 1202 1397957 1859 1878 262176 262195 AGGCTGAACTCTCCATTCAC 76 1203 1397964 N/A N/A 28317 28336 ATGTACTACCTTCTCCTCCA 70 1204 1397980 N/A N/A 52628 52647 TACCTCACACAACACCTGGC 70 1205 1398000 N/A N/A 31975 31994 CCACACTATATACATAACCT 78 1206 1398004 N/A N/A 19541 19560 CTGGACCCTACATCATCTCA 56 1207 1398017 N/A N/A 87560 87579 CCACACTGGATCCTTCATCT 55 1208 1398039 N/A N/A 98136 98155 CACAAACTACTTTCCCTGGA 99 1209 1398084 N/A N/A 37318 37337 GCTGATTACTTCCTTGTATC 37 1210 1398086 N/A N/A 27297 27316 GCATTCAGCGCACTATTCTC 49 1211 1398087 N/A N/A 231031 231050 TCCACAGTCCCTCATCCTCT 53 1212 1398089 N/A N/A 178596 178615 GTGATTTCACTAACCGGCAA 44 1213 1398094 N/A N/A 105114 105133 CCTTTCACTTAGCATTCCCA 48 1214 1398113 N/A N/A 276314 276333 CAGAACCTGTATTACATCAT 83 1215 1398135 N/A N/A 13880 13899 CAGCCAAATACTCACATGGC 44 1216 1398144 N/A N/A 45500 45519 TTGCATGCTTATACCACTAA 53 1217 1398166 N/A N/A 183620 183639 ACATCTATTCTCTATTCAGC 38 1218 1398176 N/A N/A 287693 287712 ATGCCATCTCTCTATAGTTA 33 1219 1398194 N/A N/A 95691 95710 GTACCTAATTCACAATAGTA 41 1220 1398219 N/A N/A 30294 30313 ACCAACATCGCCTCACTTCC 50 1221 1398244 N/A N/A 61106 61125 GTCCTAGCTATTACCATTGC 68 1222 1398247 N/A N/A 25715 25734 GCAGCTACCTCCAGCTGGTC 38 1223 1398249 N/A N/A 122985 123004 TACCTCCCATCTGCATAGTC 33† 1224 1398258 N/A N/A 48782 48801 GCTGCCACATTCCAAAGCAA 87 1225 1398306 N/A N/A 214088 214107 TCTCATTTAATACTGCCATT 53 1226 1398311 N/A N/A 223652 223671 AAAGGTGCAACTTTTCAAGC 39 1227 1398383 N/A N/A 38868 38887 GCAAGAGATATTATTCCCTT 27 1228 1398499 N/A N/A 55933 55952 TGCCAACCTAATACCAAGCT 87 1229 1398512 N/A N/A 102328 102347 GCTGTGTTTTAACCCAGAAC 37 1230 1398530 2439 2458 292423 292442 GTAAATCATAAAACGGGTTT 71 1231 1398557 N/A N/A 20379 20398 GCCAGCCAATATCCTTGTAC 47 1232 1398577 N/A N/A 141044 141063 GCATATTAACAATAATGGGC 41 1233 1398584 N/A N/A 199942 199961 CGGTGAACACATCTATGCCT 42 1234 1398642 494 513 N/A N/A TCACTGCATGTCTCTTTGGC 52 1235 1398674 N/A N/A 10230 10249 TCATCATCATTTAACCACAG 40 1236 1398711 N/A N/A 188118 188137 ATCCTATATTCATACCAACC 68 1237 1398727 N/A N/A 15589 15608 CCAGTTGCCACTCAATATCC 43 1238 1398729 N/A N/A 272136 272155 TGGTTTCCCTTTATTTGGAC 63 1239 1398752 N/A N/A 6193 6212 GCAGTACTAATAGCCTTGCA 24 1240 1398756 N/A N/A 104452 104471 CTGCACATATCACCAACGAC 79 1241 1398816 N/A N/A 24100 24119 ATGTGCTTCTTCCAACACCC 43 1242 1398820 N/A N/A 17274 17293 GCAGACAATTTTTTTAGAAC 46 1243 1398872 N/A N/A 42114 42133 GTCTACTTCCTACTGGAATC 80 1244 1398899 N/A N/A 131944 131963 CCACTCTTACTTGACTCATC 45 1245 1398943 N/A N/A 89053 89072 TTGACTTTTTTCTATTATCC 50 1246 1398994 N/A N/A 281985 282004 TCAGTATATTCTCTGCCCAA 45 1247 1399009 1154 1173 191553 191572 TCGAGATACTTGTCAACGGC 34 1248 1399035 N/A N/A 12677 12696 ATCTAAGTTTACCTTCACAT 62 1249 1399041 N/A N/A 208566 208585 CTGCTTCATACATCCTCTAA 63 1250 1399127 N/A N/A 86358 86377 TAGGCTTCTCTCCATTTCTC 24 1251 1399159 N/A N/A 119665 119684 TTGCCATTATACCCCCACAA 70 1252 1399160 N/A N/A 220780 220799 GGACACTGCACCTCCCTGAC 67 1253 1399164 N/A N/A 90846 90865 GCGCATATATTTTATTACAC 28 1254 1399220 N/A N/A 175471 175490 TTCCTCTTAGATCCTGGGCT 56 1255 1399221 N/A N/A 267918 267937 GGCTTCTAACAATTTCAGCA 31 1256 1399251 N/A N/A 241772 241791 GCAACTTCATCTTTTCCTGC 25 1257 1399258 N/A N/A 154268 154287 ACCAAGGACTTTCAGTCCCA 67 1258 1399317 N/A N/A 167749 167768 CCACAATCCTTTATTGATGT 32 1259 1399330 N/A N/A 108262 108281 TTCCTCATTAACCAACCCAA 80 1260 1399332 N/A N/A 283858 283877 ATGTGCTCACACTCTGATCT 70 1261 1399392 N/A N/A 258667 258686 TCTCCTGTATGACTCTCCTC 66 1262 1399435 N/A N/A 8401 8420 TGGCATCAAATTCAACATTA 41 1263 1399446 N/A N/A 10489 10508 GTTTGTCCTATTTATTCCTC 20 1264 1399476 N/A

N/A 163909 163928 GCTTCTTGTCACAATCTCTA 20 1265 1399510 N/A N/A 92322 92341 ACAGAATCTCTTTATTGTCA 32 1266 1399512 N/A N/A 47488 47507 AGTGGTTCTCCAACAGGGTA 35 1267

(323) TABLE-US-00019 TABLE 17 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 46 178 1396899 N/A N/A 199979 199998 GTTCCTTCCATTCCAAGTAA 62 1268 1397558 N/A N/A 122987 123006 CTTACCTCCCATCTGCATAG 78† 1269 1397561 N/A N/A 98285 98304 TGTACAGATATTTTTCTGGA 98 1270 1397578 N/A N/A 281986 282005 TTCAGTATATTCTCTGCCCA 78 1271 1397622 N/A N/A 84269 84288 TTTCAATATACACCCTGGGT 89 1272 1397651 N/A N/A 95780 95799 TCCTTAATTTCATTTCAGTA 90 1273 1397652 N/A N/A 22816 22835 GACTTGTTTTTCACCACATA 43 1274 1397689 N/A N/A 47520 47539 ACACTAGTCTCACCCATGTT 97 1275 1397709 N/A N/A 55993 56012 TTGATGTTTTTCACGGCCTC 76 1276 1397724 N/A N/A 12694 12713 AGTTCCTTCCCCCAGTTATC 78 1277 1397757 N/A N/A 220936 220955 CTGAGTTGCTCCTTCTGAAC 65 1278 1397770 N/A N/A 6196 6215 TCCGCAGTACTAATAGCCTT 39 1279 1397774 N/A N/A 223723 223742 CAGCTCTTTTCTCCGTTCTC 59 1280 1397800 N/A N/A 175485 175504 GCTTTTCCATTACATTCCTC 71 1281 1397831 N/A N/A 13928 13947 GTTAAGGCCACCTCTGTCCA 195 1282 1397841 N/A N/A 169813 169832 GCAGCAGCATAGACTTGGGT 59 1283 1397861 N/A N/A 214094 214113 TGCTGATCTCATTTAATACT 69 1284 1397899 2440 2459 292424 292443 AGTAAATCATAAAACGGGTT 50 1285 1397911 N/A N/A 31976 31995 GCCACACTATATACATAACC 120 1286 1397930 N/A N/A 104006 104025 AGGCATTACAATATTGCTAT 77 1287 1397978 495 514 N/A N/A CTCACTGCATGTCTCTTTGG 105 1288 1398055 1155 1174 191554 191573 CTCGAGATACTTGTCAACGG 103 1289 1398064 N/A N/A 108463 108482 TTCCAAATTTAACCTTGTCT 82 1290 1398070 N/A N/A 10232 10251 GTTCATCATCATTTAACCAC 58 1291 1398093 N/A N/A 87639 87658 TGACATACTTTCCCCATGCA 56 1292 1398130 N/A N/A 10519 10538 GGCTTATTCATCTTTTCCCT 25 1293 1398175 N/A N/A 154345 154364 GTGCTCAAAATCTAATGTTT 61 1294 1398223 N/A N/A 243500 243519 AGGATGATTTTCAACATCCA 104 1295 1398269 N/A N/A 178597 178616 TGTGATTTCACTAACCGGCA 85 1296 1398276 N/A N/A 17472 17491 GTATACATCTAACTGCCTGC 75 1297 1398285 N/A N/A 90968 90987 GCGCTTTTACTCTATCAATA 39 1298 1398294 N/A N/A 19542 19561 ACTGGACCCTACATCATCTC 82 1299 1398295 N/A N/A 154928 154947 GTGGCATCCTCTCATTGTAC 89 1300 1398361 N/A N/A 27613 27632 AGTCTTTGCCCATCAGGGTT 36 1301 1398443 N/A N/A 104468 104487 GCACACACACTCATCACTGC 99 1302 1398467 N/A N/A 288073 288092 AGGTCTCCTCCTATTGCCCC 111 1303 1398502 N/A N/A 80457 80476 TTGCATACCATCTTCAGATT 138 1304 1398565 N/A N/A 86492 86511 CCAACTTTTTGAATTATGTA 35 1305 1398579 N/A N/A 37319 37338 TGCTGATTACTTCCTTGTAT 52 1306 1398614 1864 1883 262181 262200 CGTCCAGGCTGAACTCTCCA 101 1307 1398643 N/A N/A 119667 119686 GCTTGCCATTATACCCCCAC 84 1308 1398683 N/A N/A 101035 101054 GCCATTTTTTGATAAGGAAC 51 1309 1398720 N/A N/A 272137 272156 CTGGTTTCCCTTTATTTGGA 64 1310 1398792 N/A N/A 131946 131965 ATCCACTCTTACTTGACTCA 50 1311 1398793 N/A N/A 276321 276340 GTCAACCCAGAACCTGTATT 78 1312 1398794 N/A N/A 183798 183817 GGAGAACACTATCAATGCAT 64 1313 1398795 N/A N/A 102493 102512 GCTCCCATTTTATATTTAAC 95 1314 1398800 N/A N/A 52631 52650 TGGTACCTCACACAACACCT 108 1315 1398835 N/A N/A 50737 50756 GCTTATAACTCTCATACTGT 52 1316 1398873 N/A N/A 8402 8421 CTGGCATCAAATTCAACATT 47 1317 1398923 N/A N/A 45501 45520 ATTGCATGCTTATACCACTA 91 1318 1398924 N/A N/A 258770 258789 GCATACCCATTCTGACACTT 55 1319 1398930 N/A N/A 141519 141538 TGGGTTTCATTCTCAGTGCT 96 1320 1398936 N/A N/A 15620 15639 TGGTACTGTATTTCTTCTAC 78 1321 1398995 N/A N/A 188732 188751 TGGTAATTAATTTTCTGTGC 78 1322 1399008 N/A N/A 28484 28503 ACTGGCTCACCTGCCTGCCA 111 1323 1399039 N/A N/A 38900 38919 CCTGTCCTCACACTATTCTT 128 1324 1399064 N/A N/A 268126 268145 ATACTTCCTTGTTTTACGCT 45 1325 1399085 N/A N/A 61195 61214 GCTGGTGTCTCCTCTCCCAA 70 1326 1399092 N/A N/A 92764 92783 CCCACATCTTCTTCTCATTC 77 1327 1399134 N/A N/A 105118 105137 CTGACCTTTCACTTAGCATT 122 1328 1399146 N/A N/A 284033 284052 AAGACATCTTTATTTGCTCA 101 1329 1399171 N/A N/A 34561 34580 TGGTTCTCCAATTTTAACTT 56 1330 1399214 N/A N/A 20381 20400 ATGCCAGCCAATATCCTTGT 118 1331 1399228 N/A N/A 208567 208586 CCTGCTTCATACATCCTCTA 82 1332 1399244 N/A N/A 231103 231122 GGCCATCCATCTTCCCCACT 135 1333 1399254 N/A N/A 42117 42136 TCTGTCTACTTCCTACTGGA 112 1334 1399273 N/A N/A 26553 26572 GCTGCCCTTTATATAAGCTT 63 1335 1399289 N/A N/A 66498 66517 ATGCTTGCACTCTTATCTTT 186 1336 1399300 N/A N/A 89073 89092 TGTGTCGACTTTCAAGTCTT 38 1337 1399307 N/A N/A 33493 33512 TTGTAGGATTTTCTTGGCAC 95 1338 1399328 N/A N/A 163938 163957 CTGACATGTACACCTCTCCA 81 1339 1399351 N/A N/A 159544 159563 GGTGCTCTATCACCCAGTAA 53 1340 1399352 N/A N/A 30295 30314 GACCAACATCGCCTCACTTC 73 1341 1399409 N/A N/A 49225 49244 CCGTTCCCACTCTACACAGA 54 1342 1399459 N/A N/A 7574 7593 CCCACTCCATACATTTGCAT 53 1343 1399488 N/A N/A 24102 24121 TCATGTGCTTCTTCCAACAC 79 1344

(324) TABLE-US-00020 TABLE 18 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 17 178 1397527 N/A N/A 13929 13948 TGTTAAGGCCACCTCTGTCC 72 1345 1397544 N/A N/A 125364 125383 GTGCAAGACATACCAGACAC 44 1346 1397554 N/A N/A 119668 119687 TGCTTGCCATTATACCCCCA 59 1347 1397624 N/A N/A 28753 28772 AGGCAGTGATCTCTAACCTT 60 1348 1397631 N/A N/A 102856 102875 CGGCAGTTTAAAATTCTCTT 22 1349 1397635 N/A N/A 220972 220991 TCCACCTCCACTATCTTCAT 69 1350 1397649 N/A N/A 31977 31996 AGCCACACTATATACATAAC 81 1351 1397683 N/A N/A 95922 95941 CCATGATGCTTATTTGTGTA 36 1352 1397695 N/A N/A 20393 20412 GCGACAGTCACCATGCCAGC 50 1353 1397723 N/A N/A 132173 132192 GTCCAAGTTTATTCAATACA 37 1354 1397740 N/A N/A 104007 104026 CAGGCATTACAATATTGCTA 53 1355 1397853 N/A N/A 176134 176153 CCTTCTTCATACATTATTCT 53 1356 1397918 N/A N/A 208568 208587 TCCTGCTTCATACATCCTCT 48 1357 1397923 N/A N/A 10521 10540 CAGGCTTATTCATCTTTTCC 46 1358 1398020 N/A N/A 243501 243520 AAGGATGATTTTCAACATCC 68 1359 1398026 N/A N/A 38902 38921 GCCCTGTCCTCACACTATTC 61 1360 1398043 N/A N/A 61307 61326 CTGTAGAATTCACCATCCAC 90 1361 1398145 N/A N/A 284762 284781 GGTTGATCCTAATCCACTAT 47 1362 1398149 N/A N/A 87640 87659 CTGACATACTTTCCCCATGC 46 1363 1398154 N/A N/A 184111 184130 GCAGAGCTTTCCGAGTGCCA 64 1364 1398167 N/A N/A 10276 10295 CCCATGTGAATTCTTTGGGA 56 1365 1398217 N/A N/A 19546 19565 GATCACTGGACCCTACATCA 45 1366 1398255 N/A N/A 22879 22898 TACCGTCTCTTTTCTGGTCA 63 1367 1398272 N/A N/A 178599 178618 AATGTGATTTCACTAACCGG 37 1368 1398288 N/A N/A 26554 26573 TGCTGCCCTTTATATAAGCT 54 1369 1398357 N/A N/A 8420 8439 ATTGGCCTAACATCACGCCT 57 1370 1398364 N/A N/A 56192 56211 GCCACATCTATTCACAGCCA 54 1371 1398394 N/A N/A 201548 201567 CCAGTATTTTTTACCCAGCA 49 1372 1398396 N/A N/A 92765 92784 ACCCACATCTTCTTCTCATT 56 1373 1398408 2113 2132 282147 282166 CTTTGTTTGAACCCACATCT 78 1374 1398419 N/A N/A 24103 24122 CTCATGTGCTTCTTCCAACA 65 1375 1398434 N/A N/A 80458 80477 GTTGCATACCATCTTCAGAT 70 1376 1398516 N/A N/A 34617 34636 GGTTATTTCTTCCAAAGCTC 32 1377 1398543 N/A N/A 104470 104489 CAGCACACACACTCATCACT 70 1378 1398551 N/A N/A 30365 30384 TCACTATTATTAACTAGTCA 43 1379 1398556 N/A N/A 154388 154407 CATCCATTCCACATGGCCTA 46 1380 1398563 N/A N/A 50740 50759 TGTGCTTATAACTCTCATAC 49 1381 1398622 N/A N/A 223724 223743 CCAGCTCTTTTCTCCGTTCT 47 1382 1398624 N/A N/A 33531 33550 CCGGAACTCTGTCTTGGGTA 28 1383 1398628 N/A N/A 105130 105149 ACTCTTTCAATTCTGACCTT 55 1384 1398637 N/A N/A 42123 42142 TGAATGTCTGTCTACTTCCT 56 1385 1398657 N/A N/A 27627 27646 TGGCAAGCCTTTTTAGTCTT 48 1386 1398663 N/A N/A 262503 262522 GTCTTTTCCAACAATTGGCA 38 1387 1398706 N/A N/A 170325 170344 GCTACCTTGTCCAACTGGTT 48 1388 1398818 N/A N/A 49227 49246 TGCCGTTCCCACTCTACACA 112 1389 1398857

N/A N/A 84317 84336 TAGGCATTTTTCATTCAGGA 41 1390 1398876 N/A N/A 159545 159564 TGGTGCTCTATCACCCAGTA 46 1391 1398881 N/A N/A 52675 52694 TCACTCCTCATACCTGCACA 63 1392 1398973 N/A N/A 259679 259698 AGTCTCCTCACTGCTTGCTA 61 1393 1398977 N/A N/A 154929 154948 TGTGGCATCCTCTCATTGTA 61 1394 1398999 N/A N/A 141806 141825 CAACAAGCCCACTTTCTTGC 57 1395 1399005 N/A N/A 45556 45575 GCCACAGTATTAAATTTGTT 45 1396 1399011 497 516 N/A N/A TTCTCACTGCATGTCTCTTT 95 1397 1399042 N/A N/A 98327 98346 GCCTATTAATGACATGTGCA 34 1398 1399091 N/A N/A 164614 164633 GCTTCGATACCTCTGCCTTA 34 1399 1399093 N/A N/A 101265 101284 TCTGCATCAATAGCAGGGTT 56 1400 1399099 N/A N/A 15634 15653 CCTCTATCCCTTTATGGTAC 41 1401 1399103 N/A N/A 6210 6229 CATCTAGTAACTTCTCCGCA 43 1402 1399109 N/A N/A 47523 47542 CTGACACTAGTCTCACCCAT 86 1403 1399110 N/A N/A 268167 268186 CCATCATCTGACCTTTCCAA 61 1404 1399183 N/A N/A 89339 89358 TCCCATTCTTCCTTCTGGCC 82 1405 1399203 2442 2461 292426 292445 TGAGTAAATCATAAAACGGG 52 1406 1399205 N/A N/A 276322 276341 TGTCAACCCAGAACCTGTAT 53 1407 1399219 N/A N/A 12730 12749 GTCTACAATTATTCTTTTAC 58 1408 1399257 N/A N/A 7575 7594 CCCCACTCCATACATTTGCA 53 1409 1399269 N/A N/A 272173 272192 CTTCATGACACCTCTTGCAT 70 1410 1399285 N/A N/A 288328 288347 TGGCATGGCTTCAACTGGCT 45 1411 1399309 N/A N/A 17475 17494 AAGGTATACATCTAACTGCC 25 1412 1399322 N/A N/A 231104 231123 CGGCCATCCATCTTCCCCAC 52 1413 1399327 1156 1175 191555 191574 TCTCGAGATACTTGTCAACG 70 1414 1399378 N/A N/A 37320 37339 GTGCTGATTACTTCCTTGTA 51 1415 1399402 N/A N/A 189271 189290 GTCATCTTCTCATCTTAACT 47 1416 1399403 N/A N/A 66499 66518 CATGCTTGCACTCTTATCTT 56 1417 1399455 N/A N/A 86552 86571 GCTCATTTCACATCAGACAC 28 1418 1399467 N/A N/A 109510 109529 GCCAAACTCCTACTGACTGC 54 1419 1399468 N/A N/A 91193 91212 CCACATTTCACCCACCTCCA 131 1420 1399492 N/A N/A 214956 214975 TTAGTCTCACTGTCTTGGCT 94 1421

(325) TABLE-US-00021 TABLE 19 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 19 178 1397533 1157 1176 191556 191575 GTCTCGAGATACTTGTCAAC 54 1422 1397541 N/A N/A 30624 30643 TTGGCTTTACCATAGAGCTA 18 1423 1397564 N/A N/A 34618 34637 GGGTTATTTCTTCCAAAGCT 36 1424 1397701 N/A N/A 231791 231810 GGACATTTCTTCTATCTACC 44 1425 1397747 N/A N/A 221288 221307 GCCACTTCAACTGAAGTCAC 35 1426 1397775 N/A N/A 45572 45591 TTGGTTCATTTCTTTAGCCA 29 1427 1397779 N/A N/A 164616 164635 CAGCTTCGATACCTCTGCCT 49 1428 1397813 N/A N/A 92774 92793 TGTTTCTTTACCCACATCTT 46 1429 1397815 2115 2134 282149 282168 ACCTTTGTTTGAACCCACAT 70 1430 1397818 N/A N/A 12736 12755 TCTTCTGTCTACAATTATTC 83 1431 1397935 N/A N/A 104473 104492 CCTCAGCACACACACTCATC 96 1432 1397943 N/A N/A 272177 272196 TGTCCTTCATGACACCTCTT 70 1433 1397968 N/A N/A 184355 184374 GGGTTAGTCTCCTTTCATCA 62 1434 1398014 N/A N/A 50741 50760 GTGTGCTTATAACTCTCATA 50 1435 1398028 N/A N/A 66500 66519 TCATGCTTGCACTCTTATCT 63 1436 1398054 N/A N/A 6226 6245 AGGACCAGTATTATTCCATC 36 1437 1398074 N/A N/A 203120 203139 GTGCACTGTAACTTTATCCA 50 1438 1398075 N/A N/A 10350 10369 TGTGAACCCACTTCTTGTCT 53 1439 1398186 N/A N/A 98454 98473 CAGTTTTTTCCCCAATCCAA 54 1440 1398189 N/A N/A 101365 101384 CTAGTTGTTATTTACCGGCA 39 1441 1398193 N/A N/A 112138 112157 CTCCAACTTTTCCAAGTGCA 59 1442 1398207 N/A N/A 159554 159573 CATTCTATTTGGTGCTCTAT 57 1443 1398220 N/A N/A 47531 47550 CCTTTACCCTGACACTAGTC 63 1444 1398230 N/A N/A 119670 119689 CTTGCTTGCCATTATACCCC 94 1445 1398253 N/A N/A 170578 170597 TGGCACTCTTGACTTTGAAC 53 1446 1398265 N/A N/A 10556 10575 GCACTTCATTCATCAGGATC 37 1447 1398315 N/A N/A 24104 24123 GCTCATGTGCTTCTTCCAAC 33 1448 1398319 N/A N/A 37365 37384 GTCCACCTCATCTTTTTCTT 52 1449 1398321 N/A N/A 104008 104027 CCAGGCATTACAATATTGCT 94 1450 1398338 N/A N/A 49228 49247 ATGCCGTTCCCACTCTACAC 99 1451 1398345 N/A N/A 91194 91213 CCCACATTTCACCCACCTCC 84 1452 1398355 N/A N/A 89894 89913 CCTCAACTCATCCTCTGTCC 69 1453 1398397 N/A N/A 22880 22899 ATACCGTCTCTTTTCTGGTC 37 1454 1398403 N/A N/A 7580 7599 TCCATCCCCACTCCATACAT 68 1455 1398407 N/A N/A 80461 80480 TTGGTTGCATACCATCTTCA 63 1456 1398428 N/A N/A 126835 126854 ACCTCTTTTTCAATGAGGTC 78 1457 1398466 N/A N/A 52677 52696 GGTCACTCCTCATACCTGCA 64 1458 1398470 N/A N/A 95953 95972 TGTAGATTCATCTTTATGTC 64 1459 1398508 N/A N/A 31981 32000 GCCTAGCCACACTATATACA 53 1460 1398529 N/A N/A 42258 42277 CCAACTGTTCTCATCAGTGA 59 1461 1398562 N/A N/A 86553 86572 TGCTCATTTCACATCAGACA 51 1462 1398568 N/A N/A 87645 87664 GCAACCTGACATACTTTCCC 49 1463 1398580 N/A N/A 208569 208588 GTCCTGCTTCATACATCCTC 57 1464 1398612 N/A N/A 102857 102876 TCGGCAGTTTAAAATTCTCT 36 1465 1398625 N/A N/A 27628 27647 CTGGCAAGCCTTTTTAGTCT 56 1466 1398646 N/A N/A 284837 284856 CTGCCAGTACCTCCACCTGT 92 1467 1398650 N/A N/A 105133 105152 TCCACTCTTTCAATTCTGAC 74 1468 1398655 N/A N/A 223725 223744 GCCAGCTCTTTTCTCCGTTC 33 1469 1398736 N/A N/A 13967 13986 CCTGGACAGCTCTAATGGCC 69 1470 1398739 N/A N/A 17508 17527 GTGCCAACCTTTTCAGTTCA 31 1471 1398743 N/A N/A 8465 8484 GCTGCCTTCTCTACATACCT 38 1472 1398809 N/A N/A 176161 176180 ACCCATCTAACTGATCTTCA 82 1473 1398810 N/A N/A 262527 262546 TGCCACCTATACAATGGAGT 36 1474 1398817 N/A N/A 26639 26658 GTTAAAGAATTCTTCTCTCA 57 1475 1398865 N/A N/A 141813 141832 CCTCTTCCAACAAGCCCACT 87 1476 1398868 N/A N/A 259683 259702 CGATAGTCTCCTCACTGCTT 64 1477 1398893 N/A N/A 19610 19629 CCTGGGTCCCAAAAGGTCCC 58 1478 1398941 N/A N/A 15643 15662 ACCCATTTTCCTCTATCCCT 64 1479 1398964 N/A N/A 288387 288406 CTTCATGTGACTCTCGGTAC 63 1480 1398967 N/A N/A 33567 33586 GCCAACTTCTAAGCTAACAA 44 1481 1398993 N/A N/A 84432 84451 GCTTCACATTAGATTCTTTC 66 1482 1399046 N/A N/A 154984 155003 GAGACCAATTTATCTCAAGC 34 1483 1399059 N/A N/A 268168 268187 ACCATCATCTGACCTTTCCA 63 1484 1399108 N/A N/A 178600 178619 AAATGTGATTTCACTAACCG 61 1485 1399161 N/A N/A 154389 154408 TCATCCATTCCACATGGCCT 57 1486 1399179 N/A N/A 61649 61668 GGCAATGCTTTCTTTTATAC 69 1487 1399231 N/A N/A 56527 56546 TGCTCATTTCATCACTAACA 50 1488 1399290 N/A N/A 29341 29360 TCTTGAACAACTTTCTGGGT 61 1489 1399305 N/A N/A 276323 276342 TTGTCAACCCAGAACCTGTA 76 1490 1399338 N/A N/A 132561 132580 TCCTACTATTTTTAAGCCAG 40 1491 1399358 N/A N/A 38919 38938 TCTTCATGTTTTTAAGAGCC 62 1492 1399374 N/A N/A 21102 21121 GCAGAACCAACCTAAGTGGC 46 1493 1399425 N/A N/A 243850 243869 ACAGCATTGCCATAACAGCT 83 1494 1399426 505 524 122810 122829 TGGTACTCTTCTCACTGCAT 48 1495 1399437 2443 2462 292427 292446 ATGAGTAAATCATAAAACGG 71 1496 1399460 N/A N/A 215018 215037 CATAGGCTACATCCCTGGCC 83 1497 1399489 N/A N/A 189272 189291 AGTCATCTTCTCATCTTAAC 65 1498

(326) TABLE-US-00022 TABLE 20 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 21 178 1396904 2008 2027 276338 276357 CCTCCGTCTTGATATTTGTC 108 1499 1397591 N/A N/A 12761 12780 TCAACATTTAATCACCCAAA 62 1500 1397606 N/A N/A 52799 52818 TGCTGCATAGACCTAGCCAA 74 1501 1397613 N/A N/A 26675 26694 GCTCAGAATTCACTTGACAT 66 1502 1397626 N/A N/A 164643 164662 TCTGTCCTATCTCAAGCAAC 40 1503 1397663 N/A N/A 42516 42535 GGCTCTTTTTACTAAGCCAA 78 1504 1397681 N/A N/A 92776 92795 GTTGTTTCTTTACCCACATC 43 1505 1397700 N/A N/A 24497 24516 CAGTTATTTTTTCCAGACTA 35 1506 1397737 N/A N/A 34702 34721 GTGTGCATACCTTAATCTCA 34 1507 1397776 N/A N/A 87697 87716 CCAACTTATTCTCAAGGGAA 31 1508 1397803 N/A N/A 159556 159575 TTCATTCTATTTGGTGCTCT 47 1509 1397834 N/A N/A 223726 223745 TGCCAGCTCTTTTCTCCGTT 36 1510 1397876 N/A N/A 141814 141833 TCCTCTTCCAACAAGCCCAC 100 1511 1397912 N/A N/A 105134 105153 CTCCACTCTTTCAATTCTGA 104 1512 1397954 N/A N/A 126836 126855 TACCTCTTTTTCAATGAGGT 108 1513 1397969 N/A N/A 10351 10370 ATGTGAACCCACTTCTTGTC 48 1514 1397975 N/A N/A 272182 272201 AGGTATGTCCTTCATGACAC 50 1515 1398006 N/A N/A 170606 170625 TGGTTCTCCCAATCCTGTTA 47 1516 1398048 N/A

N/A 155246 155265 ATCTCTCAATGACCAGGTAT 68 1517 1398097 N/A N/A 13989 14008 CCACAACATTCATTATGTTT 45 1518 1398117 N/A N/A 98499 98518 TTGCAGGATACTACAGGCTA 49 1519 1398136 N/A N/A 50770 50789 GTCATAACATTTACTCATCA 36 1520 1398174 N/A N/A 89895 89914 TCCTCAACTCATCCTCTGTC 59 1521 1398236 N/A N/A 56529 56548 GTTGCTCATTTCATCACTAA 68 1522 1398242 N/A N/A 189277 189296 GCTTTAGTCATCTTCTCATC 62 1523 1398256 2154 2173 282188 282207 CGCTATGACAACACCGCCCA 70 1524 1398292 N/A N/A 91195 91214 GCCCACATTTCACCCACCTC 68 1525 1398359 N/A N/A 259743 259762 GCTTTTCCACACCACCCTCA 70 1526 1398459 N/A N/A 96270 96289 CCTGAGATTTCCCTTCACTA 54 1527 1398471 N/A N/A 6252 6271 GCATGTTCCTTTTCATTTCC 30 1528 1398504 N/A N/A 31555 31574 GCCAGACCATTTTAATACCA 33 1529 1398511 N/A N/A 19627 19646 GGTTCAGAATCACATATCCT 36 1530 1398539 N/A N/A 28009 28028 GCGCATTTATACAATATACT 23 1531 1398627 N/A N/A 33576 33595 GCACACTGCGCCAACTTCTA 80 1532 1398634 N/A N/A 132720 132739 GGGTTATTTTTCCATGTCAC 28 1533 1398667 N/A N/A 112139 112158 TCTCCAACTTTTCCAAGTGC 59 1534 1398718 N/A N/A 84437 84456 CTGCAGCTTCACATTAGATT 34 1535 1398765 N/A N/A 7581 7600 ATCCATCCCCACTCCATACA 64 1536 1398786 N/A N/A 21338 21357 TCCCAATTCCAAATCTAGCT 40 1537 1398789 N/A N/A 262623 262642 TCGAAGGATAATATTCCCTA 46 1538 1398812 N/A N/A 104019 104038 ACCACCTTTTACCAGGCATT 36 1539 1398823 N/A N/A 15645 15664 CTACCCATTTTCCTCTATCC 64 1540 1398842 N/A N/A 102877 102896 GCTGCAGCACATTTGCGGAT 68 1541 1398885 N/A N/A 215094 215113 TCAGCCCTATGACAGAGTCA 53 1542 1398887 506 525 122811 122830 TTGGTACTCTTCTCACTGCA 46 1543 1398891 N/A N/A 101392 101411 ATGCTTGATTCATTTGATTC 41 1544 1398909 N/A N/A 231919 231938 GCAACATGCACAATGTAGCT 41 1545 1398925 N/A N/A 37366 37385 AGTCCACCTCATCTTTTTCT 54 1546 1398940 N/A N/A 268172 268191 CCTCACCATCATCTGACCTT 68 1547 1398945 N/A N/A 285265 285284 GTCAACTTCTCCTCTGACAT 62 1548 1398969 N/A N/A 17510 17529 GAGTGCCAACCTTTTCAGTT 30 1549 1398976 N/A N/A 45949 45968 GCTGACTATATAACCACATA 43 1550 1398980 N/A N/A 243869 243888 GCCGTAGCAAGACTTGCCCA 28 1551 1398985 N/A N/A 119671 119690 TCTTGCTTGCCATTATACCC 73 1552 1399087 N/A N/A 154394 154413 GCTCATCATCCATTCCACAT 16 1553 1399088 N/A N/A 288705 288724 CCAATCTCTTCCTCATGGCT 69 1554 1399096 N/A N/A 39067 39086 GTTCTTCCTTAAAACTTCGA 56 1555 1399143 N/A N/A 49230 49249 ACATGCCGTTCCCACTCTAC 97 1556 1399147 N/A N/A 221342 221361 TCATCAACTTTTTAGTCCTT 20 1557 1399150 2444 2463 292428 292447 AATGAGTAAATCATAAAACG 65 1558 1399163 N/A N/A 208570 208589 GGTCCTGCTTCATACATCCT 49 1559 1399168 N/A N/A 178601 178620 CAAATGTGATTTCACTAACC 72 1560 1399186 N/A N/A 8466 8485 TGCTGCCTTCTCTACATACC 53 1561 1399207 N/A N/A 104549 104568 GCTGCAGCACTCTCTGCAGT 87 1562 1399218 N/A N/A 86603 86622 AGCAAATGATTATCTAGTCC 28 1563 1399233 N/A N/A 80559 80578 GCATATTCACATCATGGTTC 46 1564 1399239 1182 1201 191581 191600 GGCATGTTCATTCTCATCCC 25 1565 1399250 N/A N/A 203152 203171 ACGAGCTCTTTAACGGCTCC 108 1566 1399264 N/A N/A 31982 32001 TGCCTAGCCACACTATATAC 66 1567 1399267 N/A N/A 22914 22933 GCATTTCATCACAATTTGTT 32 1568 1399346 N/A N/A 184458 184477 CGTGGCCATCTCCAACAGGC 75 1569 1399363 N/A N/A 47535 47554 AGCTCCTTTACCCTGACACT 54 1570 1399383 N/A N/A 29345 29364 ATTCTCTTGAACAACTTTCT 53 1571 1399388 N/A N/A 10557 10576 TGCACTTCATTCATCAGGAT 37 1572 1399393 N/A N/A 176165 176184 GTCCACCCATCTAACTGATC 69 1573 1399443 N/A N/A 67152 67171 GCTGACTCACCATTGACCCA 80 1574 1399497 N/A N/A 61676 61695 GCTACAGATGTTCTTAGCCA 51 1575

