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Cancer vaccine

Abstract

Provided herein are systems, compositions, and methods for generating immunogenic peptides or epitopes from tumor associated antigens (e.g., in vivo or ex vivo). Polynucleotides (e.g., genes) encoding the tumor associated antigens may be edited at selected target sites by nucleobase editors comprising a catalytically-inactive Cas9 and a cytosine deaminase, leading to the expression of heteroclitic or cryptic peptides that are more immunogenic than the native peptide derived from the tumor associated antigens. The heteroclitic or cryptic peptide elicit strong tumor-specific immune response (e.g., T-cell response or B-cell response), which inhibits tumor growth and metastasis.

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2012/0270273	12/2011	Zhang et al.	N/A	N/A
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Background/Summary

RELATED APPLICATIONS (1) The present application is a national stage filing under 35 U.S.C. § 371 of international PCT application, PCT/US2018/021880, filed Mar. 9, 2018, which claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S. Ser. No. 62/469,219, filed Mar. 9, 2017, the entire contents of each of which are incorporated herein by reference.

REFERENCE TO A SEQUENCE LISTING SUBMITTED AS A TEXT FILE VIA EFS-WEB

(1) The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Oct. 27, 2023, is named H082470241US01-SUBSEQ-AZW and is 3,827,234 bytes in size.

BACKGROUND OF THE INVENTION

(2) Tumor-specific immune responses may be elicited by peptides generated from proteins expressed in tumor cells or on tumor cell surface (e.g., tumor-specific antigens). Native peptides derived from tumor-specific antigens are tolerated as "self" by the immune system and do not elicit strong immune response against the tumor-specific antigen. Altered versions of the native peptides derived from tumor-specific antigens (e.g., heteroclitic peptides or cryptic peptides) may be engineered to elicit potent immune reactions through the MHC-I and MHC-II antigen presentation pathways, which also produce cross-reactive responses towards the native tumor-specific antigen sequences.

(3) It is well established that the immune system can function to kill tumor cells, including both primary and metastatic cancer cells. Indeed, evidence that the immune system recognizes the presence of neoplastic cancerous cells is supported by the existence of infiltrating lymphocytes in tumor tissues (Haskill et al., 1978, *Contemp. Top. Immunobiol.* 8: 107-170; Vose and Moore, 1985, *Semin. Hematol.* 22: 27-40). Yet, for reasons that are not completely clear, despite the presence of immune cells, tumors often prevail and not only survive but metastasize to distant sites with unrestricted growth. Recent advances in the understanding of T cell activation and recognition of target cells have begun to permit some progress in development of T cell mediated cancer immunotherapy (Schwartz, 1992, *Cell* 71: 1065-1068; Pardoll, 1992, *Curr. Opin. Immunol.* 4: 619-623).

SUMMARY OF THE INVENTION

(4) Described herein are systems, methods, compositions, and kits for producing immunogenic peptides derived from tumor specific antigens (e.g., heteroclitic epitopes or cryptic epitopes) that may be used as cancer vaccines in vivo or ex vivo. Targeted mutations are introduced into tumor-specific antigens using gene editing agents, e.g., a nucleobase editor comprising a programmable DNA binding domain (e.g., catalytically-inactive Cas9 or a Cas9 nickase) fused to a cytosine deaminase, to generate altered versions of peptides arising from the tumor-specific antigens (heteroclitic epitopes) or peptides arising from normally untranslated regions of the tumor-specific antigen genes (cryptic peptides). The heteroclitic peptides or cryptic peptides may be generated in vivo in a subject (e.g., a subject who has cancer) and presented to the adaptive immune system via the MHC class I or MHC class II pathway, which in turn induces a strong adaptive immune response, e.g., T cell response and B cell response. Such an adaptive immune response is antigen specific and is effective in reducing tumor growth and preventing metastasis.

(5) Some aspects of the present disclosure provide methods of eliciting a tumor-specific immune response in a subject in need thereof, the methods including administering to the subject a therapeutically effective amount of a composition comprising: (i) a fusion protein comprising (a) a guide nucleotide sequence-programmable DNA-binding protein domain; and (b) a cytosine deaminase domain; and (ii) a guide nucleotide sequence, wherein the guide nucleotide sequence of (ii) targets the fusion protein of (i) to a polynucleotide encoding a tumor-specific antigen in a tumor cell, wherein the fusion protein changes a target cytosine (C) base to a thymine (T) base via deamination.

(6) In some embodiments, the polynucleotide comprises a coding strand and a complementary strand. In some embodiments, the polynucleotide comprises a coding region and a non-coding region. In some embodiments, the polynucleotide encoding the tumor-specific antigen is located in the genome of the tumor cell. In some embodiments, deamination of the target C base results in a C-G base-pair to thymine-adenine (T-A) base-pair change.

(7) In some embodiments, the guide nucleotide sequence-programmable DNA binding protein domain is selected from the group consisting of: nuclease inactive Cas9 (dCas9) domains, nuclease inactive Cpf1 domains, nuclease inactive Argonaute domains, and variants thereof.

(8) In some embodiments, the guide nucleotide sequence-programmable DNA-binding protein domain is a nuclease inactive Cas9 (dCas9) domain. In some embodiments, the amino acid sequence of the dCas9 domain comprises mutations corresponding to a D10A and/or H840A mutation in SEQ ID NO: 1. In some embodiments, the amino acid sequence of the dCas9 domain comprises a mutation corresponding to a D10A mutation in SEQ ID NO: 1, and wherein the dCas9 domain comprises a histidine at the position corresponding to amino acid 840 of SEQ ID NO: 1.

(9) In some embodiments, the guide nucleotide sequence-programmable DNA-binding protein domain comprises a nuclease inactive Cpf1 (dCpf1) domain. In some embodiments, the dCpf1 domain is from a species of *Acidaminococcus* or Lachnospiraceae. In some embodiments, the guide nucleotide sequence-programmable DNA-binding protein domain comprises a nuclease inactive Argonaute (dAgo) domain. In some embodiments, the (dAgo) domain is from *Natronobacterium gregoryi* (dNgAgo).

(10) In some embodiments, the cytosine deaminase domain comprises an apolipoprotein B mRNA-editing complex (APOBEC) family deaminase. In some embodiments, the cytosine deaminase is selected from the group consisting of APOBEC1, APOBEC2, APOBEC3A, APOBEC3B, APOBEC3C, APOBEC3D, APOBEC3F, APOBEC3G deaminase, APOBEC3H deaminase, APOBEC4 deaminase, and activation-induced deaminase (AID). In some embodiments, the cytosine deaminase comprises an amino acid sequence of any of SEQ ID NOs: 27-292, 303, and 1072-1083.

(11) In some embodiments, the fusion protein of (a) further comprises a uracil glycosylase inhibitor (UGI) domain. In some embodiments, the cytosine deaminase domain is fused to the N-terminus of the guide nucleotide sequence-programmable DNA-binding protein domain. In some embodiments, the UGI domain is fused to the C-terminus of the

guide nucleotide sequence-programmable DNA-binding protein domain. In some embodiments, the cytosine deaminase and the guide nucleotide sequence-programmable DNA-binding protein domain is fused via an optional linker. In some embodiments, the UGI domain is fused to the guide nucleotide sequence-programmable DNA-binding protein domain via an optional linker.

(12) In some embodiments, the fusion protein comprises the structure NH.sub.2-[cytosine deaminase domain]-[optional linker sequence]-[guide nucleotide sequence-programmable DNA-binding protein domain]-[optional linker sequence]-[UGI domain]-COOH.

(13) In some embodiments, the optional linker comprises (GGGS).sub.n, (SEQ ID NO: 337) (GGGGS).sub.n (SEQ ID NO: 308), (G).sub.n (SEQ ID NO: 783), (EAAAK).sub.n (SEQ ID NO: 309), (GGS).sub.n(SEQ ID NO: 784), SGSETPGTSESATPES (SEQ ID NO: 310), or (XP).sub.n (SEQ ID NO: 785) motif, or a combination of any of these, wherein n is independently an integer between 1 and 30 and wherein X is any amino acid. In some embodiments, the linker comprises the amino acid sequence of SGSETPGTSESATPES (SEQ ID NO: 310). In some embodiments, the linker is (GGS).sub.n(SEQ ID NO: 784), and wherein n is 1, 3, or 7.

(14) In some embodiments, the fusion protein comprises the amino acid sequence of any one of SEQ ID NOs: 293-302, 1071, and 1084.

(15) In some embodiments, the tumor specific antigen is selected from the group consisting of: CEA; gp100; Pmel17; mammaglobin-A; Melan-A; MART-1; NY-BR-1; ERBB2; OA1; PAP; PSA; RAB38; NY-MEL-1; TRP-1; gp75; TRP-2; tyrosinase; WTi; CD33; BAGE-1; D393-CD20n; Cyclin-A1; GAGE-1,2,8; GAGE-3,4,5,6,7; GnTVf; HERV-K-MEL; KK-LC-1; KM-HN-1; LAGE-1; LY6K; MAGE-A1; MAGE-A2; MAGE-A3; MAGE-A4; MAGE-A6; MAGE-A9; MAGE-A10; MAGE-A12m; MAGE-C1; MAGE-C2; mucink; NA88-A; NY-ESO-1; LAGE-2; SAGE; Sp17; SSX-2; SSX-4; survivin; BIRC5; TAG-1; TAG-2; TRAG-3; TRP2-INT2g; XAGE-1b; GAGED2a; BCR-ABL (b3a2); adipophilin; AIM-2; ALDH1A1; BCLX(L); BING-4; CALCA; CD45; CD274; CPSF; cyclin D1; DKK1; ENAH (hMena); EpCAM; EphA3; EZH2; FGF5; glypican-3; G250; MN; CAIX; HER-2; neu; HLA-DOB; Hepsin; IDO1; IGF2B3; IL13Ralpha2; Intestinal carboxyl esterase; alpha-foetoprotein; Kallikrein 4; KIF20A; Lengsin; M-CSF; MCSP; mdm-2; Meloe; Midkine; MMP-2; MMP-7; MUC1; MUC5AC; p53; PAX5; PBF; PRAME; PSMA; RAGE-1; RGS5; RhoC; RNF43; RU2AS; secernin 1; SOX10; STEAP1; Telomerase; TPBG; and VEGF.

(16) In some embodiments, the target C base is in a target codon located in a coding region of the polynucleotide encoding the tumor-specific antigen. In some embodiments, the target codon is any one of the target codons in Tables 4 and 8.

(17) In some embodiments, the target codon is converted to a modified codon selected from any one of the modified codons in Table 4. In some embodiments, the target C base is located in a non-coding region of the polynucleotide encoding the tumor specific antigen. In some embodiments, the target C base is located in an intron in the polynucleotide encoding the tumor specific antigen.

(18) In some embodiments, the methods described herein further comprising generating an immunogenic peptide from the tumor-specific antigen. In some embodiments, the immunogenic peptide is a heteroclitic epitope. In some embodiments, the heteroclitic epitope is at least 2 fold, at least 5 fold, at least 10 fold, at least 20 fold, at least 30 fold, at least 40 fold, at least 50 fold, at least 60 fold, at least 70 fold, at least 80 fold, at least 90 fold, at least 100 fold, or more immunogenic than a native epitope from the tumor specific antigen. In some embodiments, the immunogenic peptide is a cryptic epitope. In some embodiments, the cryptic epitope is at least 2 fold, at least 5 fold, at least 10 fold, at least 20 fold, at least 30 fold, at least 40 fold, at least 50 fold, at least 60 fold, at least 70 fold, at least 80 fold, at least 90 fold, at least 100 fold, or more immunogenic than a native epitope from the tumor specific antigen.

(19) In some embodiments, the immunogenic peptide is displayed on the surface of the tumor cell via the MHC class I antigen presentation pathway. In some embodiments, the immunogenic peptide is displayed on the surface of an antigen presenting cell (APC) via the MHC class II antigen presentation pathway.

(20) In some embodiments, the method is carried out in vivo. In some embodiments, the method is carried out ex vivo.

(21) In some embodiments, the APC is selected from the group consisting of: tumor cells, dendritic cells, mononuclear phagocytes, thymic epithelial cells, and B cells.

(22) In some embodiments, the immunogenic peptide elicits adaptive immune response against the tumor-specific antigen. In some embodiments, the adaptive immune response comprises promoting the maturation of dendritic cells, activation of CD4+ T lymphocytes, activation of CD8+ T lymphocytes, activation and maturation of B lymphocytes, and/or production of tumor antigen-specific antibodies. In some embodiments, the adaptive immune response kills tumor cells, reduces tumor size, and/or prevents metastasis.

(23) In some embodiments, the guide nucleotide sequence is an RNA. In some embodiments, the RNA is chemically modified.

(24) In some embodiments, the guide nucleotide sequence is a single strand DNA (ssDNA).

(25) In some embodiments, the tumor specific antigen is gp100. In some embodiments, the gp100 is from melanoma. In some embodiments, the deamination of the target C base in codon T210 of gp100 results in a T210I mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of IIDQVPFSV (SEQ ID NO: 786) is generated, and wherein the I at position 2 corresponds to the T210I mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 724 and 870-888.

(26) In some embodiments, the deamination of the target C base in codon A288 of gp100 results in a A288V mutation. In

some embodiments, a heteroclitic epitope comprising the amino acid sequence of YLEPGPVTV (SEQ ID NO: 818) is generated, and wherein the V at position 7 corresponds to the A288V mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 725 and 889.
(27) In some embodiments, the deamination of the target C base in codon T155 of gp100 results in a T155I mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of KIWGQYWQV (SEQ ID NO: 787) is generated, and wherein the I at position 2 corresponds to the T155I mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 726 and 890-892.
(28) In some embodiments, the tumor specific antigen is melanoma antigen recognized by T cells 1 (MART-1). In some embodiments, the MART-1 antigen is from melanoma. In some embodiments, the deamination of the target C base in codon A27 of MART-1 results in a A27V mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of EVAGIGILTV (SEQ ID NO: 819) is generated, and wherein the V at position 2 corresponds to the A27V mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 727 and 893-896.
(29) In some embodiments, the tumor specific antigen is cancer/testis antigen 1B (NY-ESO-1). In some embodiments, the NY-ESO-1 antigen is from melanoma or breast cancer. In some embodiments, the deamination of the target C base in codon C165 of NY-ESO-1 results in a C165Y mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of SLLMWITQY (SEQ ID NO: 788) is generated, and wherein the C at position 9 corresponds to the C165Y mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 728 and 897.
(30) In some embodiments, the tumor specific antigen is Tyrosinase (TYR). In some embodiments, the TYR antigen is from melanoma. In some embodiments, the deamination of the target C base in codon T373 of TYR results in a T373I mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of YMNGIMSQV (SEQ ID NO: 789) is generated, and wherein the I at position 5 corresponds to the T373I mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 729 and 898-901.
(31) In some embodiments, the tumor specific antigen is tyrosinase-related protein 1 (TyRP1). In some embodiments, the TyRP1antigen is from melanoma. In some embodiments, the deamination of the target C base in codon C244 of TyRP1 results in a C244Y mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of DAEKYDICTDEY (SEQ ID NO: 790) is generated, and wherein the Y at position 5 corresponds to the C244Y mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 730 and 902.
(32) In some embodiments, the tumor specific antigen is Survivin. In some embodiments, the Survivin is from melanoma, breast cancer, or leukemia. In some embodiments, the deamination of the target C base in codon T97 of Survivin results in a T97I mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of ELILGEFLKL (SEQ ID NO: 791) is generated, and wherein the I at position 3 corresponds to the T97I mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 731 and 903.
(33) In some embodiments, the tumor specific antigen is telomerase reverse transcriptase (hTERT). In some embodiments, the hTERT is from breast cancer. In some embodiments, the deamination of the target C base in codon M549 of hTERT results in a M549I mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of ILAKFLHWLI (SEQ ID NO: 792) is generated, and wherein the I at position 10 corresponds to the M549I mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 735 and 916-920.
(34) In some embodiments, the tumor specific antigen is human epidermal growth factor receptor 2 (HER2). In some embodiments, the HER2 is from breast cancer. In some embodiments, the deamination of the target C base in codon V658 of HER2 results in a V658M mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of AMVGILLVVV (SEQ ID NO: 793) is generated, and wherein the M at position 2 corresponds to the V658M mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 732 and 904-909.
(35) In some embodiments, the deamination of the target C base in codon T912 of HER2 results in a T912I mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of IIWELMTFGA (SEQ ID NO: 794) is generated, and wherein the V at position 2 corresponds to the T912I mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 733 and 910-912.
(36) In some embodiments, the deamination of the target C base in codon A920 of HER2 results in a A920V mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of ITWELMTFGV (SEQ ID NO: 795) is generated, and wherein the V at position 10 corresponds to the A920V mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 734 and 913-915.
(37) In some embodiments, the tumor specific antigen is CD33. In some embodiments, the CD33 is from leukemia. In some embodiments, the deamination of the target C base in codon A65 of CD33 results in a A65V mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of VIISGDSPV (SEQ ID NO: 796) is generated,