(327) TABLE-US-00023 TABLE 21 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 20 178 1396902 N/A N/A 288817 288836 TGGATCTTTAATCTCCAGCC 50 1576 1397577 N/A N/A 33640 33659 TGTCAACACTAACCCAACTT 109 1577 1397645 N/A N/A 263070 263089 ATCTGCATCTCTGCAGGCCC 44 1578 1397687 2446 2465 292430 292449 ATAATGAGTAAATCATAAAA 53 1579 1397706 N/A N/A 34952 34971 TCCCATACATGATTTTAGGT 24 1580 1397708 N/A N/A 170608 170627 GTTGGTTCTCCCAATCCTGT 53 1581 1397719 N/A N/A 102953 102972 TCAAATTGTACACACCAGGC 61 1582 1397788 N/A N/A 52800 52819 TTGCTGCATAGACCTAGCCA 67 1583 1397793 N/A N/A 50771 50790 TGTCATAACATTTACTCATC 58 1584 1397823 N/A N/A 10373 10392 TTCTGTCATTACACATCCTC 63 1585 1397845 2155 2174 282189 282208 TCGCTATGACAACACCGCCC 57 1586 1397891 N/A N/A 159557 159576 ATTCATTCTATTTGGTGCTC 56 1587 1397913 N/A N/A 104551 104570 ATGCTGCAGCACTCTCTGCA 103 1588 1397946 N/A N/A 91196 91215 GGCCCACATTTCACCCACCT 73 1589 1397953 N/A N/A 61715 61734 CCCGGTCTTCAACACTCCTT 83 1590 1397960 N/A N/A 49243 49262 ATGGTTATCAAACACATGCC 95 1591 1398031 N/A N/A 42517 42536 TGGCTCTTTTTACTAAGCCA 129 1592 1398034 N/A N/A 154395 154414 TGCTCATCATCCATTCCACA 22 1593 1398037 N/A N/A 208571 208590 TGGTCCTGCTTCATACATCC 59 1594 1398040 N/A N/A 178603 178622 CGCAAATGTGATTTCACTAA 32 1595 1398104 2018 2037 276348 276367 TCAGAGATCTCCTCCGTCTT 65 1596 1398156 N/A N/A 32046 32065 CATACCCAATTACATCCAGT 93 1597 1398160 N/A N/A 285266 285285 TGTCAACTTCTCCTCTGACA 63 1598 1398203 N/A N/A 101459 101478 GCTTAATTATATATCTTCAC 33 1599 1398218 N/A N/A 223727 223746 ATGCCAGCTCTTTTCTCCGT 56 1600 1398232 N/A N/A 6279 6298 CCATTCCTCATTTAACCTCG 57 1601 1398264 N/A N/A 17696 17715 TGCAACTAATTTTTGCAATC 37 1602 1398278 N/A N/A 19671 19690 GGTCCATCTCTCCCCTTCCT 61 1603 1398287 N/A N/A 272248 272267 CCAGCTCTCTCTTCCTGTAA 51 1604 1398314 N/A N/A 86700 86719 TAGGGTCTAATTTCAGGTCC 46 1605 1398327 N/A N/A 164959 164978 ACGATTGTTTTCCAAGGGCC 57 1606 1398346 N/A N/A 120247 120266 CCCTACTTTTCTTTCTTGGA 97 1607 1398351 N/A N/A 46001 46020 CCTGCTATTTATTCAGGAAC 66 1608 1398377 N/A N/A 96344 96363 TCTCTCCTGCGACCAGCCTC 69 1609 1398436 N/A N/A 244550 244569 CTTTATCACTTTACTATGCA 52 1610 1398438 N/A N/A 215236 215255 TTATTTCTTTCACTCAGGCC 95 1611 1398454 N/A N/A 28010 28029 TGCGCATTTATACAATATAC 33 1612 1398485 N/A N/A 221344 221363 GGTCATCAACTTTTTAGTCC 21 1613 1398488 507 526 122812 122831 GTTGGTACTCTTCTCACTGC 43 1614 1398606 N/A N/A 31589 31608 GCTTATTTTCACCAAGCCTC 55 1615 1398616 N/A N/A 176179 176198 CTCTACTTATTCTTGTCCAC 61 1616 1398671 N/A N/A 22917 22936 GCAGCATTTCATCACAATTT 40 1617 1398699 N/A N/A 104020 104039 CACCACCTTTTACCAGGCAT 30 1618 1398819 N/A N/A 68100 68119 GGTCATTCTTCTATTTTGCC 46 1619 1398824 N/A N/A 8499 8518 GCCCTGGTCTAAACTCTCCT 47 1620 1398832 N/A N/A 203154 203173 CCACGAGCTCTTTAACGGCT 87 1621 1398841 N/A N/A 155251 155270 TTGCTATCTCTCAATGACCA 30 1622 1398859 N/A N/A 47536 47555 GAGCTCCTTTACCCTGACAC 67 1623 1398898 N/A N/A 15684 15703 GCTCACGGAGAATCTTAGCT 45 1624 1398907 N/A N/A 92820 92839 GCTCAGAATTACACACTAAT 46 1625 1398926 N/A N/A 24601 24620 CCTGGTTCATAGAATGAGCT 48 1626 1398954 N/A N/A 142804 142823 GCATCTCCTTCCACTGTGTC 78 1627 1398987 N/A N/A 89898 89917 GTCTCCTCAACTCATCCTCT 45 1628 1399051 N/A N/A 232183 232202 GCAACAGGCCACTAACATGC 70 1629 1399052 N/A N/A 29366 29385 ACAGATGTCTTATCATGGTC 44 1630 1399094 N/A N/A 189280 189299 CTAGCTTTAGTCATCTTCTC 51 1631 1399095 N/A N/A 80565 80584 TGGCAGGCATATTCACATCA 105 1632 1399105 N/A N/A 184557 184576 GCATTTGTTTCCTCAGGCTC 41 1633 1399126 N/A N/A 14160 14179 GTGTCCCTACAATATGACCC 51 1634 1399145 N/A N/A 22177 22196 GCAAAGCTCCTAACACGCCA 59 1635 1399148 N/A N/A 39109 39128 GCCACAGTATCACATGACCA 25 1636 1399162 N/A N/A 113517 113536 GCATACTTACAATTATGTCT 55 1637 1399170 N/A N/A 126849 126868 TACCTCTTTTTCATACCTCT 33 1638 1399253 N/A N/A 10558 10577 CTGCACTTCATTCATCAGGA 17 1639 1399259 N/A N/A 259951 259970 GTAGGTACACAACTGTACTC 49 1640 1399266 N/A N/A 105139 105158 GCCTCCTCCACTCTTTCAAT 63 1641 1399350 N/A N/A 56532 56551 GCAGTTGCTCATTTCATCAC 56 1642 1399401 1237 1256 191636 191655 GGGACATTCTCTCTCGGTGC 49 1643 1399412 N/A N/A 7590 7609 GCATTTCCCATCCATCCCCA 81 1644 1399416 N/A N/A 37370 37389 CCTTAGTCCACCTCATCTTT 103 1645 1399428 N/A N/A 98500

98519 TTTGCAGGATACTACAGGCT 39 1646 1399434 N/A N/A 268182 268201 GCATGATATTCCTCACCATC 50 1647 1399445 N/A N/A 26676 26695 AGCTCAGAATTCACTTGACA 77 1648 1399486 N/A N/A 132721 132740 AGGGTTATTTTTCCATGTCA 58 1649 1399501 N/A N/A 12782 12801 TCTCTCTCCCACCACTTGTT 61 1650 1399511 N/A N/A 87698 87717 GCCAACTTATTCTCAAGGGA 22 1651 1399513 N/A N/A 84438 84457 GCTGCAGCTTCACATTAGAT 42 1652

(328) TABLE-US-00024 TABLE 22 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 15 178 1397574 N/A N/A 92823 92842 CAGGCTCAGAATTACACACT 47 1653 1397579 N/A N/A 7591 7610 GGCATTTCCCATCCATCCCC 36 1654 1397654 N/A N/A 264160 264179 CCAGGTCTTTGATAATGAAC 46 1655 1397662 N/A N/A 10374 10393 CTTCTGTCATTACACATCCT 58 1656 1397690 N/A N/A 10588 10607 GTCCATCATTAATAAGACCT 45 1657 1397693 N/A N/A 127382 127401 GCACACGCTCACCAGTGTCT 41 1658 1397738 N/A N/A 32052 32071 CCGGTACATACCCAATTACA 62 1659 1397802 N/A N/A 80566 80585 GTGGCAGGCATATTCACATC 53 1660 1397825 N/A N/A 24618 24637 AGCACTTTTCAACAAGGCCT 38 1661 1397826 N/A N/A 120754 120773 GCTGGTACCTCTTTGGCGAC 87 1662 1397830 N/A N/A 33645 33664 CAGCATGTCAACACTAACCC 46 1663 1397846 N/A N/A 155652 155671 CTGCAGTATCTCATCTTTGC 30 1664 1397877 N/A N/A 47537 47556 AGAGCTCCTTTACCCTGACA 91 1665 1397922 N/A N/A 35072 35091 TTTCTTCGATATTATTGTCT 48 1666 1397993 N/A N/A 6280 6299 GCCATTCCTCATTTAACCTC 23 1667 1397999 N/A N/A 91199 91218 GGAGGCCCACATTTCACCCA 79 1668 1398016 N/A N/A 22179 22198 CAGCAAAGCTCCTAACACGC 70 1669 1398077 N/A N/A 86713 86732 CTACTTGTCATATTAGGGTC 30 1670 1398103 N/A N/A 259968 259987 CCTGATCCATGCACTTGGTA 84 1671 1398105 N/A N/A 56792 56811 CGATACTATTTCTATCACAT 71 1672 1398106 N/A N/A 52820 52839 CCTCAGTTATCACCTGGGTT 55 1673 1398139 658 677 122963 122982 TGTCTGCTCCGCCCCACCAG 8† 1674 1398161 N/A N/A 12794 12813 TCAACACTAACTTCTCTCTC 67 1675 1398170 2476 2495 292460 292479 CTTGTGTTACAGCACAGCTG 22 1676 1398252 N/A N/A 113542 113561 GTCCTTTATCCACTAACTCT 82 1677 1398261 N/A N/A 272249 272268 TCCAGCTCTCTCTTCCTGTA 50 1678 1398297 2019 2038 276349 276368 TTCAGAGATCTCCTCCGTCT 79 1679 1398305 N/A N/A 215826 215845 GCATTACTACTTCAAGCTAA 75 1680 1398317 N/A N/A 37381 37400 CAGTGTATTTACCTTAGTCC 32 1681 1398356 173 192 61936 61955 TCCCACTTCCCATTCTGGAC 50 1682 1398393 N/A N/A 26681 26700 ATGCAAGCTCAGAATTCACT 113 1683 1398406 N/A N/A 50772 50791 GTGTCATAACATTTACTCAT 33 1684 1398435 N/A N/A 192183 192202 TCTGGCTCACTGATTTTGCT 54 1685 1398458 N/A N/A 232992 233011 CTGAAATATTCCCTGGGCAT 49 1686 1398479 N/A N/A 88098 88117 TACTACTTACACATTTGGAA 65 1687 1398505 N/A N/A 159558 159577 CATTCATTCTATTTGGTGCT 22 1688 1398519 N/A N/A 17699 17718 CGTTGCAACTAATTTTTGCA 46 1689 1398540 N/A N/A 68101 68120 GGGTCATTCTTCTATTTTGC 66 1690 1398547 N/A N/A 96352 96371 TGGAGGCCTCTCTCCTGCGA 74 1691 1398575 N/A N/A 244552 244571 CTCTTTATCACTTTACTATG 36 1692 1398611 N/A N/A 142807 142826 CTGGCATCTCCTTCCACTGT 79 1693 1398613 N/A N/A 104597 104616 CCCTTCCATCCACTACAGCT 94 1694 1398636 N/A N/A 84537 84556 CCCAATTCCAATTCCTCTAC 60 1695 1398644 N/A N/A 221345 221364 TGGTCATCAACTTTTTAGTC 17 1696 1398647 N/A N/A 39110 39129 TGCCACAGTATCACATGACC 44 1697 1398669 N/A N/A 268188 268207 TGGACAGCATGATATTCCTC 48 1698 1398680 N/A N/A 8510 8529 CATGCATTCCTGCCCTGGTC 48 1699 1398724 N/A N/A 19675 19694 GACAGGTCCATCTCTCCCCT 50 1700 1398737 N/A N/A 22943 22962 ACGACCTTACACTAGGTTCT 28 1701 1398759 N/A N/A 165103 165122 AGTTTCTTACTTCCTGTCTC 60 1702 1398760 N/A N/A 288973 288992 TTTGCTACTTGATAATCCTA 67 1703 1398788 N/A N/A 133089 133108 GCATTAGTCTACCACCTACA 60 1704 1398803 N/A N/A 205070 205089 TGTCTGCATTTTCCAGGCAC 71 1705 1398844 N/A N/A 98555 98574 CCCAACCTATTACCCTACAA 70 1706 1398850 N/A N/A 184656 184675 CCATTTCATATTCATACTAA 60 1707 1398874 N/A N/A 104021 104040 GCACCACCTTTTACCAGGCA 35 1708 1398895 N/A N/A 154396 154415 GTGCTCATCATCCATTCCAC 25 1709 1398908 2159 2178 282193 282212 ACTGTCGCTATGACAACACC 86 1710 1398998 N/A N/A 49405 49424 TCCTGCTGCTAAAAGCCTTC 76 1711 1399004 N/A N/A 14298 14317 AATGTCTTTTTCTCTGCAAC 48 1712 1399010 N/A N/A 101460 101479 TGCTTAATTATATATCTTCA 37 1713 1399102 N/A N/A 42518 42537 TTGGCTCTTTTTACTAAGCC 43 1714 1399104 N/A N/A 102957 102976 TCATTCAAATTGTACACACC 64 1715 1399153 N/A N/A 208572 208591 GTGGTCCTGCTTCATACATC 33 1716 1399169 N/A N/A 170856 170875 GCCTCATTCTATAACAGCTA 46 1717 1399202 N/A N/A 31590 31609 TGCTTATTTTCACCAAGCCT 68 1718 1399223 N/A N/A 285543 285562 GTGGTCTATTTCAACATTGC 55 1719 1399226 N/A N/A 189288 189307 GTGCTTCCCTAGCTTTAGTC 47 1720 1399260 N/A N/A 89899 89918 AGTCTCCTCAACTCATCCTC 61 1721 1399261 N/A N/A 28029 28048 CTCATAATATCCTCATCTGT 77 1722 1399296 N/A N/A 179065 179084 TAGCACTGCAAAACCCTTCA 82 1723 1399343 N/A N/A 176192 176211 TGAGGCTTATACTCTCTACT 58 1724 1399353 N/A N/A 223737 223756 TGTCACTCAAATGCCAGCTC 22 1725 1399418 N/A N/A 105146 105165 GTCAACAGCCTCCTCCACTC 98 1726 1399442 N/A N/A 29523 29542 GCACAAACATTTTATATCTT 40 1727 1399456 N/A N/A 15788 15807 AGCATTTCCTACCTCCTCCT 79 1728 1399494 N/A N/A 46260 46279 CCTCTTGATTTCCTTTATCT 87 1729

(329) TABLE-US-00025 TABLE 23 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 19 178 1396906 N/A N/A 22216 22235 GCAACACTCACTCACCCATT 35 1730 1397534 N/A N/A 31591 31610 GTGCTTATTTTCACCAAGCC 22 1731 1397545 N/A N/A 244553 244572 TCTCTTTATCACTTTACTAT 53 1732 1397572 N/A N/A 224068 224087 TGGCAAACTCTCTTAGGTTC 20 1733 1397580 N/A N/A 22944 22963 CACGACCTTACACTAGGTTC 21 1734 1397607 N/A N/A 89900 89919 CAGTCTCCTCAACTCATCCT 46 1735 1397615 N/A N/A 14300 14319 CCAATGTCTTTTTCTCTGCA 39 1736 1397620 N/A N/A 17954 17973 ACTTCATTTATGCTATGCCT 31 1737 1397621 N/A N/A 42519 42538 GTTGGCTCTTTTTACTAAGC 59 1738 1397623 N/A N/A 101562 101581 TGCTGAGACCACATCTGTTT 48 1739 1397655 N/A N/A 159560 159579 TGCATTCATTCTATTTGGTG 22 1740 1397711 N/A N/A 11246 11265 ATCTCTTATTCTCATAAGTA 26 1741 1397792 N/A N/A 285597 285616 AGGTTCTACCATCCCAGCTA 75 1742 1397855 N/A N/A 15817 15836 CTTGGATGTTTCTACCATAA 35 1743 1397862 N/A N/A 155838 155857 TCCCTCCATTTCTTTCCGGT 41 1744 1397885 N/A N/A 208594 208613 GCATATTCATACTTGGACTA 41 1745 1397919 N/A N/A 6281 6300 AGCCATTCCTCATTTAACCT 36 1746 1397924 N/A N/A 91222 91241 GCCCACTATCAACTCTGTAA 63 1747 1397996 N/A N/A 80651 80670 ACTGCATCTTTCTAAAGGGT 47 1748 1398030 N/A N/A 12805 12824 TGTGATCACAATCAACACTA 30 1749 1398033 N/A N/A 28031 28050 CTCTCATAATATCCTCATCT 53 1750 1398060 N/A N/A 92843 92862 ACACCATATTACTTATGCAC 32 1751 1398088 N/A N/A 32084 32103 GAAGGCCCTCAACCTGCACA 70 1752 1398152 N/A N/A 7592 7611 CGGCATTTCCCATCCATCCC 35 1753 1398198 2478 2497 292462 292481 TACTTGTGTTACAGCACAGC 31 1754 1398224 N/A N/A 268343 268362 GCAGTCTTTTTCTCACTTTT 38 1755 1398233 N/A N/A 98556 98575 TCCCAACCTATTACCCTACA 35 1756 1398263 N/A N/A 50773 50792 AGTGTCATAACATTTACTCA 49 1757 1398275 N/A N/A 233132 233151 TGCTCAGCCCCATCCCTAGC 69 1758 1398286 2189 2208 282223 282242 TTCTTCAGCATCACCAAGGT 95 1759 1398337 N/A N/A 68137 68156 CCTTTTCTAATCCATACCCA 81 1760 1398446 N/A N/A 189859 189878 CTGCTTAATACATCCTGTTC 48 1761 1398452 N/A N/A 215828 215847 TGGCATTACTACTTCAAGCT 90 1762 1398455 N/A N/A 29599 29618 CCTGGTTTCATATATGGTTT 38 1763 1398480 2020 2039 276350 276369 CTTCAGAGATCTCCTCCGTC 102 1764 1398490 N/A N/A 133092 133111 GTGGCATTAGTCTACCACCT 47 1765 1398531 N/A N/A 104610 104629 CCATAGTTCCTCTCCCTTCC 76 1766 1398533 N/A N/A 184657 184676 TCCATTTCATATTCATACTA 55 1767 1398541 N/A N/A 96456 96475 CCATCAATACTGTATCTTTC 25 1768 1398571 N/A N/A 88104 88123 GGTCATTACTACTTACACAT 39 1769

1398661 N/A N/A 49657 49676 GCTACAGTTCAACTTGTCCA 51 1770 1398705 N/A N/A 56793 56812 GCGATACTATTTCTATCACA 40 1771 1398750 N/A N/A 47541 47560 GTCAAGAGCTCCTTTACCCT 60 1772 1398771 N/A N/A 24619 24638 AAGCACTTTTCAACAAGGCC 35 1773 1398790 N/A N/A 37382 37401 GCAGTGTATTTACCTTAGTC 25 1774 1398796 N/A N/A 10376 10395 GGCTTCTGTCATTACACATC 18 1775 1398821 N/A N/A 179173 179192 CCATGACTTTTTCAAATCAA 39 1776 1398843 N/A N/A 272254 272273 GTGACTCCAGCTCTCTCTTC 34 1777 1398853 N/A N/A 170857 170876 TGCCTCATTCTATAACAGCT 47 1778 1398854 N/A N/A 221517 221536 GCTGCCCTATTCTTGGGCAT 108 1779 1398894 N/A N/A 105147 105166 GGTCAACAGCCTCCTCCACT 71 1780 1398935 N/A N/A 176194 176213 GCTGAGGCTTATACTCTCTA 9 1781 1398975 N/A N/A 143205 143224 CGAGCAAATTCCTCATGTCC 56 1782 1399022 N/A N/A 205071 205090 TTGTCTGCATTTTCCAGGCA 37 1783 1399024 660 679 122965 122984 TGTGTCTGCTCCGCCCCACC 12† 1784 1399029 N/A N/A 192435 192454 CCTCCATATTATCAAACTCC 53 1785 1399178 N/A N/A 165104 165123 CAGTTTCTTACTTCCTGTCT 48 1786 1399224 N/A N/A 26744 26763 AGCCTGCTTTTCTCTTTCAC 52 1787 1399236 N/A N/A 39205 39224 TCTCATTAGCATATAAGACC 27 1788 1399247 N/A N/A 264172 264191 CAGGACAGTTTTCCAGGTCT 37 1789 1399304 N/A N/A 103082 103101 TCCTCTTTTATCACTACAAC 45 1790 1399361 N/A N/A 8514 8533 TGCCCATGCATTCCTGCCCT 39 1791 1399364 N/A N/A 259973 259992 TCCCTCCTGATCCATGCACT 48 1792 1399380 N/A N/A 35657 35676 GCAGATCATATACTATACAC 21 1793 1399407 N/A N/A 104022 104041 GGCACCACCTTTTACCAGGC 34 1794 1399408 N/A N/A 46261 46280 ACCTCTTGATTTCCTTTATC 74 1795 1399422 N/A N/A 120791 120810 AGGAAATCTTCACTTTGCAA 56 1796 1399429 N/A N/A 63461 63480 CATCATGGTTCATACTCCTT 57 1797 1399461 N/A N/A 84538 84557 TCCCAATTCCAATTCCTCTA 42 1798 1399469 N/A N/A 33649 33668 TCAACAGCATGTCAACACTA 43 1799 1399477 N/A N/A 19676 19695 TGACAGGTCCATCTCTCCCC 55 1800 1399478 N/A N/A 127481 127500 CCTCCAGATCTTAAGCAGCT 74 1801 1399480 N/A N/A 86776 86795 GCAGCACCTATATTCCTTAA 28 1802 1399481 N/A N/A 289024 289043 GCTGGTGCACAATCCAGACC 32 1803 1399502 N/A N/A 113769 113788 TTGCACCATCACCACCTACT 42 1804 1399503 N/A N/A 154398 154417 GTGTGCTCATCATCCATTCC 19 1805 1399516 N/A N/A 52872 52891 CCAAATTTCACCATGTGGCA 67 1806

(330) TABLE-US-00026 TABLE 24 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 23 178 1396903 N/A N/A 88284 88303 ACAGTATTCAAATACATCCT 36 1807 1397588 N/A N/A 101591 101610 AAGCTCTCCTCACACTGTAA 39 1808 1397636 N/A N/A 89902 89921 GTCAGTCTCCTCAACTCATC 28 1809 1397678 N/A N/A 104612 104631 TCCCATAGTTCCTCTCCCTT 54 1810 1397685 N/A N/A 272276 272295 GCTGATTTCACCCTAAGCCC 27 1811 1397686 2479 2498 292463 292482 CTACTTGTGTTACAGCACAG 9 1812 1397725 N/A N/A 26769 26788 GCAGAACTCCTTCCCAAAGA 56 1813 1397732 N/A N/A 32086 32105 TGGAAGGCCCTCAACCTGCA 51 1814 1397769 N/A N/A 47542 47561 AGTCAAGAGCTCCTTTACCC 37 1815 1397798 N/A N/A 19677 19696 ATGACAGGTCCATCTCTCCC 50 1816 1397817 N/A N/A 8515 8534 ATGCCCATGCATTCCTGCCC 21 1817 1397840 661 680 122966 122985 CTGTGTCTGCTCCGCCCCAC 8† 1818 1397948 N/A N/A 13144 13163 GAGGCATTTTTTCTTTTTGC 17 1819 1397959 N/A N/A 159561 159580 TTGCATTCATTCTATTTGGT 25 1820 1397982 N/A N/A 63472 63491 TCATCATTTCACATCATGGT 26 1821 1398082 N/A N/A 84833 84852 GCCTACTGATGAATACACTT 56 1822 1398083 N/A N/A 259975 259994 GCTCCCTCCTGATCCATGCA 44 1823 1398118 N/A N/A 179198 179217 CCATCTGAATTTGACCTCCA 53 1824 1398122 N/A N/A 120950 120969 CGGGAACTCTATTTTCTGTT 63 1825 1398125 N/A N/A 86834 86853 TCTGTATTATACTCTGGGCT 20 1826 1398128 N/A N/A 35659 35678 TGGCAGATCATATACTATAC 12 1827 1398200 N/A N/A 96460 96479 GCATCCATCAATACTGTATC 26 1828 1398213 N/A N/A 233347 233366 ATGCATCAATTCCTTTGGGT 18 1829 1398228 N/A N/A 18325 18344 GTGCACCAACAATAAATCAA 26 1830 1398231 N/A N/A 57207 57226 CTGCATTTGAACCACCCGCT 72 1831 1398270 N/A N/A 176195 176214 TGCTGAGGCTTATACTCTCT 30 1832 1398279 N/A N/A 282276 282295 AGTCAAGTTTACCTACCTCC 73 1833 1398282 N/A N/A 22218 22237 CAGCAACACTCACTCACCCA 48 1834 1398336 N/A N/A 269083 269102 GGTCACTTCAAATTCTACTC 23 1835 1398372 N/A N/A 165105 165124 TCAGTTTCTTACTTCCTGTC 40 1836 1398373 N/A N/A 104163 104182 GATGCAGAACTATTTAGGGC 34 1837 1398385 N/A N/A 80737 80756 GCTGCAGCACTCATGAGTCA 65 1838 1398420 N/A N/A 46362 46381 ACCCACACATGAAAGTACCA 44 1839 1398422 N/A N/A 205072 205091 GTTGTCTGCATTTTCCAGGC 27 1840 1398429 N/A N/A 22945 22964 CCACGACCTTACACTAGGTT 5 1841 1398585 N/A N/A 6282 6301 CAGCCATTCCTCATTTAACC 16 1842 1398587 N/A N/A 98573 98592 CTGATTATAATACTTTGTCC 37 1843 1398649 N/A N/A 7593 7612 ACGGCATTTCCCATCCATCC 20 1844 1398666 N/A N/A 113774 113793 GTTCATTGCACCATCACCAC 43 1845 1398698 N/A N/A 92927 92946 ATCTTCTTTTACCACATCAA 43 1846 1398732 N/A N/A 128188 128207 TGGCCATACGCACCCACACA 27 1847 1398746 N/A N/A 244554 244573 GTCTCTTTATCACTTTACTA 26 1848 1398747 N/A N/A 50786 50805 TATTTCCTTTCAAAGTGTCA 48 1849 1398766 N/A N/A 52888 52907 TCGCACTGAGATCCTACCAA 61 1850 1398772 N/A N/A 155923 155942 AGACATCTTCTCATTTGGGT 17 1851 1398785 N/A N/A 134292 134311 GCACCTTCAAATGTCTGACA 38 1852 1398798 N/A N/A 264375 264394 GTGCACGCAGATTTTCTCCT 45 1853 1398799 N/A N/A 10392 10411 TGTTTATCACAAATATGGCT 46 1854 1398858 N/A N/A 105169 105188 AGACATATCATCCATGCCTA 43 1855 1398886 N/A N/A 31594 31613 CCTGTGCTTATTTTCACCAA 51 1856 1398906 N/A N/A 289150 289169 GCTGTCAACAATCATTTGCA 30 1857 1398934 N/A N/A 37431 37450 CCATGCCCATTTGATTTATA 30 1858 1398959 2021 2040 276351 276370 ACTTCAGAGATCTCCTCCGT 42 1859 1398965 N/A N/A 208596 208615 TTGCATATTCATACTTGGAC 27 1860 1399012 N/A N/A 215829 215848 TTGGCATTACTACTTCAAGC 43 1861 1399063 N/A N/A 68149 68168 CCAGCCTACAAGCCTTTTCT 51 1862 1399067 N/A N/A 189861 189880 CTCTGCTTAATACATCCTGT 50 1863 1399080 N/A N/A 224104 224123 CCACTTTCATCACTTTACTA 57 1864 1399083 N/A N/A 192593 192612 AGATCTTTATTCATTCACTT 44 1865 1399141 N/A N/A 42531 42550 ACTCATATATTTGTTGGCTC 48 1866 1399149 N/A N/A 171299 171318 ACAGAATCCCTTCACCCCAT 43 1867 1399187 N/A N/A 184661 184680 GCACTCCATTTCATATTCAT 33 1868 1399199 N/A N/A 103083 103102 ATCCTCTTTTATCACTACAA 35 1869 1399201 N/A N/A 11268 11287 ATGACTTTTCTTTATGCAAC 25 1870 1399211 N/A N/A 15868 15887 ATGCAAGTCTGAACCATCTA 35 1871 1399212 N/A N/A 39408 39427 ATCCAACCCTCCAGGAACCT 59 1872 1399234 N/A N/A 154401 154420 TGTGTGTGCTCATCATCCAT 26 1873 1399298 N/A N/A 49873 49892 GCCAACAATTAAGAAACACC 31 1874 1399340 N/A N/A 28033 28052 TGCTCTCATAATATCCTCAT 37 1875 1399341 N/A N/A 24620 24639 AAAGCACTTTTCAACAAGGC 42 1876 1399359 N/A N/A 14301 14320 TCCAATGTCTTTTTCTCTGC 19 1877 1399384 N/A N/A 33676 33695 CAGAGCTTCCATCCTCGGGA 51 1878 1399386 N/A N/A 91237 91256 TCCCATCCCCTTCAGGCCCA 42 1879 1399390 N/A N/A 285598 285617 CAGGTTCTACCATCCCAGCT 41 1880 1399436 N/A N/A 221519 221538 GTGCTGCCCTATTCTTGGGC 9 1881 1399500 N/A N/A 29618 29637 GCAGAATACCAAGTTAGTAC 22 1882 1399508 N/A N/A 145247 145266 GCTGTGCTTTACCAAGTGCC 60 1883

(331) TABLE-US-00027 TABLE 25 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 38 178 1397530 N/A N/A 15902 15921 GTTCCATCACTCTAGCTGGA 28 1884 1397551 N/A N/A 22950 22969 GGACTCCACGACCTTACACT 48 1885 1397563 N/A N/A 264451 264470 AGGGCTTTGCTCAAATGGAC 75 1886 1397614 N/A N/A 158123 158142 GCGATCCTCAACTCTACTTC 17 1887 1397619 N/A N/A 86835 86854 CTCTGTATTATACTCTGGGC 104 1888 1397628 N/A N/A 146473 146492 TAGCCAGTACTTCTCCCGCA 66 1889 1397637 N/A N/A 285601 285620 GTTCAGGTTCTACCATCCCA 40 1890 1397639 N/A N/A 42533 42552 TCACTCATATATTTGTTGGC 70 1891 1397643 N/A N/A 272308 272327 GCAGGCTTACTTAGAGGTCT 52 1892 1397736 N/A N/A 113775 113794 TGTTCATTGCACCATCACCA 61 1893 1397746 N/A N/A 26879 26898 CTTCTGGTTTTTTATTGGCT

45 1894 1397763 N/A N/A 7594 7613 GACGGCATTTCCCATCCATC 45 1895 1397772 N/A N/A 282310 282329 CTCTCATAGTCTTAATTCCC 30 1896 1397799 N/A N/A 24779 24798 GCTGAACTCTTTGACTTATT 40 1897 1397804 N/A N/A 68171 68190 GCACTCCCTCACCTCGCCCT 77 1898 1397809 N/A N/A 11722 11741 CCACGGCTACAGATCACACC 49 1899 1397833 N/A N/A 193136 193155 ATGCCACTACATGCAGGGTC 149 1900 1397837 N/A N/A 165177 165196 ATTGCCTCATACTTGTTGGT 117 1901 1397867 N/A N/A 224106 224125 CCCCACTTTCATCACTTTAC 70 1902 1397963 N/A N/A 96462 96481 ATGCATCCATCAATACTGTA 85 1903 1397981 N/A N/A 28034 28053 ATGCTCTCATAATATCCTCA 48 1904 1397987 N/A N/A 46438 46457 CATCACTGTCTATATCTCTA 80 1905 1398047 N/A N/A 159562 159581 ATTGCATTCATTCTATTTGG 36 1906 1398050 N/A N/A 233436 233455 GTTCACCTTTTAATCTACAA 50 1907 1398063 N/A N/A 259979 259998 TAGGGCTCCCTCCTGATCCA 72 1908 1398099 N/A N/A 18360 18379 GCTGTTTTAAAACCATGCTT 48 1909 1398102 N/A N/A 179240 179259 GCTTACCTTCTAGTTCAGCT 39 1910 1398123 N/A N/A 128283 128302 CCATATGTGACACTCCAGCA 92 1911 1398181 N/A N/A 19721 19740 GTACATGTTTACATACCCAT 41 1912 1398190 N/A N/A 93615 93634 GCAGGTGATTCCTAAGATTC 75 1913 1398204 N/A N/A 37442 37461 ATCTTTGGTAACCATGCCCA 39 1914 1398234 N/A N/A 22219 22238 GCAGCAACACTCACTCACCC 53 1915 1398248 N/A N/A 33771 33790 GCTGGCTCCAATCATTGTCA 89 1916 1398266 662 681 122967 122986 TCTGTGTCTGCTCCGCCCCA 14 1917 1398308 N/A N/A 101593 101612 GTAAGCTCTCCTCACACTGT 133 1918 1398387 N/A N/A 52901 52920 GATCATGTGACACTCGCACT 69 1919 1398389 N/A N/A 222019 222038 CTGTAGCTTTGACACTAGCA 73 1920 1398423 2480 2499 292464 292483 TCTACTTGTGTTACAGCACA 50 1921 1398475 N/A N/A 289154 289173 ACTGGCTGTCAACAATCATT 175 1922 1398521 N/A N/A 171301 171320 GCACAGAATCCCTTCACCCC 40 1923 1398546 N/A N/A 269317 269336 GTCTACATCTATCTGGGCTT 64 1924 1398623 N/A N/A 39417 39436 TTTCCTGACATCCAACCCTC 81 1925 1398659 N/A N/A 209417 209436 TGGTTTTAATTCTCTCATCA 74 1926 1398678 N/A N/A 104225 104244 TATATATTTCAGGCATTTTC 43 1927 1398686 N/A N/A 15029 15048 CTTTCTATTTACTCACAGCC 86 1928 1398691 N/A N/A 98577 98596 GCCACTGATTATAATACTTT 85 1929 1398694 N/A N/A 176671 176690 GCAGCATCCTCCTCCCCTCT 121 1930 1398696 N/A N/A 49915 49934 GACTCTCTCACTCCCACATA 86 1931 1398701 N/A N/A 8524 8543 ACAGAATTTATGCCCATGCA 47 1932 1398704 N/A N/A 90069 90088 CACCCATGCTATTAGAGCTC 29 1933 1398713 N/A N/A 121037 121056 TGAATCTAGTTCAACTGGCC 113 1934 1398714 N/A N/A 32087 32106 GTGGAAGGCCCTCAACCTGC 78 1935 1398715 N/A N/A 104616 104635 TCCTTCCCATAGTTCCTCTC 93 1936 1398730 N/A N/A 134563 134582 ATGCTACGCTTACAATAGCA 86 1937 1398754 N/A N/A 105170 105189 CAGACATATCATCCATGCCT 90 1938 1398763 N/A N/A 216488 216507 AAGGTCTTAGAAATCTCTCT 125 1939 1398822 N/A N/A 88414 88433 CCATCCTCATCGCCATCTTT 68 1940 1398856 N/A N/A 13276 13295 TGCCACTAAATTTAATTCCA 36 1941 1398882 N/A N/A 47557 47576 GTACGGCCAATCTCCAGTCA 59 1942 1398902 N/A N/A 50888 50907 CCTTTCTATTTTTAGCAGAT 64 1943 1398938 N/A N/A 57386 57405 GCTTGGCAGCATTCCTCCCC 92 1944 1398950 N/A N/A 6512 6531 GCACTTCTCACTGATAGTTT 28 1945 1398958 N/A N/A 65806 65825 ACCTCAATTTCCTCACTGCC 126 1946 1399013 N/A N/A 154518 154537 TCCCTCTTACTCTCGGAGGC 45 1947 1399066 N/A N/A 103085 103104 TCATCCTCTTTTATCACTAC 89 1948 1399098 N/A N/A 80832 80851 CCCATGGCTTTTTTCCTATA 118 1949 1399128 2024 2043 276354 276373 TTCACTTCAGAGATCTCCTC 98 1950 1399192 N/A N/A 206434 206453 GCTAAGGTTTTCCAAACCTA 55 1951 1399200 N/A N/A 244582 244601 ATGGTTTTATTCTTACAGCA 50 1952 1399230 N/A N/A 31641 31660 GCTGCTGGCTCACTGCAGAA 74 1953 1399240 N/A N/A 10418 10437 CCTCACTGTATCTACTGTAA 57 1954 1399319 N/A N/A 35860 35879 CTGCATCAAATCCTTTCAGA 48 1955 1399471 N/A N/A 184709 184728 ATGCACTGATTTCCCTCATT 53 1956 1399496 N/A N/A 84848 84867 CCTTATTTACAACCTGCCTA 111 1957 1399506 N/A N/A 29639 29658 CTGCCTTTCTGATAAAGCTA 52 1958 (332) TABLE-US-00028 TABLE 26 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 21 178 1394453 2481 2500 292465 292484 ATCTACTTGTGTTACAGCAC 52 1959 1394555 663 682 122968 122987 GTCTGTGTCTGCTCCGCCCC 25† 1960 1397570 N/A N/A 285602 285621 TGTTCAGGTTCTACCATCCC 52 1961 1397585 N/A N/A 260048 260067 TCCCCAGCTTTGACTTCTCC 98 1962 1397593 N/A N/A 96469 96488 ATTTTCTATGCATCCATCAA 74 1963 1397599 N/A N/A 42543 42562 ACTCAGTCAGTCACTCATAT 55 1964 1397609 N/A N/A 6683 6702 ACTAAACCTTACATTCTGGA 69 1965 1397617 N/A N/A 269543 269562 CTGTTGTGTTACTTTAGCCA 39 1966 1397659 N/A N/A 53070 53089 CTGCAATCACACTCCATCAA 72 1967 1397666 N/A N/A 91246 91265 GAGCTGAAATCCCATCCCCT 81 1968 1397680 N/A N/A 206768 206787 GCTCAATTAAACTGATAGCC 44 1969 1397703 2031 2050 276361 276380 ATCCATCTTCACTTCAGAGA 92 1970 1397739 N/A N/A 101595 101614 CTGTAAGCTCTCCTCACACT 74 1971 1397771 N/A N/A 11723 11742 GCCACGGCTACAGATCACAC 61 1972 1397784 N/A N/A 103086 103105 GTCATCCTCTTTTATCACTA 45 1973 1397797 N/A N/A 8656 8675 ACACACTGTTTCAAGCATTT 45 1974 1397801 N/A N/A 15905 15924 TTTGTTCCATCACTCTAGCT 80 1975 1397816 N/A N/A 154525 154544 CAGAAGTTCCCTCTTACTCT 46 1976 1397839 N/A N/A 179243 179262 CTTGCTTACCTTCTAGTTCA 48 1977 1397856 N/A N/A 32243 32262 TGGTACTTTTCTATCGGTTC 21 1978 1397868 N/A N/A 158124 158143 TGCGATCCTCAACTCTACTT 51 1979 1397900 N/A N/A 26937 26956 CCATTGACCTATCTATGCAT 75 1980 1397927 N/A N/A 22951 22970 TGGACTCCACGACCTTACAC 72 1981 1397956 N/A N/A 104227 104246 TCTATATATTTCAGGCATTT 56 1982 1397965 N/A N/A 134832 134851 GCCCTTTCCTTCATGATGTC 65 1983 1397977 N/A N/A 31674 31693 CACTCGATCTTTCTAGGCTC 52 1984 1398027 N/A N/A 282633 282652 GCAACTTCCTACTTCTATTT 74 1985 1398036 N/A N/A 88415 88434 TCCATCCTCATCGCCATCTT 50 1986 1398061 N/A N/A 184710 184729 CATGCACTGATTTCCCTCAT 52 1987 1398071 N/A N/A 245283 245302 CTGCATGTCTTCTACAAACA 53 1988 1398119 N/A N/A 68178 68197 GCATGATGCACTCCCTCACC 71 1989 1398127 N/A N/A 15030 15049 CCTTTCTATTTACTCACAGC 69 1990 1398137 N/A N/A 272497 272516 GCTCTTGCTATAATAGTTCA 59 1991 1398142 N/A N/A 190063 190082 CCCATTTCTTTTTCAGATCA 59 1992 1398164 N/A N/A 30069 30088 CTCCCTGTATTAATCTGATC 95 1993 1398179 N/A N/A 19821 19840 GCACACACACAATAAGCCTT 67 1994 1398188 N/A N/A 93677 93696 GGTCTAACTCAAATAGTGCT 42 1995 1398206 N/A N/A 98578 98597 AGCCACTGATTATAATACTT 73 1996 1398210 N/A N/A 233534 233553 TCCTTATCATGACAAGGCAT 41 1997 1398216 N/A N/A 86865 86884 TCTACATACTCTACCAGGTT 45 1998 1398221 N/A N/A 105171 105190 TCAGACATATCATCCATGCC 80 1999 1398277 N/A N/A 22220 22239 GGCAGCAACACTCACTCACC 55 2000 1398312 N/A N/A 121395 121414 GCAGAGGTTAACCAAGTGCT 71 2001 1398332 N/A N/A 165372 165391 ATGGCTTACAAAATTCCTCT 32 2002 1398341 N/A N/A 81766 81785 CTGCCTTGTTTACCTCACCT 83 2003 1398386 N/A N/A 24826 24845 GCTTGCTTACTTAGGAGGCT 32 2004 1398415 N/A N/A 51069 51088 GTTCTTGTCTCTCATATGTA 57 2005 1398496 N/A N/A 39711 39730 AGATTACACATCCCACAGGC 47 2006 1398497 N/A N/A 113837 113856 GCTACTCTTCATCATTCACT 95 2007 1398518 N/A N/A 222030 222049 GCAAACCACTTCTGTAGCTT 15 2008 1398532 N/A N/A 28048 28067 AGTTGATACAAATAATGCTC 27 2009 1398572 N/A N/A 7693 7712 TCCCCTGCCACCTTCTGTCT 79 2010 1398586 N/A N/A 13356 13375 TGTCACACTAAACACTAGCT 43 2011 1398595 N/A N/A 49916 49935 TGACTCTCTCACTCCCACAT 83 2012 1398672 N/A N/A 176810 176829 GCCCAACATCTCAAGCTGTC 49 2013 1398684 N/A N/A 18510 18529 GGTCCTATTATACCTCTACT 49 2014 1398709 N/A N/A 209703 209722 CTCCATGTACTTCCTCTAAC 67 2015 1398717 N/A N/A 57913 57932 TGCCACTGACATCATAAAAC 87 2016 1398755 N/A N/A 84849 84868 TCCTTATTTACAACCTGCCT 67 2017 1398805 N/A N/A 65903 65922 TGGGATCTAAGACCCTTACA 84 2018 1398828 N/A N/A 146927 146946 GGACTTTTTTCTTCTTGCTA 64 2019 1398883 N/A N/A 217168 217187 AGGAGCCATCTCCCTGCCAT 113 2020 1398972 N/A N/A 264465 264484 GAAGTACTTAATCAAGGGCT 66 2021 1398986 N/A N/A 46446 46465 GTCTAATCCATCACTGTCTA 68 2022 1398997 N/A N/A 159564 159583 GTATTGCATTCATTCTATTT 53 2023 1399020 N/A N/A 47558 47577 TGTACGGCCAATCTCCAGTC 53 2024 1399061 N/A N/A 104621 104640 ACTCATCCTTCCCATAGTTC 73 2025 1399115 N/A N/A 10423

10442 TCACTCCTCACTGTATCTAC 61 2026 1399120 N/A N/A 35893 35912 TTTCTCTCTGTATACTGGTT 55 2027 1399123 N/A N/A 289167 289186 CATCTACCATCACACTGGCT 88 2028 1399175 N/A N/A 90197 90216 GCCCACTCATAAGCCATAAC 41 2029 1399217 N/A N/A 224109 224128 CCACCCCACTTTCATCACTT 64 2030 1399249 N/A N/A 37457 37476 ACACCTCTAGAATTCATCTT 79 2031 1399274 N/A N/A 129754 129773 GCTGTAATGCACCATACTCA 76 2032 1399292 N/A N/A 33848 33867 CTTCACAGTACTCACTTACA 80 2033 1399310 N/A N/A 171302 171321 GGCACAGAATCCCTTCACCC 50 2034 1399439 N/A N/A 193425 193444 GCACATTATATTCCAGAGCC 47 2035

(333) TABLE-US-00029 TABLE 27 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 21 178 1397555 2482 2501 292466 292485 CATCTACTTGTGTTACAGCA 47 2036 1397568 N/A N/A 70128 70147 TCTCACAACACTTTGGGTCT 83 2037 1397575 N/A N/A 103087 103106 AGTCATCCTCTTTTATCACT 66 2038 1397576 N/A N/A 7703 7722 GCTCATTCCTTCCCCTGCCA 49 2039 1397598 N/A N/A 171560 171579 CCCAGAGCTTACCTTCAGTT 66 2040 1397601 N/A N/A 28093 28112 TCAGCATAATATTCTACTGT 31 2041 1397605 N/A N/A 49919 49938 GCCTGACTCTCTCACTCCCA 80 2042 1397640 N/A N/A 121662 121681 CACCACTCCCTCAAGCTGTA 82 2043 1397647 N/A N/A 222031 222050 AGCAAACCACTTCTGTAGCT 39 2044 1397657 N/A N/A 6843 6862 GTAACATATTTACTCAGTAT 28 2045 1397749 N/A N/A 134848 134867 CTGTAAGTGCAATACTGCCC 66 2046 1397767 N/A N/A 233549 233568 GTTCCTTTTCACCTATCCTT 39 2047 1397789 N/A N/A 88420 88439 GTTTTTCCATCCTCATCGCC 45 2048 1397806 N/A N/A 104228 104247 GTCTATATATTTCAGGCATT 33 2049 1397807 N/A N/A 113907 113926 TCCCCAGTATCTATCTCATC 86 2050 1397811 N/A N/A 42614 42633 GCAACCATTTTATTGTTCAC 32 2051 1397812 N/A N/A 53074 53093 GCTACTGCAATCACACTCCA 72 2052 1397814 N/A N/A 265092 265111 CGGGTCTGTATCATTCAGGA 41 2053 1397844 N/A N/A 51092 51111 TCGGATATTTGACATTTACT 55 2054 1397858 N/A N/A 26938 26957 CCCATTGACCTATCTATGCA 68 2055 1397874 N/A N/A 19157 19176 CAGAAACTATGATTCTCTTC 86 2056 1397887 N/A N/A 8676 8695 GGTTACATATATATTAACTC 28 2057 1397901 N/A N/A 22952 22971 ATGGACTCCACGACCTTACA 55 2058 1397909 N/A N/A 194107 194126 TCAAGGTTTCTATCCAGCTT 98 2059 1397932 N/A N/A 207006 207025 TGTTGAACATTTATTGCTCT 51 2060 1397979 N/A N/A 105181 105200 GCTTTCTCACTCAGACATAT 74 2061 1398013 N/A N/A 165400 165419 CCATTGGTATTTCAAGCTAC 31 2062 1398041 N/A N/A 47772 47791 GCTTCTGACTTTACTGCTGT 71 2063 1398114 N/A N/A 19974 19993 CACCAATCCCACTTCTCCAA 67 2064 1398165 N/A N/A 65924 65943 CCTCTCCCACTTGCCAGATC 93 2065 1398183 N/A N/A 81767 81786 ACTGCCTTGTTTACCTCACC 99 2066 1398273 N/A N/A 190064 190083 TCCCATTTCTTTTTCAGATC 46 2067 1398309 N/A N/A 37468 37487 ACTGGAGTTTTACACCTCTA 42 2068 1398371 N/A N/A 12012 12031 CCATCTTTATTCTATGAGCC 30 2069 1398400 N/A N/A 30117 30136 TCAACCTCACCCCTATTGTT 93 2070 1398413 N/A N/A 22305 22324 TCACTTTCTTACATGCGGTT 39 2071 1398491 N/A N/A 129869 129888 TTGCTGTGTTCCCAAAGTAC 71 2072 1398520 N/A N/A 36032 36051 ACTCATCTTCTACTGCAGTA 76 2073 1398523 N/A N/A 101631 101650 ACATTCTCTTCTTCCTAGTT 61 2074 1398570 2035 2054 276365 276384 CTGCATCCATCTTCACTTCA 65 2075 1398574 N/A N/A 179248 179267 ACAGGCTTGCTTACCTTCTA 66 2076 1398583 N/A N/A 285649 285668 GTGCTCTCTCACCTGGGAAC 61 2077 1398593 N/A N/A 31676 31695 CTCACTCGATCTTTCTAGGC 49 2078 1398632 N/A N/A 274132 274151 CGGGCTTTAATTTCCTTTCA 55 2079 1398700 N/A N/A 91248 91267 CTGAGCTGAAATCCCATCCC 82 2080 1398728 N/A N/A 217903 217922 GTCCTTCTCTTTTCGCACCC 78 2081 1398734 N/A N/A 269553 269572 GCATCCACATCTGTTGTGTT 56 2082 1398749 N/A N/A 185049 185068 GCTTGTCACAATACTGCCAC 40 2083 1398769 N/A N/A 24843 24862 ATCAATTGCATTCCAAGGCT 54 2084 1398784 N/A N/A 15060 15079 GCGGAATTCCTCAAGGCACA 33 2085 1398831 N/A N/A 94190 94209 TGTTTCTCCCTATATACACT 48 2086 1398861 N/A N/A 245348 245367 TGGATGTCTTCCTCTGGTTC 54 2087 1398875 N/A N/A 154561 154580 ATGTCATGCTCTCCATGGAA 43 2088 1398890 N/A N/A 209704 209723 CCTCCATGTACTTCCTCTAA 75 2089 1398911 N/A N/A 33852 33871 CCAACTTCACAGTACTCACT 60 2090 1398928 N/A N/A 15906 15925 CTTTGTTCCATCACTCTAGC 55 2091 1398929 N/A N/A 158125 158144 TTGCGATCCTCAACTCTACT 34 2092 1398970 N/A N/A 39714 39733 TGGAGATTACACATCCCACA 33 2093 1398989 N/A N/A 84850 84869 ATCCTTATTTACAACCTGCC 73 2094 1399001 664 683 122969 122988 AGTCTGTGTCTGCTCCGCCC 10† 2095 1399014 N/A N/A 46447 46466 GGTCTAATCCATCACTGTCT 50 2096 1399032 N/A N/A 57967 57986 GTCTATGCTTTTCTAAGACT 84 2097 1399077 N/A N/A 96471 96490 TCATTTTCTATGCATCCATC 52 2098 1399089 N/A N/A 177018 177037 CTTCCACTGCACCTAGCCCT 84 2099 1399124 N/A N/A 86866 86885 CTCTACATACTCTACCAGGT 42 2100 1399132 N/A N/A 260250 260269 CTGTTTCGCATACACAGTAC 77 2101 1399166 N/A N/A 289172 289191 AGGCACATCTACCATCACAC 57 2102 1399182 N/A N/A 10431 10450 CATCTTAATCACTCCTCACT 89 2103 1399276 N/A N/A 32244 32263 TTGGTACTTTTCTATCGGTT 30 2104 1399287 N/A N/A 90260 90279 TCACCTATCATCTAGGACCT 63 2105 1399347 N/A N/A 224562 224581 TAGCTTGATCAATCACAGCT 47 2106 1399360 N/A N/A 13372 13391 GGCCAATTTTGATCCTTGTC 35 2107 1399370 N/A N/A 148175 148194 AAGTTCTTATTACCATAGCT 69 2108 1399381 N/A N/A 159588 159607 GCTACTCTGATTTACTTCAA 55 2109 1399433 N/A N/A 283633 283652 GCCTGTCCTCTTCTAATCAA 85 2110 1399464 N/A N/A 104646 104665 CCAGTAAACCACTTTCTGGC 89 2111 1399504 N/A N/A 98602 98621 TGTTTCCTCTTATCAGGCCC 47 2112

(334) TABLE-US-00030 TABLE 28 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 19 178 1397528 N/A N/A 101638 101657 TTATTTCACATTCTCTTCTT 84 2113 1397653 N/A N/A 88489 88508 GCACCAATTCTCTAGCACAC 54 2114 1397762 N/A N/A 26939 26958 CCCCATTGACCTATCTATGC 47 2115 1397764 N/A N/A 6889 6908 TCTCATCCCATTGTTCCTTA 32 2116 1397796 N/A N/A 283635 283654 CTGCCTGTCCTCTTCTAATC 83 2117 1397838 N/A N/A 274165 274184 GCTAGGGCTTTCTTTTCTCA 40 2118 1397870 N/A N/A 58436 58455 AGCGCAGCCACTCCCTGGCA 92 2119 1397880 N/A N/A 38261 38280 TCTCTCATCATCCCAGATCT 67 2120 1397916 N/A N/A 90261 90280 CTCACCTATCATCTAGGACC 43 2121 1397939 N/A N/A 30123 30142 TGGATTTCAACCTCACCCCT 81 2122 1397941 N/A N/A 158141 158160 GGCAACACAATCTCTTTTGC 29 2123 1397962 N/A N/A 31679 31698 GCCCTCACTCGATCTTTCTA 86 2124 1397983 N/A N/A 7707 7726 GTGTGCTCATTCCTTCCCCT 24 2125 1397992 N/A N/A 86870 86889 CATGCTCTACATACTCTACC 38 2126 1397995 N/A N/A 234374 234393 CCAAGTTCATTCCCCTAGCC 66 2127 1398007 N/A N/A 222034 222053 CCCAGCAAACCACTTCTGTA 58 2128 1398035 N/A N/A 98615 98634 GCTGCACAATTATTGTTTCC 42 2129 1398062 N/A N/A 53075 53094 TGCTACTGCAATCACACTCC 66 2130 1398072 N/A N/A 22306 22325 CTCACTTTCTTACATGCGGT 13 2131 1398090 N/A N/A 179400 179419 AGAGCTTTTTCTATCTCCTT 29 2132 1398126 N/A N/A 39715 39734 TTGGAGATTACACATCCCAC 58 2133 1398129 N/A N/A 10432 10451 CCATCTTAATCACTCCTCAC 52 2134 1398138 N/A N/A 33853 33872 GCCAACTTCACAGTACTCAC 34 2135 1398147 N/A N/A 134893 134912 ACCCAATGTCTTTTTAGGCA 24 2136 1398151 2483 2502 292467 292486 GCATCTACTTGTGTTACAGC 33 2137 1398171 N/A N/A 260299 260318 TGTGGTATCTACTATCACTT 78 2138 1398172 N/A N/A 96472 96491 CTCATTTTCTATGCATCCAT 36 2139 1398195 N/A N/A 51401 51420 GCCTGCCGTTACCAATGCCA 54 2140 1398197 N/A N/A 49920 49939 GGCCTGACTCTCTCACTCCC 71 2141 1398201 N/A N/A 36034 36053 AAACTCATCTTCTACTGCAG 66 2142 1398214 N/A N/A 186344 186363 CTTCCAAATATACAGTGGCA 44 2143 1398250 665 684 122970 122989 TAGTCTGTGTCTGCTCCGCC 28† 2144 1398274 N/A N/A 148301 148320 TGCCCATCATCCATCCCTGC 75 2145 1398283 N/A N/A 12013 12032 TCCATCTTTATTCTATGAGC 25 2146 1398342 N/A N/A 289342 289361 GCATCATTTTTGCTCCCCAT 52 2147 1398366 N/A N/A 94193 94212 GTCTGTTTCTCCCTATATAC 40 2148 1398378 N/A N/A 177114 177133 GCCTTTGTTTTTTAATCCAA 27 2149 1398379 N/A N/A 84878 84897 GTCCACAATCTCCACAGACA 27 2150 1398404 N/A N/A 246008 246027 GTGCTGATCTGATTTCCAAC 38 2151 1398410 N/A N/A 217904 217923 GGTCCTTCTCTTTTCGCACC 44 2152 1398449 N/A N/A

121663 121682 ACACCACTCCCTCAAGCTGT 90 2153 1398482 N/A N/A 15061 15080 TGCGGAATTCCTCAAGGCAC 36 2154 1398492 N/A N/A 42615 42634 TGCAACCATTTTATTGTTCA 33 2155 1398495 N/A N/A 285928 285947 CATCATGACTTCTTCAGGCA 52 2156 1398513 N/A N/A 20041 20060 TCATCCATCATGCATGCTTC 34 2157 1398544 N/A N/A 114470 114489 TGCCACCACCCTCAATACTT 87 2158 1398582 N/A N/A 190155 190174 TGTTCCTTCTTACATTGGCA 42 2159 1398695 N/A N/A 165667 165686 GTGGTTTTTCCTCAACCTTT 35 2160 1398708 N/A N/A 65940 65959 GACTCATTTCTACCTCCCTC 66 2161 1398742 N/A N/A 269905 269924 CCTGTTCTTTGACTATCGCC 66 2162 1398783 N/A N/A 154590 154609 ACCCACCCACACTTTTGGCT 66 2163 1398811 N/A N/A 104229 104248 GGTCTATATATTTCAGGCAT 30 2164 1398815 N/A N/A 104652 104671 AGCACTCCAGTAAACCACTT 69 2165 1398837 N/A N/A 130143 130162 TCTCACTTTATCCATTCATA 41 2166 1398845 N/A N/A 19182 19201 GAGGTCTTATAGATTCTACC 37 2167 1398864 N/A N/A 72332 72351 CCACAATGCTTTTCACACTA 70 2168 1398948 N/A N/A 23266 23285 ATGGTTGTATCCCAATGCTT 12 2169 1398949 N/A N/A 91249 91268 CCTGAGCTGAAATCCCATCC 60 2170 1398955 N/A N/A 159666 159685 GTCCATTACAAACAAGTAAC 24 2171 1398981 N/A N/A 24930 24949 CAGCATTCAGAACTTCCTGC 42 2172 1399027 N/A N/A 46451 46470 ACAGGGTCTAATCCATCACT 44 2173 1399034 N/A N/A 28139 28158 TTAGATATTTCTATACATCA 42 2174 1399047 N/A N/A 265210 265229 TGCTCATACTATACCTCTGA 44 2175 1399053 2038 2057 276368 276387 ATTCTGCATCCATCTTCACT 111 2176 1399076 N/A N/A 8699 8718 ACAGTGCTTATGCTATGCCA 23 2177 1399101 N/A N/A 194108 194127 CTCAAGGTTTCTATCCAGCT 120 2178 1399112 N/A N/A 47912 47931 GGGAAAGATTTACATTCTAC 43 2179 1399113 N/A N/A 171570 171589 GGTCTCTGCTCCCAGAGCTT 38 2180 1399129 N/A N/A 207134 207153 TCCACATCATATAGTGGCGA 39 2181 1399131 N/A N/A 32282 32301 CTGTATTATTTCTTTTACGC 38 2182 1399133 N/A N/A 15908 15927 TGCTTTGTTCCATCACTCTA 49 2183 1399265 N/A N/A 82409 82428 GCTACACCTGATGACAGCAA 85 2184 1399313 N/A N/A 105198 105217 TGTCTTCTACTCTTCTTGCT 72 2185 1399326 N/A N/A 209774 209793 AGTCATCTATCATCTGTTCT 45 2186 1399356 N/A N/A 103095 103114 TTCAACTTAGTCATCCTCTT 75 2187 1399395 N/A N/A 225512 225531 GCCATATCTTTCAATCCTGC 19 2188 1399465 N/A N/A 13493 13512 TAGATTTTCAATTCCTGTCA 36 2189

(335) TABLE-US-00031 TABLE 29 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 23 178 1396897 N/A N/A 177301 177320 GCACCTTCAGAATTCTCCCT 40 2190 1397543 N/A N/A 53168 53187 GCTCATACCTCACATGTGGC 55 2191 1397592 N/A N/A 22309 22328 GCTCTCACTTTCTTACATGC 37 2192 1397656 N/A N/A 103097 103116 TCTTCAACTTAGTCATCCTC 65 2193 1397667 N/A N/A 25017 25036 CCACACTCAGAACTTCCTTC 109 2194 1397692 N/A N/A 65942 65961 GGGACTCATTTCTACCTCCC 258 2195 1397743 N/A N/A 135854 135873 GAGACATCATACTTTCTAGT 68 2196 1397750 N/A N/A 283702 283721 GCAGAGGTTTTAATTGCTGA 84 2197 1397759 N/A N/A 105199 105218 CTGTCTTCTACTCTTCTTGC 79 2198 1397822 N/A N/A 88490 88509 GGCACCAATTCTCTAGCACA 85 2199 1397857 N/A N/A 7779 7798 TGCTTTTCTTCTTATACAAC 58 2200 1397863 N/A N/A 23459 23478 ATCCAGCTCCTCACTGGCTT 73 2201 1397884 N/A N/A 85004 85023 CCATATATTACATAGATCTC 141 2202 1397893 N/A N/A 47959 47978 GTACAATCTATATCTCGCCC 104 2203 1397896 N/A N/A 115707 115726 GAGGGACATACTCCTCAGCA 148 2204 1397973 N/A N/A 8746 8765 ACCCATTGTACATCAACATC 94 2205 1397974 N/A N/A 90262 90281 TCTCACCTATCATCTAGGAC 42 2206 1398003 N/A N/A 73312 73331 GCTCAACTCATCTAACAGGC 87 2207 1398008 N/A N/A 285929 285948 TCATCATGACTTCTTCAGGC 57 2208 1398010 N/A N/A 30124 30143 CTGGATTTCAACCTCACCCC 169 2209 1398021 N/A N/A 222487 222506 AGGCATGCATTTTTAGGGAC 108 2210 1398046 N/A N/A 195741 195760 GCACCATCCCACTAAGACTC 79 2211 1398051 N/A N/A 165668 165687 TGTGGTTTTTCCTCAACCTT 80 2212 1398067 N/A N/A 274765 274784 ATGGTGCTACTTCCCCTTCA 60 2213 1398095 N/A N/A 190207 190226 TGGTGCCTTTACACAGCTGC 169 2214 1398158 N/A N/A 12020 12039 GTGCTTATCCATCTTTATTC 50 2215 1398191 N/A N/A 246643 246662 GCCAGAAGTTTCACCAACTC 94 2216 1398302 N/A N/A 39735 39754 ACTGGATTCTGACACTGTAC 87 2217 1398352 N/A N/A 28164 28183 TGTTTTCACTTATATCGGTA 32 2218 1398353 N/A N/A 49921 49940 TGGCCTGACTCTCTCACTCC 87 2219 1398374 N/A N/A 207700 207719 CCTTCCCATTCACTATCTGT 77 2220 1398392 N/A N/A 32353 32372 AATCAATCACCAATGCTGGC 94 2221 1398395 N/A N/A 96473 96492 CCTCATTTTCTATGCATCCA 66 2222 1398411 N/A N/A 234375 234394 ACCAAGTTCATTCCCCTAGC 194 2223 1398445 N/A N/A 26942 26961 TTGCCCCATTGACCTATCTA 109 2224 1398456 N/A N/A 159759 159778 GTTCACAGTTTACCCCAAGC 36 2225 1398486 N/A N/A 43083 43102 ATCTTCCTTAGACTATGCCT 88 2226 1398526 N/A N/A 36035 36054 GAAACTCATCTTCTACTGCA 66 2227 1398566 N/A N/A 186345 186364 GCTTCCAAATATACAGTGGC 54 2228 1398590 N/A N/A 101640 101659 GATTATTTCACATTCTCTTC 68 2229 1398597 N/A N/A 171691 171710 CCTCTGGTTTTACCAGTACT 118 2230 1398630 N/A N/A 19227 19246 CCAGATATTACTTTCTTCAT 85 2231 1398651 N/A N/A 86871 86890 GCATGCTCTACATACTCTAC 143 2232 1398719 N/A N/A 91386 91405 AGTGAACTAGTTCCTACCTT 44 2233 1398741 N/A N/A 121796 121815 AGATCAGATTTCTCAACCCC 101 2234 1398745 N/A N/A 6893 6912 ATGATCTCATCCCATTGTTC 50 2235 1398761 N/A N/A 13611 13630 TTGCATTTAAATTTTCTGGA 28 2236 1398762 N/A N/A 15100 15119 ACCTAATTATTTCTCCGTCT 65 2237 1398807 N/A N/A 180615 180634 CCTCCAGCATATCCTGGGAT 183 2238 1398910 N/A N/A 15909 15928 TTGCTTTGTTCCATCACTCT 87 2239 1398918 N/A N/A 38277 38296 GTCCTACCTGCCTTTCTCTC 120 2240 1398960 N/A N/A 148442 148461 CCAGGTTCCTTCTCCAGGCT 63 2241 1398984 2484 2503 292468 292487 GGCATCTACTTGTGTTACAG 42 2242 1398991 N/A N/A 94716 94735 CCTCATCATAACCATTTGTA 55 2243 1399003 2043 2062 276373 276392 TCGGAATTCTGCATCCATCT 124 2244 1399068 N/A N/A 83178 83197 CCTGCTCTTATTCCAAGTAA 86 2245 1399069 N/A N/A 58490 58509 CGGCATCCTCACCTGCATCA 75 2246 1399122 N/A N/A 31681 31700 CAGCCCTCACTCGATCTTTC 191 2247 1399135 N/A N/A 158504 158523 GCAAAGATTTGAATCTGGAC 76 2248 1399140 N/A N/A 10433 10452 ACCATCTTAATCACTCCTCA 65 2249 1399154 N/A N/A 226487 226506 CCATTCATTTGACAAAGCAT 121 2250 1399172 N/A N/A 270073 270092 GCAGACTCTCAGTCTTCATC 125 2251 1399245 N/A N/A 209779 209798 CTAGGAGTCATCTATCATCT 80 2252 1399263 N/A N/A 265408 265427 CTGTATCTCATTATATGGCT 30 2253 1399281 N/A N/A 154630 154649 TCCTGATGACTCTACAGCAA 100 2254 1399286 N/A N/A 260383 260402 GCATACACATTCATCTTGAC 90 2255 1399294 N/A N/A 20110 20129 ACTCAGTCAACATCCATGCT 149 2256 1399311 N/A N/A 33855 33874 ATGCCAACTTCACAGTACTC 84 2257 1399329 666 685 122971 122990 ATAGTCTGTGTCTGCTCCGC 44† 2258 1399369 N/A N/A 46453 46472 GAACAGGGTCTAATCCATCA 58 2259 1399375 N/A N/A 51577 51596 GTTAAGTTATCATATTGTCT 176 2260 1399432 N/A N/A 104231 104250 TTGGTCTATATATTTCAGGC 28 2261 1399451 N/A N/A 218042 218061 GCTGCTTTTCACTTCCACAA 146 2262 1399462 N/A N/A 104660 104679 TCAGACACAGCACTCCAGTA 132 2263 1399473 N/A N/A 289345 289364 TGGGCATCATTTTTGCTCCC 94 2264 1399475 N/A N/A 98616 98635 AGCTGCACAATTATTGTTTC 88 2265 1399491 N/A N/A 130153 130172 GGGCTGATATTCTCACTTTA 291 2266