and wherein the V at position 1 corresponds to the A65V mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 740 and 930-932.
(38) In some embodiments, the tumor specific antigen is Synovial Sarcoma X Breakpoint 2 (SSX2). In some embodiments, the deamination of the target C base in codon A42 of SSX2 results in a A42V mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of KVSEKIFYV (SEQ ID NO: 797) is generated, and wherein the V at position 2 corresponds to the A42V mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 737 and 921.
(39) In some embodiments, the tumor specific antigen is Wilm's tumor 1 (WT1) protein. In some embodiments, the WT1 is from leukemia. In some embodiments, the deamination of the target C base in codon C235 of WT1 results in a C235Y mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of YMTWNQMNL (SEQ ID NO: 798) is generated, and wherein the Y at position 1 corresponds to the C235Y mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 738 and 922-925.
(40) In some embodiments, the deamination of the target C base in codon M236 of WT1 results in a M236I mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of CITWNQMNL (SEQ ID NO: 799) is generated, and wherein the I at position 2 corresponds to the M236I mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 739 and 926-929.
(41) In some embodiments, the tumor specific antigen is Epithelial cell adhesion molecule precursor (EpCAM). In some embodiments, the deamination of the target C base in codon T192 of EpCAM results in a T192I mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of ILYENNVII (SEQ ID NO: 800) is generated, and wherein the I at position 9 corresponds to the T192I mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 741 and 933-934.
(42) In some embodiments, the tumor specific antigen is carcinoembryonic antigen-related cell adhesion molecules (CEA-CAM). In some embodiments, the CEA-CAM is from colorectal cancer, lung cancer, or breast cancer. In some embodiments, the deamination of the target C base in codon T314 of CEA-CAM results in a T314I mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of LLTFWNPPI (SEQ ID NO: 801) is generated, and wherein the I at position 9 corresponds to the T314I mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 742 and 935-936.
(43) In some embodiments, the deamination of the target C base in codon T311 of CEA-CAM results in a T3111 mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of RITVTTITV (SEQ ID NO: 802) is generated, and wherein the V at position 2 corresponds to the T3111 mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 743 and 937-940.
(44) In some embodiments, the deamination of the target C base in codon T688 of CEA-CAM results in a T688V mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of AVVGIMIGV (SEQ ID NO: 803) is generated, and wherein the V at position 2 corresponds to the T688V mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 744 and 941-947.
(45) In some embodiments, the deamination of the target C base in codon V695 of CEA-CAM results in a V695M mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of IMIGMLVGV (SEQ ID NO: 804) is generated, and wherein the M at position 5 corresponds to the V695M mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 745 and 948-953.
(46) In some embodiments, the tumor specific antigen is melanoma-associated antigen A3 (MAGEA3). In some embodiments, the deamination of the target C base in codon H118 of MAGEA3 results in a H118Y mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of KVAELVYFL (SEQ ID NO: 805) is generated, and wherein the Y at position 7 corresponds to the H118Y mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 746 and 954.
(47) In some embodiments, the tumor specific antigen is melanoma-associated antigen (MAGE) common antigen A3, A1, A4, A2, or A12. In some embodiments, the deamination of the target C base in codon C181 of MAGE common antigen A3, A1, A4, A2, or A12results in a C181Y mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of YLGLSYDGLL (SEQ ID NO: 806) is generated, and wherein the Y at position 1 corresponds to the C181Y mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 747-750 and 955-983.
(48) In some embodiments, the tumor specific antigen is MUC-1. In some embodiments, the deamination of the target C base in codon T93 of MUC-1 results in a T93I mutation. In some embodiments, a heteroclitic epitope comprising the amino acid sequence of AIWGQDVTSV (SEQ ID NO: 807) is generated, and wherein the I at position 2 corresponds to the T93I mutation. In some embodiments, the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 751 and 984-985.
(49) In some embodiments, the target C base is located in intron 4 of the premelanosome protein (PMEL) gene. In some embodiments, the deamination of the target C base results in a cryptic peptide comprising the amino acid sequence of

VYFFLPDHL (SEQ ID NO: 808). In some embodiments, the guide nucleotide sequence comprises a nucleotide selected from the group consisting of SEQ ID NOs: 752-753 and 986-998.
(50) In some embodiments, the target C base is located on the complementary strand of open reading frame 1 (ORF1) of TYRP1 gene. In some embodiments, the target C base is located in the complementary strain of the first start codon (ATG) of ORF1 of the TYRP1 gene. In some embodiments, the deamination of the target C base results in a cryptic peptide comprising the amino acid sequence of MSLQRQFLR (SEQ ID NO: 809). In some embodiments, the guide nucleotide sequence comprises a nucleotide selected from the group consisting of SEQ ID NOs: 754 and 999-1005.
(51) In some embodiments, the target C base is located on the complementary strand of the last base of intron 2 of the mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl glucosaminyltransferase (MGAT5) gene. In some embodiments, the deamination of the target C base results in a cryptic peptide comprising the amino acid sequence of VLPDVFIRCV (SEQ ID NO: 810). In some embodiments, the cryptic peptide is translated from exon 3 of the MGAT5 gene. In some embodiments, the guide nucleotide sequence comprises a nucleotide selected from the group consisting of SEQ ID NOs: 755 and 1006-1008.
(52) In some embodiments, the target C base is located in open reading frame 1 (ORF1) of cancer/testis antigen 2 (LAGE-1) gene. In some embodiments, the target C base is located in the complementary strand of the first start codon of ORF1 of the LAGE-1 gene. In some embodiments, the deamination of the target C base results in a cryptic peptide comprising the amino acid sequence of selected from the group consisting of: MLMAQEALAFL (SEQ ID NO: 811), LAAQERRVPR (SEQ ID NO: 812), APRGVRMAV (SEQ ID NO: 813), QGAMLAAQERRVPRAAEVPR (SEQ ID NO: 814), and CLSRRPWKRSWSAGSCPGMPHL (SEQ ID NO: 815). In some embodiments, the guide nucleotide sequence comprises a nucleotide selected from the group consisting of SEQ ID NOs: 756 and 1009-1014.
(53) In some embodiments, the target C base is located in intron 2 of tyrosinase-related protein 2 (TRP-2) gene. In some embodiments, the target C base is located on the complementary strand of the first base of intron 2 of the TRP-2 gene. In some embodiments, the deamination of the target C base results in a cryptic peptide comprising the amino acid sequence of EVISCKLIKR (SEQ ID NO: 816). In some embodiments, the guide nucleotide sequence comprises a nucleotide selected from the group consisting of SEQ ID NOs: 757-758 and 1015-1023.
(54) In some embodiments, the target C base is located in intron 2 of baculoviral IAP repeat containing 5 (BIRC5) gene. In some embodiments, the target C base is located on the spliceosome branch site of intron 2 of the BIRC5 gene. In some embodiments, the target C base is located in the complementary strand of the last base of intron 2 of the BIRC5 gene. In some embodiments, the deamination of the target C base results in a cryptic peptide comprising the amino acid sequence of AYACNTSTL (SEQ ID NO: 817). In some embodiments, the guide nucleotide sequence comprises a nucleotide selected from the group consisting of SEQ ID NOs: 759 and 1024-1029.
(55) In some embodiments, the target C base is located in intron 1 acceptor site of BCR/ABL fusion proteins (BCR/ABL-OOF) gene. In some embodiments, the target C base is located in intron 2 acceptor site of BCR/ABL fusion proteins (BCR/ABL-OOF) gene. In some embodiments, the deamination of the target C base results in a cryptic peptide comprising the amino acid sequence of any one of SSKALQRPV (SEQ ID NO: 603), GFKQSSKAL (SEQ ID NO: 604), and ATGFKQSSKALQRPVAS (SEQ ID NO: 605). In some embodiments, the guide nucleotide sequence comprises a nucleotide selected from the group consisting of SEQ ID NOs: 761 and 1032-1045. In some embodiments, the guide nucleotide sequence comprises a nucleotide selected from the group consisting of SEQ ID NOs: 762 and 1046-1056.
(56) In some embodiments, the methods further comprising administering to the subject a therapeutically effective amount of an immune checkpoint inhibitor. In some embodiments, the immune checkpoint inhibitor inhibits binding of CTLA-4, PD-1, PD-L1, TIM3, LAG3, B7-H3, B7-H4, BTLA, GAL9, Chk1, or A2aR to a cognate binding partner. In some embodiments, the immune checkpoint inhibitor is an antibody or a fragment thereof. In some embodiments, the antibody is selected from anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-TIM3 antibodies, anti-LAG3 antibodies, anti-B7-H3 antibodies, anti-B7-H4 antibodies, anti-BTLA antibodies, anti-GAL9 antibodies, anti-Chk1 antibodies, and anti-A2aR antibodies. In some embodiments, the antibody is selected from pembrolizumab, nivolumab, and ipilimumab.
(57) In some embodiments, the immune checkpoint inhibitor is a small molecule.
(58) In some embodiments, the immune checkpoint inhibitor is a recombinant protein.
(59) In some embodiments, the immune checkpoint inhibitor is a nucleic acid aptamer.
(60) In some embodiments, the immune checkpoint inhibition is performed by genome editing of a gene selected from the group consisting of: CTLA-4, PD-1, PD-L1, TIM3, LAG3, B7-H3, B7-H4, BTLA, GAL9, Chk1, or A2aR.
(61) Other aspects of the present disclosure provide methods of treating cancer, the methods including administering to a subject in need thereof a therapeutically effective amount of a composition comprising: (i) a fusion protein comprising (a) a guide nucleotide sequence-programmable DNA-binding protein domain; and (b) a cytosine deaminase domain; and (ii) a guide nucleotide sequence; wherein the fusion protein of (i) and the guide nucleotide sequence of (ii) enters a tumor cell, and wherein the guide nucleotide sequence targets the fusion protein of (i) to a polynucleotide encoding a tumor-specific antigen, wherein the fusion protein changes a target cytosine (C) residue to a (T) residue in the polynucleotide.
(62) In some embodiments, the methods include administering to the subject a therapeutically effective amount of an immune checkpoint inhibitor.
(63) Further provided herein are methods of inducing a tumor-specific immune response in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a composition comprising: (i) a

fusion protein comprising (a) a guide nucleotide sequence-programmable DNA-binding protein domain; and (b) a nuclease domain; and (ii) a guide nucleotide sequence; wherein the fusion protein of (i) and the guide nucleotide sequence of (ii) enters the tumor cell, and wherein the guide nucleotide sequence targets the fusion protein of (i) to a polynucleotide encoding a tumor-specific antigen, wherein the fusion protein introduces an indel in the polynucleotide. In some embodiments, the nuclease is a FokI nuclease.

(64) Further provided herein are methods of inducing a tumor-specific immune response in a subject in need thereof, the methods including administering to the subject a therapeutically effective amount of a composition comprising: (i) a guide nucleotide sequence-programmable nuclease; and (ii) a guide nucleotide sequence; wherein the fusion protein of (i) and the guide nucleotide sequence of (ii) enters the tumor cell, and wherein the guide nucleotide sequence targets the fusion protein of (i) to a polynucleotide encoding a tumor-specific antigen, wherein the guide nucleotide sequence-programmable nuclease introduces an indel in the polynucleotide.

(65) In some embodiments, the guide nucleotide sequence-programmable nuclease comprises a Cas9, a Cpf1, an Argonaute, or a variant thereof. In some embodiments, the indel causes a mutation or frame shift.

(66) Method of inducing a tumor-specific immune response in a subject in need thereof are also provided, the methods including administering to a subject in need thereof a therapeutically effective amount of a composition comprising a fusion protein comprising (a) a programmable DNA-binding protein domain; and (b) a deaminase domain; wherein the fusion protein enters the tumor cell and changes a target base in the polynucleotide via deamination.

(67) In some embodiments, the deaminase domain comprises a cytosine deaminase and the target base is a cytosine (C) base. In some embodiments, the programmable DNA-binding domain comprises a zinc finger nuclease (ZFN). In some embodiments, the programmable DNA-binding domain comprises a transcription activator-like effector (TALE).

(68) In some embodiments, the programmable DNA-binding domain is a guide nucleotide sequence-programmable DNA binding protein domain. In some embodiments, the programmable DNA-binding domain is selected from the group consisting of: nuclease-inactive Cas9 domains, nuclease inactive Cpf1 domains, nuclease inactive Argonaute domains, and variants thereof. In some embodiments, the programmable DNA-binding domain is associated with a guide nucleotide sequence. In some embodiments, the deamination of the target C base results in a C to thymine (T) change. In some embodiments, the deamination of the target C base results in a C-G base pair to thymine-adenine (T-A) change in a translated codon, resulting in the incorporation of a different amino acid in an immunogenic or heteroclitic peptide. In some embodiments, the deamination of the target C base results in a C-G basepair to thymine-adenine (T-A) change in an non-coding intron region of a gene, resulting in alternative splicing and translation of immunogenic or cryptic peptide sequences. In some embodiments, the deamination of the target C base results in a C-G basepair to thymine-adenine (T-A) change in the start (Met) codon of the open reading frame of a gene, resulting in the translation of an alternative open reading frame comprising immunogenic or cryptic peptide sequences.

(69) Other aspects of the present disclosure provide compositions comprising: (i) a fusion protein comprising (a) a guide nucleotide sequence-programmable DNA-binding protein domain; and (b) a cytosine deaminase domain; and (ii) a guide nucleotide sequence targeting the fusion protein of (i) to a polynucleotide encoding a tumor specific antigen.

(70) Yet other aspects of the present disclosure provide compositions comprising a polynucleotide encoding a fusion protein and a guide nucleotide sequence, wherein the fusion protein comprises (a) a guide nucleotide sequence-programmable DNA-binding protein domain; and (b) a cytosine deaminase domain, and wherein the guide nucleotide sequence targets the fusion protein to a polynucleotide encoding a tumor specific antigen.

(71) Yet other aspects of the present disclosure provide cancer vaccines comprising: (i) a fusion protein comprising (a) a guide nucleotide sequence-programmable DNA-binding protein domain; and (b) a cytosine deaminase domain; and (ii) a guide nucleotide sequence targeting the fusion protein of (i) to a polynucleotide encoding a tumor specific antigen.

(72) Further provided herein are cancer vaccine comprising a polynucleotide encoding a fusion protein and a guide nucleotide sequence, wherein the fusion protein comprises (a) a guide nucleotide sequence-programmable DNA-binding protein domain; and (b) a cytosine deaminase domain, and wherein the guide nucleotide sequence targets the fusion protein to a polynucleotide encoding a tumor specific antigen.