(336) TABLE-US-00032 TABLE 30 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ SEQ ID SEQ ID No: 1 ID No: No: 2 ID No: Compound Start 1 Stop Start 2 Stop APP SEQ ID Number Site Site Site Site Sequence (5′ to 3′) (% UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 20 178 1397539 N/A N/A 234724 234743 CCAGCTTTTCCTTTCACATC 47 2267 1397560 N/A N/A 103102 103121 GCTACTCTTCAACTTAGTCA 58 2268 1397571 N/A N/A 25019 25038 ATCCACACTCAGAACTTCCT 97 2269 1397587 N/A N/A 159824 159843 GCATGCTACTACTGAGGCCT 71 2270 1397600 N/A N/A 36061 36080 GTTCCATCAACAAAGGGCTA 74 2271 1397604 N/A N/A 85005 85024 ACCATATATTACATAGATCT 45 2272 1397633 N/A N/A 13698 13717 GCTGCCTTTACATTCAAACA 114 2273 1397677 N/A N/A 43189 43208 GTAGTAGCCTTCCCTTCCTT 49 2274 1397718 N/A N/A 207764 207783 AGCATGTATACCATTCAGCA 74 2275 1397726 N/A N/A 40005 40024 GTCCTTTATAACCCATTGAC 52 2276 1397795 N/A N/A 222488 222507 AAGGCATGCATTTTTAGGGA 24 2277

1397829 N/A N/A 10434 10453 AACCATCTTAATCACTCCTC 44 2278 1397851 N/A N/A 53176 53195 CCGTTCCTGCTCATACCTCA 80 2279 1397886 N/A N/A 285939 285958 ACCAAAGCTTTCATCATGAC 73 2280 1397902 N/A N/A 33891 33910 CAGAGTTTCATCTTACCCAA 76 2281 1397925 N/A N/A 15130 15149 CCTCCTCTATTATAGCCTTT 85 2282 1397971 2047 2066 276377 276396 CATGTCGGAATTCTGCATCC 78 2283 1397991 N/A N/A 46463 46482 CTGCAACTATGAACAGGGTC 90 2284 1397994 N/A N/A 101641 101660 GGATTATTTCACATTCTCTT 47 2285 1398056 N/A N/A 86872 86891 GGCATGCTCTACATACTCTA 33 2286 1398096 667 686 122972 122991 CATAGTCTGTGTCTGCTCCG 59† 2287 1398109 N/A N/A 218043 218062 GGCTGCTTTTCACTTCCACA 59 2288 1398163 N/A N/A 9447 9466 GCCAGTGTATAAACTTGCTC 41 2289 1398169 N/A N/A 28165 28184 ATGTTTTCACTTATATCGGT 21 2290 1398178 N/A N/A 7781 7800 TCTGCTTTTCTTCTTATACA 68 2291 1398184 N/A N/A 196046 196065 GTGGTGGTACTCTACCAACA 61 2292 1398226 N/A N/A 47960 47979 TGTACAATCTATATCTCGCC 67 2293 1398268 N/A N/A 83252 83271 CCTCCCCCTATCTCTCACTA 78 2294 1398320 N/A N/A 165669 165688 CTGTGGTTTTTCCTCAACCT 38 2295 1398369 N/A N/A 66353 66372 CTGCAATTCCCCAAGGTGCT 61 2296 1398381 N/A N/A 51673 51692 GTCCATACCCTTTAATATCT 60 2297 1398401 N/A N/A 158953 158972 TATTTCAATATACAGTGTAT 39 2298 1398414 N/A N/A 49922 49941 CTGGCCTGACTCTCTCACTC 109 2299 1398426 N/A N/A 98831 98850 TGGCTACATCCTCAATTCAT 51 2300 1398427 N/A N/A 38283 38302 GCATGTGTCCTACCTGCCTT 70 2301 1398433 N/A N/A 265827 265846 GCCAGATCATTTCACGATCT 71 2302 1398447 N/A N/A 91411 91430 GACCAATTACCTCTTCTTTT 44 2303 1398461 N/A N/A 190221 190240 GCAGGGCATATTCCTGGTGC 61 2304 1398464 N/A N/A 30125 30144 CCTGGATTTCAACCTCACCC 49 2305 1398489 N/A N/A 15940 15959 CACTGCTGTCCACACAGGGC 39 2306 1398550 N/A N/A 177517 177536 CTCTTGTTAAATCATGGCAT 20 2307 1398581 N/A N/A 32356 32375 GCCAATCAATCACCAATGCT 47 2308 1398588 N/A N/A 289346 289365 TTGGGCATCATTTTTGCTCC 87 2309 1398592 N/A N/A 274792 274811 CCCAGCTTTCCACAAAGACC 72 2310 1398605 N/A N/A 130155 130174 GTGGGCTGATATTCTCACTT 73 2311 1398645 N/A N/A 23495 23514 TCTGATCCCCTTCATACCCT 75 2312 1398654 N/A N/A 226647 226666 AGGTCTGTAACCTCAAGTCT 89 2313 1398676 N/A N/A 186379 186398 TTCCTAGTACATCACTGCTT 83 2314 1398685 N/A N/A 20259 20278 GCATGCTTAACTTCAAGGTT 58 2315 1398725 N/A N/A 104232 104251 GTTGGTCTATATATTTCAGG 39 2316 1398731 N/A N/A 105673 105692 ATGCCATCAGTCTCTTCTCA 92 2317 1398753 N/A N/A 12184 12203 GCTACTACATATCACTTTTC 70 2318 1398767 N/A N/A 210196 210215 TCACCACCTTTATTGTCTTT 68 2319 1398773 N/A N/A 122200 122219 GCACAAATCTAGATTAGCAT 83 2320 1398834 N/A N/A 90263 90282 TTCTCACCTATCATCTAGGA 39 2321 1398848 N/A N/A 74558 74577 GCACATCATAATCCTGAGTT 50 2322 1398855 N/A N/A 172144 172163 GATCCATCACATCTAGGCAT 116 2323 1398884 N/A N/A 58491 58510 ACGGCATCCTCACCTGCATC 91 2324 1398932 2486 2505 292470 292489 CAGGCATCTACTTGTGTTAC 52 2325 1398946 N/A N/A 260386 260405 GGTGCATACACATTCATCTT 28 2326 1398947 N/A N/A 283736 283755 CCCCAATTTCCATCAGCAGC 74 2327 1399025 N/A N/A 135887 135906 CTACCTTCATTTTTATAGCA 57 2328 1399043 N/A N/A 19244 19263 TGAACAACTCAACATCTCCA 78 2329 1399065 N/A N/A 88565 88584 ACACATGCATCTCCCATGAC 136 2330 1399078 N/A N/A 96475 96494 TGCCTCATTTTCTATGCATC 68 2331 1399114 N/A N/A 271036 271055 TGGATGGTTTTCTCCCACCA 52 2332 1399188 N/A N/A 31682 31701 ACAGCCCTCACTCGATCTTT 139 2333 1399210 N/A N/A 94735 94754 TCCACTTTCTTCTTTGATTC 162 2334 1399213 N/A N/A 104672 104691 ATCATGTAATACTCAGACAC 80 2335 1399299 N/A N/A 6949 6968 CCTGGGATATAAACCTGGCT 76 2336 1399335 N/A N/A 26944 26963 GTTTGCCCCATTGACCTATC 47 2337 1399355 N/A N/A 151234 151253 CCGCAACGCATTGCACGGTA 230 2338 1399400 N/A N/A 154701 154720 GCTCTAGCTTAAATTGGACC 120 2339 1399438 N/A N/A 115880 115899 CCTATCTTTCTGTACTGCCA 88 2340 1399466 N/A N/A 22456 22475 ACAGCAGCAATTTATAGCAG 62 2341

(337) TABLE-US-00033 TABLE 31 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ SEQ ID SEQ No: 1 ID No: No: 2 ID No: Compound Start 1 Stop Start 2 Stop APP SEQ ID Number Site Site Site Site Sequence (5′ to 3′) (% UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 33 178 1396898 N/A N/A 66354 66373 GCTGCAATTCCCCAAGGTGC 70 2342 1396901 N/A N/A 49925 49944 GCACTGGCCTGACTCTCTCA 73 2343 1397569 N/A N/A 222521 222540 TGCTTGTATTTATAAGCACA 36 2344 1397581 N/A N/A 186468 186487 AGGCTATTACCTCCCTTCCT 69 2345 1397594 N/A N/A 207838 207857 TAGCAAGATTTTATCGAACT 65 2346 1397608 N/A N/A 283742 283761 GCTCCACCCCAATTTCCATC 59 2347 1397658 N/A N/A 90272 90291 GGTTTCTTTTTCTCACCTAT 36 2348 1397715 N/A N/A 85022 85041 TAGGACATTCATTTTTGACC 40 2349 1397722 N/A N/A 88566 88585 CACACATGCATCTCCCATGA 78 2350 1397727 N/A N/A 285978 285997 CGGGCATTTTTCACTCTAAA 33 2351 1397742 N/A N/A 103103 103122 GGCTACTCTTCAACTTAGTC 72 2352 1397748 N/A N/A 228774 228793 CTAAATCAGTTCTCTTGCTA 66 2353 1397758 N/A N/A 159826 159845 CAGCATGCTACTACTGAGGC 43 2354 1397785 N/A N/A 7205 7224 CTGCATTCAGCCCCTTACCT 73 2355 1397848 N/A N/A 74564 74583 TGTGTAGCACATCATAATCC 60 2356 1397917 N/A N/A 104673 104692 GATCATGTAATACTCAGACA 85 2357 1397926 N/A N/A 30126 30145 GCCTGGATTTCAACCTCACC 63 2358 1397945 N/A N/A 130298 130317 GCCAAGTATTTTCCTGCATC 30 2359 1397952 N/A N/A 28245 28264 GCTACTGACATAATACACAT 79 2360 1398107 N/A N/A 20318 20337 TCCCAGACACAGCACTGGCA 58 2361 1398187 N/A N/A 40668 40687 TGCAATTTTTATTAACACAC 66 2362 1398199 N/A N/A 10435 10454 GAACCATCTTAATCACTCCT 31 2363 1398212 N/A N/A 180718 180737 GTCAGGCCTACACCTCTGCA 52 2364 1398240 N/A N/A 271136 271155 CCTACCGTTTAATTTCTTTC 97 2365 1398257 N/A N/A 105717 105736 GCTCCAACAATCTGCAACTC 78 2366 1398301 N/A N/A 43305 43324 GCTAAGCTTACGCTAAGGGC 50 2367 1398329 N/A N/A 265988 266007 TCTACATATTATATCTAGGT 35 2368 1398333 N/A N/A 47961 47980 CTGTACAATCTATATCTCGC 69 2369 1398384 N/A N/A 158955 158974 GATATTTCAATATACAGTGT 47 2370 1398412 N/A N/A 31684 31703 ACACAGCCCTCACTCGATCT 100 2371 1398430 N/A N/A 9500 9519 CTGTTCACAGTTCCTTGCAC 35 2372 1398462 N/A N/A 8042 8061 CCTAGAGCAATCATTGTACT 69 2373 1398469 N/A N/A 86873 86892 AGGCATGCTCTACATACTCT 40 2374 1398473 N/A N/A 96476 96495 TTGCCTCATTTTCTATGCAT 59 2375 1398474 N/A N/A 115885 115904 GTATTCCTATCTTTCTGTAC 90 2376 1398507 N/A N/A 210617 210636 TGGCATCTTATCATAATAGA 72 2377 1398522 N/A N/A 101642 101661 CGGATTATTTCACATTCTCT 35 2378 1398537 2605 2624 292589 292608 GCACTAGTTTGATACAGCTA 52 2379 1398573 N/A N/A 16032 16051 GCTTTCAAAGAACAAGCACA 60 2380 1398594 N/A N/A 196386 196405 TGGCATTCATTCTTTGTATA 75 2381 1398599 N/A N/A 22457 22476 GACAGCAGCAATTTATAGCA 64 2382 1398668 N/A N/A 59221 59240 GCTTCTTGACTTTACAGCTA 66 2383 1398670 2071 2090 276401 276420 GATGATGAACTTCATATCCT 76 2384 1398688 N/A N/A 46464 46483 TCTGCAACTATGAACAGGGT 41 2385 1398721 N/A N/A 98846 98865 TCCTTTTCCAATATTTGGCT 58 2386 1398723 N/A N/A 33955 33974 CTTCATCCCTACTTTGGTCA 70 2387 1398757 N/A N/A 25020 25039 CATCCACACTCAGAACTTCC 71 2388 1398758 N/A N/A 172146 172165 AGGATCCATCACATCTAGGC 114 2389 1398774 N/A N/A 51680 51699 CCACATTGTCCATACCCTTT 68 2390 1398778 N/A N/A 53335 53354 AGCTTCTTTTCTCCTACATT 51 2391 1398781 N/A N/A 234726 234745 AGCCAGCTTTTCCTTTCACA 54 2392 1398806 743 762 152005 152024 TCGGCTTCTTCTTCTTCCAC 18† 2393 1398846 N/A N/A 36063 36082 TTGTTCCATCAACAAAGGGC 60 2394 1398917 N/A N/A 32357 32376 AGCCAATCAATCACCAATGC 63 2395 1398933 N/A N/A 247463 247482 GCTGATTTGATAACCACAAT 57 2396 1398944 N/A N/A 27003 27022 AGACACTTTTATCTTGCACT 32 2397 1398992 N/A N/A 122406 122425 GCTCACTCCTACCTCCCTTA 90 2398 1399002 N/A N/A 104233 104252 TGTTGGTCTATATATTTCAG 41 2399 1399018 N/A N/A 23570 23589 TGGGTCTGCTATTTCTCGAT 49 2400 1399036 N/A N/A 19413 19432 ATTGTCTTAAAGCTCCTGGC 52 2401 1399073 N/A N/A 190328 190347 CGTTTTGATTTTTTCCCTCC 31 2402 1399097 668 687 122973 122992 GCATAGTCTGTGTCTGCTCC 14† 2403 1399107 N/A N/A 166225 166244 GTGATTTTCCCAATTCTGGA 33 2404 1399142 N/A N/A 177518 177537 TCTCTTGTTAAATCATGGCA 33 2405 1399152 N/A N/A 136218 136237 CCTTGGCTCCAATTTTCCAA 55 2406 1399174 N/A N/A 94736 94755 GTCCACTTTCTTCTTTGATT 43 2407 1399198 N/A N/A 15168 15187 GTTCAAATTCTGCCTGCCTT 73 2408 1399225 N/A N/A 274802 274821 TCCCTACCTTCCCAGCTTTC 82 2409 1399271 N/A N/A 83555 83574 GCTCTACCTCTGACCAAGCT 93 2410 1399277 N/A N/A 38376 38395 CTCAAACTCATTCCTAAGCA 75 2411 1399284 N/A N/A 13699 13718 AGCTGCCTTTACATTCAAAC 91 2412 1399308 N/A N/A 154733 154752 TCTATATTTTGGTCCCAACC

71 2413 1399323 N/A N/A 260566 260585 CCTCATTAGATTTCCTCCAA 86 2414 1399342 N/A N/A 289347 289366 CTTGGGCATCATTTTTGCTC 90 2415 1399389 N/A N/A 92206 92225 ATCAGTTTTTCTCTAGGTAT 45 2416 1399411 N/A N/A 12284 12303 ACTCTTCAGTTATATCCTCA 33 2417 1399457 N/A N/A 218044 218063 CGGCTGCTTTTCACTTCCAC 46 2418

(338) TABLE-US-00034 TABLE 32 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in SH-SY5Y cells SEQ ID SEQ SEQ ID SEQ No: 1 ID No: No: 2 ID No: Compound Start 1 Stop Start 2 Stop APP SEQ ID Number Site Site Site Site Sequence (5′ to 3′) (% UTC) NO 1354057 N/A N/A 158958 158977 GCAGATATTTCAATATACAG 17 178 1394556 669 688 122974 122993 TGCATAGTCTGTGTCTGCTC 33† 2419 1397532 1511 1530 218264 218283 CGGACATACTTCTTTAGCAT 54 2420 1397537 N/A N/A 74671 74690 GCTTTTCCATACCAGTCCCT 69 2421 1397540 N/A N/A 19417 19436 CCAGATTGTCTTAAAGCTCC 48 2422 1397557 N/A N/A 235275 235294 GCCTTTTCCATCCAAGGACT 41 2423 1397559 N/A N/A 247481 247500 GCCTTTTCATACCCATCTGC 54 2424 1397610 N/A N/A 10436 10455 GGAACCATCTTAATCACTCC 30 2425 1397612 N/A N/A 25024 25043 CCAACATCCACACTCAGAAC 73 2426 1397634 N/A N/A 283785 283804 TCCTCACACTGCTCATCCAC 102 2427 1397642 N/A N/A 136220 136239 GTCCTTGGCTCCAATTTTCC 63 2428 1397669 3339 3358 293323 293342 TGCCACTTCCATTTTCATCT 71 2429 1397691 N/A N/A 83558 83577 CCTGCTCTACCTCTGACCAA 70 2430 1397735 N/A N/A 86957 86976 CATCAGTTACACCTATGTCC 49 2431 1397766 N/A N/A 59222 59241 TGCTTCTTGACTTTACAGCT 76 2432 1397777 N/A N/A 48017 48036 GATGTCTTTTTGACATGTCT 64 2433 1397778 N/A N/A 105774 105793 AGACTGTCACTCTCACGCCC 75 2434 1397808 N/A N/A 30158 30177 TTTCACTTAGCTTAAGGCCA 49 2435 1397881 N/A N/A 51695 51714 TCTGGTACATACATTCCACA 55 2436 1397894 N/A N/A 85109 85128 ACCAGGTGAAATCTTCTTTC 31 2437 1397897 N/A N/A 16183 16202 CTGTTTCAATAACACCAGCA 31 2438 1397906 N/A N/A 222522 222541 TTGCTTGTATTTATAAGCAC 45 2439 1397920 N/A N/A 22543 22562 GCCTTTCCTTATTTTTGCTA 54 2440 1397938 N/A N/A 260600 260619 GCCCATGATGACCTTTCCCT 72 2441 1397942 N/A N/A 166367 166386 GTGGTGACATTTCATGAGCC 49 2442 1397944 N/A N/A 43321 43340 ATGACTCAACCATTTGGCTA 71 2443 1397951 N/A N/A 13702 13721 GTAAGCTGCCTTTACATTCA 75 2444 1397958 N/A N/A 153124 153143 CCTTTAGTTCTTTTAGTTCA 31 2445 1397966 N/A N/A 130873 130892 GCCATCCCTCTTCTGCCCAT 75 2446 1397988 N/A N/A 92207 92226 TATCAGTTTTTCTCTAGGTA 56 2447 1397997 N/A N/A 7211 7230 CTGGTCCTGCATTCAGCCCC 53 2448 1398044 N/A N/A 159947 159966 GTGCATCCTCTCCATCTTCA 36 2449 1398049 N/A N/A 46664 46683 AGACTTTCAAATTCTAGCCA 54 2450 1398057 N/A N/A 9536 9555 TTGCTAGCAAAGATTCTACT 51 2451 1398069 N/A N/A 196682 196701 GTGCAACTCTGAACTAGGTA 31 2452 1398091 N/A N/A 28246 28265 TGCTACTGACATAATACACA 77 2453 1398134 N/A N/A 190811 190830 GCAACATATACTGCTATATT 36 2454 1398141 N/A N/A 266245 266264 GTACAAACTCTCTACCAGGC 41 2455 1398148 N/A N/A 210708 210727 AGCTTATTACTTGACAGTTC 31 2456 1398173 N/A N/A 271262 271281 CCATCACAGAACATTCTTGT 67 2457 1398196 N/A N/A 49936 49955 CCTACTCTTTAGCACTGGCC 85 2458 1398281 N/A N/A 36102 36121 GCTGTTCCAATGATTTTCCT 38 2459 1398303 N/A N/A 27078 27097 CCTTCCTTCTATGTACAGTC 20 2460 1398347 N/A N/A 31686 31705 CCACACAGCCCTCACTCGAT 96 2461 1398348 N/A N/A 277174 277193 CCATGATCTTACTCTTGCAA 77 2462 1398349 N/A N/A 98868 98887 GGGCTATTCTTTCTTTTCCC 34 2463 1398367 N/A N/A 101645 101664 TTCCGGATTATTTCACATTC 39 2464 1398431 N/A N/A 207865 207884 TCTTGTTACATACTTCCCAT 52 2465 1398510 N/A N/A 38397 38416 CAGCACATTTAGCCTTATTA 39 2466 1398542 N/A N/A 228776 228795 TGCTAAATCAGTTCTCTTGC 43 2467 1398552 N/A N/A 289359 289378 ACGCCATTTGAACTTGGGCA 68 2468 1398610 N/A N/A 96477 96496 TTTGCCTCATTTTCTATGCA 67 2469 1398633 N/A N/A 186566 186585 CAGCAATACCAACATCACAT 41 2470 1398679 N/A N/A 104235 104254 AATGTTGGTCTATATATTTC 70 2471 1398710 N/A N/A 33956 33975 ACTTCATCCCTACTTTGGTC 46 2472 1398722 N/A N/A 32393 32412 GCCTCTGAAAACATCTGGCA 71 2473 1398904 N/A N/A 8043 8062 TCCTAGAGCAATCATTGTAC 68 2474 1398927 N/A N/A 115886 115905 CGTATTCCTATCTTTCTGTA 73 2475 1398939 N/A N/A 53336 53355 GAGCTTCTTTTCTCCTACAT 57 2476 1399040 N/A N/A 95334 95353 CCATAGAGCTCTCAATCCCA 43 2477 1399071 N/A N/A 103104 103123 AGGCTACTCTTCAACTTAGT 80 2478 1399074 N/A N/A 285979 285998 GCGGGCATTTTTCACTCTAA 55 2479 1399136 N/A N/A 158956 158975 AGATATTTCAATATACAGTG 35 2480 1399184 N/A N/A 274805 274824 CTATCCCTACCTTCCCAGCT 74 2481 1399204 N/A N/A 154735 154754 TCTCTATATTTTGGTCCCAA 42 2482 1399243 N/A N/A 23665 23684 TGGTGCCACCTCTAGTGGTC 63 2483 1399302 N/A N/A 20324 20343 GCATTGTCCCAGACACAGCA 22 2484 1399324 N/A N/A 88569 88588 TCCCACACATGCATCTCCCA 56 2485 1399333 N/A N/A 104715 104734 TCAAACTCTCCATACTCCCA 74 2486 1399367 N/A N/A 12285 12304 TACTCTTCAGTTATATCCTC 34 2487 1399379 N/A N/A 90273 90292 GGGTTTCTTTTTCTCACCTA 42 2488 1399410 N/A N/A 172755 172774 ACTCATCCCTGATTGCCTCA 57 2489 1399421 N/A N/A 66369 66388 TTGTTTGCCTTCAATGCTGC 72 2490 1399441 N/A N/A 41109 41128 GTGCATCATATTCTACACTA 41 2491 1399453 N/A N/A 122502 122521 GTAGCAGTCTCCACTGGTGA 67 2492 1399474 N/A N/A 177757 177776 GGAGGCTCTTTCTCTACTTC 48 2493 1399487 N/A N/A 15196 15215 GTTCACCTTCACACATCCTT 50 2494 1399498 N/A N/A 180976 180995 CTCCTGTCTTTACAACGACC 46 2495

Example 2: Effect of Mixed Backbone Gapmers on Human APP RNA In Vitro, Single Dose

(339) Modified oligonucleotides complementary to human APP nucleic acid were synthesized and tested for their effect on APP RNA levels in vitro. The modified oligonucleotides were tested in experiment A or experiment B using the same culture conditions, as indicated in the tables below. “Start site” in all the tables below indicates the 5′-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. “Stop site” in all the tables below indicates the 3′-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are complementary to SEQ ID NO: 1 (described herein above), SEQ ID NO: 2 (described herein above), or SEQ ID NO: 8 (GENBANK Accession No. NM_201414.2). ‘N/A’ indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity.

(340) Cultured SH-SY5Y cells at a density of 20,000 cells per well were transfected treated with 4,000 nM of modified oligonucleotide using by electroporation with 4000 nM of modified oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and APP RNA levels were measured by quantitative real-time RTPCR. Human APP primer probe set RTS35572 (described herein above) was used to measure APP RNA levels. APP RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented as percent of APP RNA, relative to untreated control cells (% UTC). The values marked by the symbol “f” indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the activity of the modified oligonucleotides complementary to the amplicon region.

(341) The modified oligonucleotides in the tables below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length. The sugar motif of the gapmers is (from 5′ to 3′): eeeeeddddddddddeeeee; wherein each ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and each ‘e’ represents a 2′-MOE sugar moiety. The internucleoside motif of the gapmers is (from 5′ to 3′): soooossssssssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methyl cytosine.

(342) TABLE-US-00035 TABLE 33 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ SEQ ID SEQ ID SEQ ID ID No: No: 1 No: 2 No: 2 Compound 1 Start Stop Start Stop APP Expt. SEQ ID Number Site Site Site Site Sequence (5′ to 3′) (% UTC) ID NO 1332176 2409 2428 292393 292412 ACATTATTCTATAAATGGAC 59 A 2496 1332177 2030 2049 276360 276379 TCCATCTTCACTTCAGAGAT 69 A 2497 1332178 2095 2114 N/A N/A CTTCTGCAAAGAACACCAAT 74 A 2498 1332179 2090 2109 N/A N/A GCAAAGAACACCAATTTTTG 66 A 2499 1332180 2133 2152 282167 282186 CATGAGTCCAATGATTGCAC 63 A 2500 1332181 2151 2170 282185 282204 TATGACAACACCGCCCACCA 78 B 2501 1332182 2144 2163 282178 282197 ACACCGCCCACCATGAGTCC 65 B 2502 1332183 2441 2460 292425 292444 GAGTAAATCATAAAACGGGT 22 B 2503 1332184 3364 3383 293348 293367 GCATGCCTTCCTCATCCCCT 80 A 2504 1332185 2416 2435 292400 292419 TCTTCCCACATTATTCTATA 47 A 2505 1332186 2029 2048 276359 276378 CCATCTTCACTTCAGAGATC 65 A 2506 1332187

1895 1914 262212 262231 TCAGCCCCAAAAGAATGCCA 70 A 2507 1332188 1341 1360 198780 198799 CAAAGATTCCACTTTCTCCT 51 A 2508 1332189 1342 1361 198781 198800 CCAAAGATTCCACTTTCTCC 51 A 2509 1332190 1407 1426 198846 198865 CATGGCTTCCACTCTGGCCA 67 B 2510 1332192 1343 1362 198782 198801 TCCAAAGATTCCACTTTCTC 40 B 2511 1332193 1638 1657 219328 219347 CATGCGCTCATAAATCACAC 59† A 2512 1332194 3318 3337 293302 293321 CTTTTGTATCATAAATGAAA 6 A 2513 1332195 1894 1913 262211 262230 CAGCCCCAAAAGAATGCCAC 23 A 2514 1332196 1302 1321 198016 198035 CTTCTTATCAGCTTTAGGCA 53 A 2515 1332197 573 592 122878 122897 ACACACAAACTCTACCCCTC 44 A 2516 1332198 567 586 122872 122891 AAACTCTACCCCTCGGAACT 52 A 2517 1332199 683 702 N/A N/A TCTTCACTCCCATCTGCATA 3† B 2518 1332200 562 581 122867 122886 CTACCCCTCGGAACTTGTCA 12 B 2519 1332201 726 745 151988 152007 CACCTCAGCCACTTCTTCCT 6† A 2520 1332202 611 630 122916 122935 GCAGAATCCACATTGTCACT 5 A 2521 1332203 706 725 151968 151987 CCTCTGCTACTTCTACTACT 2† A 2522 1332204 1258 1277 197972 197991 CTTCCCATTCTCTCATGACC 12 A 2523 1332205 734 753 151996 152015 TCTTCTTCCACCTCAGCCAC 3† A 2524 1332206 N/A N/A 3189 3208 GCTCAGAGCCAGGCGAGTCA 13 A 2525 1332207 392 411 120655 120674 GCATCACTTACAAACTCACC 16 B 2526 1332208 2950 2969 292934 292953 TGTGCACATAAAACAGGCAC 47 B 2527 1332209 181 200 61944 61963 GATCTGAATCCCACTTCCCA 11 A 2528 1332210 172 191 61935 61954 CCCACTTCCCATTCTGGACA 12 A 2529 1332211 162 181 61925 61944 ATTCTGGACATTCATGTGCA 12 A 2530 1332212 391 410 120654 120673 CATCACTTACAAACTCACCA 8 A 2531 1332213 452 471 120715 120734 GTTTCGCAAACATCCATCCT 7 A 2532

(343) TABLE-US-00036 TABLE 34 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ ID No: 8 No: 8 SEQ Compound Start Stop APP Expt. ID Number Site Site Sequence (5′ to 3′) (% UTC) ID NO 1332165 1053 1072 GTAGGAACTCGAACCACCTC 125 A 2533 1332166 1048 1067 AACTCGAACCACCTCTTCCA 104 A 2534 1332167 1047 1066 ACTCGAACCACCTCTTCCAC 71 A 2535 1332168 1049 1068 GAACTCGAACCACCTCTTCC 99 A 2536 1332169 1052 1071 TAGGAACTCGAACCACCTCT 14 A 2537 1332170 1051 1070 AGGAACTCGAACCACCTCTT 103 A 2538 1332171 1050 1069 GGAACTCGAACCACCTCTTC 103 A 2539 1332172 1055 1074 TTGTAGGAACTCGAACCACC 85 A 2540 1332173 1056 1075 GTTGTAGGAACTCGAACCAC 59 A 2541 1332174 1059 1078 GCTGTTGTAGGAACTCGAAC 85 A 2542

(344) The modified oligonucleotides in the table below are 3-10-3 cEt gapmers. The gapmers are 16 nucleosides in length. The sugar motif of the gapmers is (from 5′ to 3′): kkkddddddddddkkk; wherein each ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and each ‘k’ represents a cEt sugar moiety. The internucleoside motif of the gapmers is (from 5′ to 3′): soosssssssssos, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methyl cytosine.

(345) TABLE-US-00037 TABLE 35 Reduction of APP RNA by 3-10-3 cEt gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ SEQ ID SEQ ID No: 1 ID No: No: 2 No: 2 SEQ Compound Start 1 Stop Start Stop APP Expt. ID Number Site Site Site Site Sequence (5′ to 3′) (% UTC) ID NO 1333912 3351 3366 293335 293350 CCTTATATTGCCACTT 45 B 2543 1333913 3349 3364 293333 293348 TTATATTGCCACTTCC 20 A 2544 1333914 2378 2393 292362 292377 AGCAATGGTTTTGCTG 55 A 2545 1333915 2022 2037 276352 276367 TCAGAGATCTCCTCCG 39 A 2546 1333916 1784 1799 262101 262116 CGTAACTGATCCTTGG 25 A 2547 1333917 1154 1169 191553 191568 GATACTTGTCAACGGC 14 A 2548 1333918 2066 2081 276396 276411 CTTCATATCCTGAGTC 38 A 2549 1333919 2002 2017 276332 276347 GATATTTGTCAACCCA 24 B 2550 1333920 3348 3363 293332 293347 TATATTGCCACTTCCA 43 B 2551 1333921 3355 3370 293339 293354 ATCCCCTTATATTGCC 45 A 2552 1333922 527 542 122832 122847 TGCCGTAGTCATGCAA 44 A 2553 1333923 453 468 120716 120731 TCGCAAACATCCATCC 21 A 2554 1333924 3131 3146 293115 293130 GTACAATCATCCTGCA 39 A 2555 1333925 2617 2632 292601 292616 CTATTCATGCACTAGT 33 A 2556 1333926 1153 1168 191552 191567 ATACTTGTCAACGGCA 13 A 2557 1333927 525 540 122830 122845 CCGTAGTCATGCAAGT 12 B 2558 1333928 752 767 152014 152029 CATCATCGGCTTCTTC 9† B 2559 1333929 3130 3145 293114 293129 TACAATCATCCTGCAG 15 A 2560 1333930 451 466 120714 120729 GCAAACATCCATCCTC 17 A 2561 1333931 3150 3165 293134 293149 TGTCATAAGCAATGAT 33 A 2562 1333932 2501 2516 292485 292500 TAATTCAAGTTCAGGC 24 A 2563 1333933 2476 2491 292460 292475 TGTTACAGCACAGCTG 17 A 2564 1333934 2500 2515 292484 292499 AATTCAAGTTCAGGCA 72 A 2565 1333935 2483 2498 292467 292482 CTACTTGTGTTACAGC 18 B 2566

(346) The modified oligonucleotides in the table below are 3-10-3 gapmers. The gapmers are 16 nucleosides in length. The sugar motif of the gapmers is (from 5′ to 3′): kkkdyddddddddkkk; wherein each ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, each ‘y’ represents a 2′-O-Me sugar moiety, and each ‘k’ represents a cEt sugar moiety. The internucleoside motif of the gapmers is (from 5′ to 3′): soosssssssssos, wherein each “s” represents a phosphorothioate internucleoside linkage, and each ‘o’ represents a phosphodiester internucleoside linkage. Each 2′-OMe cytosine nucleoside is not methylated and is indicated by a bold underlined C Each other cytosine nucleoside is a 5-methylcytosine.

(347) TABLE-US-00038 TABLE 36 Reduction of APP RNA by 3-10-3 cEt gapmers having a 2′-OMe at position 2 of the gap and mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ SEQ ID SEQ ID No: 1 ID No: No: 2 No: 2 SEQ Compound Start 1 Stop Start Stop APP Expt. ID Number Site Site Site Site Sequence (5′ to 3′) (% UTC) ID NO 1335695 527 542 122832 122847 TGCCGTAGTCATGCAA 73 B 2553 1335696 2476 2491 292460 292475 TGTTACAGCACAGCTG 48 A 2564 1335697 2617 2632 292601 292616 CTATUCATGCACTAGT 23 A 2567 1335698 2483 2498 292467 292482 CTACUTGTGTTACAGC 22 A 2568 1335699 3130 3145 293114 293129 TACAATCATCCTGCAG 37 A 2560 1335700 3131 3146 293115 293130 GTACAATCATCCTGCA 22 A 2555 1335701 752 767 152014 152029 CATCATCGGCTTCTTC 9† A 2559 1335702 451 466 120714 120729 GCAAACATCCATCCTC 10 B 2561 1335703 2501 2516 292485 292500 TAATUCAAGTTCAGGC 49 B 2569 1335704 525 540 122830 122845 CCGTAGTCATGCAAGT 26 A 2558 1335705 453 468 120716 120731 TCGCAAACATCCATCC 20 A 2554 1335706 3150 3165 293134 293149 TGTCATAAGCAATGAT 53 A 2562 1335707 2500 2515 292484 292499 AATT**C**AAGTTCAGGCA 17 A 2565 1335708 1153 1168 191552 191567 ATACUTGTCAACGGCA 9 A 2570 1335709 3355 3370 293339 293354 ATCC**C**CTTATATTGCC 10 A 2552 1335710 2022 2037 276352 276367 TCAGAGATCTCCTCCG 35 B 2546 1335711 3348 3363 293332 293347 TATAUTGCCACTTCCA 81 B 2571 1335712 1154 1169 191553 191568 GATA**C**TTGTCAACGGC 16 A 2548 1335713 2002 2017 276332 276347 GATAUTTGTCAACCCA 27 A 2572 1335714 2066 2081 276396 276411 CTTCATATCCTGAGTC 51 A 2549 1335715 2378 2393 292362 292377 AGCAATGGTTTTGCTG 66 A 2545 1335716 3349 3364 293333 293348 TTATATTGCCACTTCC 39 A 2544 1335717 1784 1799 262101 262116 CGTAACTGATCCTTGG 11 A 2547 1335718 3351 3366 293335 293350 CCTTATATTGCCACTT 41 B 2543

Example 3: Effect of Mixed Backbone 5-10-5 MOE Gapmers on Human APP RNA In Vitro, Single Dose

(348) Modified oligonucleotides complementary to an APP nucleic acid were synthesized and tested for their effect on APP RNA levels in vitro. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each separate experiment are presented in separate tables below.