(73) Kits comprising the cancer vaccines described herein are also provided.

(74) The details of certain embodiments of the disclosure are set forth in the Detailed Description of Certain Embodiments, as described below. Other features, objects, and advantages of the disclosure will be apparent from the Definitions, Examples, Figures, and Claims.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) The accompanying drawings, which constitute a part of this specification, illustrate several embodiments of the disclosure and together with the description, serve to explain the principles of the disclosure.

(2) FIG. **1** shows strategies to engineer heteroclitic and cryptic epitopes using genome base editing.

(3) FIG. **2**A shows strategies to introduce immunogenic heteroclitic epitopes by editing conservative anchor residues to match the binding preference of the main HLA allele supertypes. The example shows a base-editing reaction that turns an alanine residue at anchor position 9 of a weakly immunogenic peptide epitope into a preferred valine residue for binding HLA-A2.

(4) FIG. **2**B shows anchor-residue binding preference and population coverage of the main HLA allele supertypes (MHC-I pathway). The peptides in FIG. **2**B are as follows: HLA A1, A2, A3, and A24 (SEQ ID NOs: 878-881) and HLA B7, B27, B44, B58, and B62 (SEQ ID NOs: 882-886).
(5) FIG. **3** shows a proposed mechanism for anti-cancer vaccination by heteroclitic/cryptic epitopes introduced by genome base-editing reactions programmed by guide-RNAs. The edited tumor cells produce heteroclitic and cryptic epitopes in cancer-specific genes, which chemotactically attract immature dendritic cells (DCs) (1a), inducing DC maturation (1b). Edited tumor cells produce apoptotic bodies (2a) that are taken up by DCs (2b), contributing to maturation of DCs (1b) and B cells (2b′). Mature DCs activate CD4+ T lymphocytes (1c) and CD8+ T lymphocytes (1c′). Activated CD4+ T lymphocytes further stimulate B-lymphocyte activation (1d) and provide IL-2 for CD8+ T lymphocytes (1d′). B lymphocytes produce TAA-specific antibodies to cell-surface proteins that result in antibody-dependent cell-mediated cytotoxicity or complement-mediated tumor cell death (1e). Activated CD8+ T lymphocytes then kill tumor cells via recognition of MHC class I molecules in association with TAA epitopes (1e′).
(6) FIG. **4** shows comparison of cancer lineages that display high frequency of mutagenesis, which may harbor non-synonymous hitchhiker mutations and “neo-epitopes”.
DEFINITIONS
(7) As used herein and in the claims, the singular forms “a,” “an,” and “the” include the singular and the plural reference unless the context clearly indicates otherwise. Thus, for example, a reference to “an agent” includes a single agent and a plurality of such agents.
(8) An “immunogenic peptide” or “antigenic peptide” is a peptide or epitope that can be recognized by the immune system and elicit an immune response. Immunogenic peptides or antigenic peptide may comprise a motif such that the peptide will bind an MHC molecule and induce a T cell response, or can be recognized by the B cell receptor on the B cell to induce antibody production. These terms are used interchangeably herein.
(9) An “immunogenic epitope” or “antigenic epitope” refers to a part of an antigen is recognized by the immune system, e.g., by antibodies, B cells, or T cells. In some embodiments, the epitope is the specific piece of the antigen to which an antibody binds. Although epitopes are usually non-self proteins, sequences derived from the host can, in some instances, be recognized.
(10) “Immune response” is how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful to the body. In its general form, the immune response begins with the sensitization of helper (TH, CD4+) and cytotoxic (CD8+) T cell subsets through their interaction with antigen presenting cells (APC) that express major histocompatibility (MHC)-class I or class II molecules associated with antigenic fragments (i.e., specific amino acid sequences derived from the antigen which bind to MHC I and/or MHC II for presentation on the cell surface). The sensitized or primed CD4+ T cells produce lymphokines that participate in the activation of B cells as well as various T cell subsets. The sensitized CD8+ T cells increase in numbers in response to lymphokines and are capable of destroying any cells that express the specific antigenic fragments associated with matching MHC-encoded class I molecules. Thus, in the course of a cancerous tumor, CTL eradicate cells expressing cancer associated or cancer specific antigens, thereby limiting the progression of tumor spread and disease development.
(11) The “adaptive immune system,” also known as the acquired immune system, is a subsystem of the overall immune system that is composed of highly specialized, systemic cells and processes that eliminate or prevent pathogen growth. The adaptive immune system is one of the two main immunity strategies found in vertebrates (the other being the innate immune system). Adaptive immunity creates immunological memory after an initial response to a specific pathogen, and leads to an enhanced response to subsequent encounters with that pathogen. This process of acquired immunity is the basis of vaccination. Like the innate system, the adaptive system includes both humoral immunity components and cell-mediated immunity components.
(12) Unlike the innate immune system, the adaptive immune system is highly specific to a particular pathogen or antigen. Adaptive immunity can also provide long-lasting protection. The adaptive system response destroys invading pathogens and any toxic molecules they produce. In accordance with the present disclosure, the adaptive immune system response destroys tumor or cancer cells. Sometimes the adaptive system is unable to distinguish harmful from harmless foreign molecules. The cells that carry out the adaptive immune response are white blood cells known as lymphocytes. Two main broad classes-antibody responses and cell mediated immune response—are also carried by two different lymphocytes (B cells and T cells). In antibody responses, B cells are activated to secrete antibodies, which are proteins also known as immunoglobulins. Antibodies travel through the bloodstream and bind to the foreign antigen causing it to inactivate, which does not allow the antigen to bind to the host.
(13) In adaptive immunity, pathogen-specific receptors are “acquired” during the lifetime of the organism (whereas in innate immunity pathogen-specific receptors are already encoded in the germline). The acquired response is called “adaptive” because it prepares the body's immune system for future challenges (though it can actually also be maladaptive when it results in autoimmunity).
(14) The immune system is highly adaptable because of somatic hypermutation (a process of accelerated somatic mutations), and V(D)J recombination (an irreversible genetic recombination of antigen receptor gene segments). This mechanism allows a small number of genes to generate a vast number of different antigen receptors, which are then uniquely expressed on each individual lymphocyte. Since the gene rearrangement leads to an irreversible change in the DNA of each cell, all progeny (offspring) of that cell inherit genes that encode the same receptor specificity, including the

memory B cells and memory T cells that are the keys to long-lived specific immunity.
(15) A “T cell” or “T lymphocyte” is a type of lymphocyte (a subtype of white blood cell) that plays a central role in cell-mediated immunity. T cells can be distinguished from other lymphocytes, such as B cells and natural killer cells, by the presence of a T-cell receptor on the cell surface. They are called T cells because they mature in the thymus from thymocytes. The several subsets of T cells each have a distinct function. The majority of human T cells rearrange their alpha and beta chains on the cell receptor and are termed alpha beta T cells (αβ T cells) and are part of the adaptive immune system. Specialized gamma delta T cells, (a small minority of T cells in the human body, more frequent in ruminants), have invariant T cell receptors with limited diversity, that can effectively present antigens to other T cells and are considered to be part of the innate immune system. Effector T cell broadly includes various T cell types that actively respond to a stimulus, such as co-stimulation. This includes helper, killer, regulatory, and potentially other T cell types. One skilled in the art is familiar with different types of T cells and their respective roles in adaptive immune response.
(16) A “human leukocyte antigen (HLA) system” is a gene complex encoding the major histocompatibility complex (MHC) proteins in humans. These cell-surface proteins are responsible for the regulation of the immune system in humans. The HLA gene complex resides on a 3 Mbp stretch within chromosome 6p21. HLA genes are highly polymorphic, which means that they have many different alleles, allowing them to fine-tune the adaptive immune system. The proteins encoded by certain genes are also known as antigens, as a result of their historic discovery as factors in organ transplants. Different classes have different functions:
(17) HLAs encoding major histocompatibility complex (MHC) class I MHC class I (A, B, and C) molecules, which present peptides from inside the cell. “Major histocompatibility complex (MHC) class I” or “MHC class I” molecules are found on the cell surface of all nucleated cells in the body. Their function is to display peptide fragments of antigens from within the cell to cytotoxic T cells; this will trigger an immediate response from the immune system against a particular non-self antigen displayed with the help of an MHC class I protein. Because MHC class I molecules present peptides derived from cytosolic proteins, the pathway of MHC class I presentation is often called cytosolic or endogenous pathway.
(18) Class I MHC molecules bind peptides generated mainly from degradation of cytosolic proteins by the proteasome. The MHC I peptide complex is then inserted via endoplasmic reticulum into the external plasma membrane of the cell. The epitope peptide is bound on extracellular parts of the class I MHC molecule. Thus, the function of the class I MHC is to display intracellular proteins to cytotoxic T cells (CTLs). However, class I MHC can also present peptides generated from exogenous proteins, in a process known as cross-presentation.
(19) A normal cell will display peptides from normal cellular protein turnover on its class I MHC, and CTLs will not be activated in response to them due to central and peripheral tolerance mechanisms. When a cell expresses foreign proteins, such as after viral infection, a fraction of the class I MHC will display these peptides on the cell surface. Consequently, CTLs specific for the MHC:peptide complex will recognize and kill presenting cells. Alternatively, class I MHC itself can serve as an inhibitory ligand for natural killer cells (NKs). Reduction in the normal levels of surface class I MHC, a mechanism employed by some viruses during immune evasion or in certain tumors, will activate NK cell killing. Antigens or antigenic epitopes presented by MHC class II molecules are recognized by cytotoxic T cells.
(20) HLAs encoding MHC class II (DP, DM, DOA, DOB, DQ, and DR) molecules, which present antigens from outside of the cell to T-lymphocytes. “Major histocompatibility complex class II” or “MHC class II” molecules are a family of molecules normally found only on antigen-presenting cells such as dendritic cells, mononuclear phagocytes, some endothelial cells, thymic epithelial cells, and B cells. The antigens presented by class II peptides are usually derived from extracellular proteins (not cytosolic as in class I); hence, the MHC class II-dependent pathway of antigen presentation is called the endocytic or exogenous pathway. Loading of a MHC class II molecule occurs by phagocytosis; extracellular proteins are endocytosed, digested in lysosomes, and the resulting epitopic peptide fragments are loaded onto MHC class II molecules prior to their migration to the cell surface. Antigens or antigenic epitopes presented by MHC class II molecules are recognized by T helper cells and stimulate the multiplication of T-helper cells, which in turn stimulate antibody-producing B-cells to produce antibodies to that specific antigen. Self-antigens are suppressed by regulatory T cells.
(21) An “antigen-presenting cell (APC)” is a cell that displays antigen complexed with major histocompatibility complexes (MHCs) on their surfaces; this process is known as antigen presentation. T cells may recognize these complexes using their T cell receptors (TCRs). These cells process antigens and present them to T-cells. Antigen-presenting cells fall into two categories: professional and non-professional. Those that express MHC class II molecules along with co-stimulatory molecules and pattern recognition receptors are often called professional antigen-presenting cells. The non-professional APCs express MHC class I molecules.
(22) Professional APCs specialize in presenting antigen to T cells. They are very efficient at internalizing antigens, either by phagocytosis (macrophages and dendritic cells) or by receptor-mediated endocytosis (B cells), processing the antigen into peptide fragments and then displaying those peptides, bound to a class II MHC molecule, on their membrane.[1] The T cell recognizes and interacts with the antigen-class II MHC molecule complex on the membrane of the antigen-presenting cell. An additional co-stimulatory signal is then produced by the antigen-presenting cell, leading to activation of the T cell. The expression of co-stimulatory molecules and MHC class II are defining features of professional APCs.
(23) Almost all cell types can serve as a non-professional APC. They are found in a variety of tissue types. Professional antigen-presenting cells, including dendritic cells, mononuclear phagocytes, thymic epithelial cells, and B cells, present

foreign antigens to helper T cells, while other cell types can present antigens originating inside the cell to cytotoxic T cells. In addition to the MHC family of proteins, antigen presentation relies on other specialized signaling molecules on the surfaces of both APCs and T cells.
(24) A “B lymphocyte” or “B cell” is a type of white blood cell of the lymphocyte subtype. B cells function in the humoral immunity component of the adaptive immune system by secreting antibodies. Additionally, B cells present antigen (they are also classified as professional antigen-presenting cells (APCs)) and secrete cytokines. In mammals, B cells mature in the bone marrow, which is at the core of most bones. B cells express B cell receptors (BCRs) on their cell membrane. BCRs allow the B cell to bind a specific antigen, against which it will initiate an antibody response.
(25) “Cancer immunotherapy” refers to a type of cancer treatment designed to boost the body's natural defenses to fight the cancer. It uses substances either made by the body or in a laboratory to improve or restore immune system function.
(26) “Tumor specific antigen (TSA)” or “tumor associated antigen (TAA)” refers to a protein that is specifically expressed or upregulated in cells of the respective tumor, as compared to non-cancerous cells of the same origin. A tumor specific antigen, or epitopes derived therefrom, can be recognized by the immune system to induce a immune response. Herein, the terms “tumor associated antigen” and “tumor specific antigen” are used interchangeably. The tumor specific antigen may be from all protein classes, e.g., enzymes, receptors, transcription factors, etc.
(27) A “heteroclitic epitope” or “heteroclitic analog” refers to an altered version of an endogenous peptide sequence (i.e., an analog) engineered to elicit potent immune reactions. Heteroclitic epitopes have increased stimulatory capacity or potency for a specific T cell, as measured by increased responses to a given dose, or by a requirement of lesser amounts to achieve the same response and therefore provide benefit as vaccine components since these epitopes induce T cell responses stronger than those induced by the native epitope.
(28) A “self-antigen” refers to an antigen that originates from within the body. The immune system usually does not react to self-antigens under normal homeostatic conditions. Epitopes from self-antigens (i.e., self-epitopes) are found in high concentration on the surface of Antigen-presenting cells (APC's) in association with its major histocompatibility complex (MHC) are known as dominant epitopes. These are stimulants of negative selection mechanisms to remove potentially self-destructing autoreactive T cells. Their “self” antigens are displayed to a developing T-cell and signal those “self-reactive” T-cells to die via programmed cell death (apoptosis) and thereby deletion from the T cell repertoire, preventing autoimmunity.
(29) A “cryptic epitope” refers to an epitope derived from a self-antigen that does not necessarily undergo antigen processing/presentation and are ‘hidden’ from immune recognition. Cryptic epitopes usually appear in very low concentration on APC and do not delete auto-reactive T cells. Cryptic epitopes are not presented for recognition by T cells unless they are produced in unusually large concentrations or unless they are freed from the configuration of their native antigen. Cryptic epitopes derived from tumor-specific antigens may be used to break the tolerance of T cells to the tumor and induce potent immune response against the tumor. Such principles have been described in Pardoll, et al., *PNAS*, Vol. 96, pp. 5340-5342 (1999), the entire contents of which are incorporated herein by reference.
(30) A “neoepitope” refers to an antigenic epitope generated via random somatic mutations occurring in tumor cells. Neoepitopes are usually derived from individually specific tumor antigens or unique antigens and is thus specific to the lineage of tumor cells it is derived from. Neoepitopes are regarded in the art to be responsible for the immunogenicity of tumors ((Srivastava et al., 1993, Duan et al., 2009; van der Bruggen et al., 2013), and mathematic modeling has predicted the existence of tens to hundreds of neoepitopes in individual human tumors (Srivastava 2009). The recent revolution in high-throughput DNA sequencing and accompanying bioinformatics approaches has finally made it possible to actually identify the individually specific neoepitopes in individual cancers.
(31) “Cancer vaccine,” as used herein, refers to a composition that induces tumor-specific immunoresponse against a tumor or a tumor-specific antigen. Such immunoresponse is effective in inhibiting tumor growth and/or preventing reoccurrence of tumor.
(32) An “intron” refers to any nucleotide sequence within a gene that is removed by RNA splicing during maturation of the final RNA product. The term intron refers to both the DNA sequence within a gene and the corresponding sequence in RNA transcripts. Sequences that are joined together in the final mature RNA after RNA splicing are exons. Introns are found in the genes of most organisms and many viruses, and can be located in a wide range of genes, including those that generate proteins, ribosomal RNA (rRNA), and transfer RNA (tRNA). When proteins are generated from intron-containing genes, RNA splicing takes place as part of the RNA processing pathway that follows transcription and precedes translation.
(33) An “exon” refers to any part of a gene that will become a part of the final mature RNA produced by that gene after introns have been removed by RNA splicing. The term exon refers to both the DNA sequence within a gene and to the corresponding sequence in RNA transcripts. In RNA splicing, introns are removed and exons are covalently joined to one another as part of generating the mature messenger RNA.
(34) “RNA splicing” refers to the processing of a newly synthesized messenger RNA transcript (also referred to as a primary mRNA transcript). After splicing, introns are removed and exons are joined together (ligated) for form mature mRNA molecule containing a complete open reading frame that is decoded and translated into a protein. For nuclear-encoded genes, splicing takes place within the nucleus either co-transcriptionally or immediately after transcription. The molecular mechanism of RNA splicing has been extensively described, e.g., in Pagani et al., *Nature Reviews Genetics* 5, 389-396, 2004; Clancy et al., *Nature Education* 1 (1): 31, 2011; Cheng et al., Molecular Genetics and Genomics 286 (5-