(349) The modified oligonucleotides are all 5-10-5 MOE gapmers. The sugar motif of the gapmers is (from 5′ to 3′): eeeeeddddddddddeeeee; wherein each ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and each ‘e’ represents a 2′-MOE sugar moiety. The internucleoside linkage motif for the gapmers is (from 5′ to 3′): soooosssssssssssooss; wherein each ‘o’ represents a phosphodiester internucleoside linkage and each ‘s’ represents a phosphorothioate internucleoside linkage. All cytosine nucleobases throughout each modified oligonucleotide are 5-methylcytosines.

(350) “Start site” indicates the 5′-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. “Stop site” indicates the 3′-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are complementary to either SEQ ID NO: 1 (described herein above) or to SEQ ID NO: 2 (described herein above) or to both. ‘N/A’ indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity.

(351) Cultured A431 cells at a density of 10,000 cells per well were treated by free uptake with 4000 nM of modified oligonucleotide. After a treatment period of approximately 48 hours, RNA was isolated from the cells and APP RNA levels were measured by quantitative real-time RTPCR. Human primer probe set RTS35432 (forward sequence GACAGACAGCACACCCTAAA, designated herein as SEQ ID NO: 14; reverse sequence CACACGGAGGTGTGTCATAA, designated herein as SEQ ID NO: 15; probe sequence ATCCCAAGAAAGCCGCTCAGATCC, designated herein as SEQ ID NO: 16) was used to measure RNA levels. APP RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Results are presented as percent APP RNA, relative to untreated control cells (% UTC). The values marked by the symbol "f" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the activity of the modified oligonucleotides complementary to the amplicon region.

(352) TABLE-US-00039 TABLE 37 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP SEQ Number Site Site Site Site Sequence (5′ to 3′) (% UTC) ID NO 1397572 N/A N/A 224068 224087 TGGCAAACTCTCTTAGGTTC 8 1733 1399147 N/A N/A 221342 221361 TCATCAACTTTTTAGTCCTT 9 1557 1463174 N/A N/A 220783 220802 CTGGGACACTGCACCTCCCT 86 2573 1463179 N/A N/A 222439 222458 TCTGAATTTTAGTATGCTAT 12 2574 1463181 N/A N/A 221006 221025 TCTCTGTTCTCAATTCATGG 14 2575 1463194 N/A N/A 220050 220069 TGTACTATTTTTCCAAGTTC 10 2576 1463200 N/A N/A 220135 220154 TCAGTTTCCTGGTTTTGATA 13 2577 1463212 N/A N/A 219242 219261 GGTTCTTTTTCTTTCTTTTT 44 2578 1463220 N/A N/A 222110 222129 GTATTGTTTTAAATGTTCCT 4 2579 1463226 N/A N/A 220397 220416 GATACATATTGCTTATATGT 39 2580 1463237 N/A N/A 226908 226927 GTATCTGTTTGCCAATGGTA 9 2581 1463249 N/A N/A 229341 229360 CATATTTCAAAATTAATCTC 71 2582 N/A N/A 229374 229393 1463252 N/A N/A 221138 221157 TGGAGAACTTCTTTACACTT 11 2583 1463254 N/A N/A 220458 220477 CTGTATCTATTTCCAACCCA 43 2584 1463260 N/A N/A 219944 219963 ATGGCTTCCCTGCTCAGCCA 70 2585 1463269 N/A N/A 218616 218635 GTCATTGGTTTTAATCAGTT 21 2586 1463272 N/A N/A 222523 222542 ATTGCTTGTATTTATAAGCA 117 2587 1463274 N/A N/A 219076 219095 TCTTGTTCTCCTATTTCTGT 78 2588 1463283 N/A N/A 222735 222754 CTCAGCATGACTCCATTCTT 48 2589 1463286 N/A N/A 220244 220263 TCATGTGGTATTTTATTCTC 18 2590 1463288 N/A N/A 229285 229304 TCACTGATTTTTTTCCCCTC 9 2591 1463289 N/A N/A 221316 221335 GGCTTATTTCCCTATAGTTA 10 2592 1463297 N/A N/A 220057 220076 ACCTCTCTGTACTATTTTTC 33 2593 1463299 N/A N/A 219602 219621 GCGACATTCCTCCAGTCTTA 20 2594 1463302 N/A N/A 225700 225719 CCTAGTCTACTTTGGACCCA 54 2595 1463310 N/A N/A 225364 225383 CTTTATTTCCTACTGCCTTT 31 2596 1463317 N/A N/A 222585 222604 CCATTATTTAATTAAACCAT 78 2597 1463321 N/A N/A 221637 221656 CCCCTAATATGTTCTTAATC 76 2598 1463323 N/A N/A 220971 220990 CCACCTCCACTATCTTCATA 53 2599 1463335 N/A N/A 225455 225474 CCGCATCTGGTTTATAATAA 59 2600 1463338 N/A N/A 221521 221540 TTGTGCTGCCCTATTCTTGG 16 2601 1463340 N/A N/A 224096 224115 ATCACTTTACTATCTGGGCT 8 2602 1463346 N/A N/A 220480 220499 TGCTCTGATTCCAGATGATA 29 2603 1463358 N/A N/A 221089 221108 TACTGATGTCTATTCTCCAA 26 2604 1463359 N/A N/A 222727 222746 GACTCCATTCTTCCTCATTT 17 2605 1463364 N/A N/A 221216 221235 ACCATGTTTTCTAGAAGATT 16 2606 1463371 N/A N/A 228219 228238 CTGCAGCCTCAGCCACCCCA 72 2607 1463406 N/A N/A 222776 222795 TTTAATGTCAATTTTCCCCT 67 2608 1463407 N/A N/A 233894 233913 GCCAACATTACCTACTGCAA 35 2609 1463409 N/A N/A 222678 222697 GCATAATTTACTGAAGCAGA 10 2610 1463426 N/A N/A 234807 234826 TTCCACTTTCATGTTCCCTT 12 2611 1463436 N/A N/A 228946 228965 ATGCCTCAGGCTCCATCCAT 73 2612 1463452 N/A N/A 234059 234078 CCTTCCTTTTTAATCAGAAT 54 2613 1463466 N/A N/A 221999 222018 GCTCAGATAGTGTACAGGGT 7 2614 1463468 N/A N/A 234235 234254 GCTCTCCTGTTACTGTTAAT 23 2615 1463469 N/A N/A 224596 224615 GCTTTGTTATCTTGGCCAAC 26 2616 1463473 N/A N/A 220944 220963 GCTCAACACTGAGTTGCTCC 57 2617 1463477 N/A N/A 232117 232136 ACTCTTATGTCTGATCCCTT 21 2618 1463483 N/A N/A 220746 220765 CTGCAAGTTATGTAGCTCAA 12 2619 1463488 N/A N/A 229154 229173 ACACATCTGCTCTAGTGTTC 58 2620 1463489 N/A N/A 231289 231308 CCTGTGTCCTTATTTCTTCA 12 2621 1463490 N/A N/A 234371 234390 AGTTCATTCCCCTAGCCTGC 50 2622 1463500 N/A N/A 233352 233371 ATCCAATGCATCAATTCCTT 20 2623 1463524 N/A N/A 234353 234372 GCACTGATTCCTCTTTTTCT 34 2624 1463526 N/A N/A 222753 222772 CCGATAGCATTCCTTCTTCT 22 2625 1463528 N/A N/A 222744 222763 TTCCTTCTTCTCAGCATGAC 27 2626 1463532 N/A N/A 224124 224143 GGCAGGTCTTGGCTTCCACC 43 2627 1463534 N/A N/A 233434 233453 TCACCTTTTAATCTACAACT 20 2628 1463535 N/A N/A 231282 231301 CCTTATTTCTTCAATCTCCT 29 2629 1463536 N/A N/A 222721 222740 ATTCTTCCTCATTTTCACCC 13 2630 1463540 N/A N/A 221735 221754 TGTTCTTTATTTTTATTATA 70 2631 1463546 N/A N/A 226513 226532 CTGTCTTAATAGTATACCGT 14 2632 1463549 N/A N/A 231033 231052 ACTCCACAGTCCCTCATCCT 86 2633 1463559 N/A N/A 220679 220698 ATCATCACTTGACACATGCC 24 2634 1463564 N/A N/A 230913 230932 TTGCATGTCATCCTTGTGCA 46 2635 1463567 N/A N/A 223618 223637 AGCAGCTTTTTTTTTTTCTT 11 2636 1463568 N/A N/A 218641 218660 TACAACTTTTGTTTTTCTCA 57 2637 1463578 N/A N/A 220897 220916 AAGTTGCTTTTTTTCTCTTC 9 2638 1463580 N/A N/A 231654 231673 AGTCTTTAGTCTTATTCATC 11 2639 1463587 N/A N/A 223728 223747 AATGCCAGCTCTTTTCTCCG 18 2640 1463589 N/A N/A 222548 222567 GTTTGACTGCATTAAGCACA 9 2641 1463595 N/A N/A 222458 222477 TTCTCCTTTTGCCAGTGTCT 6 2642 1463596 N/A N/A 222761 222780 CCCCTTCACCGATAGCATTC 55 2643 1463597 N/A N/A 229342 229361 ACATATTTCAAAATTAATCT 83 2644 N/A N/A 229375 229394 1463608 N/A N/A 225370 225389 TTCCCTCTTTATTTCCTACT 31 2645 1463620 N/A N/A 221302 221321 TAGTTATTACCTATGCCACT 28 2646 1463622 N/A N/A 233074 233093 GTGCTTTTCCAACAAGTTCC 30 2647 1463630 N/A N/A 218917 218936 GCCTAAATACATTTCTTTGC 77 2648

(353) TABLE-US-00040 TABLE 38 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP SEQ Number Site Site Site Site Sequence (5′ to 3′) (% UTC) ID NO 1397572 N/A N/A 224068 224087 TGGCAAACTCTCTTAGGTTC 9 1733 1463172 N/A N/A 220892 220911 GCTTTTTTTCTCTTCTTTTT 9 2649 1463173 N/A N/A 223714 223733 TCTCCGTTCTCTATGCAAAT 24 2650 1463175 N/A N/A 234061 234080 CTCCTTCCTTTTTAATCAGA 48 2651 1463185 N/A N/A 220401 220420 GCCAGATACATATTGCTTAT 9 2652 1463186 N/A N/A 220958 220977 CTTCATAAATTCTTGCTCAA 39 2653 1463188 N/A N/A 221139 221158 TTGGAGAACTTCTTTACACT 11 2654 1463196 N/A N/A 222745 222764 ATTCCTTCTTCTCAGCATGA 20 2655 1463197 N/A N/A 220459 220478 CCTGTATCTATTTCCAACCC 39 2656 1463213 N/A N/A 231655 231674 CAGTCTTTAGTCTTATTCAT 11 2657 1463214 N/A N/A 231022 231041 CCTCATCCTCTCAGCCCCTG 51 2658 1463215 N/A N/A 221563 221582 AGTTATCTAAATATCCTCCC 54 2659 1463229 N/A N/A 220058 220077 GACCTCTCTGTACTATTTTT 38 2660 1463230 N/A N/A 218625 218644 CTCATTTTAGTCATTGGTTT 39 2661 1463231 N/A N/A 222762 222781 TCCCCTTCACCGATAGCATT 38 2662 1463238 N/A N/A 226582 226601 TCACACATTTGTATCTTGCT 8 2663 1463247 N/A N/A 222728 222747 TGACTCCATTCTTCCTCATT 56 2664 1463259 N/A N/A 221090 221109 TTACTGATGTCTATTCTCCA 38 2665 1463261 N/A N/A 222440 222459 CTCTGAATTTTAGTATGCTA 18 2666 1463266 N/A N/A 228278 228297 TCTTCCTTTTTTTGAGACAG 11 2667 1463270 N/A N/A 229211 229230 GCCCTTGTTCCAGTCTAAAA 47 2668 1463273 N/A N/A 225701 225720 ACCTAGTCTACTTTGGACCC 84 2669 1463275 N/A N/A 224105 224124 CCCACTTTCATCACTTTACT 65 2670 1463276 N/A N/A 220747 220766 TCTGCAAGTTATGTAGCTCA 20 2671 1463279 N/A N/A 233397 233416 GCATTTTTTTTCTATGAATT 28 2672 1463280 N/A N/A 221639 221658 ACCCCCTAATATGTTCTTAA 51 2673 1463287 N/A N/A 219243 219262 TGGTTCTTTTTCTTTCTTTT 41 2674 1463290 N/A N/A 222554 222573 ACAGATGTTTGACTGCATTA 19 2675 1463294 N/A N/A 220898 220917 GAAGTTGCTTTTTTTCTCTT 5 2676 1463295 N/A N/A 220681 220700 ACATCATCACTTGACACATG 42 2677 1463303 N/A N/A 234355 234374 CTGCACTGATTCCTCTTTTT 57 2678 1463308 N/A N/A 231290 231309 TCCTGTGTCCTTATTTCTTC 14 2679 1463314 N/A N/A 218642 218661 ATACAACTTTTGTTTTTCTC 48 2680 1463328 N/A N/A 219710 219729 GCATCATAATTTGAGAGCCA 33 2681 1463329 N/A N/A 224598 224617 ATGCTTTGTTATCTTGGCCA 39 2682 1463331 N/A N/A 233907 233926 GTTAGCATTTCCAGCCAACA 78 2683 1463342 N/A N/A 220973

220992 CTCCACCTCCACTATCTTCA 49 2684 1463345 N/A N/A 222737 222756 TTCTCAGCATGACTCCATTC 45 2685 1463354 N/A N/A 227156 227175 GTTGATATTTAATTCCTCAA 11 2686 1463356 N/A N/A 231283 231302 TCCTTATTTCTTCAATCTCC 22 2687 1463365 N/A N/A 222637 222656 ACTGGCAGTTCCCCAGACTG 79 2688 1463379 N/A N/A 222459 222478 TTTCTCCTTTTGCCAGTGTC 9 2689 1463386 N/A N/A 220237 220256 GTATTTTATTCTCTTTCCAA 13 2690 1463389 N/A N/A 220262 220281 TTGGCAGCTGACAGAGACTC 26 2691 1463395 N/A N/A 233131 233150 GCTCAGCCCCATCCCTAGCT 108 2692 1463401 N/A N/A 221273 221292 GTCACATGTGAAAACAGGCT 23 2693 1463414 N/A N/A 229343 229362 AACATATTTCAAAATTAATC 57 2694 N/A N/A 229376 229395 1463438 N/A N/A 223842 223861 ACATCTCTATATGGCGGTCC 22 2695 1463443 N/A N/A 224215 224234 ACCCAGTGCTTTCACATTGA 21 2696 1463448 N/A N/A 233435 233454 TTCACCTTTTAATCTACAAC 38 2697 1463453 N/A N/A 222783 222802 TCACAAATTTAATGTCAATT 68 2698 1463454 N/A N/A 221317 221336 TGGCTTATTTCCCTATAGTT 12 2699 1463458 N/A N/A 219056 219075 TCTCTAACTTTTTGAGCTCA 68 2700 1463460 N/A N/A 234328 234347 GTTTCTTATTTTTTCAGTTT 8 2701 1463463 N/A N/A 225365 225384 TCTTTATTTCCTACTGCCTT 47 2702 1463486 N/A N/A 221306 221325 CCTATAGTTATTACCTATGC 54 2703 1463491 N/A N/A 234565 234584 CCCACTTAATTTTTCATCCT 34 2704 1463494 N/A N/A 229286 229305 ATCACTGATTTTTTTCCCCT 19 2705 1463505 N/A N/A 222528 222547 TCCTAATTGCTTGTATTTAT 27 2706 1463508 N/A N/A 221874 221893 GCATCTGGTATATTTAGAAT 9 2707 1463511 N/A N/A 220051 220070 CTGTACTATTTTTCCAAGTT 7 2708 1463518 N/A N/A 222006 222025 ACTAGCAGCTCAGATAGTGT 80 2709 1463527 N/A N/A 222715 222734 CCTCATTTTCACCCATAAAA 40 2710 1463530 N/A N/A 219085 219104 CTTTATTTTTCTTGTTCTCC 155 2711 1463531 N/A N/A 232176 232195 GCCACTAACATGCCATCTGC 46 2712 1463542 N/A N/A 221343 221362 GTCATCAACTTTTTAGTCCT 8 2713 1463545 N/A N/A 221081 221100 TCTATTCTCCAAGTATACCT 33 2714 1463547 N/A N/A 225371 225390 GTTCCCTCTTTATTTCCTAC 16 2715 1463565 N/A N/A 222722 222741 CATTCTTCCTCATTTTCACC 50 2716 1463575 N/A N/A 234808 234827 ATTCCACTTTCATGTTCCCT 10 2717 1463576 N/A N/A 229345 229364 GAAACATATTTCAAAATTAA 93 2718 N/A N/A 229378 229397 1463590 N/A N/A 220485 220504 CTGGGTGCTCTGATTCCAGA 81 2719 1463591 N/A N/A 231066 231085 GCCAAATTGAACCTCTGTGC 15 2720 1463593 N/A N/A 228947 228966 CATGCCTCAGGCTCCATCCA 90 2721 1463602 N/A N/A 219949 219968 CACTCATGGCTTCCCTGCTC 37 2722 1463615 N/A N/A 222754 222773 ACCGATAGCATTCCTTCTTC 29 2723 1463623 N/A N/A 222139 222158 TTTCAACTATATTCCTACTA 55 2724 1463629 N/A N/A 225469 225488 GCCAGAGATCTTTCCCGCAT 26 2725

(354) TABLE-US-00041 TABLE 39 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP SEQ Number Site Site Site Site Sequence (5′ to 3′) (% UTC) ID NO 1397572 N/A N/A 224068 224087 TGGCAAACTCTCTTAGGTTC 4 1733 1463177 N/A N/A 223844 223863 CCACATCTCTATATGGCGGT 14 2726 1463178 N/A N/A 225366 225385 CTCTTTATTTCCTACTGCCT 22 2727 1463204 N/A N/A 220402 220421 TGCCAGATACATATTGCTTA 20 2728 1463205 N/A N/A 222738 222757 CTTCTCAGCATGACTCCATT 48 2729 1463208 N/A N/A 229407 229426 ACTCATGTCATTCCCAGTTA 17 2730 1463209 N/A N/A 222716 222735 TCCTCATTTTCACCCATAAA 48 2731 1463216 N/A N/A 222747 222766 GCATTCCTTCTTCTCAGCAT 22 2732 1463224 N/A N/A 221082 221101 GTCTATTCTCCAAGTATACC 14 2733 1463232 N/A N/A 229215 229234 ACCAGCCCTTGTTCCAGTCT 31 2734 1463244 N/A N/A 231284 231303 GTCCTTATTTCTTCAATCTC 18 2735 1463246 N/A N/A 221308 221327 TCCCTATAGTTATTACCTAT 26 2736 1463251 N/A N/A 219991 220010 CCCACTATCTTTTAAGTTTA 63 2737 1463262 N/A N/A 221641 221660 GCACCCCCTAATATGTTCTT 28 2738 1463263 N/A N/A 221474 221493 ACCACCATCTGTTCTGTGGA 56 2739 1463268 N/A N/A 222414 222433 CTGAACTGACTCCAAATCTA 34 2740 1463282 N/A N/A 234062 234081 TCTCCTTCCTTTTTAATCAG 49 2741 1463292 N/A N/A 234344 234363 CCTCTTTTTCTCTAAAGTTT 22 2742 1463315 N/A N/A 224108 224127 CACCCCACTTTCATCACTTT 40 2743 1463319 N/A N/A 233398 233417 TGCATTTTTTTTCTATGAAT 35 2744 1463322 N/A N/A 228286 228305 AGTCTTTTTCTTCCTTTTTT 15 2745 1463334 N/A N/A 231786 231805 TTTCTTCTATCTACCGCATT 35 2746 1463344 N/A N/A 229287 229306 CATCACTGATTTTTTTCCCC 16 2747 1463349 N/A N/A 221149 221168 CTACAACTTTTTGGAGAACT 14 2748 1463352 N/A N/A 233439 233458 GTTGTTCACCTTTTAATCTA 13 2749 1463362 N/A N/A 231101 231120 CCATCCATCTTCCCCACTGA 49 2750 1463363 N/A N/A 223716 223735 TTTCTCCGTTCTCTATGCAA 45 2751 1463373 N/A N/A 220503 220522 ACATCCATCTACAACATCCT 41 2752 1463374 N/A N/A 220900 220919 ATGAAGTTGCTTTTTTTCTC 16 2753 1463376 N/A N/A 222441 222460 TCTCTGAATTTTAGTATGCT 16 2754 1463378 N/A N/A 220964 220983 CACTATCTTCATAAATTCTT 70 2755 1463383 N/A N/A 220766 220785 CCTGACATATGAAGTTTCTT 78 2756 1463388 N/A N/A 220893 220912 TGCTTTTTTTCTCTTCTTTT 4 2757 1463391 N/A N/A 226583 226602 TTCACACATTTGTATCTTGC 11 2758 1463393 N/A N/A 221610 221629 ATGGCTGTTTTTTTTTTTCT 23 2759 1463394 N/A N/A 220239 220258 TGGTATTTTATTCTCTTTCC 6 2760 1463398 N/A N/A 224607 224626 CCCTGATTTATGCTTTGTTA 22 2761 1463403 N/A N/A 232190 232209 GCCAGCAGCAACAGGCCACT 86 2762 1463410 N/A N/A 218626 218645 TCTCATTTTAGTCATTGGTT 20 2763 1463412 N/A N/A 220067 220086 GATGCATGAGACCTCTCTGT 60 2764 1463421 N/A N/A 219069 219088 CTCCTATTTCTGTTCTCTAA 90 2765 1463424 N/A N/A 222764 222783 TTTCCCCTTCACCGATAGCA 15 2766 1463431 N/A N/A 234567 234586 GTCCCACTTAATTTTTCATC 41 2767 1463434 N/A N/A 234357 234376 GCCTGCACTGATTCCTCTTT 42 2768 1463437 N/A N/A 222015 222034 AGCTTTGACACTAGCAGCTC 73 2769 1463439 N/A N/A 219086 219105 ACTTTATTTTTCTTGTTCTC 38 2770 1463441 N/A N/A 234897 234916 TTGACCATTTTTAGCACTTT 20 2771 1463445 N/A N/A 220368 220387 ACACACTAAATCTCCAGTAT 28 2772 1463449 N/A N/A 225805 225824 GTTCATCCTTGACTAACAAT 14 2773 1463451 N/A N/A 219746 219765 ATGAGTTTTTTTCCCCATTA 8 2774 1463455 N/A N/A 221318 221337 ATGGCTTATTTCCCTATAGT 8 2775 1463456 N/A N/A 220974 220993 ACTCCACCTCCACTATCTTC 64 2776 1463461 N/A N/A 229344 229363 AAACATATTTCAAAATTAAT 121 2777 N/A N/A 229377 229396 1463462 N/A N/A 225531 225550 GCGAATTTCTTGATTCCCCG 12 2778 1463475 N/A N/A 222485 222504 GCATGCATTTTTAGGGACTT 23 2779 1463484 N/A N/A 222663 222682 GCAGATATACCTCTCCCACT 22 2780 1463492 N/A N/A 221965 221984 TTCTCTTTCTATAGAGAACA 74 2781 1463495 N/A N/A 219244 219263 ATGGTTCTTTTTCTTTCTTT 50 2782 1463497 N/A N/A 220710 220729 CCGTCCATTAATGTGCAGTA 5 2783 1463502 N/A N/A 233924 233943 ACCCAAGTTTCTTACAAGTT 25 2784 1463509 N/A N/A 222533 222552 GCACATCCTAATTGCTTGTA 8 2785 1463520 N/A N/A 221091 221110 CTTACTGATGTCTATTCTCC 38 2786 1463525 N/A N/A 225372 225391 TGTTCCCTCTTTATTTCCTA 11 2787 1463533 N/A N/A 231291 231310 ATCCTGTGTCCTTATTTCTT 19 2788 1463539 N/A N/A 222755 222774 CACCGATAGCATTCCTTCTT 40 2789 1463543 N/A N/A 220052 220071 TCTGTACTATTTTTCCAAGT 14 2790 1463544 N/A N/A 222723 222742 CCATTCTTCCTCATTTTCAC 36 2791 1463551 N/A N/A 220460 220479 ACCTGTATCTATTTCCAACC 34 2792 1463566 N/A N/A 222784 222803 CTCACAAATTTAATGTCAAT 39 2793 1463569 N/A N/A 228951 228970 AGACCATGCCTCAGGCTCCA 59 2794 1463570 N/A N/A 224415 224434 GCATCTGCCTTTTTATCCTG 14 2795 1463571 N/A N/A 233239 233258 TCTCACCTATTTATTAACTT 42 2796 1463574 N/A N/A 231023 231042 CCCTCATCCTCTCAGCCCCT 74 2797 1463592 N/A N/A 221287 221306 CCACTTCAACTGAAGTCACA 82 2798 1463599 N/A N/A 222560 222579 CTCTCTACAGATGTTTGACT 28 2799 1463616 N/A N/A 228103 228122 GCCATGTTTCCCATTCTGGT 48 2800 1463617 N/A N/A 218681 218700 GCCATACTTCAGTTGAACCA 50 2801 1463633 N/A N/A 222729 222748 ATGACTCCATTCTTCCTCAT 35 2802

(355) TABLE-US-00042 TABLE 40 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP SEQ Number Site Site Site Site Sequence (5′ to 3′) (% UTC) ID NO 1397572 N/A N/A 224068 224087 TGGCAAACTCTCTTAGGTTC 6 1733 1397795 N/A N/A 222488 222507 AAGGCATGCATTTTTAGGGA 7 2277 1463187 N/A N/A 222757 222776 TTCACCGATAGCATTCCTTC 51 2803 1463192 N/A N/A 220894 220913 TTGCTTTTTTTCTCTTCTTT 8 2804 1463193 N/A N/A 221966 221985 CTTCTCTTTCTATAGAGAAC 66 2805 1463199 N/A N/A 220028 220047 GTGAGAGTACAATTATTTCA 5 2806 1463202 N/A N/A 233400 233419 CATGCATTTTTTTTCTATGA 11 2807 1463203 N/A N/A 220240 220259 GTGGTATTTTATTCTCTTTC 4 2808 1463211 N/A N/A 229569

229588 CCTTCTATGATTTACTTTCT 35 2809 1463217 N/A N/A 222826 222845 TCACAAGCATGATGAACCCT 104 2810 1463222 N/A N/A 222717 222736 TTCCTCATTTTCACCCATAA 47 2811 1463223 N/A N/A 220712 220731 TTCCGTCCATTAATGTGCAG 23 2812 1463227 N/A N/A 233778 233797 GCACATCATTTACCCTTTAA 6 2813 1463233 N/A N/A 221289 221308 TGCCACTTCAACTGAAGTCA 39 2814 1463235 N/A N/A 218631 218650 GTTTTTCTCATTTTAGTCAT 76 2815 1463236 N/A N/A 234590 234609 TGCGATTTAGTAATTCACAA 6 2816 1463239 N/A N/A 221084 221103 ATGTCTATTCTCCAAGTATA 28 2817 1463242 N/A N/A 224113 224132 GCTTCCACCCCACTTTCATC 47 2818 1463243 N/A N/A 222534 222553 AGCACATCCTAATTGCTTGT 37 2819 1463245 N/A N/A 220461 220480 AACCTGTATCTATTTCCAAC 35 2820 1463256 N/A N/A 234898 234917 CTTGACCATTTTTAGCACTT 15 2821 1463271 N/A N/A 224608 224627 ACCCTGATTTATGCTTTGTT 16 2822 1463277 N/A N/A 221157 221176 TGTACCTTCTACAACTTTTT 19 2823 1463296 N/A N/A 226652 226671 CCTGCAGGTCTGTAACCTCA 107 2824 1463298 N/A N/A 228106 228125 CTTGCCATGTTTCCCATTCT 52 2825 1463300 N/A N/A 232203 232222 GTATGATTTAATAGCCAGCA 21 2826 1463306 N/A N/A 220070 220089 ATGGATGCATGAGACCTCTC 63 2827 1463313 N/A N/A 234350 234369 CTGATTCCTCTTTTTCTCTA 10 2828 1463332 N/A N/A 222730 222749 CATGACTCCATTCTTCCTCA 23 2829 1463333 N/A N/A 222739 222758 TCTTCTCAGCATGACTCCAT 37 2830 1463347 N/A N/A 220967 220986 CTCCACTATCTTCATAAATT 61 2831 1463351 N/A N/A 229324 229343 CTCAATTTGGATTCATCTCC 25 2832 1463355 N/A N/A 221488 221507 TTCAAGATATCTGAACCACC 14 2833 1463367 N/A N/A 220929 220948 GCTCCTTCTGAACAAAAGCT 52 2834 1463368 N/A N/A 225532 225551 TGCGAATTTCTTGATTCCCC 7 2835 1463375 N/A N/A 229098 229117 CTGACTTCACTTCCCAATCA 43 2836 1463377 N/A N/A 219183 219202 GGTTATTTTTCTTACCAAGC 43 2837 1463382 N/A N/A 233250 233269 CTACAATGGATTCTCACCTA 36 2838 1463385 N/A N/A 231444 231463 GCTTCTTAACTGTTTATCCA 32 2839 1463396 N/A N/A 221631 221650 ATATGTTCTTAATCCAACCT 43 2840 1463416 N/A N/A 223720 223739 CTCTTTTCTCCGTTCTCTAT 17 2841 1463417 N/A N/A 225377 225396 GCCTTTGTTCCCTCTTTATT 20 2842 1463422 N/A N/A 225367 225386 CCTCTTTATTTCCTACTGCC 30 2843 1463425 N/A N/A 221322 221341 TGTAATGGCTTATTTCCCTA 9 2844 1463429 N/A N/A 218682 218701 TGCCATACTTCAGTTGAACC 50 2845 1463432 N/A N/A 224416 224435 AGCATCTGCCTTTTTATCCT 20 2846 1463433 N/A N/A 222442 222461 GTCTCTGAATTTTAGTATGC 14 2847 1463446 N/A N/A 221002 221021 TGTTCTCAATTCATGGTGTA 12 2848 1463447 N/A N/A 220505 220524 GTACATCCATCTACAACATC 47 2849 1463450 N/A N/A 228768 228787 CAGTTCTCTTGCTACTTCTA 10 2850 1463459 N/A N/A 222664 222683 AGCAGATATACCTCTCCCAC 30 2851 1463465 1693 1712 219383 219402 CCTGAATCTCCTCGGCCACT 26 2852 1463474 N/A N/A 221643 221662 CTGCACCCCCTAATATGTTC 27 2853 1463479 N/A N/A 220054 220073 TCTCTGTACTATTTTTCCAA 27 2854 1463481 N/A N/A 222770 222789 GTCAATTTTCCCCTTCACCG 12 2855 1463485 N/A N/A 222564 222583 GTATCTCTCTACAGATGTTT 7 2856 1463501 N/A N/A 231025 231044 GTCCCTCATCCTCTCAGCCC 31 2857 1463503 N/A N/A 225847 225866 GTGACAGCTCTCTATTTGCT 28 2858 1463510 N/A N/A 222424 222443 GCTATTTGTACTGAACTGAC 12 2859 1463513 N/A N/A 233939 233958 GCTTAAACCATTTCCACCCA 37 2860 1463517 N/A N/A 219070 219089 TCTCCTATTTCTGTTCTCTA 84 2861 1463519 N/A N/A 221309 221328 TTCCCTATAGTTATTACCTA 55 2862 1463523 N/A N/A 231789 231808 ACATTTCTTCTATCTACCGC 28 2863 1463537 N/A N/A 231285 231304 TGTCCTTATTTCTTCAATCT 21 2864 1463550 N/A N/A 229282 229301 CTGATTTTTTTCCCCTCCTC 30 2865 1463555 N/A N/A 220407 220426 GGATATGCCAGATACATATT 22 2866 1463556 N/A N/A 234131 234150 ACTTTATTTTGACTGACATC 22 2867 1463557 N/A N/A 222724 222743 TCCATTCTTCCTCATTTTCA 28 2868 1463561 N/A N/A 229346 229365 GGAAACATATTTCAAAATTA 45 2869 N/A N/A 229379 229398 1463573 N/A N/A 234358 234377 AGCCTGCACTGATTCCTCTT 47 2870 1463581 N/A N/A 222016 222035 TAGCTTTGACACTAGCAGCT 53 2871 1463583 N/A N/A 222748 222767 AGCATTCCTTCTTCTCAGCA 17 2872 1463585 N/A N/A 231102 231121 GCCATCCATCTTCCCCACTG 56 2873 1463600 N/A N/A 220371 220390 ACTACACACTAAATCTCCAG 25 2874 1463603 N/A N/A 220769 220788 CTCCCTGACATATGAAGTTT 73 2875 1463609 N/A N/A 219940 219959 CTTCCCTGCTCAGCCATCAA 59 2876 1463614 N/A N/A 221092 221111 CCTTACTGATGTCTATTCTC 38 2877 1463632 N/A N/A 223845 223864 GCCACATCTCTATATGGCGG 73 2878

(356) TABLE-US-00043 TABLE 41 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1397572 N/A N/A 224068 224087 TGGCAAACTCTCTTAGGTTC 5 1733 1463176 N/A N/A 221323 221342 TTGTAATGGCTTATTTCCCT 9 2879 1463180 N/A N/A 221732 221751 TCTTTATTTTTATTATACTT 73 2880 1463184 N/A N/A 231105 231124 ACGGCCATCCATCTTCCCCA 57 2881 1463190 N/A N/A 221158 221177 TTGTACCTTCTACAACTTTT 22 2882 1463207 N/A N/A 229339 229358 TATTTCAAAATTAATCTCAA 110 2883 N/A N/A 229372 229391 1463210 N/A N/A 221296 221315 TTACCTATGCCACTTCAACT 56 2884 1463219 N/A N/A 229652 229671 GTCAACATTCCTTTGGACAC 71 2885 1463221 N/A N/A 221635 221654 CCTAATATGTTCTTAATCCA 40 2886 1463234 N/A N/A 224121 224140 AGGTCTTGGCTTCCACCCCA 72 2887 1463240 N/A N/A 222959 222978 GCACTGGGATTCAGTACGCT 40 2888 1463241 N/A N/A 218687 218706 TTGCCTGCCATACTTCAGTT 70 2889 1463248 N/A N/A 221004 221023 TCTGTTCTCAATTCATGGTG 8 2890 1463250 N/A N/A 220127 220146 CTGGTTTTGATAATGGACTA 36 2891 1463253 N/A N/A 225293 225312 GCTACATTTTTAGCCTTGAG 11 2892 1463255 N/A N/A 222758 222777 CTTCACCGATAGCATTCCTT 42 2893 1463257 N/A N/A 234185 234204 GCTTCAAGCATTCTCAGTAT 19 2894 1463258 N/A N/A 220773 220792 GCACCTCCCTGACATATGAA 32 2895 1463281 N/A N/A 221310 221329 TTTCCCTATAGTTATTACCT 54 2896 1463284 N/A N/A 218632 218651 TGTTTTTCTCATTTTAGTCA 22 2897 1463301 N/A N/A 220456 220475 GTATCTATTTCCAACCCAAT 27 2898 1463304 N/A N/A 222427 222446 TATGCTATTTGTACTGAACT 27 2899 1463307 N/A N/A 220048 220067 TACTATTTTTCCAAGTTCTT 9 2900 1463312 N/A N/A 222725 222744 CTCCATTCTTCCTCATTTTC 40 2901 1463318 N/A N/A 234361 234380 CCTAGCCTGCACTGATTCCT 65 2902 1463320 N/A N/A 220055 220074 CTCTCTGTACTATTTTTCCA 37 2903 1463325 1700 1719 219390 219409 ACTTCATCCTGAATCTCCTC 43 2904 1463326 N/A N/A 233971 233990 TCTGACATTTTCACTGATCG 16 2905 1463327 N/A N/A 225875 225894 GTCACACCTATGTTCTTATA 14 2906 1463330 N/A N/A 222741 222760 CTTCTTCTCAGCATGACTCC 36 2907 1463339 N/A N/A 234351 234370 ACTGATTCCTCTTTTTCTCT 14 2908 1463341 N/A N/A 234983 235002 ACATCTGATTTTTGCACCCC 16 2909 1463348 N/A N/A 222718 222737 CTTCCTCATTTTCACCCATA 32 2910 1463350 N/A N/A 221086 221105 TGATGTCTATTCTCCAAGTA 40 2911 1463353 N/A N/A 231286 231305 GTGTCCTTATTTCTTCAATC 9 2912 1463366 N/A N/A 233780 233799 TTGCACATCATTTACCCTTT 7 2913 1463369 N/A N/A 222731 222750 GCATGACTCCATTCTTCCTC 9 2914 1463387 N/A N/A 226791 226810 GCACTATATTTACAGATTCC 6 2915 1463390 N/A N/A 222052 222071 CCCAGAAAAGCTATTCTCCC 73 2916 1463392 N/A N/A 231613 231632 ACATGGTTTTCCTGAGCCTA 41 2917 1463411 N/A N/A 233401 233420 GCATGCATTTTTTTTTCTATG 48 2918 1463413 N/A N/A 222543 222562 ACTGCATTAAGCACATCCTA 32 2919 1463418 N/A N/A 220932 220951 GTTGCTCCTTCTGAACAAAA 9 2920 1463419 N/A N/A 225547 225566 GCATCCTTTCATTATTGCGA 34 2921 1463423 N/A N/A 231030 231049 CCACAGTCCCTCATCCTCTC 37 2922 1463430 N/A N/A 232567 232586 ACGCAAAATTCTCTGCTGCC 32 2923 1463435 N/A N/A 233251 233270 GCTACAATGGATTCTCACCT 22 2924 1463440 N/A N/A 222771 222790 TGTCAATTTTCCCCTTCACC 9 2925 1463442 N/A N/A 221972 221991 TGCAAACTTCTCTTTCTATA 8 2926 1463467 N/A N/A 222751 222770 GATAGCATTCCTTCTTCTCA 25 2927 1463471 N/A N/A 224441 224460 CCCACTTCATCAGTCCAAGT 13 2928 1463472 N/A N/A 220725 220744 GTATAATTTCAGATTCCGTC 7 2929 1463478 N/A N/A 223721 223740 GCTCTTTTCTCCGTTCTCTA 5 2930 1463482 N/A N/A 220379 220398 GTTGGTAGACTACACACTAA 9 2931 1463498 N/A N/A 220895 220914 GTTGCTTTTTTTCTCTTCTT 5 2932 1463499 N/A N/A 222570 222589 ACCATTGTATCTCTCTACAG 13 2933 1463504 N/A N/A 221489 221508 ATTCAAGATATCTGAACCAC 27 2934 1463514 N/A N/A 234592 234611 GTTGCGATTTAGTAATTCAC 5 2935 1463538 N/A N/A 219071 219090 TTCTCCTATTTCTGTTCTCT 71 2936 1463548 N/A N/A 220507 220526 GGGTACATCCATCTACAACA 18 2937 1463552 N/A N/A

225368 225387 CCCTCTTTATTTCCTACTGC 27 2938 1463553 N/A N/A 220241 220260 TGTGGTATTTTATTCTCTTT 4 2939 1463560 N/A N/A 225379 225398 ATGCCTTTGTTCCCTCTTTA 9 2940 1463562 N/A N/A 229283 229302 ACTGATTTTTTTCCCCTCCT 12 2941 1463563 N/A N/A 221097 221116 AGGTTCCTTACTGATGTCTA 11 2942 1463584 N/A N/A 222665 222684 AAGCAGATATACCTCTCCCA 19 2943 1463586 N/A N/A 220968 220987 CCTCCACTATCTTCATAAAT 110 2944 1463588 N/A N/A 219941 219960 GCTTCCCTGCTCAGCCATCA 37 2945 1463598 N/A N/A 219187 219206 CCCAGGTTATTTTTCTTACC 74 2946 1463604 N/A N/A 223983 224002 CCCATATGCTGCCTTTGTGT 18 2947 1463607 N/A N/A 228107 228126 TCTTGCCATGTTTCCCATTC 31 2948 1463610 N/A N/A 222506 222525 GCACAAACTTCTATACAAAA 11 2949 1463612 N/A N/A 222444 222463 GTGTCTCTGAATTTTAGTAT 7 2950 1463613 N/A N/A 231790 231809 GACATTTCTTCTATCTACCG 30 2951 1463618 N/A N/A 229102 229121 TGGTCTGACTTCACTTCCCA 62 2952 1463619 N/A N/A 220477 220496 TCTGATTCCAGATGATAACC 58 2953 1463624 N/A N/A 229325 229344 TCTCAATTTGGATTCATCTC 25 2954 1463628 N/A N/A 228937 228956 GCTCCATCCATTTGGTTGAG 63 2955

(357) TABLE-US-00044 TABLE 42 Reduction of APP RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop APP (% SEQ ID Number Site Site Site Site Sequence (5′ to 3′) UTC) NO 1397572 N/A N/A 224068 224087 TGGCAAACTCTCTTAGGTTC 7 1733 1399436 N/A N/A 221519 221538 GTGCTGCCCTATTCTTGGGC 58 1881 1463182 N/A N/A 222668 222687 CTGAAGCAGATATACCTCTC 37 2956 1463183 N/A N/A 221124 221143 ACACTTATTTAATACATAGT 37 2957 1463189 N/A N/A 226832 226851 GTCATTATCAATGACTTCCA 81 2958 1463191 N/A N/A 222546 222565 TTGACTGCATTAAGCACATC 66 2959 1463195 N/A N/A 220732 220751 GCTCAAAGTATAATTTCAGA 11 2960 1463198 N/A N/A 221973 221992 TTGCAAACTTCTCTTTCTAT 20 2961 1463201 N/A N/A 220970 220989 CACCTCCACTATCTTCATAA 79 2962 1463206 N/A N/A 225359 225378 TTTCCTACTGCCTTTCTCAT 48 2963 1463218 N/A N/A 234370 234389 GTTCATTCCCCTAGCCTGCA 47 2964 1463225 N/A N/A 221005 221024 CTCTGTTCTCAATTCATGGT 13 2965 1463228 N/A N/A 231288 231307 CTGTGTCCTTATTTCTTCAA 18 2966 1463264 N/A N/A 225381 225400 TTATGCCTTTGTTCCCTCTT 27 2967 1463265 N/A N/A 223617 223636 GCAGCTTTTTTTTTTTCTTT 9 2968 1463267 N/A N/A 231032 231051 CTCCACAGTCCCTCATCCTC 85 2969 1463278 N/A N/A 221192 221211 CTTCAGTTCATTAAGACTGA 100 2970 1463285 N/A N/A 222732 222751 AGCATGACTCCATTCTTCCT 20 2971 1463291 N/A N/A 219075 219094 CTTGTTCTCCTATTTCTGTT 62 2972 1463293 N/A N/A 220129 220148 TCCTGGTTTTGATAATGGAC 77 2973 1463305 N/A N/A 222571 222590 AACCATTGTATCTCTCTACA 10 2974 1463311 N/A N/A 235334 235353 CTGTGCTTCACTTGGCCCCA 55 2975 1463316 N/A N/A 229326 229345 ATCTCAATTTGGATTCATCT 23 2976 1463324 N/A N/A 221315 221334 GCTTATTTCCCTATAGTTAT 12 2977 1463336 N/A N/A 225369 225388 TCCCTCTTTATTTCCTACTG 25 2978 1463337 N/A N/A 234802 234821 CTTTCATGTTCCCTTGAGGA 22 2979 1463343 N/A N/A 222742 222761 CCTTCTTCTCAGCATGACTC 22 2980 1463357 N/A N/A 220563 220582 GCCAGCTGTTCCCTTGAGCG 55 2981 1463360 N/A N/A 222720 222739 TTCTTCCTCATTTTCACCCA 29 2982 1463361 N/A N/A 220896 220915 AGTTGCTTTTTTTCTCTTCT 7 2983 1463370 N/A N/A 232980 232999 CTGGGCATGGTATTTGCAAT 30 2984 1463372 N/A N/A 222752 222771 CGATAGCATTCCTTCTTCTC 39 2985 1463380 N/A N/A 221341 221360 CATCAACTTTTTAGTCCTTT 5 2986 1463381 N/A N/A 222428 222447 GTATGCTATTTGTACTGAAC 7 2987 1463384 N/A N/A 222772 222791 ATGTCAATTTTCCCCTTCAC 14 2988 1463397 N/A N/A 224442 224461 GCCCACTTCATCAGTCCAAG 26 2989 1463399 N/A N/A 231620 231639 GCATATTACATGGTTTTCCT 9 2990 1463400 N/A N/A 220457 220476 TGTATCTATTTCCAACCCAA 38 2991 1463402 N/A N/A 219533 219552 GTTCCAGCCTGACAGTTTCA 52 2992 1463404 N/A N/A 220056 220075 CCTCTCTGTACTATTTTTCC 53 2993 1463405 N/A N/A 220937 220956 ACTGAGTTGCTCCTTCTGAA 17 2994 1463408 N/A N/A 229106 229125 ACTGTGGTCTGACTTCACTT 92 2995 1463415 N/A N/A 225614 225633 GCTGCATTTTTCCTGAAGAG 21 2996 1463420 N/A N/A 233345 233364 GCATCAATTCCTTTGGGTTT 15 2997 1463427 N/A N/A 218640 218659 ACAACTTTTGTTTTTCTCAT 54 2998 1463428 N/A N/A 220479 220498 GCTCTGATTCCAGATGATAA 24 2999 1463444 N/A N/A 229858 229877 ACTCATGCTTTTAGGAGCAT 45 3000 1463457 N/A N/A 229340 229359 ATATTTCAAAATTAATCTCA 86 3001 N/A N/A 229373 229392 1463464 N/A N/A 220242 220261 ATGTGGTATTTTATTCTCTT 5 3002 1463470 N/A N/A 234015 234034 GCCACAGTAGAGTATAGTAT 17 3003 1463476 N/A N/A 221734 221753 GTTCTTTATTTTTATTATAC 16 3004 1463480 N/A N/A 224123 224142 GCAGGTCTTGGCTTCCACCC 41 3005 1463487 N/A N/A 234195 234214 TGGTTAGTTTGCTTCAAGCA 9 3006 1463496 N/A N/A 228109 228128 GGTCTTGCCATGTTTCCCAT 28 3007 1463506 N/A N/A 221087 221106 CTGATGTCTATTCTCCAAGT 19 3008 1463507 N/A N/A 223722 223741 AGCTCTTTTCTCCGTTCTCT 6 3009 1463512 N/A N/A 229284 229303 CACTGATTTTTTTCCCCTCC 15 3010 1463515 N/A N/A 228944 228963 GCCTCAGGCTCCATCCATTT 86 3011 1463516 N/A N/A 220394 220413 ACATATTGCTTATATGTTGG 13 3012 1463521 N/A N/A 220049 220068 GTACTATTTTTCCAAGTTCT 8 3013 1463522 N/A N/A 222448 222467 GCCAGTGTCTCTGAATTTTA 11 3014 1463529 N/A N/A 222760 222779 CCCTTCACCGATAGCATTCC 65 3015 1463541 N/A N/A 231112 231131 ATGCATCACGGCCATCCATC 58 3016 1463554 N/A N/A 233403 233422 ATGCATGCATTTTTTTTCTA 61 3017 1463558 N/A N/A 222726 222745 ACTCCATTCTTCCTCATTTT 46 3018 1463572 N/A N/A 221300 221319 GTTATTACCTATGCCACTTC 23 3019 1463577 N/A N/A 226498 226517 ACCGTACTTTGCCATTCATT 8 3020 1463579 N/A N/A 222520 222539 GCTTGTATTTATAAGCACAA 58 3021 1463582 N/A N/A 221636 221655 CCCTAATATGTTCTTAATCC 49 3022 1463601 N/A N/A 219943 219962 TGGCTTCCCTGCTCAGCCAT 80 3023 1463605 N/A N/A 220776 220795 ACTGCACCTCCCTGACATAT 39 3024 1463606 N/A N/A 219188 219207 GCCCAGGTTATTTTTCTTAC 59 3025 1463611 N/A N/A 218738 218757 TGGGCTTCATTTAGGCTCAC 98 3026 1463621 N/A N/A 233880 233899 CTGCAATTTCTCTATAATCT 14 3027 1463625 N/A N/A 231902 231921 GCTGATATTCATGTTCTCTT 5 3028 1463626 N/A N/A 224045 224064 GTTCAATTTCTTCAACTGTA 4 3029 1463627 N/A N/A 234352 234371 CACTGATTCCTCTTTTTCTC 33 3030 1463631 N/A N/A 222079 222098 AGGACTATAGATGACAACTA 35 3031

Example 4: Dose-Dependent Inhibition of Human APP in SH-SY5Y Cells by Modified Oligonucleotides

(358) Modified oligonucleotides selected from the examples above were tested at various doses in SH-SY5Y cells. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and were transfected using electroporation with modified oligonucleotides at various doses, as specified in the tables below. After a treatment period of approximately 24 hours, APP RNA levels were measured as previously described using the human APP primer-probe set RTS35572 (described herein above). APP RNA levels were normalized to total RNA, as measured by RIBOGREEN®. Results are presented as percent APP RNA, relative to untreated control cells (% UTC).

(359) The half maximal inhibitory concentration (IC.sub.50) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in Excel and is also presented in the tables below. N.D in the table below refers to instances where the value was Not Defined. Compound IDs 912255, 912262, 912263, 912267, 912272, 912294, 912295, 912298, and 912301 were previously described in PCT/US20/15701.

(360) TABLE-US-00045 TABLE 43 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 78 nM 312 nM 1250 nM 5000 nM (μM) 1353637 84 55 29 15 0.48 1353643 94 77 42 22 1.01 1353645 110 91 52 27 1.64 1353653 86 58 38 18 0.62 1353833 91 84 43 23 1.12 1353849 103 76 53 31 1.54 1353867 92 66 36 27 0.86 1353889 88 77 33 19 0.78 1353899 80 66 30 13 0.52 1353901 103 86 43 21 1.19 1353910 102 76 49 18 1.11 1353917 104 101 58 29 2.05 1353978 104 85 47 28 1.43 1353989 102 82 52 26 1.46 1354007 88 60 33 10 0.56 1354030 103 82 40 22 1.10 1354037 103 80 53 26 1.42 1354055 123 99 59 21 1.74 1354057 69 46 33 13 0.29

(361) TABLE-US-00046 TABLE 44 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 78 nM 312 nM 1250 nM 5000 nM (μM) 1353647 111 83 51 15 1.19 1353731 93 28 43 11 0.43 1353733 88 68 35 15 0.67 1353736 92 73 44 19 0.92 1353750 80 48 64 29 1.07 1353830 106 95 87 41 >5.0 1353875 107 82 51 20 1.27 1353889 97 82 42 21 1.06

1353913 83 55 41 21 0.63 1353959 94 100 72 47 >5.0 1353992 108 73 43 25 1.16 1354021 110 88 60 35 2.23 1354048 109 103 55 34 2.21 1354049 85 74 57 24 1.25 1354052 126 116 80 66 >5.0 1354060 123 111 65 32 2.60 1354063 97 110 97 62 >5.0 1354072 84 64 37 20 0.68 1354081 98 68 55 35 1.60

(362) TABLE-US-00047 TABLE 45 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 78 nM 312 nM 1250 nM 5000 nM (μM) 1353655 98 89 52 40 2.30 1353664 129 109 80 43 4.45 1353671 84 78 48 23 1.08 1353686 104 85 54 22 1.42 1353710 111 83 39 17 1.06 1353723 138 120 97 64 >5.0 1353749 118 95 69 52 >5.0 1353753 115 105 72 40 3.69 1353762 117 96 62 42 2.95 1353792 120 67 38 25 1.08 1353815 81 68 40 16 0.67 1353839 117 98 63 34 2.47 1353884 110 80 60 35 2.08 1353889 100 84 47 19 1.16 1353911 131 106 66 33 2.57 1353931 132 119 86 47 >5.0 1353976 129 122 114 59 >5.0 1354031 93 69 41 24 0.93 1354067 97 84 58 26 1.61

(363) TABLE-US-00048 TABLE 46 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 78 nM 312 nM 1250 nM 5000 nM (μM) 1332169 105 104 105 73 >5.0 1332194 90 90 85 49 >5.0 1332202 117 98 48 30 1.74 1332204 64 29 18 10 0.13 1332206 114 108 110 91 >5.0 1332209 69 68 25 23 0.47 1332210 70 58 38 23 0.49 1332211 81 48 8 5 0.29 1332212 115 92 60 41 2.75 1332213 74 77 48 24 0.98 1333917 55 38 9 11 0.10 1333926 60 38 24 18 0.14 1333929 74 62 34 12 0.47 1335707 85 71 30 20 0.68 1335708 64 35 19 11 0.16 1335709 86 75 52 43 2.22 1335712 72 40 14 7 0.22 1335717 76 29 12 15 0.19 1354057 93 62 34 9 0.62

(364) TABLE-US-00049 TABLE 47 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 78 nM 312 nM 1250 nM 5000 nM (μM) 912255 104 99 68 39 3.44 912262† 30 22 9 5 <0.1 912263† 29 20 9 5 <0.1 912267† 58 32 11 7 0.10 912272† 25 10 4 3 <0.1 912294 120 96 67 36 2.73 912295† 36 20 11 5 <0.1 912298 86 73 42 20 0.87 912301 110 82 32 19 0.98 1332183 85 57 30 17 0.54 1332200 89 97 108 56 >5.0 1332207 119 91 63 20 1.66 1333927 84 50 25 11 0.41 1333935 66 38 18 13 0.17 1335702 62 36 24 7 0.15 1354057 85 40 19 15 0.34

(365) TABLE-US-00050 TABLE 48 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 125 nM 500 nM 2000 nM 8000 nM (μM) 1354057 91 42 15 10 0.58 1397573 79 73 40 21 1.24 1397586 91 82 64 36 3.90 1397705 106 87 80 32 4.88 1397786 111 76 46 17 1.75 1398012 97 52 48 17 1.21 1398133 99 82 63 34 3.56 1398494 100 87 65 18 2.48 1398569 96 95 61 48 6.95 1398653 96 68 48 16 1.46 1398916 105 79 63 26 2.70 1399000 109 99 86 64 >8.0 1399084 95 92 66 23 3.02 1399137 110 104 106 97 >8.0 1399215 109 79 63 33 3.32 1399216 90 80 57 13 1.72 1399291 99 89 65 53 >8.0 1399365 91 59 36 26 1.21 1399507 111 90 86 52 >8.0

(366) TABLE-US-00051 TABLE 49 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 125 nM 500 nM 2000 nM 8000 nM (μM) 1354057 88 40 21 7 0.55 1397616 98 96 88 62 >8.0 1397821 86 62 27 14 0.85 1397824 75 36 14 7 0.35 1397860 84 62 39 19 1.06 1397882 91 90 63 29 3.27 1397883 78 49 24 13 0.56 1397940 97 90 64 27 3.12 1398227 95 70 36 13 1.20 1398440 97 42 46 11 0.94 1398681 75 62 24 13 0.67 1398748 107 106 75 30 4.80 1398829 65 37 24 11 0.28 1398830 112 101 78 44 7.84 1398922 95 78 42 27 1.84 1399070 97 67 41 11 1.22 1399404 104 83 37 10 1.42 1399427 82 44 15 7 0.49 1399430 95 88 58 37 3.84

(367) TABLE-US-00052 TABLE 50 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 125 nM 500 nM 2000 nM 8000 nM (μM) 1354057 88 68 18 9 0.81 1397541 118 96 72 39 5.31 1397700 95 69 43 18 1.40 1397706 93 76 45 27 1.82 1397713 112 88 71 48 7.23 1398034 93 61 36 14 1.06 1398203 107 63 30 14 1.16 1398406 85 72 50 22 1.62 1398534 117 86 47 32 2.64 1398539 82 50 23 13 0.62 1398644 90 73 31 14 1.12 1398760 105 98 80 50 >8.0 1399010 99 93 56 24 2.64 1399026 95 75 57 49 5.46 1399147 86 59 31 12 0.85 1399261 103 83 65 27 3.03 1399295 90 65 53 14 1.37 1399442 106 97 48 28 2.64 1399511 68 42 22 14 0.35

(368) TABLE-US-00053 TABLE 51 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 125 nM 500 nM 2000 nM 8000 nM (μM) 1354057 85 44 21 21 0.63 1397534 117 98 62 23 2.98 1397572 71 37 21 10 0.35 1397580 98 73 32 22 1.39 1397620 96 68 32 13 1.12 1397948 92 58 34 14 0.96 1398033 91 99 60 20 2.62 1398060 111 85 41 19 1.82 1398125 114 95 42 25 2.29 1398128 103 83 39 16 1.60 1398213 87 61 36 15 0.98 1398429 58 25 14 29 <0.1 1398541 94 72 38 11 1.20 1398772 87 67 31 16 1.02 1398935 93 84 41 18 1.59 1399141 99 78 68 52 >8.0 1399380 111 77 47 19 1.84 1399436 71 45 29 19 0.49 1399500 104 63 35 23 1.37

(369) TABLE-US-00054 TABLE 52 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 125 nM 500 nM 2000 nM 8000 nM (μM) 1354057 69 39 18 9 0.33 1397576 88 68 67 86 >8.0 1397631 97 68 31 11 1.08 1397656 112 93 89 46 >8.0 1397765 82 64 34 8 0.84 1397842 71 46 12 6 0.37 1397884 114 82 58 26 2.62 1398342 109 109 63 40 5.28 1398371 84 61 29 24 0.97 1398456 109 63 54 15 1.65 1398752 73 62 35 12 0.76 1398762 107 95 52 19 2.29 1398948 90 56 43 18 1.12 1398955 108 83 43 19 1.81 1399033 90 74 44 24 1.61 1399164 112 80 42 20 1.83 1399176 80 53 24 11 0.62 1399204 108 88 59 18 2.30 1399473 100 90 91 68 >8.0

(370) TABLE-US-00055 TABLE 53 Dose-dependent reduction of human APP RNA in SH-SY5Y cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 125 nM 500 nM 2000 nM 8000 nM (μM) 1354057 65 31 18 6 0.23 1397604 101 76 52 25 2.10 1397614 94 71 37 22 1.40 1397772 93 88 52 28 2.44 1397795 80 55 34 14 0.76 1397925 96 80 61 22 2.33 1398169 95 64 32 27 1.30 1398187 96 86 53 30 2.67 1398341 112 114 172 92 >8.0 1398518 86 56 29 14 0.81 1398537 103 76 50 32 2.43 1398550 86 53 24 13 0.71 1398668 94 94 70 46 >8.0 1398686 103 89 95 53 >8.0 1398806 25 23 12 5 <0.1 1399025 141 121 101 58 >8.0 1399198 111 130 98 35 >8.0 1399200 110 75 37 18 1.56

Example 5: Dose-Dependent Inhibition of Human APP in A431 Cells by Modified Oligonucleotides

(371) Certain modified oligonucleotides described in the studies above exhibiting significant in vitro inhibition of APP RNA were selected and tested at various doses in A431 cells. The modified oligonucleotides were tested in a series of experiments using the same culture conditions. The results for each experiment are presented in separate tables shown below. Cells plated at a density of 10,000 cells per well were treated with modified oligonucleotides at various doses by free uptake, as specified in the tables below. After a treatment period of approximately 48 hours, APP RNA levels were measured as previously described using the Human APP primer-probe set RTS35432 (described herein above). APP RNA levels were normalized to total RNA, as measured by RIBOGREEN®. Results are presented as percent APP RNA, relative to untreated control cells (% UTC). The half maximal inhibitory concentration (IC.sub.50) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in Excel and is also presented in the tables below. N.D in the table below refers to instances where the value was Not Defined.

(372) TABLE-US-00056 TABLE 54 Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 31.25 nM 125.0 nM 500.0 nM 2000.0 nM (μM) 1397572 75 33 18 11 0.09 1399147 77 53 35 20 0.19 1463194 67 49 26 18 0.11 1463220 62 34 18 11 0.05 1463237 74 55 22 19 0.15 1463238 95 49 24 14 0.2 1463288 95 59 28 24 0.27 1463289 71 38 22 11 0.09 1463294 68 39 16 14 0.08 1463340 70 35 21 14 0.08 1463409 72 46 30 18 0.13 1463460 81 32 20 14 0.1 1463466 55 23 13 11 0.02 1463511 96 62 37 20 0.31 1463567 69 50 31 20 0.14 1463578 66 35 17 9 0.07 1463580 79 42 25 13 0.13 1463589 87 51 25 18 0.19 1463595 58 38 17 11 0.05

(373) TABLE-US-00057 TABLE 55 Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 31.25 nM 125.0 nM 500.0 nM 2000.0 nM (μM) 1397572 70 34 17 11 0.07 1463172 41 17 10 8 0.00 1463185 67 37 13 12 0.07 1463213 65 37 23 17 0.07 1463266 71 57 26 20 0.15 1463354 126 76 42 27 0.53 1463379 78 38 25 17 0.12 1463388 50 24 12 9 0.02 1463391 138 90 50 30 0.69 1463394 50 20 11 7 0.02 1463451 53 42 22 13 0.04 1463455 73 50 27 17 0.14 1463462 122 72 44 31 0.55 1463497 72 31 18 9 0.08 1463508 58 34 15 17 0.04 1463509 92 72 44 31 0.47 1463525 121 76 37 28 0.49 1463542 58 30 16 12 0.04 1463575 75 59 35 25 0.22

(374) TABLE-US-00058 TABLE 56 Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 31.25 nM 125.0 nM 500.0 nM 2000.0 nM (μM) 1397572 68 34 21 11 0.07 1397795 53 28 19 12 0.02 1463192 75 46 24 17 0.13 1463199 65 36 18 10 0.07 1463203 48 20 13 9 0.01 1463227 70 39 20 15 0.09 1463236 71 40 23 14 0.10 1463313 73 55 35 24 0.20 1463368 75 50 31 20 0.16 1463387 79 44 24 16 0.13 1463425 91 60 34 23 0.28 1463450 82 57 34 22 0.23 1463472 89 45 28 16 0.18 1463478 58 30

19 12 0.04 1463485 96 65 35 22 0.32 1463498 44 23 15 10 0.01 1463514 57 27 14 11 0.03 1463553 60 29 17 11 0.04 1463612 84 53 29 18 0.20
(375) TABLE-US-00059 TABLE 57 Dose-dependent reduction of human APP RNA in A431 cells by modified oligonucleotides Compound APP RNA (% UTC) IC.sub.50 No. 31.25 nM 125.0 nM 500.0 nM 2000.0 nM (μM) 1397572 66 27 15 11 0.05 1463248 98 68 42 25 0.39 1463265 73 39 25 18 0.10 1463307 79 54 32 22 0.20 1463361 49 28 17 11 0.02 1463366 87 61 39 23 0.29 1463369 82 55 34 22 0.22 1463380 65 32 18 12 0.06 1463381 86 49 34 18 0.20 1463399 87 55 32 19 0.22 1463442 72 42 24 15 0.11 1463464 54 25 13 10 0.02 1463482 90 38 48 30 0.28 1463487 80 44 28 15 0.15 1463507 55 27 16 11 0.03 1463521 76 42 26 18 0.13 1463577 71 41 23 18 0.10 1463625 39 19 10 8 0.00 1463626 56 29 14 10 0.03
Example 6: Design of MOE Gapmer Modified Oligonucleotides with Mixed PO/PS Internucleoside Linkages Complementary to a Human APP Nucleic Acid
(376) Modified oligonucleotides complementary to human APP nucleic acid were designed and synthesized. “Start site” in all the tables below indicates the 5′-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. “Stop site” in all the tables below indicates the 3′-most nucleoside of the target sequence to which the modified oligonucleotide is complementary. As shown in the tables below, the modified oligonucleotides are complementary to either SEQ ID NO: 1 (described hereinabove), and/or to SEQ ID NO: 2 (described hereinabove). ‘N/A’ indicates that the modified oligonucleotide is not complementary to that particular target sequence with 100% complementarity.
(377) The modified oligonucleotides in the table below are 5-10-5 MOE gapmers. The sugar motif of the gapmers is (from 5′ to 3′): eeeeeddddddddddeeeee; wherein ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and ‘e’ represents a 2′-MOE sugar moiety. The internucleoside motif of the gapmers is (from 5′ to 3′): soooossssssssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage, and each ‘o’ represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methylcytosine.
(378) TABLE-US-00060 TABLE 58 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Site SEQ ID No. Sequence (5′ to 3′) Site Site Site Stop No. 1478917 ATCCCACTTCCCATTCTGGA 174 193 61937 61956 3032 1478919 GGCATCACTTACAAACTCAC 393 412 120656 120675 3033 1478925 GAAGCTTACATCATTTTCTT N/A N/A 25103 25122 3038 1478926 AAGCTTACATCATTTTCTTG N/A N/A 25102 25121 3039 1498072 TCTTGATATTTGTCAACCCA 2002 2021 276332 276351 3034 1498073 CTTGATATTTGTCAACCCAG 2001 2020 276331 276350 3035
(379) The modified oligonucleotides in the table below are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length. The sugar motif of the gapmers is (from 5′ to 3′): eeeeeddddddddddeeee; wherein ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and ‘e’ represents a 2′-β-D-MOE sugar moiety. The internucleoside motif of the gapmers is (from 5′ to 3′): sooooossssssssssoss, wherein each “s” represents a phosphorothioate internucleoside linkage, and each ‘o’ represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methylcytosine.
(380) TABLE-US-00061 TABLE 59 6-10-4 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Site SEQ ID No. Sequence (5′ to 3′) Site Site Site Stop No. 1478902 CATCACTTACAAACTCACCA 391 410 120654 120673 2531 1478903 CCCACTTCCCATTCTGGACA 172 191 61935 61954 2529 1478904 GATCTGAATCCCACTTCCCA 181 200 61944 61963 2528 1478905 TCCAAAGATTCCACTTTCTC 1343 1362 198782 198801 2511 1478906 GCTTACATCATTTTCTTGCA N/A N/A 25100 25119 111 1478907 CTTCCCATTCTCTCATGACC 1258 1277 197972 197991 2523 1498058 GTCTTGATATTTGTCAACCC 2003 2022 276333 276352 3036 1498059 TCTTGATATTTGTCAACCCA 2002 2021 276332 276351 3034 1498060 CTTGATATTTGTCAACCCAG 2001 2020 276331 276350 3035 1498061 TTGATATTTGTCAACCCAGA 2000 2019 276330 276349 428 1498062 TGATATTTGTCAACCCAGAA 1999 2018 276329 276348 3037 1498065 TCTCGAGATACTTGTCAACG 1156 1175 191555 191574 1414 1498066 CTCGAGATACTTGTCAACGG 1155 1174 191554 191573 1289 1498067 TCGAGATACTTGTCAACGGC 1154 1173 191553 191572 1248 1498068 CGAGATACTTGTCAACGGCA 1153 1172 191552 191571 1129 1498069 GAGATACTTGTCAACGGCAT 1152 1171 191551 191570 1037 1498070 AGATACTTGTCAACGGCATC 1151 1170 191550 191569 960 1498071 GATACTTGTCAACGGCATCA 1150 1169 191549 191568 892
(381) The modified oligonucleotides in the table below are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length. The sugar motif of the gapmers is (from 5′ to 3′): eeeeeddddddddddeeee; wherein ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and ‘e’ represents a 2′-MOE sugar moiety. The internucleoside motif of the gapmers is (from 5′ to 3′): soooossssssssssoss, wherein each “s” represents a phosphorothioate internucleoside linkage, and each ‘o’ represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methylcytosine.
(382) TABLE-US-00062 TABLE 60 6-10-4 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Site SEQ ID No. Sequence (5′ to 3′) Site Site Site Stop No. 1498105 CTTGATATTTGTCAACCCAG 2001 2020 276331 276350 3035 1498106 GAGATACTTGTCAACGGCAT 1152 1171 191551 191570 1037
(383) The modified oligonucleotides in the table below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length. The sugar motif of the gapmers is (from 5′ to 3′): eeeeeddddddddddeeeee; wherein ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and ‘e’ represents a 2′-MOE sugar moiety. The internucleoside motif of the gapmers is (from 5′ to 3′): ssoossssssssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage, and each ‘o’ represents a phosphodiester internucleoside linkage. Each cytosine nucleoside is a 5-methylcytosine.
(384) TABLE-US-00063 TABLE 61 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Site SEQ ID No. Sequence (5′ to 3′) Site Site Site Stop No. 1478908 CATCACTTACAAACTCACCA 391 410 120654 120673 2531 1478909 CCCACTTCCCATTCTGGACA 172 191 61935 61954 2529 1478910 GATCTGAATCCCACTTCCCA 181 200 61944 61963 2528 1478911 TCCAAAGATTCCACTTTCTC 1343 1362 198782 198801 2511 1478912 GCTTACATCATTTTCTTGCA N/A N/A 25100 25119 111 1478913 CTTCCCATTCTCTCATGACC 1258 1277 197972 197991 2523
Example 7: Tolerability of Modified Oligonucleotides Comprising 2′-MOE Nucleosides Complementary to Human APP in Wild-Type Mice, 3 Hour Study
(385) Modified oligonucleotides described above were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Wild-type female C57/Bl6 mice each received a single ICV dose of modified oligonucleotide at 700 μg. Each treatment group consisted of 2-4 mice. A group of 2-4 mice received PBS as a negative control for each experiment. Each experiment is identified in separate tables below. At 3 hours post-injection, mice were evaluated according to seven different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.
(386) TABLE-US-00064 TABLE 62 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1332165 2.00 1332166 0.00 1332167 0.00 1332168 1.00 1332170 1.00 1332171 2.50 1332172 2.00 1332173 1.00 1332174 4.00 1332176 0.00 1332177 0.50 1332178 0.50 1332179 3.00 1332180 5.50 1332182 1.00 1332183 2.00 1332184 0.00 1332185 0.00 1332186 0.50 1332187 0.00 1332188 7.00 1332189 0.00 1332190 1.00 1332192 1.00 1332193 3.50 1332194 0.50 1332195 0.50 1332196 1.00 1332197 1.00 1332198 1.00 1332199 1.00 1332200 0.50 1332201 0.50 1332202 1.50 1332203 1.00 1332204 0.50 1332205 0.50 1332206 3.00 1332207 1.00 1332208 1.00 1332209 0.00 1332210 1.00 1332211 1.00 1332212 1.00 1332213 1.00

(387) TABLE-US-00065 TABLE 63 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1332169 0.00 1332181 4.00 1353640 2.00 1353707 2.50 1353716 0.00 1353744 1.00 1353747 1.50 1353809 0.00 1353877 0.00 1353892 0.00 1353950 0.00 1354003 0.00 1354037 1.00

(388) TABLE-US-00066 TABLE 64 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1332192 0.00 1332197 0.00 1332204 0.00 1332209 0.00 1332210 0.00 1332212 0.00 1332213 0.00 1353645 0.00 1353763 0.00 1353889 0.00

(389) TABLE-US-00067 TABLE 65 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1478904 0.00 1478907 0.00 1478908 0.00 1478909 0.00 1478910 0.25 1478913 1.00 1478919 0.75 1498061 4.75 1498072 5.00

(390) TABLE-US-00068 TABLE 66 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1353977 1.00 1353993 2.75 1399125 1.00 1478914 1.00 1478920 1.00 1478921 0.00 1478922 1.00 1478923 1.25 1478924 0.00

(391) TABLE-US-00069 TABLE 67 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1332169 1.00 1332200 1.00 1332207 0.00 1333927 6.33 1353643 1.00 1353760 0.00 1353776 0.67 1353802 0.00 1353818 0.00 1353869 0.00 1353981 1.00 1354046 0.00 1354060 0.00 1354072 0.33 1354075 0.00 1394454 2.33 1394455 1.67 1397904 2.33 1478925 0.00 1478926 1.33 1478927 0.33 1498064 1.00

(392) TABLE-US-00070 TABLE 68 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1353658 1.00 1353681 0.00 1353690 0.67 1353694 0.00 1353734 0.00 1353762 0.00 1353783 0.00 1353804 0.00 1353808 0.00 1353846 1.00 1353884 0.00 1353899 0.00 1353931 1.33 1353974 0.00 1354007 0.00 1354012 0.00 1354033 0.00 1354050 0.00 1354092 0.00 1397572 1.33 1397795 1.67 1397824 1.67 1398213 0.00 1398518 0.00 1398644 0.00 1399147 0.67 1399295 4.00

(393) TABLE-US-00071 TABLE 69 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1353648 3.33 1353649 0.33 1353664 2.33 1353686 0.00 1353723 0.67 1353725 2.67 1353733 0.00 1353753 0.67 1353796 1.00 1353815 1.00 1353886 0.00 1353935 1.00 1353937 0.00 1353957 2.00 1353986 0.00 1353992 1.67 1353996 0.67 1354081 1.00

Example 8: Tolerability of Modified Oligonucleotides Comprising cEt Nucleosides Complementary to Human APP in Wild-Type Mice, 3 Hour Study

(394) Modified oligonucleotides described above were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Wild-type female C57/Bl6 mice each received a single ICV dose of modified oligonucleotide at 300 μg. Each treatment group consisted of 2-4 mice. A group of 2-4 mice received PBS as a negative control for each experiment. Each experiment is identified in separate tables below. At 3 hours post-injection, mice were evaluated according to seven different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.