6): 395-410, 2014; Taggart et al., *Nature Structural & Molecular Biology* 19 (7): 719-2, 2012, the contents of each of which are incorporated herein by reference. One skilled in the art is familiar with the mechanism of RNA splicing.
(35) "Alternative splicing" refers to a regulated process during gene expression that results in a single gene coding for multiple proteins. In this process, particular exons of a gene may be included within or excluded from the final, processed messenger RNA (mRNA) produced from that gene. Consequently, the proteins translated from alternatively spliced mRNAs will contain differences in their amino acid sequence and, often, in their biological functions. Notably, alternative splicing allows the human genome to direct the synthesis of many more proteins than would be expected from its 20,000 protein-coding genes. Alternative splicing is sometimes also termed differential splicing. Alternative splicing occurs as a normal phenomenon in eukaryotes, where it greatly increases the biodiversity of proteins that can be encoded by the genome; in humans, ˜95% of multi-exonic genes are alternatively spliced. There are numerous modes of alternative splicing observed, of which the most common is exon skipping. In this mode, a particular exon may be included in mRNAs under some conditions or in particular tissues, and omitted from the mRNA in others. Abnormal variations in splicing are also implicated in disease; a large proportion of human genetic disorders result from splicing variants. Abnormal splicing variants are also thought to contribute to the development of cancer, and splicing factor genes are frequently mutated in different types of cancer. The regulation of alternative splicing is also described in the art, e.g., in Douglas et al., *Annual Review of Biochemistry* 72 (1): 291-336, 2003; Pan et al., *Nature Genetics* 40 (12): 1413-1415, 2008; Martin et al., *Nature Reviews* 6 (5): 386-398, 2005; Skotheim et al., *The international journal of biochemistry & cell biology* 39 (7-8): 1432-49, 2007, the entire contents of each of which is incorporated herein by reference.
(36) A "coding frame" or "open reading frame" refers to a stretch of codons that encodes a polypeptide. Since DNA is interpreted in groups of three nucleotides (codons), a DNA strand has three distinct reading frames. The double helix of a DNA molecule has two anti-parallel strands so, with the two strands having three reading frames each, there are six possible frame translations. A functional protein may be produced when translation proceeds in the correct coding frame. An insertion or a deletion of one or two bases in the open reading frame causes a shift in the coding frame that is also referred to as a "frameshift mutation." A frameshift mutation typical results in premature translation termination and/or truncated or non-functional protein.
(37) The term "proteome" refers to the entire set of proteins expressed by a genome, cell, tissue, or organism at a certain time. More specifically, it is the set of expressed proteins in a given type of cell or organism, at a given time, under certain conditions. The term is a blend of proteins and genome. "Proteome-wide" refers to each and every protein in the proteome without any bias.
(38) The term "genome" refers to the genetic material of a cell or organism. It typically includes DNA (or RNA in the case of RNA viruses). The genome includes both the genes, the coding regions, the noncoding DNA, and the genomes of the mitochondria and chloroplasts. A genome does not typically include genetic material that is artificially introduced into a cell or organism, e.g., a plasmid that is transformed into a bacteria is not a part of the bacterial genome.
(39) A "programmable DNA-binding protein," as used herein, refers to DNA binding proteins that can be programmed to navigate to any desired target nucleotide sequence within the genome. To program the DNA-binding protein to bind a desired nucleotide sequence, the DNA binding protein may be modified to change its binding specificity, e.g., zinc finger nuclease (ZFN) or transcription activator-like effector proteins (TALE). ZFNs are artificial restriction enzymes generated by fusing a zinc finger DNA-binding domain to a DNA-cleavage domain. Zinc finger domains can be engineered to target specific desired DNA sequences and this enables zinc-finger nucleases to target unique sequences within complex genomes. Transcription activator-like effector nucleases (TALEN) are restriction enzymes that can be engineered to cut specific sequences of DNA. They are made by fusing a TAL effector DNA-binding domain to a DNA cleavage domain (a nuclease which cuts DNA strands). Transcription activator-like effectors (TALEs) can be engineered to bind practically any desired DNA sequence, so when combined with a nuclease, DNA can be cut at specific locations. The restriction enzymes can be introduced into cells, for use in gene editing or for genome editing in situ, Methods of programming ZFNs and TALEs are familiar to one skilled in the art. For example, such methods are described in Maeder, et al., *Mol. Cell* 31 (2): 294-301, 2008; Carroll et al., *Genetics Society of America*, 188 (4): 773-782, 2011; Miller et al., *Nature Biotechnology* 25 (7): 778-785, 2007; Christian et al., *Genetics* 186 (2): 757-61, 2008; Li et al., *Nucleic Acids Res* 39 (1): 359-372, 2010; and Moscou et al., *Science* 326 (5959): 1501, 2009, the entire contents of each of which are incorporated herein by reference.
(40) A "guide nucleotide sequence-programmable DNA-binding protein," as used herein, refers to a protein, a polypeptide, or a domain that is able to bind DNA, and the binding to its target DNA sequence is mediated by a guide nucleotide sequence. Thus, it is appreciated that the guide nucleotide sequence-programmable DNA-binding protein binds to a guide nucleotide sequence. The "guide nucleotide" may be a RNA molecule or a DNA molecule (e.g., a single-stranded DNA or ssDNA molecule) that is complementary to the target sequence and can guide the DNA binding protein to the target sequence. In some embodiments, the guide nucleotide sequence is an oligonucleotide sequence. As such, a guide nucleotide sequence-programmable DNA-binding protein may be a RNA-programmable DNA-binding protein (e.g., a Cas9 protein), or an ssDNA-programmable DNA-binding protein (e.g., an Argonaute protein). "Programmable" means the DNA-binding protein may be programmed to bind any DNA sequence that the guide nucleotide targets.
(41) In some embodiments, the guide nucleotide sequence exists as a single nucleotide molecule and comprises comprise two domains: (1) a domain that shares homology to a target nucleic acid (e.g., and directs binding of a guide nucleotide sequence-programmable DNA-binding protein to the target); and (2) a domain that binds a guide nucleotide sequence-

programmable DNA-binding protein. In some embodiments, the guide nucleotide is a guide RNA (gRNA). In some embodiments, domain (2) of the gRNA corresponds to a sequence known as a tracrRNA, and comprises a stem-loop structure. For example, in some embodiments, domain (2) is identical or homologous to a tracrRNA as provided in Jinek et al., *Science* 337:816-821(2012), the entire contents of which is incorporated herein by reference. Other examples of gRNAs (e.g., those including domain 2) can be found in U.S. Provisional Patent Application, U.S. Ser. No. 61/874,682, filed Sep. 6, 2013, entitled "Switchable Cas9 Nucleases And Uses Thereof," and U.S. Provisional Patent Application, U.S. Ser. No. 61/874,746, filed Sep. 6, 2013, entitled "Delivery System For Functional Nucleases," the entire contents of each are hereby incorporated by reference in their entirety.

(42) Because the guide nucleotide sequence hybridizes to target DNA sequence, the guide nucleotide sequence-programmable DNA-binding proteins are able to be targeted, in principle, to any sequence specified by the guide nucleotide sequence. Methods of using guide nucleotide sequence-programmable DNA-binding protein, such as Cas9, for site-specific cleavage (e.g., to modify a genome) are known in the art (see e.g., Cong, L. et al. *Science* 339, 819-823 (2013); *Mali*, P. et al. *Science* 339, 823-826 (2013); Hwang, W. Y. et al. *Nature biotechnology* 31, 227-229 (2013); Jinek, M. et al. eLife 2, e00471 (2013); Dicarlo, J. E. et al. *Nucleic acids research* (2013); Jiang, W. et al. *Nature biotechnology* 31, 233-239 (2013); the entire contents of each of which are incorporated herein by reference).

(43) It is to be understood that any DNA binding domain that is programmable by a guide nucleotide sequence may be used in accordance with the present disclosure. For example, in some embodiments, the guide nucleotide sequence-programmable DNA binding protein may be a Cas9 protein, or a variant thereof. One skilled in the art would understand that the present disclosure is not limited to the use of Cas9 as the guide nucleotide sequence-programmable DNA binding protein, but that other DNA binding proteins that adopt similar mechanism of target sequence binding may also be used.

(44) As used herein, the term "Cas9" or "Cas9 nuclease" refers to an RNA-guided nuclease comprising a Cas9 protein, a fragment, or a variant thereof. A Cas9 nuclease is also referred to sometimes as a casnI nuclease or a CRISPR (clustered regularly interspaced short palindromic repeat)-associated nuclease. CRISPR is an adaptive immune system that provides protection against mobile genetic elements (viruses, transposable elements and conjugative plasmids). CRISPR clusters contain spacers, sequences complementary to antecedent mobile elements, and target invading nucleic acids. CRISPR clusters are transcribed and processed into CRISPR RNA (crRNA). In type II CRISPR systems correct processing of pre-crRNA requires a trans-encoded small RNA (tracrRNA), endogenous ribonuclease 3 (mc) and a Cas9 protein. The tracrRNA serves as a guide for ribonuclease 3-aided processing of pre-crRNA. Subsequently, Cas9/crRNA/tracrRNA endonucleolytically cleaves linear or circular dsDNA target complementary to the spacer. The target strand not complementary to crRNA is first cut endonucleolytically, then trimmed 3′-5′ exonucleolytically. In nature, DNA-binding and cleavage typically requires protein and both RNAs. However, single guide RNAs ("sgRNA", or simply "gNRA") can be engineered so as to incorporate aspects of both the crRNA and tracrRNA into a single RNA species. See, e.g., Jinek et al., *Science* 337:816-821(2012), the entire contents of which is incorporated herein by reference.

(45) Cas9 nuclease sequences and structures are well known to those of skill in the art (see, e.g., Ferretti et al., *Proc. Natl. Acad. Sci.* 98:4658-4663(2001); Deltcheva E. et al., *Nature* 471:602-607(2011); and Jinek et al., *Science* 337:816-821(2012), the entire contents of each of which are incorporated herein by reference). Cas9 orthologs have been described in various species, including, but not limited to, *S. pyogenes* and *S. thermophilus*. Additional suitable Cas9 nucleases and sequences will be apparent to those of skill in the art based on this disclosure, and such Cas9 nucleases and sequences include Cas9 sequences from the organisms and loci disclosed in Chylinski et al., (2013) *RNA Biology* 10:5, 726-737; the entire contents of which are incorporated herein by reference. In some embodiments, wild type Cas9 corresponds to Cas9 from *Streptococcus pyogenes* (*NCBI Reference Sequence*: NC_002737.2, SEQ ID NO: 4 (nucleotide); and Uniport Reference Sequence: Q99ZW2, SEQ ID NO: 1 (amino acid).

(46) TABLE-US-00001 (SEQ ID NO: 4)

ATGGATAAGAAATACTCAATAGGCTTAGATATCGGCACAAATAGCGTCGGATGGGCGGTGATCAC
TGATGAATATAAGGTTCCGTCTAAAAAGTTCAAGGTTCTGGGAAATACAGACCGCCACAGTATCA
AAAAAAATCTTATAGGGGCTCTTTTATTTGACAGTGGAGAGACAGCGGAAGCGACTCGTCTCAAA
CGGACAGCTCGTAGAAGGTATACACGTCGGAAGAATCGTATTTGTTATCTACAGGAGATTTTTTCA
AATGAGATGGCGAAAGTAGATGATAGTTTCTTTCATCGACTTGAAGAGTCTTTTTTGGTGGAAGAA
GACAAGAAGCATGAACGTCATCCTATTTTTGGAAATATAGTAGATGAAGTTGCTTATCATGAGAAA
TATCCAACTATCTATCATCTGCGAAAAAAATTGGTAGATTCTACTGATAAAGCGGATTTGCGCTTA
ATCTATTTGGCCTTAGCGCATATGATTAAGTTTCGTGGTCATTTTTTGATTGAGGGAGATTTAAATC
CTGATAATAGTGATGTGGACAAACTATTTATCCAGTTGGTACAAACCTACAATCAATTATTTGAAG
AAAACCCTATTAACGCAAGTGGAGTAGATGCTAAAGCGATTCTTTCTGCACGATTGAGTAAATCAA
GACGATTAGAAAATCTCATTGCTCAGCTCCCCGGTGAGAAGAAAAATGGCTTATTTGGGAATCTCA
TTGCTTTGTCATTGGGTTTGACCCCTAATTTTAAATCAAATTTTGATTTGGCAGAAGATGCTAAATT
ACAGCTTTCAAAAGATACTTACGATGATGATTTAGATAATTTATTGGCGCAAATTGGAGATCAATA
TGCTGATTTGTTTTTGGCAGCTAAGAATTTATCAGATGCTATTTTACTTTCAGATATCCTAAGAGTA
AATACTGAAATAACTAAGGCTCCCCTATCAGCTTCAATGATTAAACGCTACGATGAACATCATCAA
GACTTGACTCTTTTAAAAGCTTTAGTTCGACAACAACTTCCAGAAAAGTATAAAGAAATCTTTTTT
GATCAATCAAAAAACGGATATGCAGGTTATATTGATGGGGGAGCTAGCCAAGAAGAATTTTATAA
ATTTATCAAACCAATTTTAGAAAAAATGGATGGTACTGAGGAATTATTGGTGAAACTAAATCGTGA