(395) TABLE-US-00072 TABLE 70 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1333912 4.50 1333913 5.00 1333914 5.50 1333915 4.00 1333916 6.00 1333917 5.00 1333918 1.00 1333919 1.00 1333920 1.00 1333921 1.00 1333922 1.00 1333923 1.00 1333924 1.00 1333925 1.00 1333926 1.00 1333927 4.50 1333928 5.00 1333929 1.00 1333930 1.00 1333931 4.00 1333932 4.50 1333933 3.00 1333934 5.00 1333935 1.00 1335695 1.00 1335696 4.00 1335697 1.00 1335698 3.00 1335699 1.00 1335700 2.00 1335701 1.00 1335702 1.00 1335703 4.00 1335704 4.00 1335705 1.00 1335706 2.00 1335707 6.00 1335708 1.00 1335709 1.00 1335710 3.50 1335711 3.50 1335712 5.00 1335713 1.00 1335714 1.00 1335715 6.50 1335716 4.50 1335717 4.00 1335718 3.50

Example 9: Tolerability of Modified Oligonucleotides Complementary to Human APP in Rats, 3 Hour Study

(396) Modified oligonucleotides described above were tested in rats to assess the tolerability of the oligonucleotides. Sprague Dawley rats each received a single intrathecal (IT) dose of oligonucleotide at doses indicated in the tables below. Compounds comprising MOE nucleosides were administered at a dose of 3 mg and compounds comprising cEt nucleosides were administered at a dose of 2.4 mg. Each treatment group consisted of 3 rats. A group of 3 rats received PBS as a negative control. Each experiment is identified in separate tables below. At 3 hours post-injection, movement in 7 different parts of the body were evaluated for each rat. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed (the functional observational battery score or FOB). After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and all other evaluated body parts were moving 3 hours after the 3 mg IT dose, it would receive a summed score of 0. If another rat was not moving its tail 3 hours after the 3 mg IT dose but all other evaluated body parts were moving, it would receive a score of 1. Results are presented as the average score for each treatment group.

(397) TABLE-US-00073 TABLE 71 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1332179 3 1.33 1332199 3 1.33 1332201 3 3.00 1332202 3 3.00 1332204 3 0.67 1332207 3 1.00 1332212 3 0.00 1333926 2.4 2.33 1335708 2.4 3.00 1335714 2.4 3.00

(398) TABLE-US-00074 TABLE 72 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1332173 3 3.00 1332182 3 2.00 1332183 3 3.67 1332187 3 1.67 1332189 3 0.33 1332192 3 0.33 1332196 3 1.67 1332197 3 0.33 1332198 3 1.67 1332200 3 3.00 1332206 3 5.00 1332208 3 0.67 1332209 3 0.33 1332210 3 0.33 1332211 3 2.00 1333924 2.4 1.33 1333927 2.4 1.33 1333932 2.4 4.67 1335696 2.4 5.00 1335700 2.4 0.33 1335704 2.4 5.67

(399) TABLE-US-00075 TABLE 73 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1332169 3 2.33 1332176 3 0.67 1332181 3 4.33 1332186 2.4 2.00 1332193 3 0.33 1332195 3 2.33 1332203 3 1.33 1332213 3 0.67 1333925 3 3.67 1333931 3 4.67 1335695 2.4 2.67 1335697 2.4 3.00 1335703 2.4 4.33 1335706 2.4 5.67 1335718 2.4 3.33

(400) TABLE-US-00076 TABLE 74 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1353641 3 0.00 1353642 3 0.00 1353643 3 2.00 1353645 3 0.00 1353692 3 0.67 1353730 3 0.67 1353731 3 0.33 1353750 3 0.00 1353760 3 1.67 1353763 3 0.00 1353776 3 2.67 1353802 3 1.33 1353818 3 1.67 1353828 3 0.33 1353844 3 4.33 1353869 3 2.00 1353889 3 0.00 1353953 3 1.00 1353956 3 0.00 1353962 3 0.67 1353972 3 0.33 1353977 3 1.67 1353981 3 1.67 1354008 3 0.00 1354020 3 0.00 1354030 3 1.00 1354046 3 1.67 1354060 3 0.33 1354072 3 1.67 1354075 3 0.00 1354092 3 0.00

(401) TABLE-US-00077 TABLE 75 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1353648 3 1.33 1353658 3 1.33 1353664 3 2.67 1353681 3 0.00 1353690 3 0.00 1353694 3 0.00 1353725 3 2.00 1353734 3 0.67 1353762 3 1.33 1353783 3 1.33 1353804 3 1.67 1353808 3 0.00 1353815 3 0.00 1353846 3 2.00 1353884 3 0.00 1353886 3 0.00 1353899 3 0.33 1353913 3 0.67 1353931 3 1.33 1353974 3 1.33 1353986 3 0.00 1353993 3 1.67 1354007 3 2.00 1354012 3 0.00 1354028 3 0.00 1354031 3 2.67 1354033 3 0.00 1354050 3 0.67

(402) TABLE-US-00078 TABLE 76 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1353649 3 0.33 1353686 3 0.33 1353723 3 0.33 1353733 3 0.67 1353753 3 0.67 1353796 3 2.67 1353935 3 1.67 1353937 3 0.33 1353957 3 2.33 1353992 3 3.00 1353996 3 1.67 1354081 3 1.33

(403) TABLE-US-00079 TABLE 77 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1397572 3 3.00 1397586 3 2.33 1397616 3 0.33 1397620 3 2.00 1397631 3 1.33 1397656 3 1.67 1397705 3 0.33 1397706 3 2.00 1397713 3 0.00 1397765 3 2.67 1397772 3 1.67 1397786 3 0.67 1397795 3 2.00 1397821 3 0.00 1397824 3 3.00 1397842 3 0.33 1397883 3 1.67 1397925 3 2.00 1397948 3 2.00 1398033 3 0.00 1398060 3 0.33 1398125 3 1.00 1398133 3 2.00 1398203 3 0.00 1398213 3 0.33 1398227 3 0.00 1398341 3 0.33

(404) TABLE-US-00080 TABLE 78 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1398342 3 2.33 1398371 3 0.00 1398406 3 0.00 1398429 3 0.00 1398440 3 0.00 1398456 3 3.00 1398518 3 0.33 1398534 3 0.00 1398539 3 0.00 1398550 3 2.00 1398644 3 2.00 1398681 3 0.00 1398686 3 1.00 1398748 3 0.00 1398760 3 2.33 1398762 3 0.00 1398806 3 0.00 1398829 3 0.67 1398830 3 0.00 1398916 3 1.67

1398955 3 0.00 1399000 3 1.67 1399010 3 0.00 1399025 3 0.33 1399026 3 0.00
(405) TABLE-US-00081 TABLE 79 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1332171 3 1.33 1332194 3 0.67 1335713 3 3.33 1353640 3 3.33 1353707 3 3.33 1353716 3 0.33 1353744 3 2.33 1353747 3 2.33 1353809 3 2.00 1399141 3 2.00 1399147 3 0.67 1399164 3 0.33 1399176 3 0.00 1399198 3 2.00 1399200 3 1.00 1399215 3 0.00 1399216 3 0.00 1399291 3 0.00 1399295 3 4.33 1399365 3 0.33 1399380 3 0.00 1399404 3 0.00 1399427 3 0.00 1399430 3 1.00 1399473 3 0.33 1399500 3 0.33 1399511 3 1.33
(406) TABLE-US-00082 TABLE 80 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1332192 3 0.33 1332204 3 0.00 1353877 3 0.00 1353892 3 2.00 1353985 3 0.00 1354003 3 1.33 1399125 3 2.00 1478902 3 1.67 1478903 3 2.00 1478904 3 0.00 1478905 3 0.67 1478906 3 1.67 1478907 3 0.67 1478908 3 0.33 1478909 3 0.33 1478910 3 0.00 1478911 3 1.00 1478912 3 0.00 1478913 3 0.33
(407) TABLE-US-00083 TABLE 81 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1478917 3 0.00 1478919 3 0.00 1478925 3 0.33 1478926 3 0.67 1478914 3 0.33 1478920 3 0.00 1478921 3 0.00 1478922 3 0.00 1478923 3 0.00 1478924 3 0.00 1478927 3 0.67
(408) TABLE-US-00084 TABLE 82 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1394454 3 2.33 1394455 3 3.00 1397904 3 4.67 1498061 3 3.33 1498069 3 4.00 1498072 3 3.00 1498064 3 1.00
Example 10: Activity of Modified Oligonucleotides Complementary to Human APP in Tel Transgenic Mice
(409) The aneuploid mouse line (Tel), expressing human APP, previously described in O'Doherty A., et al., *An Aneuploid Mouse Strain Carrying Human Chromosome* 21 *with Down Syndrome Phenotypes*, Science 2005, 309(5743): 2033-2037, was used to test activity of modified oligonucleotides described above.
(410) Treatment
(411) Tc1 mice were divided into groups of 2-3 mice each (the n for each study is indicated in the tables below). Each mouse received a single ICV bolus of 300 μg of modified oligonucleotide. A group of 3-4 mice received PBS as a negative control.
(412) RNA Analysis
(413) Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (forward sequence CCCACTTTGTGATTCCCTACC, designated herein as SEQ ID NO: 17; reverse sequence ATCCATCCTCTCCTGGTGTAA, designated herein as SEQ ID NO: 18; probe sequence TGATGCCCTTCTCGTTCCTGACAA, designated herein as SEQ ID NO: 19). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A. Mouse cyclophilin A was amplified using primer probe set m_cyclo24 (forward sequence TCGCCGCTTGCTGCA, designated herein as SEQ ID NO: 20; reverse sequence ATCGGCCGTGATGTCGA, designated herein as SEQ ID NO: 21; probe sequence CCATGGTCAACCCCACCGTGTTC, designated herein as SEQ ID NO: 22).
(414) The values marked by the symbol "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set RTS35572 (described herein above), or the human primer probe set HS.PT.56a.38768352 (Integrated DNA Technologies, Inc.) were used to further assess the activity of the modified oligonucleotides.
(415) TABLE-US-00085 TABLE 83 Reduction of human APP RNA in Tc1 transgenic mice, n = 2 APP RNA (% control) APP RNA (% control) RTS35571 RTS35572 SPINAL SPINAL Compound No. CORD CORTEX CORD CORTEX PBS 100 100 100 100 1332176 117 94 110 96 1332179 87 75 91 79 1332192 42 40 61‡ 41 1332193 73 56 72 53 1332197 72 77 78 79 1332204 59 46 59 38 1332208 109 94 98 90 1332209 66 51 68 52 1332210 63 37 42 45 1332212 75† 22† 67 30 1332213 149† 92† 76 43 1335700 113 129 111 113 1353641 100 109 98 100 1353642 95 90 95 92 1353645 51 41 52 43 1353692 89 78 90 80 1353730 104 129 107 123 1353731 85 104 81 86 1353750 69 81 71 87 1353763 80 66 84 61 1353828 84 85 80 82 1353889 59 63 63 61 1353953 86 94 90 95 1353956 84 78 88 75 1353962 60 52 62 55 1353972 63 60 70 62 1354008 65 58 68 59 1354020 81 96 85 96 1354030 62 60 66 66
(416) TABLE-US-00086 TABLE 84 Reduction of human APP RNA in Tc1 transgenic mice, n = 2 APP RNA (% control) RTS35571 Compound No. SPINAL CORD CORTEX PBS 100 100 1332173 94 74 1332182 72 67 1332186 79 72 1332187 101 85 1332195 102 88 1332196 88 99 1332198 101 84 1332211 70 71 1333924 95 101 1333926 27 22 1335695 82 124 1335697 110 113 1335713 32 26 1335714 61 78
(417) TABLE-US-00087 TABLE 85 Reduction of human APP RNA in Tc1 transgenic mice, n = 2 APP RNA (% control) APP RNA (% control) RTS35571 HS.PT.56a.38768352 SPINAL SPINAL Compound No. CORD CORTEX CORD CORTEX PBS 100 100 100 100 1333919 40 32 36 29 1335708 35 38 29 34 1353707 77 64 77 66 1353985 64† 56† 68 61 1478902 67† 72† 79 79 1478903 33 63‡ 45‡ 58‡ 1478904 54 32‡ 51‡ 32‡ 1478905 59 51 56 47 1478906 58 51 57 52 1478907 59 41 58 42 1478908 71† 50† 69 58 1478909 55 50 50 48 1478910 61 42 61 42 1478911 69 55 63 52 1478912 62 57 61 56 1478913 63 48 62 49 1478917 81 84 74 80 1478919 35† 21† 47 33 1332212 42† 28† 47 36
‡indicates that fewer than 2 samples were available for PCR
(418) TABLE-US-00088 TABLE 86 Reduction of human APP RNA in Tc1 transgenic mice, n = 2 APP RNA (% control) RTS35571 Compound No. SPINAL CORD CORTEX PBS 100 100 1498059 52 55 1498060 57‡ 62‡ 1498061 71‡ 42‡ 1498065 68 62 1498066 50‡ 81‡ 1498067 62 59 1498068 54‡ 61 1498069 66 84 1498070 69 68 1498071 65 57 1498072 42‡ 46 1498073 52 51 1498105 62 52 1498106 81 73 1498058 53 51 1498062 86‡ 76 ‡indicates that fewer than 2 samples were available for PCR
(419) TABLE-US-00089 TABLE 87 Reduction of human APP RNA in Tc1 transgenic mice, n = 3 APP RNA (% control) RTS35571 Compound No. SPINAL CORD CORTEX PBS 100 100 1332204 65‡ 53 1332209 73 56 1332210 58 53 1353645 59 47 1478919 49 22 1478908 49 29 1478904 54 35 ‡indicates that fewer than 3 samples were available for PCR
(420) TABLE-US-00090 TABLE 88 Reduction of human APP RNA in Tc1 transgenic mice, n = 2 APP RNA (% control) RTS35571 Compound No. SPINAL CORD CORTEX PBS 100 100 1332169 82 79 1353686 34 30 1353694 62 69 1353723 75 85 1353733 39 45 1353760 63 70 1353776 92 104 1353802 61 59 1353815 30 42 1353818 68 80 1353869 70 77 1353884 45 37 1353899 50 51 1353913 34 30 1353977 73 88 1353981 78 84 1353993 52 72 1354007 54 64 1354060 49 45 1354072 62 65 1354075 80 79 1354081 50 60 1354092 70 84 1397620 47 64 1397772 44 35 1397824 40 57 1398203 48 51 1398227 35 33 1398440 41 46 1398456 44 25 1398681 42 41 1399147 57 70 1399164 40 42 1399176 41 44 1399404 55 64 1478925 75 98 1478926 91 103
Example 11: Design of Modified Oligonucleotides Complementary to Human APP Nucleic Acid
(421) Modified oligonucleotides complementary to a human APP nucleic acid were designed, as described in the table below. "Start site" indicates the 5′-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3′-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to SEQ ID NO: 1 (described herein above), to SEQ ID NO: 2 (described herein above), or to both. 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.
(422) The modified oligonucleotides in the table below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5′ to 3′): eeeeeddddddddddeeeee; wherein each 'd' represents a 2′-β-D-deoxyribosyl sugar moiety, and each 'e' represents a 2′-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5′ to 3′): sooossssssssssooss; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.
(423) TABLE-US-00091 TABLE 89 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID SEQ ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop SEQ ID Number Site Site Site Site Sequence (5′ to 3′) NO 1478914 184 203 61947 61966 ATGGATCTGAATCCCACTTC 3040 1478920 387 406 N/A N/A ACTTACAAACTCACCAACTA 3041 1478921 386 405 N/A N/A CTTACAAACTCACCAACTAA 3042 1478922 1346 1365 198785 198804 TGTTCCAAAGATTCCACTTT 3043 1478923 1345 1364 198784 198803 GTTCCAAAGATTCCACTTTC 3044 1478924 1344 1363

198783 198802 TTCCAAAGATTCCACTTTCT 3045 1478927 N/A N/A 25098 25117 TTACATCATTTTCTTGCAGT 3046 1539237 N/A N/A 158797 158816 TGGTTTACCTTTAACATTCC 3047 1539238 N/A N/A 158796 158815 GGTTTACCTTTAACATTCCT 3048 1539239 N/A N/A 158794 158813 TTTACCTTTAACATTCCTCA 3049 1539240 N/A N/A 158793 158812 TTACCTTTAACATTCCTCAT 3050 1539241 N/A N/A 282311 282330 TCTCTCATAGTCTTAATTCC 3051 1539242 N/A N/A 282309 282328 TCTCATAGTCTTAATTCCCA 3052 1539243 N/A N/A 34555 34574 TCCAATTTTAACTTGCACCA 3053 1539244 N/A N/A 159758 159777 TTCACAGTTTACCCCAAGCT 3054 1539245 N/A N/A 159757 159776 TCACAGTTTACCCCAAGCTT 3055 1539246 N/A N/A 12585 12604 CATTCTCTTATATTCCTTAC 3056

The modified oligonucleotide in the table below is a 5-10-5 MOE gapmer. The gapmer is 20 nucleosides in length, wherein the sugar motif for the gapmer is (from 5′ to 3′): eeeeeddddddddddeeeee; wherein each ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and each ‘e’ represents a 2′-MOE sugar moiety. The gapmer has an internucleoside linkage motif of (from 5′ to 3′): soooosssssssssssooos; wherein each “s” represents a phosphorothioate internucleoside linkage, and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

(424) TABLE-US-00092 TABLE 90 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop SEQ ID Number Site Site Site Site Sequence (5′ to 3′) NO 1532152 393 412 120656 120675 GGCATCACTTACAAACTCAC 3033

(425) The modified oligonucleotides in the table below are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5′ to 3′): eeeeeeddddddddddeeee; wherein each ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and each ‘e’ represents a 2′-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5′ to 3′): sooooossssssssssoss; wherein each “s” represents a phosphorothioate internucleoside linkage, and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

(426) TABLE-US-00093 TABLE 91 6-10-4 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop SEQ ID Number Site Site Site Site Sequence (5′ to 3′) NO 1498064 1997 2016 276327 276346 ATATTTGTCAACCCAGAACC 3057 1532149 393 412 120656 120675 GGCATCACTTACAAACTCAC 3033

(427) The modified oligonucleotides in the table below are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5′ to 3′): eeeeeeddddddddddeeee; wherein each ‘d’ represents a 2′-β-D-deoxyribosyl sugar moiety, and each ‘e’ represents a 2′-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5′ to 3′): soooossssssssssoss; wherein each “s” represents a phosphorothioate internucleoside linkage, and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

(428) TABLE-US-00094 TABLE 92 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID ID No: 1 No: 1 No: 2 No: 2 Compound Start Stop Start Stop SEQ ID Number Site Site Site Site Sequence (5′ to 3′) NO 1532150 393 412 120656 120675 GGCATCACTTACAAACTCAC 3033 1539865 N/A N/A 282310 282329 CTCTCATAGTCTTAATTCCC 1896 1539866 N/A N/A 178598 178617 ATGTGATTTCACTAACCGGC 238 1539867 N/A N/A 158795 158814 GTTTACCTTTAACATTCCTC 452 1539868 N/A N/A 159759 159778 GTTCACAGTTTACCCCAAGC 2225 1539869 N/A N/A 34556 34575 CTCCAATTTTAACTTGCACC 1064 1539870 N/A N/A 12586 12605 GCATTCTCTTATATTCCTTA 273

Example 12: Activity of Modified Oligonucleotides Complementary to Human APP in Tel Transgenic Mice

(429) The aneuploid mouse line (Tel), expressing human APP, previously described in O'Doherty A., et al., *An Aneuploid Mouse Strain Carrying Human Chromosome* 21 *with Down Syndrome Phenotypes*, Science 2005, 309(5743): 2033-2037, was used to test activity of modified oligonucleotides described above.

(430) Treatment

(431) Tc1 mice were divided into groups of 2 mice each. Each mouse received a single ICV bolus of 300 μg of modified oligonucleotide. A group of 3-4 mice received PBS as a negative control.

(432) RNA Analysis

(433) Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A. The values marked by the symbol “f” indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set HS.PT.56a.38768352 (Integrated DNA Technologies, Inc.) were used to further assess the activity of the modified oligonucleotides.

(434) TABLE-US-00095 TABLE 93 Reduction of human APP RNA in Tc1 transgenic mice, n = 2 APP RNA (% control) RTS35571 Compound No. SPINAL CORD CORTEX PBS 100 100 1353648 61 65 1353658 69 74 1353664 55 65 1353681 53‡ 55 1353690 52 57 1353725 74 67 1353753 65 73 1353762 45 49 1353783 68 78 1353796 44 58 1353804 59 72 1353808 63 61 1353886 46 39 1353931 36 25 1353957 50 51 1353974 47 43 1353986 69 51 1353992 63 76 1354050 88 90 1397572 56 42 1398213 70 64 ‡Indicates that fewer than 2 samples were available for PCR

(435) TABLE-US-00096 TABLE 94 Reduction of human APP RNA in Tc1 transgenic mice, n = 2 APP RNA (% control) APP RNA (% control) RTS35571 HS.PT.56a.38768352 SPINAL SPINAL Compound No. CORD CORTEX CORD CORTEX PBS 100 100 100 100 1353643 36 44 37 40 1353649 68 96 71 95 1353734 77 98 76 89 1353937 69 99 66 94 1354012 54 60 54 63 1354033 54 79 53 81 1354046 57 123 61 111 1394454 38 70 42 69 1397631 43 81 41 78 1397656 55 104 56 96 1397706 47 64 46 67 1397713 61 106 60 94 1397765 51 106 48 90 1397786 25 61 29 60 1397883 37 91 40 86 1398371 37 84 38 83 1398406 45‡ 86‡ 46‡ 84‡ 1398429 40 82 39 74 1398539 25 69 26 53 1398686 56 145 52 109 1398830 47 147 49 96 1398955 46 85 48 79 1399000 49 135 52 104 1399033 23 40 25 44 1399365 39 123 38 97 1399380 35 108 40 90 1399473 56 96 56 101 1399500 53 114 56 99 1399511 46 102 47 83 1478914 44 108 51 94 1478920 41† 106† 48 86 1478921 51† 97† 50 89 1478927 26 66 30 67 1498064 42 107 46 90 1532149 20 34 31 49 1532150 11 20 21 44 1532152 16 40 25 53 1539237 38 83 38 82 1539238 24 82 35 89 1539239 27 63 36 63 1539240 27 79 45 69 1539241 26 67 30 75 1539242 20 53 27 52 1539243 27 53 30 56 1539244 29 71 29 71 1539245 19 53 24 62 1539246 35‡ 81‡ 54‡ 90‡ 1539865 24 39 26 43 1539866 27 94 33 102 1539867 24 33 22 30 1539868 20 40 19 36 1539869 20 33 18 36 1539870 22 48 21 62 ‡Indicates that fewer than 2 samples were available for PCR

Example 13: Activity of Modified Oligonucleotides Complementary to Human APP in YAC-APP Transgenic Mice, Single Dose

(436) YAC transgenic mice, expressing human APP with London V7171 and Swedish K670N/M671L mutations (YAC-APP transgenic mice), previously described in Lamb B., et al., *Altered metabolism of familial Alzheimer's disease-linked amyloid precursor protein variants in yeast artificial chromosome transgenic mice*. Hum Mol Genet 1997 September; 6(9): 1535-41, were used to test activity of modified oligonucleotides described above.

(437) Treatment

(438) YAC-APP transgenic mice were divided into groups of 2 mice each. Each mouse received a single ICV bolus of 300 μg of modified oligonucleotide. A group of 3-4 mice received PBS as a negative control.

(439) RNA Analysis

(440) Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A. The values marked by the symbol “f” indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set HS.PT.56a.38768352 (Integrated DNA

Technologies, Inc.) was used to further assess the activity of the modified oligonucleotides.
(441) TABLE-US-00097 TABLE 95 Reduction of human APP RNA in YAC-APP transgenic mice, n = 2 APP RNA (% control) APP RNA (% control) RTS35571 HS.PT.56a.38768352 SPINAL SPINAL Compound No. CORD CORTEX CORD CORTEX PBS 100 100 100 100 1332176 69 69 72 72 1332194 92 80 99 79 1332208 86 75 88 80 1332212 36† 61† 41 68 1353686 22 42 22 44 1353884 28 37 27 40 1353886 37 55 38 61 1353931 39 44 44 51 1397772 37 56 38 58 1398227 28 25 28 27 1398456 20 36 19 37 1498064 84 87 83 91 1532149 37† 36† 52 59 1532150 28† 29† 44 57 1532152 43† 30† 50 47
(442) TABLE-US-00098 TABLE 96 Reduction of human APP RNA in YAC-APP transgenic mice, n = 2 APP RNA (% control) RTS35571 Compound No. SPINAL CORD CORTEX PBS 100 100 1332183 79 106 1353643 27 73 1353677 69 30‡ 1353734 70 101 1353759 76 108 1353762 32 54 1353785 65 78 1353796 38 67 1353850 56 96 1353974 39 70 1354002 73 70 1354035 39 35 1354046 62 85 1354059 65 92 1394453 70 81 1398198 80 80 1398644 46 62 ‡Indicates that fewer than 2 samples available
(443) TABLE-US-00099 TABLE 97 Reduction of human APP RNA in YAC-APP transgenic mice, n = 2 APP RNA (% control) RTS35571 Compound No. SPINAL CORD CORTEX PBS 100 100 1332192 61 74 1353677 34 34 1353913 50 60 1398005 48 69 1398089 40 61 1398269 38 31 1399033 37 44 1478922 90 92 1478923 69 83 1478924 70 78 1539865 31 38
Example 14: Activity of Modified Oligonucleotides Complementary to Human APP in YAC-APP Transgenic Mice, Multiple Dose
(444) YAC-APP transgenic mice, described herein above, were used to test activity of modified oligonucleotides described above.
(445) Treatment
(446) YAC-APP transgenic mice were divided into groups of 4 mice each. Each mouse received a single ICV bolus of 30 μg, 100 μg, 300 μg or 700 μg of modified oligonucleotide. A group of 4 mice received PBS as a negative control.
(447) RNA Analysis
(448) Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for quantitative real time RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A. ED50 were calculated from log transformed dose and individual animal mRNA levels using the built in GraphPad formula “log(agonist) vs. response—Find ECanything”, with the following constraints: bottom=0, top=100, and F=50.
(449) TABLE-US-00100 TABLE 98 Dose-dependent reduction of human APP RNA in YAC-APP transgenic mice Spinal Cord Cortex Hippocampus Compound Dose APP RNA ED50 APP RNA ED50 APP RNA ED50 ID (μg) (% control) (μg) (% control) (μg) (% control) (μg) 1353884 30 70 70 57 81 65 82 100 38 60 48 300 22‡ 29 33 700 20 11 15 1397772 30 58 81 75 347 67 381 100 56 70 68 300 46 48 53 700 35 42 42 1398227 30 76 96 82 124 92 156 100 46 46 55 300 28 36 33 700 18 21 23 1398456 30 74 73 81 96 43 19 100 37 44 36 300 20 24 23 700 16 13 15 ‡Indicates that fewer than 4 samples available
Example 15: Tolerability of Modified Oligonucleotides Comprising 2′-MOE Nucleosides Complementary to Human APP in Wild-Type Mice, 3 Hour Study
(450) Modified oligonucleotides described above were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Wild-type female C57/Bl6 mice each received a single ICV dose of modified oligonucleotide at 700 μg. Each treatment group consisted of 4 mice. A group of 4 mice received PBS as a negative control for each experiment. Each experiment is identified in separate tables below. At 3 hours post-injection, mice were evaluated according to seven different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a sub-score of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.
(451) TABLE-US-00101 TABLE 99 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1397631 0.00 1397656 0.00 1397706 1.25 1397713 0.25 1397765 1.25 1397786 2.00 1398125 2.50 1398133 1.00 1398371 0.75 1398406 0.00 1398429 0.00 1398539 0.00 1398550 0.00 1398686 0.00 1398760 1.00 1398830 1.00 1398955 1.00 1399026 0.25 1399365 0.00 1399380 0.00
(452) TABLE-US-00102 TABLE 100 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1397883 0.00 1398916 0.25 1399000 0.00 1399033 0.00 1399473 0.00 1399500 0.25 1399511 1.00 1532149 0.00 1532150 0.00 1532152 0.00 1539237 0.00 1539238 0.25 1539239 0.00 1539240 0.00 1539241 0.00 1539242 0.00 1539243 0.50 1539244 0.00 1539245 0.00 1539246 0.00
(453) TABLE-US-00103 TABLE 101 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1397772 0.25 1398227 2.75 1539865 0.75 1539866 0.00 1539867 2.75 1539868 0.00 1539869 0.00 1539870 1.25
Example 16: Tolerability of Modified Oligonucleotides Complementary to Human APP in Rats, 3-Hour Study
(454) Modified oligonucleotides described above were tested in rats to assess the tolerability of the oligonucleotides. Sprague Dawley rats each received a single intrathecal (IT) dose of oligonucleotide at doses indicated in the tables below. Modified oligonucleotides were administered at a dose of 3 mg. Each treatment group consisted of 4 rats. A group of 4 rats received PBS as a negative control. Each experiment is identified in separate tables below. At 3 hours post-injection, movement in 7 different parts of the body were evaluated for each rat. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed (the functional observational battery score or FOB). After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and all other evaluated body parts were moving 3 hours after the 3 mg IT dose, it would receive a summed score of 0. If another rat was not moving its tail 3 hours after the 3 mg IT dose but all other evaluated body parts were moving, it would receive a score of 1. Results aye presented as the average score for each treatment group.
(455) TABLE-US-00104 TABLE 102 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1353686 3 0.00 1353884 3 0.00 1398227 3 0.00 1398456 3 0.00 1399033 3 0.00 1478908 3 0.00 1532149 3 0.00 1532150 3 0.00 1532152 3 0.25 1539237 3 0.00 1539238 3 0.25
(456) TABLE-US-00105 TABLE 103 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1539239 3 0.00 1539240 3 0.00 1539241 3 0.25 1539242 3 0.00 1539243 3 0.50 1539244 3 0.00 1539245 3 0.25 1539246 3 0.00 1539865 3 0.50 1539866 3 1.50 1539867 3 0.00
(457) TABLE-US-00106 TABLE 104 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1539868 3 2.50 1539869 3 2.75 1539870 3 0.25
(458) TABLE-US-00107 TABLE 105 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1353677 3 1.75 1354035 3 0.75 1398005 3 0.50 1398089 3 1.75 1398269 3 0.75
Example 17: Tolerability of Modified Oligonucleotides Complementary to Human APP in Wild-Type Mice, 3 Hour Study
(459) Modified oligonucleotides described above were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Wild-type female C57/Bl6 mice each received a single ICV dose of modified oligonucleotide at 700 μg. Each treatment group consisted of 4 mice. A group of 4 mice received PBS as a negative control for each experiment. Each experiment is identified in separate tables below. At 3 hours post-injection, mice were evaluated according to seven different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a sub-score of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After

all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.