AGATTTGCTGCGCAAGCAACGGACCTTTGACAACGGCTCTATTCCCCATCAAATTCACTTGGGTGA
GCTGCATGCTATTTTGAGAAGACAAGAAGACTTTTATCCATTTTTAAAAGACAATCGTGAGAAGAT
TGAAAAAATCTTGACTTTTCGAATTCCTTATTATGTTGGTCCATTGGCGCGTGGCAATAGTCGTTTT
GCATGGATGACTCGGAAGTCTGAAGAAACAATTACCCCATGGAATTTTGAAGAAGTTGTCGATAA
AGGTGCTTCAGCTCAATCATTTATTGAACGCATGACAAACTTTGATAAAAATCTTCCAAATGAAAA
AGTACTACCAAAACATAGTTTGCTTTATGAGTATTTTACGGTTTATAACGAATTGACAAAGGTCAA
ATATGTTACTGAAGGAATGCGAAAACCAGCATTTCTTTCAGGTGAACAGAAGAAAGCCATTGTTG
ATTTACTCTTCAAAACAAATCGAAAAGTAACCGTTAAGCAATTAAAAGAAGATTATTTCAAAAAA
ATAGAATGTTTTGATAGTGTTGAAATTTCAGGAGTTGAAGATAGATTTAATGCTTCATTAGGTACC
TACCATGATTTGCTAAAAATTATTAAAGATAAAGATTTTTTGGATAATGAAGAAAATGAAGATATC
TTAGAGGATATTGTTTTAACATTGACCTTATTTGAAGATAGGGAGATGATTGAGGAAAGACTTAAA
ACATATGCTCACCTCTTTGATGATAAGGTGATGAAACAGCTTAAACGTCGCCGTTATACTGGTTGG
GGACGTTTGTCTCGAAAATTGATTAATGGTATTAGGGATAAGCAATCTGGCAAAACAATATTAGAT
TTTTTGAAATCAGATGGTTTTGCCAATCGCAATTTTATGCAGCTGATCCATGATGATAGTTTGACAT
TTAAAGAAGACATTCAAAAAGCACAAGTGTCTGGACAAGGCGATAGTTTACATGAACATATTGCA
AATTTAGCTGGTAGCCCTGCTATTAAAAAAGGTATTTTACAGACTGTAAAAGTTGTTGATGAATTG
GTCAAAGTAATGGGGCGGCATAAGCCAGAAAATATCGTTATTGAAATGGCACGTGAAAATCAGAC
AACTCAAAAGGGCCAGAAAAATTCGCGAGAGCGTATGAAACGAATCGAAGAAGGTATCAAAGAA
TTAGGAAGTCAGATTCTTAAAGAGCATCCTGTTGAAAATACTCAATTGCAAAATGAAAAGCTCTAT
CTCTATTATCTCCAAAATGGAAGAGACATGTATGTGGACCAAGAATTAGATATTAATCGTTTAAGT
GATTATGATGTCGATCACATTGTTCCACAAAGTTTCCTTAAAGACGATTCAATAGACAATAAGGTC
TTAACGCGTTCTGATAAAAATCGTGGTAAATCGGATAACGTTCCAAGTGAAGAAGTAGTCAAAAA
GATGAAAAACTATTGGAGACAACTTCTAAACGCCAAGTTAATCACTCAACGTAAGTTTGATAATTT
AACGAAAGCTGAACGTGGAGGTTTGAGTGAACTTGATAAAGCTGGTTTTATCAAACGCCAATTGG
TTGAAACTCGCCAAATCACTAAGCATGTGGCACAAATTTTGGATAGTCGCATGAATACTAAATACG
ATGAAAATGATAAACTTATTCGAGAGGTTAAAGTGATTACCTTAAAATCTAAATTAGTTTCTGACT
TCCGAAAAGATTTCCAATTCTATAAAGTACGTGAGATTAACAATTACCATCATGCCCATGATGCGT
ATCTAAATGCCGTCGTTGGAACTGCTTTGATTAAGAAATATCCAAAACTTGAATCGGAGTTTGTCT
ATGGTGATTATAAAGTTTATGATGTTCGTAAAATGATTGCTAAGTCTGAGCAAGAAATAGGCAAA
GCAACCGCAAAATATTTCTTTTACTCTAATATCATGAACTTCTTCAAAACAGAAATTACACTTGCA
AATGGAGAGATTCGCAAACGCCCTCTAATCGAAACTAATGGGGAAACTGGAGAAATTGTCTGGGA
TAAAGGGCGAGATTTTGCCACAGTGCGCAAAGTATTGTCCATGCCCCAAGTCAATATTGTCAAGAA
AACAGAAGTACAGACAGGCGGATTCTCCAAGGAGTCAATTTTACCAAAAAGAAATTCGGACAAGC
TTATTGCTCGTAAAAAAGACTGGGATCCAAAAAAATATGGTGGTTTTGATAGTCCAACGGTAGCTT
ATTCAGTCCTAGTGGTTGCTAAGGTGGAAAAAGGGAAATCGAAGAAGTTAAAATCCGTTAAAGAG
TTACTAGGGATCACAATTATGGAAAGAAGTTCCTTTGAAAAAAATCCGATTGACTTTTTAGAAGCT
AAAGGATATAAGGAAGTTAAAAAAGACTTAATCATTAAACTACCTAAATATAGTCTTTTTGAGTTA
GAAAACGGTCGTAAACGGATGCTGGCTAGTGCCGGAGAATTACAAAAAGGAAATGAGCTGGCTCT
GCCAAGCAAATATGTGAATTTTTTATATTTAGCTAGTCATTATGAAAAGTTGAAGGGTAGTCCAGA
AGATAACGAACAAAAACAATTGTTTGTGGAGCAGCATAAGCATTATTTAGATGAGATTATTGAGC
AAATCAGTGAATTTTCTAAGCGTGTTATTTTAGCAGATGCCAATTTAGATAAAGTTCTTAGTGCAT
ATAACAAACATAGAGACAAACCAATACGTGAACAAGCAGAAAATATTATTCATTTATTTACGTTG
ACGAATCTTGGAGCTCCCGCTGCTTTTAAATATTTTGATACAACAATTGATCGTAAACGATATACG
TCTACAAAAGAAGTTTTAGATGCCACTCTTATCCATCAATCCATCACTGGTCTTTATGAAACACGC
ATTGATTTGAGTCAGCTAGGAGGTGACTGA (SEQ ID NO: 1)
MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLEDSGETAEATRLKRTAR
RRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLR
KKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDA
KAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDN
LLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEK
YKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHL
GELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA
SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFK
TNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT
LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN
FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVI
EMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQEL
DINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRK
FDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSD
FRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKA
TAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQ

TGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME
RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLA
SHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENI
IHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGD (single underline: HNH domain; double underline: RuvC domain) In some embodiments, wild type Cas9 corresponds to Cas9 from *Streptococcus aureus*. *S. aureus* Cas9 wild type (SEQ ID NO: 6)
MKRNYILGLDIGITSVGYGIIDYETRDVIDAGVRLFKEANVENNEGRRSKRGARRLKRRRRHRIQRVKK
LLFDYNLLTDHSELSGINPYEARVKGLSQKLSEEEFSAALLHLAKRRGVHNVNEVEEDTGNELSTKEQI
SRNSKALEEKYVAELQLERLKKDGEVRGSINRFKTSDYVKEAKQLLKVQKAYHQLDQSFIDTYIDLLE
TRRTYYEGPGEGSPFGWKDIKEWYEMLMGHCTYFPEELRSVKYAYNADLYNALNDLNNLVITRDENE
KLEYYEKFQIIENVFKQKKKPTLKQIAKEILVNEEDIKGYRVTSTGKPEFTNLKVYHDIKDITARKEIIEN
AELLDQIAKILTIYQSSEDIQEELTNLNSELTQEEIEQISNLKGYTGTHNLSLKAINLILDELWHTNDNQIA
IFNRLKLVPKKVDLSQQKEIPTTLVDDFILSPVVKRSFIQSIKVINAIIKKYGLPNDIIIELAREKNSKDAQK
MINEMQKRNRQTNERIEEIIRTTGKENAKYLIEKIKLHDMQEGKCLYSLEAIPLEDLLNNPFNYEVDHIIP
RSVSFDNSFNNKVLVKQEENSKKGNRTPFQYLSSSDSKISYETFKKHILNLAKGKGRISKTKKEYLLEER
DINRFSVQKDFINRNLVDTRYATRGLMNLLRSYFRVNNLDVKVKSINGGFTSFLRRKWKFKKERNKGY
KHHAEDALIIANADFIFKEWKKLDKAKKVMENQMFEEKQAESMPEIETEQEYKEIFITPHQIKHIKDFK
DYKYSHRVDKKPNRELINDTLYSTRKDDKGNTLIVNNLNGLYDKDNDKLKKLINKSPEKLLMYHHDP
QTYQKLKLIMEQYGDEKNPLYKYYEETGNYLTKYSKKDNGPVIKKIKYYGNKLNAHLDITDDYPNSR
NKVVKLSLKPYRFDVYLDNGVYKFVTVKNLDVIKKENYYEVNSKCYEEAKKLKKISNQAEFIASFYNN
DLIKINGELYRVIGVNNDLLNRIEVNMIDITYREYLENMNDKRPPRIIKTIASKTQSIKKYSTDILGNLYE
VKSKKHPQIIKKG In some embodiments, wild type Cas9 corresponds to Cas9 from *Streptococcus thermophilus*. *Streptococcus thermophilus* wild type CRISPR3 Cas9 (St3Cas9) (SEQ ID NO: 7)
MTKPYSIGLDIGTNSVGWAVITDNYKVPSKKMKVLGNTSKKYIKKNLLGVLLFDSGITAEGRRLKRTA
RRRYTRRRNRILYLQEIFSTEMATLDDAFFQRLDDSFLVPDDKRDSKYPIFGNLVEEKVYHDEFPTIYHL
RKYLADSTKKADLRLVYLALAHMIKYRGHFLIEGEFNSKNNDIQKNFQDFLDTYNAIFESDLSLENSKQ
LEEIVKDKISKLEKKDRILKLFPGEKNSGIFSEFLKLIVGNQADFRKCFNLDEKASLHESKESYDEDLETL
LGYIGDDYSDVFLKAKKLYDAILLSGFLTVTDNETEAPLSSAMIKRYNEHKEDLALLKEYIRNISLKTYN
EVFKDDTKNGYAGYIDGKTNQEDFYVYLKNLLAEFEGADYFLEKIDREDFLRKQRTFDNGSIPYQIHLQ
EMRAILDKQAKFYPFLAKNKERIEKILTFRIPYYVGPLARGNSDFAWSIRKRNEKITPWNFEDVIDKESS
AEAFINRMTSFDLYLPEEKVLPKHSLLYETFNVYNELTKVRFIAESMRDYQFLDSKQKKDIVRLYFKDK
RKVTDKDIIEYLHAIYGYDGIELKGIEKQFNSSLSTYHDLLNIINDKEFLDDSSNEAIIEEIIHTLTIFEDRE
MIKQRLSKFENIFDKSVLKKLSRRHYTGWGKLSAKLINGIRDEKSGNTILDYLIDDGISNRNFMQLIHDD
ALSFKKKIQKAQIIGDEDKGNIKEVVKSLPGSPAIKKGILQSIKIVDELVKVMGGRKPESIVVEMARENQ
YTNQGKSNSQQRLKRLEKSLKELGSKILKENIPAKLSKIDNNALQNDRLYLYYLQNGKDMYTGDDLDI
DRLSNYDIDHIIPQAFLKDNSIDNKVLVSSASNRGKSDDFPSLEVVKKRKTFWYQLLKSKLISQRKFDNL
TKAERGGLLPEDKAGFIQRQLVETRQITKHVARLLDEKENNKKDENNRAVRTVKIITLKSTLVSQFRKD
FELYKVREINDFHHAHDAYLNAVIASALLKKYPKLEPEFVYGDYPKYNSFRERKSATEKVYFYSNIMNI
FKKSISLADGRVIERPLIEVNEETGESVWNKESDLATVRRVLSYPQVNVVKKVEEQNHGLDRGKPKGL
FNANLSSKPKPNSNENLVGAKEYLDPKKYGGYAGISNSFAVLVKGTIEKGAKKKITNVLEFQGISILDRI
NYRKDKLNFLLEKGYKDIELIIELPKYSLFELSDGSRRMLASILSTNNKRGEIHKGNQIFLSQKFVKLLYH
AKRISNTINENHRKYVENHKKEFEELFYYILEFNENYVGAKKNGKLLNSAFQSWQNHSIDELCSSFIGPT
GSERKGLFELTSRGSAADFEFLGVKIPRYRDYTPSSLLKDATLIHQSVTGLYETRIDLAKLGEG *Streptococcus thermophilus* CRISPR1 Cas9 wild type (St1Cas9) (SEQ ID NO: 8)
MSDLVLGLDIGIGSVGVGILNKVTGEIIHKNSRIFPAAQAENNLVRRTNRQGRRLTRRKKHRRVRLNRL
FEESGLITDFTKISINLNPYQLRVKGLTDELSNEELFIALKNMVKHRGISYLDDASDDGNSSIGDYAQIVK
ENSKQLETKTPGQIQLERYQTYGQLRGDFTVEKDGKKHRLINVFPTSAYRSEALRILQTQQEFNPQITDE
FINRYLEILTGKRKYYHGPGNEKSRTDYGRYRTSGETLDNIFGILIGKCTFYPDEFRAAKASYTAQEFNL
LNDLNNLTVPTETKKLSKEQKNQIINYVKNEKAMGPAKLFKYIAKLLSCDVADIKGYRIDKSGKAEIHT
FEAYRKMKTLETLDIEQMDRETLDKLAYVLTLNTEREGIQEALEHEFADGSFSQKQVDELVQFRKANS
SIFGKGWHNFSVKLMMELIPELYETSEEQMTILTRLGKQKTTSSSNKTKYIDEKLLTEEIYNPVVAKSVR
QAIKIVNAAIKEYGDFDNIVIEMARETNEDDEKKAIQKIQKANKDEKDAAMLKAANQYNGKAELPHSV
FHGHKQLATKIRLWHQQGERCLYTGKTISIHDLINNSNQFEVDHILPLSITFDDSLANKVLVYATANQE
KGQRTPYQALDSMDDAWSFRELKAFVRESKTLSNKKKEYLLTEEDISKFDVRKKFIERNLVDTRYASR
VVLNALQEHFRAHKIDTKVSVVRGQFTSQLRRHWGIEKTRDTYHHHAVDALIIAASSQLNLWKKQKN
TLVSYSEDQLLDIETGELISDDEYKESVFKAPYQHFVDTLKSKEFEDSILFSYQVDSKFNRKISDATIYAT
RQAKVGKDKADETYVLGKIKDIYTQDGYDAFMKIYKKDKSKFLMYRHDPQTFEKVIEPILENYPNKQI
NEKGKEVPCNPFLKYKEEHGYIRKYSKKGNGPEIKSLKYYDSKLGNHIDITPKDSNNKVVLQSVSPWR
ADVYFNKTTGKYEILGLKYADLQFEKGTGTYKISQEKYNDIKKKEGVDSDSEFKFTLYKNDLLLVKDT
ETKEQQLFRFLSRTMPKQKHYVELKPYDKQKFEGGEALIKVLGNVANSGQCKKGLGKSNISIYKVRTD
VLGNQHIIKNEGDKPKLDF

(47) In some embodiments, the Cas9 domain of any of the fusion proteins provided herein is a Cas9 from archaea (e.g. nanoarchaea), which constitute a domain and kingdom of single-celled prokaryotic microbes. In some embodiments, the Cas9 domain is CasX or CasY, which have been described in, for example, Burstein et al., "New CRISPR-Cas systems from uncultivated microbes." *Cell Res.* 2017 Feb. 21. doi: 10.1038/cr.2017.21, which is incorporated herein by reference. Using genome-resolved metagenomics, a number of CRISPR-Cas systems were identified, including the first reported Cas9 in the archaeal domain of life. This divergent Cas9 protein was found in nanoarchaea as part of an active CRISPR-Cas system. In bacteria, two previously unknown systems were discovered, CRISPR-CasX and CRISPR-CasY, which are among the most compact systems yet discovered. In some embodiments, Cas9 refers to CasX, or a variant of CasX. In some embodiments, Cas9 refers to a CasY, or a variant of CasY. It should be appreciated that other RNA-guided DNA binding proteins may be used as a nucleic acid programmable DNA binding protein (napDNAbp) and are within the scope of this disclosure.

(48) In some embodiments, the Cas9 domain comprises an amino acid sequence that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to a naturally-occurring CasX or CasY protein. In some embodiments, the Cas9 domain is a naturally-occurring CasX or CasY protein. In some embodiments, the Cas9 domain comprises an amino acid sequence that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to any one of SEQ ID NOs: 336-337 or 3000. In some embodiments, the Cas9 domain comprises an amino acid sequence of any one SEQ ID NOs: 336-337 or 3000. It should be appreciated that CasX and CasY from other bacterial species may also be used in accordance with the present disclosure.

(49) In some embodiments, wild-type Cas9 refers to CasX from *Sulfolobus islandicus* (strain REY15A).

(50) TABLE-US-00002 (SEQ ID NO: 338)
MEVPLYNIFGDNYIIQVATEAENSTIYNNKVEIDDEELRNVLNLAYKIAKNNEDAAAE
RRGKAKKKKGEEGETTTSNIILPLSGNDKNPWTETLKCYNFPTTVALSEVFKNFSQV
KECEEVSAPSFVKPEFYKFGRSPGMVERTRRVKLEVEPHYLIMAAAGWVLTRLGKA
KVSEGDYVGVNVFTPTRGILYSLIQNVNGIVPGIKPETAFGLWIARKVVSSVTNPNVS
VVSIYTISDAVGQNPTTINGGFSIDLTKLLEKRDLLSERLEAIARNALSISSNMRERYIV
LANYIYEYLTGSKRLEDLLYFANRDLIMNLNSDDGKVRDLKLISAYVNGELIRGEG In some embodiments, wild-type Cas9 refers to CasX from *Sulfolobus islandicus* (strain REY15A). (SEQ ID NO: 339)
MEVPLYNIFGDNYIIQVATEAENSTIYNNKVEIDDEELRNVLNLAYKIAKNNEDAAAE
RRGKAKKKKGEEGETTTSNIILPLSGNDKNPWTETLKCYNFPTTVALSEVFKNFSQV
KECEEVSAPSFVKPEFYEFGRSPGMVERTRRVKLEVEPHYLIIAAAGWVLTRLGKAK
VSEGDYVGVNVFTPTRGILYSLIQNVNGIVPGIKPETAFGLWIARKVVSSVTNPNVSV
VRIYTISDAVGQNPTTINGGFSIDLTKLLEKRYLLSERLEAIARNALSISSNMRERYIVL
ANYIYEYLTGSKRLEDLLYFANRDLIMNLNSDDGKVRDLKLISAYVNGELIRGEG In some embodiments, wild-type Cas9 refers to CasY from a *Parcubacteria* group *bacterium*. CasY (ncbi.nlm.nih.gov/protein/APG80656.1) >APG80656.1 CRISPR-associated protein CasY [uncultured *Parcubacteria* group *bacterium*] (SEQ ID NO: 3000)
MSKRHPRISGVKGYRLHAQRLEYTGKSGAMRTIKYPLYSSPSGGRTVPREIVSAINDDYVGLYGLSNFD
DLYNAEKRNEEKVYSVLDFWYDCVQYGAVFSYTAPGLLKNVAEVRGGSYELTKTLKGSHLYDELQID
KVIKFLNKKEISRANGSLDKLKKDIIDCFKAEYRERHKDQCNKLADDIKNAKKDAGASLGERQKKLFR
DFFGISEQSENDKPSFTNPLNLTCCLLPFDTVNNNRNRGEVLENKLKEYAQKLDKNEGSLEMWEYIGIG
NSGTAFSNFLGEGFLGRLRENKITELKKAMMDITDAWRGQEQEEELEKRLRILAALTIKLREPKFDNHW
GGYRSDINGKLSSWLQNYINQTVKIKEDLKGHKKDLKKAKEMINRFGESDTKEEAVVSSLLESIEKIVP
DDSADDEKPDIPAIAIYRRFLSDGRLTLNRFVQREDVQEALIKERLEAEKKKKPKKRKKKSDAEDEKETI
DFKELFPHLAKPLKLVPNFYGDSKRELYKKYKNAAIYTDALWKAVEKIYKSAFSSSLKNSFFDTDFDK
DFFIKRLQKIFSVYRRFNTDKWKPIVKNSFAPYCDIVSLAENEVLYKPKQSRSRKSAAIDKNRVRLPSTE
NIAKAGIALARELSVAGFDWKDLLKKEEHEEYIDLIELHKTALALLLAVTETQLDISALDFVENGTVKD
FMKTRDGNLVLEGRFLEMFSQSIVFSELRGLAGLMSRKEFITRSAIQTMNGKQAELLYIPHEFQSAKITT
PKEMSRAFLDLAPAEFATSLEPESLSEKSLLKLKQMRYYPHYFGYELTRTGQGIDGGVAENALRLEKSP
VKKREIKCKQYKTLGRGQNKIVLYVRSSYYQTQFLEWFLHRPKNVQTDVAVSGSFLIDEKKVKTRWN
YDALTVALEPVSGSERVFVSQPFTIFPEKSAEEEGQRYLGIDIGEYGIAYTALEITGDSAKILDQNFISDPQ
LKTLREEVKGLKLDQRRGTFAMPSTKIARIRESLVHSLRNRIHHLALKHKAKIVYELEVSRFEEGKQKIK
KVYATLKKADVYSEIDADKNLQTTVWGKLAVASEISASYTSQFCGACKKLWRAEMQVDETITTQELIG
TVRVIKGGTLIDAIKDFMRPPIFDENDTPFPKYRDFCDKHHISKKMRGNSCLFICPFCRANADADIQASQ
TIALLRYVKEEKKVEDYFERFRKLKNIKVLGQMKKI

(51) In some embodiments, Cas9 refers to Cas9 from: *Corynebacterium ulcerans* (NCBI Refs: NC_015683.1, NC_017317.1); *Corynebacterium diphtheria* (NCBI Refs: NC_016782.1, NC_016786.1); *Spiroplasma syrphidicola* (NCBI Ref: NC_021284.1); *Prevotella intermedia* (NCBI Ref: NC_017861.1); *Spiroplasma taiwanense* (NCBI Ref: NC_021846.1); *Streptococcus iniae* (NCBI Ref: NC_021314.1); *Belliella baltica* (NCBI Ref: NC_018010.1); *Psychroflexus torquisl* (NCBI Ref: NC_018721.1); *Listeria innocua* (NCBI Ref: NP_472073.1), *Campylobacter jejuni*

(NCBI Ref: YP_002344900.1) or *Neisseria. meningitidis* (NCBI Ref: YP_002342100.1) or to a Cas9 from any of the organisms listed in Example 1 (SEQ ID NOs: 11-260).

(52) To be used as in the fusion protein of the present disclosure as the guide nucleotide sequence-programmable DNA binding protein domain, a Cas9 protein needs to be nuclease inactive. A nuclease-inactive Cas9 protein may interchangeably be referred to as a "dCas9" protein (for nuclease-"dead" Cas9). Methods for generating a Cas9 protein (or a fragment thereof) having an inactive DNA cleavage domain are known (See, e.g., Jinek et al., *Science.* 337:816-821(2012); Qi et al., (2013) *Cell.* 28; 152(5):1173-83, the entire contents of each of which are incorporated herein by reference). For example, the DNA cleavage domain of Cas9 is known to include two subdomains, the HNH nuclease subdomain and the RuvC1 subdomain. The HNH subdomain cleaves the strand complementary to the gRNA, whereas the RuvC1 subdomain cleaves the non-complementary strand. Mutations within these subdomains can silence the nuclease activity of Cas9. For example, the mutations D10A and H840A completely inactivate the nuclease activity of *S. pyogenes* Cas9 (Jinek et al., *Science.* 337:816-821(2012); Qi et al., *Cell.* 28; 152(5):1173-83 (2013)). dCas9 (D10A and H840A)

(53) TABLE-US-00003 (SEQ ID NO: 2)

MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTAR
RRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLR
KKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDA
KAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDN
LLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEK
YKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHL
GELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA
SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFK
TNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT
LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN
FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVI
EMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQEL
DINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRK
FDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSD
FRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKA
TAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQ
TGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME
RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLA
SHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENI
IHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGD (single underline: HNH domain; double underline: RuvC domain)

(54) The dCas9 of the present disclosure encompasses completely inactive Cas9 or partially inactive Cas9. For example, the dCas9 may have one of the two nuclease domain inactivated, while the other nuclease domain remains active. Such a partially active Cas9 may also be referred to as a Cas9 nickase, due to its ability to cleave one strand of the targeted DNA sequence. The Cas9 nickase suitable for use in accordance with the present disclosure has an active HNH domain and an inactive RuvC domain and is able to cleave only the strand of the target DNA that is bound by the sgRNA. The Cas9 nickase of the present disclosure may comprise mutations that inactivate the RuvC domain, e.g., a D10A mutation. It is to be understood that any mutation that inactivates the RuvC domain may be included in a Cas9 nickase, e.g., insertion, deletion, or single or multiple amino acid substitution in the RuvC domain. In a Cas9 nickase described herein, while the RuvC domain is inactivated, the HNH domain remains activate. Thus, while the Cas9 nickase may comprise mutations other than those that inactivate the RuvC domain (e.g., D10A), those mutations do not affect the activity of the HNH domain. In a non-limiting Cas9 nickase example, the histidine at position 840 remains unchanged. The sequence of an exemplary Cas9 nickase suitable for the present disclosure is provided below.

(55) TABLE-US-00004 Cas9 Nickase (D10A) (SEQ ID NO: 3)

MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLEDSGETAEATRLKRTAR
RRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLR
KKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDA
KAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDN
LLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEK
YKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHL
GELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA
SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFK
TNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT
LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN
FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVI
EMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQEL
DINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRK
FDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSD

FRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKA
TAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQ
TGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME
RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLA
SHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENI
IHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGD (single underline:
HNH domain; double underline: RuvC domain) *S. aureus* Cas9 Nickase (D10A) (SEQ ID NO: 5)
MKRNYILGLAIGITSVGYGIIDYETRDVIDAGVRLFKEANVENNEGRRSKRGARRLKRRRRHRIQRVKK
LLFDYNLLTDHSELSGINPYEARVKGLSQKLSEEEFSAALLHLAKRRGVHNVNEVEEDTGNELSTKEQI
SRNSKALEEKYVAELQLERLKKDGEVRGSINRFKTSDYVKEAKQLLKVQKAYHQLDQSFIDTYIDLLE
TRRTYYEGPGEGSPFGWKDIKEWYEMLMGHCTYFPEELRSVKYAYNADLYNALNDLNNLVITRDENE
KLEYYEKFQIIENVFKQKKKPTLKQIAKEILVNEEDIKGYRVTSTGKPEFTNLKVYHDIKDITARKEIIEN
AELLDQIAKILTIYQSSEDIQEELTNLNSELTQEEIEQISNLKGYTGTHNLSLKAINLILDELWHTNDNQIA
IFNRLKLVPKKVDLSQQKEIPTTLVDDFILSPVVKRSFIQSIKVINAIIKKYGLPNDIIIELAREKNSKDAQK
MINEMQKRNRQTNERIEEIIRTTGKENAKYLIEKIKLHDMQEGKCLYSLEAIPLEDLLNNPFNYEVDHIIP
RSVSFDNSFNNKVLVKQEENSKKGNRTPFQYLSSSDSKISYETFKKHILNLAKGKGRISKTKKEYLLEER
DINRFSVQKDFINRNLVDTRYATRGLMNLLRSYFRVNNLDVKVKSINGGFTSFLRRKWKFKKERNKGY
KHHAEDALIIANADFIFKEWKKLDKAKKVMENQMFEEKQAESMPEIETEQEYKEIFITPHQIKHIKDFK
DYKYSHRVDKKPNRELINDTLYSTRKDDKGNTLIVNNLNGLYDKDNDKLKKLINKSPEKLLMYHHDP
QTYQKLKLIMEQYGDEKNPLYKYYEETGNYLTKYSKKDNGPVIKKIKYYGNKLNAHLDITDDYPNSR
NKVVKLSLKPYRFDVYLDNGVYKFVTVKNLDVIKKENYYEVNSKCYEEAKKLKKISNQAEFIASFYNN
DLIKINGELYRVIGVNNDLLNRIEVNMIDITYREYLENMNDKRPPRIIKTIASKTQSIKKYSTDILGNLYE
VKSKKHPQIIKKG

(56) It is appreciated that when the term “dCas9” or “nuclease-inactive Cas9” is used herein, it refers to Cas9 variants that are inactive in both HNH and RuvC domains as well as Cas9 nickases. For example, the dCas9 used in the present disclosure may include the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 3. In some embodiments, the dCas9 may comprise other mutations that inactivate RuvC or HNH domain. Additional suitable mutations that inactivate Cas9 will be apparent to those of skill in the art based on this disclosure and knowledge in the field, and are within the scope of this disclosure. Such additional exemplary suitable nuclease-inactive Cas9 domains include, but are not limited to, D839A and/or N863A (See, e.g., Prashant et al., *Nature Biotechnology.* 2013; 31(9): 833-838, the entire contents of which are incorporated herein by reference), or K603R (See, e.g., Chavez et al., *Nature Methods* 12, 326-328, 2015, the entire contents of which is incorporated herein by reference). The term Cas9, dCas9, or Cas9 variant also encompasses Cas9, dCas9, or Cas9 variant from any organism. Also appreciated is that dCas9, Cas9 nickase, or other appropriate Cas9 variants from any organisms may be used in accordance with the present disclosure.

(57) A “deaminase” refers to an enzyme that catalyzes the removal of an amine group from a molecule, or deamination. In some embodiments, the deaminase is a cytidine deaminase, catalyzing the hydrolytic deamination of cytidine or deoxycytidine to uridine or deoxyuridine, respectively. In some embodiments, the deaminase is a cytosine deaminase, catalyzing the hydrolytic deamination of cytosine to uracil (e.g., in RNA) or thymine (e.g., in DNA). In some embodiments, the deaminase is a naturally-occurring deaminase from an organism, such as a human, chimpanzee, gorilla, monkey, cow, dog, rat, or mouse. In some embodiments, the deaminase is a variant of a naturally-occurring deaminase from an organism, that does not occur in nature. For example, in some embodiments, the deaminase or deaminase domain is at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75% at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to a naturally-occurring deaminase from an organism.

(58) A “cytosine deaminase” refers to an enzyme that catalyzes the chemical reaction “cytosine+H.sub.2O.fwdarw.uracil+NH.sub.3” or “5-methyl-cytosine+H2O.fwdarw.thymine+NH.sub.3.” As it may be apparent from the reaction formula, such chemical reactions result in a C to U/T nucleobase change. In the context of a gene, such nucleotide change, or mutation, may in turn lead to an amino acid residue change in the protein, which may affect the protein function, e.g., loss-of-function or gain-of-function.

(59) One exemplary suitable class of cytosine deaminases is the apolipoprotein B mRNA-editing complex (APOBEC) family of cytosine deaminases encompassing eleven proteins that serve to initiate mutagenesis in a controlled and beneficial manner. The apolipoprotein B editing complex 3 (APOBEC3) enzyme provides protection to human cells against a certain HIV-1 strain via the deamination of cytosines in reverse-transcribed viral ssDNA. These cytosine deaminases all require a Zn.sup.2+-coordinating motif (His-X-Glu-X.sub.23-26-Pro-Cys-X.sub.24-Cys; SEQ ID NO: 820) and bound water molecule for catalytic activity. The Glu residue acts to activate the water molecule to a zinc hydroxide for nucleophilic attack in the deamination reaction. Each family member preferentially deaminates at its own particular “hotspot”, ranging from WRC (W is A or T, R is A or G) for hAID, to TTC for hAPOBEC3F. A recent crystal structure of the catalytic domain of APOBEC3G revealed a secondary structure comprised of a five-stranded 3-sheet core flanked by six α-helices, which is believed to be conserved across the entire family. The active center loops have been shown to be responsible for both ssDNA binding and in determining “hotspot” identity. Overexpression of these enzymes has been linked to genomic instability and cancer, thus highlighting the importance of sequence-specific targeting.

Another suitable cytosine deaminase is the activation-induced cytidine deaminase (AID), which is responsible for the maturation of antibodies by converting cytosines in ssDNA to uracils in a transcription-dependent, strand-biased fashion.
(60) Herein, a “nucleobase editor” refers to to a protein that edits a nucleotide base. “Edit” refers to the conversion of one nucleotide base to another. For example, the nucleobase may target C bases in a nucleic acid sequence and convert the C to T base. In some embodiments, the C to T editing is carried out by a deaminase, e.g., a cytosine deaminase. Other types of base conversions are also contemplated. In some embodiments, the nucleobase editor comprises a DNA binding domain that directs it to a target sequence.
(61) As such, a base editor may be a cytosine deaminase-dCas9 fusion protein. In some embodiments, the base editor may be a deaminase-dCas9-UGI fusion protein. In some embodiments, the base editor may be a APOBEC1-dCas9-UGI fusion protein. In some embodiments, the base editor may be APOBEC1-Cas9 nickase-UGI fusion protein. In some embodiments, the base editor may be APOBEC1-dCpf1-UGI fusion protein. In some embodiments, the base editor may be APOBEC1-dNgAgo-UGI fusion protein. In some embodiments, the base editor may be a pmCDA1-Cas9 nickase-UGI fusion protein. In some embodiments, the base editor may be a human APOBEC3G-Cas9 nickase UGI fusion protein. In some embodiments, the base editor may comprise a second UGI domain. Non-limiting exemplary sequences of the nucleobase editors described herein are provided in Example 1, SEQ ID NOs: 293-302, 1071, and 1084. Such nucleobase editors and methods of using them for genome editing have been described in the art, e.g., in U.S. Pat. No. 9,068,179, US Patent Application Publications US 2015/0166980, US 2015/0166981, US 2015/0166982, US20150166984, and US20150165054, and US Provisional Applications, U.S. Ser. No. 62/245,828, filed Oct. 23, 2015; 62/279,346, filed Jan. 15, 2016; 62/311,763, filed Mar. 22, 2016; 62/322,178, filed Apr. 13, 2016, 62/357,352, filed Jun. 30, 2016, U.S. Pat. No. 62,370,700, filed Aug. 3, 2016; 62/398,490, filed Sep. 22, 2016; 62/408,686, filed Oct. 14, 2016; PCT Application PCT/US2016/058344, filed Oct. 22, 2016, U.S. patent application Ser. No. 15/311,852, filed Oct. 22, 2016; Komor et al. (2017) Improved Base Excision Repair Inhibition and Bateriophage Mu Gam Protein Yields C:G-to-T:A base editors with higher efficiency and product purity. Sci Adv, 3: eaao4774; and in Komor et al., Nature, Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage, 533, 420-424 (2016), the entire contents of each of which are incorporated herein by reference.
(62) The term “target site” or “target sequence” refers to a sequence within a nucleic acid molecule (e.g., a DNA molecule) that is deaminated by the fusion protein provided herein. In some embodiments, the target sequence is a polynucleotide (e.g., a DNA), wherein the polynucleotide comprises a coding strand and a complementary strand. The meaning of a “coding strand” and “complementary strand” is the common meaning of the terms in the art. In some embodiments, the target sequence is a sequence in the genome of a mammal. In some embodiments, the target sequence is a sequence in the genome of a human. The term “target codon” refers to the amino acid codon that is edited by the base editor and converted to a different codon via deamination of C base. In some embodiments, the target codon is edited in the coding strand. In some embodiments, the target codon is edited in the complementary strand.
(63) The term “linker,” as used herein, refers to a chemical group or a molecule linking two molecules or moieties, e.g., two domains of a fusion protein, such as, for example, a nuclease-inactive Cas9 domain and a nucleic acid editing domain (e.g., a deaminase domain). Typically, the linker is positioned between, or flanked by, two groups, molecules, or other moieties and connected to each one via a covalent bond, thus connecting the two. In some embodiments, the linker is an amino acid or a plurality of amino acids (e.g., a peptide or protein). In some embodiments, the linker is an organic molecule, group, polymer, or chemical moiety. In some embodiments, the linker is 2-100 amino acids in length, for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 30-35, 35-40, 40-45, 45-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-150, or 150-200 amino acids in length. Longer or shorter linkers are also contemplated.
(64) The term “mutation,” as used herein, refers to a substitution of a residue within a sequence, e.g., a nucleic acid or amino acid sequence, with another residue, or a deletion or insertion of one or more residues within a sequence. Mutations are typically described herein by identifying the original residue followed by the position of the residue within the sequence and by the identity of the newly substituted residue. Various methods for making the amino acid substitutions (mutations) provided herein are well known in the art, and are provided by, for example, Green and Sambrook, *Molecular Cloning: A Laboratory Manual* (4.sup.th ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2012)).
(65) The terms “nucleic acid” and “nucleic acid molecule,” as used herein, refer to a compound comprising a nucleobase and an acidic moiety, e.g., a nucleoside, a nucleotide, or a polymer of nucleotides. Typically, polymeric nucleic acids, e.g., nucleic acid molecules comprising three or more nucleotides are linear molecules, in which adjacent nucleotides are linked to each other via a phosphodiester linkage. In some embodiments, “nucleic acid” refers to individual nucleic acid residues (e.g. nucleotides and/or nucleosides). In some embodiments, “nucleic acid” refers to an oligonucleotide chain comprising three or more individual nucleotide residues. As used herein, the terms “oligonucleotide” and “polynucleotide” can be used interchangeably to refer to a polymer of nucleotides (e.g., a string of at least three nucleotides). In some embodiments, “nucleic acid” encompasses RNA as well as single and/or double-stranded DNA. Nucleic acids may be naturally occurring, for example, in the context of a genome, a transcript, an mRNA, tRNA, rRNA, siRNA, snRNA, a plasmid, cosmid, chromosome, chromatid, or other naturally occurring nucleic acid molecule. On the other hand, a nucleic acid molecule may be a non-naturally occurring molecule, e.g., a recombinant DNA or RNA, an artificial chromosome, an engineered genome, or fragment thereof, or a synthetic DNA, RNA, DNA/RNA hybrid, or including non-naturally occurring nucleotides or nucleosides. Furthermore, the terms “nucleic acid,” “DNA,” “RNA,”

and/or similar terms include nucleic acid analogs, e.g., analogs having other than a phosphodiester backbone. Nucleic acids can be purified from natural sources, produced using recombinant expression systems and optionally purified, chemically synthesized, etc. Where appropriate, e.g., in the case of chemically synthesized molecules, nucleic acids can comprise nucleoside analogs such as analogs having chemically modified bases or sugars, and backbone modifications. A nucleic acid sequence is presented in the 5′ to 3′ direction unless otherwise indicated. In some embodiments, a nucleic acid is or comprises natural nucleosides (e.g. adenosine, thymidine, guanosine, cytidine, uridine, deoxyadenosine, deoxythymidine, deoxyguanosine, and deoxycytidine); nucleoside analogs (e.g., 2-aminoadenosine, 2-thiothymidine, inosine, pyrrolo-pyrimidine, 3-methyl adenosine, 5-methylcytidine, 2-aminoadenosine, C5-bromouridine, C5-fluorouridine, C5-iodouridine, C5-propynyl-uridine, C5-propynyl-cytidine, C5-methylcytidine, 2-aminoadenosine, 7-deazaadenosine, 7-deazaguanosine, 8-oxoadenosine, 8-oxoguanosine, 0(6)-methylguanine, and 2-thiocytidine); chemically modified bases; biologically modified bases (e.g., methylated bases); intercalated bases; modified sugars (e.g., 2′-fluororibose, ribose, 2′-deoxyribose, arabinose, and hexose); and/or modified phosphate groups (e.g., phosphorothioates and 5′-N-phosphoramidite linkages).

(66) The terms “protein,” “peptide,” and “polypeptide” are used interchangeably herein, and refer to a polymer of amino acid residues linked together by peptide (amide) bonds. The terms refer to a protein, peptide, or polypeptide of any size, structure, or function. Typically, a protein, peptide, or polypeptide will be at least three amino acids long. A protein, peptide, or polypeptide may refer to an individual protein or a collection of proteins. One or more of the amino acids in a protein, peptide, or polypeptide may be modified, for example, by the addition of a chemical entity such as a carbohydrate group, a hydroxyl group, a phosphate group, a farnesyl group, an isofarnesyl group, a fatty acid group, a linker for conjugation, functionalization, or other modification, etc. A protein, peptide, or polypeptide may also be a single molecule or may be a multi-molecular complex. A protein, peptide, or polypeptide may be just a fragment of a naturally occurring protein or peptide. A protein, peptide, or polypeptide may be naturally occurring, recombinant, or synthetic, or any combination thereof. The term “fusion protein” as used herein refers to a hybrid polypeptide which comprises protein domains from at least two different proteins. One protein may be located at the amino-terminal (N-terminal) portion of the fusion protein or at the carboxy-terminal (C-terminal) protein thus forming an “amino-terminal fusion protein” or a “carboxy-terminal fusion protein,” respectively. A protein may comprise different domains, for example, a nucleic acid binding domain (e.g., the gRNA binding domain of Cas9 that directs the binding of the protein to a target site) and a nucleic acid cleavage domain or a catalytic domain of a nucleic-acid editing protein. In some embodiments, a protein comprises a proteinaceous part, e.g., an amino acid sequence constituting a nucleic acid binding domain, and an organic compound, e.g., a compound that can act as a nucleic acid cleavage agent. In some embodiments, a protein is in a complex with, or is in association with, a nucleic acid, e.g., RNA. Any of the proteins provided herein may be produced by any method known in the art. For example, the proteins provided herein may be produced via recombinant protein expression and purification, which is especially suited for fusion proteins comprising a peptide linker. Methods for recombinant protein expression and purification are well known, and include those described by Green and Sambrook, *Molecular Cloning: A Laboratory Manual* (4.sup.th ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2012)), the entire contents of which are incorporated herein by reference.

(67) The term “subject,” as used herein, refers to an individual organism, for example, an individual mammal. In some embodiments, the subject is a human. In some embodiments, the subject is a non-human mammal. In some embodiments, the subject is a non-human primate. In some embodiments, the subject is a rodent. In some embodiments, the subject is a sheep, a goat, a cattle, a cat, or a dog. In some embodiments, the subject is a vertebrate, an amphibian, a reptile, a fish, an insect, a fly, or a nematode. In some embodiments, the subject is a research animal. In some embodiments, the subject is genetically engineered, e.g., a genetically engineered non-human subject. The subject may be of either sex and at any stage of development.

(68) The term “recombinant” as used herein in the context of proteins or nucleic acids refers to proteins or nucleic acids that do not occur in nature, but are the product of human engineering. For example, in some embodiments, a recombinant protein or nucleic acid molecule comprises an amino acid or nucleotide sequence that comprises at least one, at least two, at least three, at least four, at least five, at least six, or at least seven mutations as compared to any naturally occurring sequence.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

(69) The immune system is critical in preventing the outgrowth of cancers, and “immunosurveillance” exists to provide immunological resistance against cancer development (e.g., as described in Old et al., *Annu Rev Med* 1964; 15: 167-186; Burnet et al., *Prog Exp Tumor Res* 1970; 13: 1-27; and Graziano et al., *Cancer Treat Res* 2005; 123: 89-111, each of which is incorporated herein by reference).

(70) Despite the presence of immunosurveillance, cancers can develop in apparently immunocompetent animals and humans, due to the ability of cancer cells to evade immunosurveillance (e.g., as described in Hanahan et al., *Cell* 2000; 100: 57-70 and Zitvogel et al., *Nat Rev Immunol* 2006; 6: 715-727, each of which in incorporated herein by reference). The evasion of cancer cells from immunosurveillance occurs via various well-characterized mechanisms, including induction of T-cell tolerance by autochthonous tumors (e.g., as described in Willimsky et al., *Nature* 2005; 437: 141-146, incorporated herein by reference), cancer immunoediting (e.g., as described in Dunn et al., *Nat Immunol* 2002; 3: 991-998, incorporated herein by reference), and development of an immune suppressive cancer microenvironment (e.g., as described in Zou et al., *Nat Rev Cancer* 2005; 5: 263-274, incorporated herein by reference). Therapeutic cancer vaccines

or adoptive immunotherapy are being developed and tested as potential approaches to strengthen the immune responses after tumor arise in order to slow their progression and prevent their recurrence. Immunotherapeutic approaches, e.g., cancer vaccines have been described but are only partially successful (e.g., as described in Finn et al., *Nat Rev Immunol* 2003; 3: 630-641, incorporated herein by reference).

(71) Described herein are systems, methods, compositions, and kits for producing immunogenic peptides derived from tumor specific antigens (e.g., heteroclitic epitopes or cryptic epitopes) that may be used as cancer vaccines in vivo or ex vivo. Targeted mutations are introduced into tumor-specific antigens using a gene editing agent, e.g., a nucleobase editor comprising a programmable DNA binding domain (e.g., a catalytically-inactive Cas9 or Cas9 nickase) fused to a cytosine deaminase, to generate altered versions of peptides arising from the tumor-specific antigens (heteroclitic epitopes) or peptides arising from normally untranslated regions of the tumor-specific antigen genes (cryptic peptides). The heteroclitic peptides or cryptic peptides may be generated in vivo in a subject (e.g., a subject who has cancer) and presented to the adaptive immune system via the MHC class I or MHC class II pathway, which in turn induces a strong adaptive immune response, e.g., T cell response and B cell response. Such an adaptive immune response is antigen specific and is effective in reducing tumor growth and preventing metastasis.

(72) The advantage of the cancer vaccines of the present disclosure is that the vaccine (e.g., antigenic peptides derived from tumor-specific antigens) is generated from the genome and the proteome of the malignant cells in vivo and is highly personalized. The cancer vaccines described herein are also highly cancer-specific and do not induce unwanted immune response against “self,” since the immunogenic epitopes are derived from tumor-specific antigens. Further, the adaptive immune response induced by the cancer vaccine described herein confer “memory” to the immune system, promoting the immune system to efficiently recognize “neoepitopes” generated due to the highly mutagenic nature of the cancer genome, thus preventing metastasis and facilitate remission. To enhance the efficacy of the cancer vaccines described herein, combination therapies using an immune checkpoint inhibitor in conjunction with the cancer vaccine is also contemplated, aiming to enhance the tumor antigen specific immune response.

(73) The methods of producing endogenous cancer vaccines in vivo are enabled by the targeted nucleobase editing technology described herein. Such base editing technology is described in the art, e.g., in U.S. Pat. No. 9,068,179, US Patent Application Publications US 2015/0166980, US 2015/0166981, US 2015/0166982, US20150166984, and US20150165054, and US Provisional Applications, U.S. Ser. No. 62/245,828, filed Oct. 23, 2015; 62/279,346, filed Jan. 15, 2016; 62/311,763, filed Mar. 22, 2016; 62/322,178, filed Apr. 13, 2016, 62/357,352, filed Jun. 30, 2016, U.S. Pat. No. 62,370,700, filed Aug. 3, 2016; 62/398,490, filed Sep. 22, 2016; 62/408,686, filed Oct. 14, 2016; PCT Application PCT/US2016/058344, filed Oct. 22, 2016, U.S. patent application Ser. No. 15/311,852, filed Oct. 22, 2016; and in Komor et al., *Nature*, Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage, 533, 420-424 (2016), the entire contents of each of which are incorporated herein by reference.

(74) Immunogenic Peptides or Epitopes

(75) Some aspects of the present disclosure provide immunogenic peptides or epitopes derived from tumor-specific antigens and how these peptides or epitopes elicit tumor-specific immune response. A large number of proteins that specifically express in tumor cells or are upregulated in tumor cells have been identified (Hassane et al., Holland-Frei Cancer Medicine. 6th edition). The known tumor specific antigens are classified into different classes.

(76) a) Cancer-testis antigens: The first TAAs ever identified that can be recognized by T cells belong to this class, which was originally called cancer-testis (CT) antigens because of the expression of its members in histologically different human tumors and, among normal tissues, only in spermatocytes/spermatogonia of testis and, occasionally, in placenta. Since the cells of testis do not express class I and II HLA molecules, these antigens cannot be recognized by T cells in normal tissues and can therefore be considered as immunologically tumor-specific. Well-known examples of CT antigens are the MAGE family members or NY-ESO-1.

(77) b) Differentiation antigens: These TAAs are shared between tumors and normal tissue from which the tumor arose; most are found in melanomas and normal melanocytes. Many of these melanocyte lineage-related proteins are involved in the biosynthesis of melanin and are therefore not tumor specific but nevertheless are widely used for cancer immunotherapy. Examples include, but are not limited to, tyrosinase and Melan-A/MART-1 for melanoma, and PSA for prostate cancer.

(78) c) Overexpressed TAAs: Genes encoding widely expressed TSAs have been detected in histologically different types of tumors as well as in many normal tissues, generally with lower expression levels. It is possible that many of the epitopes processed and potentially presented by normal tissues are below the threshold level for T-cell recognition, while their overexpression in tumor cells can trigger an anticancer response by breaking previously established tolerance. Examples of this class of TAAs are Her-2/neu, Survivin, Telomerase and WT1.

(79) d) Tumor specific antigens: These unique TAAs arise from mutations of normal genes (such as β-catenin, CDK4, etc.). Some of these molecular changes are associated with neoplastic transformation and/or progression. Tumor specific antigens are generally able to induce strong immune responses without bearing the risk for autoimmune reactions against normal tissues. On the other hand, these TAAs are in most cases only relevant to the exact tumor on which they were identified and are usually not shared between many individual tumors.

(80) e) TAAs arising from abnormal post-translational modifications: Such TSAs may arise from proteins which are neither specific nor overexpressed in tumors but nevertheless become tumor associated by posttranslational processes primarily active in tumors. Examples for this class arise from altered glycosylation patterns leading to novel epitopes in

tumors (e.g., MUC1).
(81) f) Oncoviral proteins: These TSAs are viral proteins that may play a critical role in the oncogenic process, and because they are foreign (not of human origin), they can evoke a T-cell response. Examples of such proteins are the human papilloma type 16 virus proteins, E6 and E7, which are expressed in cervical carcinoma.
(82) TAAs are a starting point for the development of a tumor vaccine. The methods for identifying and characterizing the TAAs are based on the use of cytoxic T lymphocytes (CTL) that can be isolated from patients or healthy subjects, or they are based on the generation of differential transcription profiles or differential peptide expression patterns between tumors and normal tissues.
(83) In some embodiments, the tumor-specific antigen is expressed in a broad range of different types of cancers. In some embodiments, the tumor-specific antigen is expressed only in one or a few types of cancers. The anti-cancer immune response described herein is antigen-specific. As such, an immune response induced by a tumor-specific antigen is specific to cancer types where the said antigen is expressed. Non-limiting, exemplary tumor-specific antigens that may be edited to generate immunogenic epitopes are provided in Tables 1-3. It is appreciated that the examples are for illustration purpose only, and the methods described herein may be applied to any tumor-specific antigen.
(84) In some embodiments, the immunogenic peptide or epitope is a portion of the tumor-specific antigen. For example, the immunogenic peptide or epitope may be a portion of the tumor-specific antigen that is 5-40 amino acids long. In some embodiments, the immunogenic peptide or epitope is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 amino acids long. In some embodiments, the immunogenic peptide or epitope comprises modifications, e.g., amino acid substitutions (also termed “heteroclitic epitopes”), as compared to the native sequence in the tumor specific antigen. In some embodiments, the immunogenic peptide or epitope comprises more than one amino acid substitutions (e.g., 2, 3, 4, 5, or more) compared to the native sequence of the tumor-specific antigen it is derived from. In some embodiments, a heteroclitic peptide or epitope may be at least 60%, at least 70%, at least 80%, at least 90%, at least 98%, or at least 99% identical to the native sequence that it is derived from. In some embodiments, a heteroclitic peptide or epitope is 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to the native sequence that it is derived from.
(85) In some embodiments, a heteroclitic peptide or epitope is more immunogenic than a peptide of its native sequence. For example, a heteroclitic epitope may be at least 30% more immunogenic (i.e., induces a stronger immune response) than its corresponding native peptide. In some embodiments, a heteroclitic epitope may be at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 60-fold, at least 70-fold, at least 80-fold, at least 90-fold, at least 100-fold, or more immunogenic than its corresponding native peptide.
(86) In some embodiments, the immunogenic peptide or epitope is a cryptic peptide or epitope, e.g., generated from translation of a non-coding region of the tumor specific antigen gene or translation of a different reading frame of a coding region of the tumor specific antigen. A cryptic peptide or epitope may be more immunogenic (i.e., induces a stronger immune response) than any native peptide derived from the tumor associated antigen. For example, a cryptic peptide or epitope may be at least 30% more immunogenic than any native peptide derived from the tumor associated antigen. In some embodiments, a cryptic peptide or epitope may be at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 60-fold, at least 70-fold, at least 80-fold, at least 90-fold, at least 100-fold, or more immunogenic than any native peptide derived from the tumor associated antigen. One skilled in the art is familiar with how to assess the immune response induced by an antigen, e.g., measuring antibody titers.
(87) Tumor specific antigens from which antigenic epitopes (e.g., heteroclitic epitopes and cryptic epitopes) may be derived are provided in Tables 1-3. (HLA—human leukocyte antigen type)
(88) TABLE-US-00005 TABLE 1 Tumor associated antigen - Differentiation HLA SEQ Gene/ frequency ID protein Tumor HLA (%) Peptide NO Position CEA gut A2 44 YLSGANLNL 340 605-613 carcinoma A2 44 IMIGVLVGV 341 691-699 A2 44 GVLVGVALI 342 694-702 A2 44 LLTFWNPPT 343 24-33 A3 22 HLFGYSWYK 344 61-69 A24 20 QYSWFVNGTF 345 268-277 A24 20 TYACFVSNL 346 652-660 DR3 21 AYVCGIQNSVSANRS 347 568-582 DR4 24 DTGFYTLHVIKSDLVNEEA 348 116-140 TGQFRV DR4 24 YSWRINGIPQQHTQV 349 625-639 DR7 25 TYYRPGVNLSLSC 350 425-437 DR7 25 EIIYPNASLLION 351 99-111 DR9 3 YACFVSNLATGRNNS 352 653-667 DR11 25 LWWVNNQSLPVSP 353 177-189, 355-367 DR13 19 LWWVNNQSLPVSP 354 177-189, 355-367 DR14 6 LWWVNNQSLPVSP 355 177-189, 355-367 DR14 6 EIIYPNASLLIQN 356 99-111 DR14 6 NSIVKSITVSASG 357 666-678 gp100/ melanoma A2 44 KTWGQYWQV 358 154-162 Pmel17 A2 44 (A)MLGTHTMEV 359 177(8)-186 A2 44 ITDQVPFSV 360 209-217 A2 44 YLEPGPVTA 361 280-288 A2 44 LLDGTATLRL 362 457-466 A2 44 VLYRYGSFSV 363 476-485 A2 44 SLADTNSLAV 364 570-579 A2 44 RLMKQDFSV 365 619-627 A2 44 RLPRIFCSC 366 639-647 A3 22 LIYRRRLMK 367 614-622 A3 22 ALLAVGATK 368 17-25 A3 22 IALNFPGSQK 369 86-95 A3 22 RSYVPLAHR 370 195-202 and 191 or 192 A3 22 ALNFPGSQK 371 87-95 A11 13 ALNFPGSQK 372 87-95 A24 20 VYFFLPDHL 373 intron 4 A32 8 RTKQLYPEW 374 40-42 and 47-52 A68 8 HTMEVTVYHR 375 182-191 B7 17 SSPGCQPPA 376 529-537 B35 20 VPLDCVLYRY 377 471-480 B35 20 LPHSSSHWL 378 630-638 Cw8 — SNDGPTLI 379 71-78 DQ6 63 GRAMLGTHTMEVTVY 380 175-189 DR4 24 WNRQLYPEWTEAQRLD 381 44-59

DR7 25 TTEWVETTARELPIPEPE 382 420-437 DR7 25 TGRAMLGTHTMEVTVYH 383 174-190 DR53 49 GRAMLGTHTMEVTVY 384 175-189 mammagl breast A3 22 PLLENVISK 385 23-31 obin-A cancer Melan-A/ melanoma A2 44 (E)AAGIGILTV 386 26(27)-35 MART-1 A2 44 ILTVILGVL 387 32-40 B35 20 EAAGIGILTV 388 26-35 B45 2 AEEAAGIGIL(T) 389 24-33(34) Cw7 41 RNGYRALMDKS 390 51-61 DP5 3 YTTAEEAAGIGILTVILGV 391 21-50 LLLIGCWYCRR DQ6 63 EEAAGIGILTVI 392 25-36 DR1 18 AAGIGILTVILGVL 393 27-40 DR1 18 APPAYEKLpSAEQf 394 100-111 DR3 21 EEAAGIGILTVI 395 25-36 DR4 24 RNGYRALMDKSLHVGTQC 396 51-73 ALTRR DR11 25 MPREDAHFIYGYPKKGHGH 397 1-20 S DR52 41 KNCEPVVPNAPPAYEKLSA 398 91-110 E NY-BR-1 breast A2 44 SLSKILDTV 399 904-912 cancer ERBB2 breast A2 44 IVWELMTFGA 400 911-921 cancer OA1 melanoma A24 20 LYSACFWWL 401 126-134 PAP prostate A2 44 FLFLLFFWL 402 18-26 cancer A2 44 TLMSAMTNL 403 112-120 A2 44 ALDVYNGLL 404 299-307 PSA prostate A2 44 FLTPKKLQCV 405 165-174 carcinoma A2 44 VISNDVCAQV 406 178-187 RAB38/ melanoma A2 44 VLHWDPETV 407 50-58 NY-MEL-1 TRP-1/ melanoma A31 5 MSLQRQFLR 408 alt. ORF gp75 DR4 24 ISPNSVFSQWRVVCDSLED 409 277-297 YD DR15 20 SLPYWNFATG 410 245-254 DR17 21 SQWRVVCDSLEDYDT 411 284-298 TRP-2 melanoma A2 44 SVYDFFVWL 412 180-188 A2 44 TLDSQVMSL 413 360-368 A31 5 LLGPGRPYR 414 197-205 A33 5 LLGPGRPYR 415 197-205 Cw8 — ANDPIFVVL 416 387-395 DR3 21 QCTEVRADTRPWSGP 417 60-74 DR15 20 ALPYWNFATG 418 241-250 tyrosinase melanoma A1 26 KCDICTDEY 419 243-251 A1 26 SSDYVIPIGTY 420 146-156 A2 44 MLLAVLYCL 421 1-9 A2 44 CLLWSFQTSA 422 8-17 A2 44 YMDGTMSQV 423 369-377 A24 20 AFLPWHRLF 424 206-214 A24 20 IYMDGTADFSF 425 368-373 and 336-340e A26 8 QCSGNFMGF 426 90-98 B35 20 TPRLPSSADVEF 427 309-320 B35 20 LPSSADVEF 428 312-320 B38 5 LHHAFVDSIF 429 388-397 B44 21 SEIWRDIDFd 430 192-200 DR4 24 QNILLSNAPLGPQFP 431 56-70 DR4 24 SYLQDSDPDSFQD 432 450-462 DR15 20 FLLHHAFVDSIFEQWLQRH 433 386-406 RP WT1 testis, A1 26 TSEKRPFMCAY 434 317-327 ovary, A24 20 CMTWNQMNL 435 235-243 bone DP5 3 LSHLQMHSRKH 436 337-347 marrow, DP5 3 KRYFKLSHLQMHSRKH 437 332-347 spleen DR4 24 KRYFKLSHLQMHSRKH 438 332-347 CD33 leukemia A2 44 AIISGDSPV 439 65-73

(89) TABLE-US-00006 TABLE 2 Tumor specific antigen - Tumor specific HLA SEQ frequency ID Gene/protein HLA (%) Peptide NO Position BAGE-1 Cw16 7 AARAVFLAL 440 1-10 D393-CD20n DR4 24 KPLFRRMSSLELVIA 441 28-42 Cyclin-A1 A2 44 FLDRFLSCM 442 227-235 A2 44 SLIAAAAFCLA 443 341-351 GAGE-1,2,8 Cw6 18 YRPRPRRY 444 9-16 GAGE-3,4,5,6,7 A29 6 YYWPRPRRY 445 10-18 GnTVf A2 44 VLPDVFIRC(V) 446 intron HERV-K-MEL A2 44 MLAVISCAV 447 1-9 KK-LC-1 B15 13 RQKRILVNL 448 76-84 KM-HN-1 A24 20 NYNNFYRFL 449 196-204 A24 20 EYSKECLKEF 450 499-508 A24 20 EYLSLSDKI 451 770-778 LAGE-1 A2 44 MLMAQEALAFL 452 alt. ORF (1-11) A2 44 SLLMWITQC 453 157-165 A31 5 LAAQERRVPR 454 alt. ORF (18-27) A68 8 ELVRRILSR 455 103-111 B7 17 APRGVRMAV 456 alt. ORF (46-54) DP4 75 SLLMWITQCFLPVF 457 157-170 DR3 21 QGAMLAAQERRVPRAAEVPR 458 alt. ORF (14-33) DR4 24 AADHRQLQLSISSCLQQL 459 139-156 DR11 25 CLSRRPWKRSWSAGSCPGMPHL 460 alt. ORFT (81-102) DR12 5 CLSRRPWKRSWSAGSCPGMPHL 461 alt. ORFT (81-102) DR13 19 ILSRDAAPLPRPG 462 108-120 DR15 20 AGATGGRGPRGAGA 463 37-50 LY6K A24 20 RYCNLEGPPI 464 119-128 DP5 3 KWTEPYCVIAAVKIFPRFFMVAKQ 465 61-84 DR15 20 KCCKIRYCNLEGPPINSSVF 466 114-133 MAGE-A1 A1 26 EADPTGHSY 467 161-169 A2 44 KVLEYVIKV 468 278-286 A3 22 SLFRAVITK 469 96-104 A68 8 EVYDGREHSA 470 222-231 B7 17 RVRFFFPSL 471 289-298 B35 20 EADPTGHSY 472 161-169 B37 3 REPVTKAEML 473 120-129 B44 21 KEADPTGHSY 474 160-169 B53 2 DPARYEFLW 475 258-266 B57 8 ITKKVADLVGF 476 102-112 Cw2 10 SAFPTTINF 477 62-70 Cw3 17 SAYGEPRKL 478 230-238 Cw7 41 RVRFFFPSL 479 289-298 Cw16 7 SAYGEPRKL 480 230-238 DP4 75 TSCILESLFRAVITK 481 90-104 DP4 75 PRALAETSYVKVLEY 482 268-282 DR13 19 FLLLKYRAREPVTKAE 483 112-127 DR15 20 EYVIKVSARVRF 484 281-292 MAGE-A2 A2 44 YLQLVFGIEV 485 157-166 A24 20 EYLQLVFGI 486 156-164 B37 3 REPVTKAEML 487 127-136 Cw7 41 EGDCAPEEK 488 212-220 DR13 19 LLKYRAREPVTKAE 489 121-134 MAGE-A3 A1 26 EVDPIGHLY 490 168-176 A2 44 FLWGPRALVd 491 271-279 A2 44 KVAELVHFL 492 112-120 A24