(460) TABLE-US-00108 TABLE 106 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1353677 1.00 1353913 0.00 1354035 0.00 1398005 0.50 1398089 2.00 1398269 1.25 1398456 3.25

Example 18: Activity of Modified Oligonucleotides Complementary to Human APP in Tel Transgenic Mice, Multiple Dose

(461) The aneuploid mouse line (Tel), expressing human APP, previously described in O'Doherty A., et al., *An Aneuploid Mouse Strain Carrying Human Chromosome* 21 *with Down Syndrome Phenotypes*, Science 2005, 309(5743): 2033-2037, was used to test activity of modified oligonucleotides described above.

(462) Treatment

(463) Tc1 transgenic mice were divided into groups of 3 mice each. Each mouse received a single ICV bolus of 30 μg, 100 μg, 300 μg or 700 μg of modified oligonucleotide. A group of 3 mice received PBS as a negative control.

(464) RNA Analysis

(465) Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue, hippocampus, and spinal cord for quantitative real time RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A.

(466) TABLE-US-00109 TABLE 107 Dose-dependent reduction of human APP RNA in Tc1 transgenic mice Spinal Cord Cortex Hippocampus Compound Dose APP RNA ED50 APP RNA ED50 APP RNA ED50 ID (μg) (% control) (μg) (% control) (μg) (% control) (μg) PBS 0 100 100 100 1332212 30 85 162 74 87 68 75 100 59 45 39 300 36 23 31 700 20 16 21 1353931 30 51 659 76 131 98 298 100 54 59 85 300 59 22 22 700 34 31 51 1398456 30 81 168 83 124 86 302 100 50 45 70 300 40 36 47 700 34 22 37

Example 19: Activity of Modified Oligonucleotides Complementary to Human APP in YAC-APP Transgenic Mice, Multiple Dose

(467) YAC-APP transgenic mice, described herein above, were used to test activity of modified oligonucleotides described above.

(468) Treatment

(469) YAC-APP transgenic mice were divided into groups of 3 mice each. Each mouse received a single ICV bolus of 30 μg, 100 μg, 300 μg or 700 μg of modified oligonucleotide. A group of 3 mice received PBS as a negative control.

(470) RNA Analysis

(471) Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue, hippocampus, and spinal cord for quantitative real time RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A. N.D. means that a value was not determined.

(472) TABLE-US-00110 TABLE 108 Dose-dependent reduction of human APP RNA in YAC-APP transgenic mice Spinal Cord Cortex Hippocampus Compound Dose APP RNA ED50 APP RNA ED50 APP RNA ED50 ID (μg) (% control) (μg) (% control) (μg) (% control) (μg) PBS 0 100 100 100 1353686 30 49 28 78 217 79 231 100 35 62 63 300 22 33 45 700 18 16 34 1399033 30 66 105 82 223 84 282 100 49 65 70 300 37 43 46 700 29 29 35 1539865 30 85 165 91 211 107 331 100 54 72 85 300 40 38 42 700 25 21 37 1539868 30 49 246 79 115 84 94 100 46 51 41 300 18 14 20 700 14 12 22 1539869 30 84 148 91 222 104 271 100 55 74 73 300 33 39 44 700 27 22 29

(473) TABLE-US-00111 TABLE 109 Dose-dependent reduction of human APP RNA in YAC-APP transgenic mice Spinal Cord Cortex Hippocampus Compound Dose APP RNA ED50 APP RNA ED50 APP RNA ED50 ID (μg) (% control) (μg) (% control) (μg) (% control) (μg) PBS 0 100 100 100 1354035 30 72 98 101 147 89 219 100 49 44 41 300 40 31 35 700 44 29 53 1398269 30 84 N.D. 105 437 99 323 100 53 90 72 300 51 62 48 700 44 34 37 1539867 30 63 117 95 140 75 91 100 50 49 42 300 30 30 26 700 25 22 25

(474) TABLE-US-00112 TABLE 110 Dose-dependent reduction of human APP RNA in YAC-APP transgenic mice Spinal Cord Cortex Hippocampus Compound Dose APP RNA ED50 APP RNA ED50 APP RNA ED50 ID (μg) (% control) (μg) (% control) (μg) (% control) (μg) PBS 0 100 — 100 — 100 — 1353677 30 78 115 71 88 68 70 100 42 42 35 300 35 32 32 700 29 20 27 1353886 30 52‡ 210 84‡ 296 74‡ 457 100 65 72 70 300 37 44 47 700 28 28 32 1353931 30 53‡ 119 52‡ 150 56‡ 147 100 51 55 52 300 32 41 39 700 24 22 29 ‡Indicates that fewer than 3 animals were available

Example 20: Design of Modified Oligonucleotides Complementary to Human APP Nucleic Acid

(475) Modified oligonucleotides complementary to a human APP nucleic acid were designed, as described in the table below. “Start site” indicates the 5′-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. “Stop site” indicates the 3′-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to SEQ ID NO: 1 (described herein above) and to SEQ ID NO: 2 (described herein above).

(476) The modified oligonucleotides in the table below are 3-10-3 cEt gapmers. The gapmers are 16 nucleosides in length. The sugar motif of the gapmers is (from 5′ to 3′): kkkddddddddddkkk; wherein each “d” represents a 2′-β-D-deoxyribosyl sugar moiety, and each “k” represents a cEt sugar moiety. The internucleoside linkage motif of the gapmers is described in the table below, wherein each “s” represents a phosphorothioate internucleoside linkage, each “o” represents a phosphodiester internucleoside linkage, and each “z” represents a mesyl phosphoramidate internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

(477) TABLE-US-00113 TABLE 111 3-10-3 cEt gapmers with mixed PO, PS, and mesyl phosphoramidate internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID SEQ ID Internucleoside No: 1 No: 1 No: 2 No: 2 SEQ Compound Linkage Motif Start Stop Start Stop ID No. Sequence (5′ to 3′) (5′ to 3′) Site Site Site Site No. 1555471 ATACTTGTCAACGGCA soozzsssssssssos 1153 1168 191552 191567 2557 1555472 ATACTTGTCAACGGCA soozzzsssssssos 1153 1168 191552 191567 2557 1555473 ATACTTGTCAACGGCA soozzzzsssssssos 1153 1168 191552 191567 2557 1555474 ATACTTGTCAACGGCA soozzzzzsssssos 1153 1168 191552 191567 2557 1555475 ATACTTGTCAACGGCA zoozzzzsssssssoz 1153 1168 191552 191567 2557 1555476 ATACTTGTCAACGGCA soosssssssszzsos 1153 1168 191552 191567 2557 1555477 ATACTTGTCAACGGCA soosssssssszzos 1153 1168 191552 191567 2557 1555478 ATACTTGTCAACGGCA soosssssssszzs 1153 1168 191552 191567 2557

(478) The modified oligonucleotides in the table below are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length. The sugar motif of the gapmers is (from 5′ to 3′): eeeeeeddddddddddeeee; wherein each “d” represents a 2′-β-D-deoxyribosyl sugar moiety, and “e” represents a 2′-β-D-MOE sugar moiety. The internucleoside linkage motif of the gapmers is described in the table below, wherein each “s” represents a phosphorothioate internucleoside linkage, each “o” represents a phosphodiester internucleoside linkage, and each “z” represents a mesyl phosphoramidate internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

(479) TABLE-US-00114 TABLE 112 6-10-4 MOE gapmers with mixed PO, PS, and mesyl phosphoramidate internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID SEQ ID Internucleoside No: 1 No: 1 No: 2 No: 2 SEQ Compound Linkage Motif Start Stop Start Stop ID No. Sequence (5′ to 3′) (5′ to 3′) Site Site Site Site No. 1555479 GATCTGAATCCCACTTCCCA soooozzsssssssssoss 181 200 61944 61963 2528 1555480 GATCTGAATCCCACTTCCCA soooozzzsssssssoss 181 200 61944 61963 2528 1555481 GATCTGAATCCCACTTCCCA soooozzzzsssssssoss 181 200 61944 61963 2528 1555482 GATCTGAATCCCACTTCCCA soooozzzzzsssssoss 181 200 61944 61963 2528 1555483 GATCTGAATCCCACTTCCCA zoooozzzzzsssssozz 181 200 61944 61963 2528 1555484 GATCTGAATCCCACTTCCCA soooossssssszzsoss 181 200 61944 61963 2528 1555485 GATCTGAATCCCACTTCCCA soooossssssszzoss 181 200 61944 61963 2528 1555486 GATCTGAATCCCACTTCCCA soooossssssssszzss 181 200 61944 61963 2528

(480) The modified oligonucleotides in the table below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif

for the gapmers is (from 5′ to 3′): eeeeeddddddddddeeeee; wherein each “d” represents a 2′-β-D-deoxyribosyl sugar moiety, and each “e” represents a 2′-MOE sugar moiety. The internucleoside linkage motif of the gapmers is described in the table below, wherein each “s” represents a phosphorothioate internucleoside linkage, each “o” represents a phosphodiester internucleoside linkage, and each “z” represents a mesyl phosphoramidate internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

(481) TABLE-US-00115 TABLE 113 5-10-5 MOE gapmers with mixed PO, PS, and mesyl phosphoramidate internucleoside linkages complementary to human APP SEQ ID SEQ ID SEQ ID Internucleoside No: 1 No: 1 No: 2 No: 2 SEQ Compound Linkage Motif Start Stop Start Stop ID No. Sequence (5′ to 3′) (5′ to 3′) Site Site Site Site No. 1555487 GGCATCACTTACAAACTCAC sooszzsssssssssooss 393 412 120656 120675 3033 1555488 GGCATCACTTACAAACTCAC soooszzzsssssssooss 393 412 120656 120675 3033 1555489 GGCATCACTTACAAACTCAC soooszzzzsssssooss 393 412 120656 120675 3033 1555490 GGCATCACTTACAAACTCAC soooszzzzzsssssooss 393 412 120656 120675 3033 1555491 GGCATCACTTACAAACTCAC zoooszzzzsssssoozz 393 412 120656 120675 3033 1555492 GGCATCACTTACAAACTCAC sooosssssssszzsooss 393 412 120656 120675 3033 1555493 GGCATCACTTACAAACTCAC sooosssssssszzooss 393 412 120656 120675 3033 1555494 GGCATCACTTACAAACTCAC sooosssssssszzoss 393 412 120656 120675 3033

Example 21: Tolerability of Modified Oligonucleotides Comprising cEt Nucleosides Complementary to Human APP in Wild-Type Mice, 3 Hour Study

(482) Modified oligonucleotides described above were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Wild-type female C57/Bl6 mice each received a single ICV dose of modified oligonucleotide at 540 μg. Each treatment group consisted of 4 mice. A group of 4 mice received PBS as a negative control for each experiment. Each experiment is identified in separate tables below. At 3 hours post-injection, mice were evaluated according to seven different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a sub-score of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.

(483) TABLE-US-00116 TABLE 114 Tolerability scores in mice Compound No. 3 hr. FOB PBS 0.00 1333926 4.50 1555471 1.00 1555472 1.50 1555473 2.00 1555474 2.00 1555475 2.00 1555476 1.50 1555477 2.75 1555478 2.00

Example 22: Tolerability of Modified Oligonucleotides Comprising 2′-MOE Nucleosides Complementary to Human APP in Wild-Type Mice, 3 Hour Study

(484) Modified oligonucleotides described above were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Wild-type female C57/Bl6 mice each received a single ICV dose of modified oligonucleotide at 700 μg. Each treatment group consisted of 3-4 mice (the n for each study is indicated in the tables below). A group of 3-4 mice received PBS as a negative control for each experiment. Each experiment is identified in separate tables below. At 3 hours post-injection, mice were evaluated according to seven different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a sub-score of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.

(485) TABLE-US-00117 TABLE 115 Tolerability scores in mice, n = 3 Compound No. 3 hr. FOB PBS 0.00 1478904 0.00 1478919 0.00 1555479 0.00 1555480 0.00 1555481 0.00 1555482 0.00 1555483 0.00 1555484 0.00 1555485 0.00 1555486 0.00 1555487 0.00 1555488 0.00 1555489 0.00 1555490 0.00 1555491 0.00 1555492 0.67 1555493 0.00 1555494 0.33

Example 23: Tolerability of Modified Oligonucleotides Complementary to Human APP in Rats, 3 Hour Study

(486) Modified oligonucleotides described above were tested in rats to assess the tolerability of the oligonucleotides. Sprague Dawley rats each received a single intrathecal (IT) dose of oligonucleotide at doses indicated in the tables below. Compounds comprising MOE nucleosides were administered at a dose of 3 mg and compounds comprising cEt nucleosides were administered at a dose of 2.4 mg. Each treatment group consisted of 3-4 rats (the n for each study is indicated in the tables below). A group of 3-4 rats received PBS as a negative control. Each experiment is identified in separate tables below. At 3 hours post-injection, movement in 7 different parts of the body were evaluated for each rat. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed (the functional observational battery score or FOB). After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and all other evaluated body parts were moving 3 hours after the IT dose, it would receive a summed score of 0. If another rat was not moving its tail 3 hours after the IT dose but all other evaluated body parts were moving, it would receive a score of 1. Results are presented as the average score for each treatment group.

(487) TABLE-US-00118 TABLE 116 Tolerability scores in rats, n = 4 Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1333926 2.4 3.00‡ 1555471 2.4 1.00 1555472 2.4 1.00 1555473 2.4 1.25 1555474 2.4 1.00‡ 1555475 2.4 1.25 1555476 2.4 0.33‡ 1555477 2.4 1.00‡ 1555478 2.4 1.50 ‡Indicates fewer than 4 samples available

(488) TABLE-US-00119 TABLE 117 Tolerability scores in rats, n = 3 Compound No. Dose (mg) 3 hr. FOB PBS 0 0.00 1478904 3 0.00 1478919 3 0.67 1555479 3 0.00 1555480 3 2.00 1555481 3 1.00 1555482 3 0.33 1555483 3 0.00 1555484 3 0.00 1555485 3 0.67 1555486 3 2.33 1555487 3 0.67 1555488 3 0.00 1555489 3 0.67 1555490 3 0.00 1555491 3 0.00 1555492 3 0.00 1555493 3 0.00 1555494 3 0.33

Example 24: Activity of Modified Oligonucleotides Complementary to Human APP in YAC-APP Transgenic Mice, Single Dose

(489) YAC-APP transgenic mice, described herein above, were used to test activity of modified oligonucleotides described above.

(490) Treatment

(491) YAC-APP transgenic mice were divided into groups of 2-3 mice each (the n for each study is indicated in the tables below). Each mouse received a single ICV bolus of 300 μg of modified oligonucleotide. A group of 3-4 mice received PBS as a negative control.

(492) RNA Analysis

(493) Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for quantitative real time RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A (% control). The values marked by the symbol “f” indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set HS.PT.56a.38768352 (Integrated DNA Technologies, Inc.) was used to further assess the activity of the modified oligonucleotides.

(494) TABLE-US-00120 TABLE 118 Reduction of human APP RNA in YAC-APP transgenic mice, n = 3 APP RNA (% control) APP RNA (% control) RTS35571 HS.PT.56a.38768352 SPINAL SPINAL Compound No. CORD CORTEX CORD CORTEX PBS 100 100 100 100 1333926 31 42 30 38 1555471 26 40 25 36 1555472 31 37 31 33 1555473 26‡ 43‡ 25‡ 37‡ 1555474 32 39 31 35 1555475 31 50 30 45 1555476 33 44 32 40 1555477 27 32 28 28 1555478 23 36 24 31 ‡Indicates fewer than 3 samples available

(495) TABLE-US-00121 TABLE 119 Reduction of human APP RNA in YAC-APP transgenic mice, n = 2 APP RNA (% control) APP RNA (% control) RTS35571 HS.PT.56a.38768352 SPINAL SPINAL Compound No. CORD CORTEX CORD CORTEX PBS 100 100 100 100

1478904 44 46 45 47 1478919 26† 44† 34 56 1555479 52 71 51 72 1555480 61 73 56 71 1555481 64 95 60 92 1555482 71 82 64 82 1555483 80 85 76 81 1555484 50 63 53 66 1555485 45 64 43 64 1555486 51‡ 51‡ 49‡ 49‡ 1555487 34‡† 38‡† 38‡ 48‡ 1555488 34† 39† 37 46 1555489 39† 63† 45 75 1555490 41‡† 77‡† 43‡ 86‡ 1555491 50† 54† 51 61 1555492 43† 53† 50 65 1555493 34† 40† 43 51 1555494 27† 40† 37 51 ‡Indicates fewer than 2 samples available

Example 25: Design of RNAi Compounds with Antisense RNAi Oligonucleotides Complementary to a Human APP Nucleic Acid

(496) RNAi compounds comprising antisense RNAi oligonucleotides complementary to a human APP nucleic acid and sense RNAi oligonucleotides complementary to the antisense RNAi oligonucleotides were designed as follows.

(497) The RNAi compounds in the tables below consist of an antisense RNAi oligonucleotide and a sense RNAi oligonucleotide. Each antisense RNAi oligonucleotide is 23 nucleosides in length; has a sugar motif (from 5′ to 3′) of: efyyyyyyyyyyyfyfyyyyyyy, wherein each “e” represents a 2′-MOE sugar, each “y” represents a 2′-O-methylribosyl sugar moiety, and each “f” represents a 2′-fluororibosyl sugar moiety; and has an internucleoside linkage motif (from 5′ to 3′) of: ssooooooooooooooooooss, wherein each “o” represents a phosphodiester internucleoside linkage, and each “s” represents a phosphorothioate internucleoside linkage. Each antisense RNAi oligonucleotide contains a 5′-vinylphosphonate (“vP”). Each sense RNAi oligonucleotide is 21 nucleosides in length; has a sugar motif (from 5′ to 3′) of: yyyyyyfyfffyyyyyyyyyy, wherein each “y” represents a 2′-O-methylribosyl sugar moiety, and each “f” represents a 2′-fhrororibosyl sugar moiety; and has an internucleoside linkage motif (from 5′ to 3′) of: ssooo[C16muP]ooooooooooooss, wherein each “o” represents a phosphodiester internucleoside linkage, each “s” represents a phosphorothioate internucleoside linkage, and each “[C16muP]” represents a modified phosphoramidate internucleoside linkage, as shown below:

(498) ##STR00035##

(499) Each antisense RNAi oligonucleotide is complementary to the target nucleic acid (APP), and each sense RNAi oligonucleotide is complementary to the first of the 21 nucleosides of the antisense RNAi oligonucleotide (from 5′ to 3′) wherein the last two 3′-nucleosides of the antisense RNAi oligonucleotides are unpaired overhanging nucleosides.

(500) “Start site” indicates the 5′-most nucleoside to which the antisense RNAi oligonucleotide is complementary in the human gene sequence. “Stop site” indicates the 3′-most nucleoside to which the antisense RNAi oligonucleotide is complementary in the human gene sequence. Each modified antisense RNAi oligonucleotide listed in the tables below is complementary to SEQ ID NO: 1 (described herein above). Non-complementary nucleobases are specified in the Antisense Sequence column in  custom character

(501) TABLE-US-00122 TABLE 120 RNAi compounds targeting human APP SEQ ID No: 1 SEQ ID SEQ ID Antisense SEQ NO: 1 NO: 1 SEQ Compound Antisense Sequence ID Antisense Antisense Sense Sense Sequence ID Number oligo ID (5′ to 3′) NO Start Site Stop Site oligo ID (5′ to 3′) NO 1581405 1551732  custom character GAACUUGUAGGUU 3058 2305 2326 1579196 AAAAUCCAACCUA 3064 GGAUUUUCG CAAGUUCA 1581406 1551735 TAAUUUAUUUAUGU 3059 3179 3201 1551736 CUGUAUUACAUAA 3065 AAUACAGUG AUAAAUUA 1581407 1551737  custom character AAGAAACAAACGU 3060 2927 2948 1551741 GAUACACACGUUU 3066 GUGUAUCCU GUUUCUUA 1581408 1551739  custom character GAGACUGAUUCAU 3061 1646 1667 1551740 UGAGCGCAUGAAU 3067 GCGCUCAUA CAGUCUCA 1581409 1551742  custom character UCUGAAAUACUUA 3062 2822 2843 1551743 ACAUUUUUAAGUA 3068 AAAAUGUUU UUUCAGAA 1581410 1551744  custom character GGGCAUCACUUAC 3063 392 413 1551745 UGAGUUUGUAAGU 3069 AAACUCACC GAUGCCCA

Example 26: Activity of RNAi Compounds on Human APP in YAC-APP Transgenic Mice, Single Dose

(502) YAC-APP transgenic mice, described herein above, were used to test activity of double-stranded RNAi compounds described above.

(503) Treatment

(504) YAC-APP transgenic mice were divided into groups of 2 mice each. Each mouse received a single ICV bolus of 150 μg of double-stranded RNAi. Compound No. 1332212, a modified oligonucleotide benchmark described herein above, was administered at a dose of 300 μg. A group of 3 mice received PBS as a negative control.

(505) RNA Analysis

(506) Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for quantitative real time RTPCR analysis to measure amount of APP RNA using human primer probe set RTS35571 (described herein above). Results are presented as percent human APP RNA relative to PBS control, normalized to mouse cyclophilin A (% control). The values marked by the symbol “f” indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. In such cases, human primer probe set HS.PT.56a.38768352 (Integrated DNA Technologies, Inc.) was used to further assess the activity of the modified oligonucleotides.

(507) TABLE-US-00123 TABLE 121 Reduction of human APP RNA in YAC-APP transgenic mice, n = 2 APP RNA (% control) APP RNA (% control) RTS35571 HS.PT.56a.38768352 Dose SPINAL SPINAL Compound No. (μg) CORD CORTEX CORD CORTEX PBS 0 100 100 100 100 1332212 300 40† 36† 50 42 1581405 150 14 27 15 26 1581406 150 17 41 19 41 1581407 150 27 49 27 50 1581408 150 43 64 41 63 1581409 150 49 41 49 41 1581410 150 43 68 46 65

Example 27: Activity of Modified Oligonucleotides on Human APP RNA In Vitro, Single Dose

(508) Modified oligonucleotides complementary to human APP nucleic acid (described herein above) were tested for their single dose effects on human APP RNA in vitro. Comparator Compound No. 1369632, described herein above and in WO/2005/042777 was also tested.

(509) Cultured SH-SY5Y cells at a density of 20,000 cells per well were treated with modified oligonucleotide at a concentration of 4000 nM using electroporation. After a treatment period of approximately 24 hours, total RNA was isolated from the cells and human APP RNA levels were measured by quantitative real-time RTPCR. Human APP RNA levels were measured by probe set RTS35572 (described herein above). Human APP RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of human APP RNA is presented in the tables below as percent APP RNA relative to the amount in untreated control cells (% UTC).

(510) TABLE-US-00124 TABLE 122 Reduction of human APP RNA in SH-SY5Y cells Compound Number APP (% UTC) 1398227 19 1398456 16 1369632 85

Example 28: Tolerability of Modified Oligonucleotides Complementary to Human APP in Wild-Type Mice, 3 Hour Study

(511) Modified oligonucleotides (described herein above) were tested in wild-type female C57/Bl6 mice to assess the tolerability of the oligonucleotides. Comparator Compound Nos. 156352, 1369361, and 1369362 (described herein above) were also tested. Wild-type female C57/Bl6 mice each received a single ICV dose of modified oligonucleotide at 700 μg. Each treatment group consisted of 2-4 mice (the n for each study is indicated in the tables below). A group of 3-4 mice received PBS as a negative control for each experiment. Each experiment is identified in separate tables below. At 3 hours post-injection, mice were evaluated according to seven different criteria. The criteria are (1) the mouse was bright, alert, and responsive; (2) the mouse was standing or hunched without stimuli; (3) the mouse showed any movement without stimuli; (4) the mouse demonstrated forward movement after it was lifted; (5) the mouse demonstrated any movement after it was lifted; (6) the mouse responded to tail pinching; (7) regular breathing. For each of the 7 criteria, a mouse was given a subscore of 0 if it met the criteria and 1 if it did not (the functional observational battery score or FOB). After all 7 criteria were evaluated, the scores were summed for each mouse and averaged within each treatment group. The results are presented in the tables below.

(512) Also tested in this assay are Compound Nos. 828428 and 828565, which are described in WO 2020/160163. Compound No. 828428 has a nucleobase sequence (from 5′ to 3′): CTTCCTTGGTATCAATGC (SEQ ID NO: 3072). Compound No. 828565 has a nucleobase sequence (from 5′ to 3′): GATACTTGTCAACGGCAT (SEQ ID NO: 3073). The sugar motif for both Compound No. 828428 and Compound No. 828565 is (from 5′ to 3′): eeeeeddddddddkkeee; wherein each “d” represents a 2′-β-D-deoxyribosyl sugar moiety, each “k” represents a cEt sugar moiety and each “e” represents a 2′-MOE sugar moiety. The internucleoside linkage motif for both Compound No. 828428 and Compound No. 828565 is (from 5′ to 3′):

soooossssssssooss; wherein each “s” represents a phosphorothioate internucleoside linkage, and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue in both Compound No. 828428 and Compound No. 828565 is a 5-methyl cytosine.
(513) TABLE-US-00125 TABLE 123 Tolerability scores in mice; n = 3 Compound No. 3 hr. FOB PBS 0.00 156352 6.00
(514) TABLE-US-00126 TABLE 124 Tolerability scores in mice; n = 2 Compound No. 3 hr. FOB PBS 0.00 1369631 6.00 1369632 2.50
(515) TABLE-US-00127 TABLE 125 Tolerability scores in mice; n = 4 Compound No. 3 hr. FOB PBS 0.00 828428 5.75 828565 5.25
Example 29: Tolerability of RNAi Compounds and Modified Oligonucleotides that Target Human APP in Rats, 3-Hour Study
(516) RNAi compounds and modified oligonucleotides described herein above were tested in rats to assess the tolerability of the oligonucleotides.
(517) Additionally, Compound No. 1581404 was tested as a comparator compound. Compound No. 1581404 consists of the antisense RNAi oligonucleotide Compound No. 1551732 (described herein above) and the sense RNAi oligonucleotide, Compound No. 1551733. The antisense RNAi oligonucleotide is complementary to the target nucleic acid (APP), and the sense RNAi oligonucleotide is complementary to the first of the 21 nucleosides of the antisense RNAi oligonucleotide (from 5′ to 3′) wherein the last two 3′-nucleosides of the antisense RNAi oligonucleotide are not paired with the sense RNAi oligonucleotide (are overhanging nucleosides).
(518) The sense RNAi oligonucleotide is described in the table below. The sense RNAi oligonucleotide is 21 nucleosides in length. In the table below, a subscript “y” represents a 2′-O-methylribosyl sugar, a subscript “f” represents a 2′-fluororibosyl sugar, a subscript “o” represents a phosphodiester internucleoside linkage, and a subscript “s” represents a phosphorothioate internucleoside linkage. A subscript “[16C2r]” represents a 2′-O-hexadecyl modified nucleoside as shown below:
(519) ##STR00036##
wherein Bx is a heterocyclic base moiety
(520) TABLE-US-00128 TABLE 126 Design of sense strand modified oligonucleotides targeted to human APP, SEQ ID NO: 2 Sense Strand Compound SEQ ID No. Chemistry Notation (5′ to 3′) NO. 1551733
A.sub.ysA.sub.ysA.sub.yoA.sub.yoU.sub.yoC.sub.
[16C2r]oC.sub.foA.sub.yoA.sub.foC.sub.foC.sub.foU.sub.yoA.sub.yoC.sub.yoA.sub.yoA.sub.yoG.sub.yoU.sub.yoU.sub.ysC.sub.ysA.sub.y 3064
(521) Sprague Dawley rats each received a single intrathecal (IT) dose of 1.5 mg of RNAi compound. Each treatment group consisted of 3 rats. A group of 3 rats received PBS as a negative control. At 3 hours post-injection, movement in 7 different parts of the body were evaluated for each rat. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed (the functional observational battery score or FOB). After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and all other evaluated body parts were moving 3 hours after the IT dose, it would receive a summed score of 0. If another rat was not moving its tail 3 hours after the IT dose but all other evaluated body parts were moving, it would receive a score of 1. Results are presented as the average score for each treatment group.
(522) TABLE-US-00129 TABLE 127 Tolerability scores in rats Compound No. 3 hr. FOB PBS 0.00 1581404 0.67 1581405 0.00 1581406 1.00 1581407 0.00 1581408 0.33 1581409 0.00 1581410 0.00
Example 30: Tolerability of RNAi Compounds and Modified Oligonucleotides Complementary to Human APP in Rats, Long-Term Assessment
(523) Selected modified oligonucleotide and RNAi compounds described above were tested in Sprague Dawley rats to assess long-term tolerability. Sprague Dawley rats each received a single intrathecal (IT) delivered dose of 1.5 mg RNAi compound or PBS. Each treatment group consisted of 3 rats. A group of 3 rats received PBS as a negative control. Beginning 2 weeks post-treatment, the animals were assessed periodically, and a functional observational battery score was calculated for each animal as follows: Each rat was evaluated for movement in 7 different parts of the body. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed (the functional observational battery score or FOB). After each of the 7 body parts were evaluated, the sub-scores were summed for each rat. For example, if a rat's tail, head, and all other evaluated body parts were moving, it would receive a summed score of 0. If another rat was not moving its tail, but all other evaluated body parts were moving, it would receive a score of 1. Results are presented as greatest FOB score for each animal during an assessment period greater than four weeks.
(524) TABLE-US-00130 TABLE 128 Long-term tolerability in rats at 1.5 mg dose Compound Number FOB Individual rats PBS 0, 0, 0 1581404 0, 3, 0 1581405 1, 0, 0 1581406 0, 0, 0 1581407 0, 0, 0 1581408 0, 0, 0 1581409 0, 0, 0 1581410 2, 0, 2
Example 31: Tolerability of Modified Oligonucleotides Complementary to Human APP in Rats, 3-Hour Study
(525) Modified oligonucleotides described above were tested in rats to assess the tolerability of the oligonucleotides. Sprague Dawley rats each received a single intrathecal (IT) dose of 3 mg of modified oligonucleotide. Modified oligonucleotides were administered at a dose of 3 mg. Each treatment group consisted of 3-4 rats. A group of 4 rats received PBS as a negative control. Each experiment is identified in separate tables below. At 3 hours post-injection, movement in 7 different parts of the body were evaluated for each rat. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed (the functional observational battery score or FOB). After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and all other evaluated body parts were moving 3 hours after the 3 mg IT dose, it would receive a summed score of 0. If another rat was not moving its tail 3 hours after the 3 mg IT dose but all other evaluated body parts were moving, it would receive a score of 1. Results are presented as the average score for each treatment group.
(526) TABLE-US-00131 TABLE 129 Tolerability scores in rats Compound No. Dose (mg) 3 hr. FOB PBS 0 0 1353686 3 0.00 1353884 3 0.00 1353931 3 1.33 1354035 3 0.50 1398227 3 0.25 1398456 3 2.50

Claims

1. A modified oligonucleotide according to the following chemical structure: ##STR00037## ##STR00038## ##STR00039## or a pharmaceutically acceptable salt thereof.
2. The modified oligonucleotide of claim 1, which is the sodium salt or the potassium salt.
3. A modified oligonucleotide according to the following chemical structure: ##STR00040##
4. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:
G.sub.esT.sub.eoT.sub.eoT.sub.eoA.sub.es.sup.mC.sub.ds.sup.mC.sub.dsT.sub.dsT.sub.dsT.sub.dsA.sub.dsA.sub.ds.sup.mC.sub.dsA.sub.dsT.sub.dsT.sub.eo.s
(SEQ ID NO: 452), wherein: A=an adenine nucleobase, .sup.mC=a 5-methylcytosine nucleobase, G=a guanine nucleobase, T=a thymine nucleobase, e=a 2′-O(CH.sub.2).sub.2OCH.sub.3 ribosyl sugar moiety, d=a 2′-β-D deoxyribosyl sugar moiety, s=a phosphorothioate internucleoside linkage, and o=a phosphodiester internucleoside linkage.
5. A population of modified oligonucleotides of claim 1, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
6. A pharmaceutical composition comprising a modified oligonucleotide of claim 1 and a pharmaceutically acceptable diluent.
7. The pharmaceutical composition of claim 6, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).

8. The pharmaceutical composition of claim 7, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.
9. The pharmaceutical composition of claim 7, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.
10. A pharmaceutical composition comprising the modified oligonucleotide of claim 2 and a pharmaceutically acceptable diluent.
11. The pharmaceutical composition of claim 10, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).
12. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.
13. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.
14. A pharmaceutical composition comprising the modified oligonucleotide of claim 3 and a pharmaceutically acceptable diluent.
15. The pharmaceutical composition of claim 14, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).
16. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.
17. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.
18. A pharmaceutical composition comprising the oligomeric compound of claim 4 and a pharmaceutically acceptable diluent.
19. The pharmaceutical composition of claim 18, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).
20. The pharmaceutical composition of claim 19, wherein the pharmaceutical composition consists essentially of the oligomeric compound and artificial cerebrospinal fluid.
21. The pharmaceutical composition of claim 19, wherein the pharmaceutical composition consists essentially of the oligomeric compound and PBS.
22. A population of modified oligonucleotides of claim 2, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
23. A population of modified oligonucleotides of claim 3, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
24. A population of oligomeric compounds of claim 4, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.
25. A pharmaceutical composition comprising the population of modified oligonucleotides of claim 5 and a pharmaceutically acceptable diluent.
26. A pharmaceutical composition comprising the population of modified oligonucleotides of claim 22 and a pharmaceutically acceptable diluent.
27. A pharmaceutical composition comprising the population of modified oligonucleotides of claim 23 and a pharmaceutically acceptable diluent.
28. A pharmaceutical composition comprising the population of oligomeric compounds of claim 24 and a pharmaceutically acceptable diluent.
29. The pharmaceutical composition of claim 25, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).
30. The pharmaceutical composition of claim 26, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).
31. The pharmaceutical composition of claim 27, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).
32. The pharmaceutical composition of claim 28, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS).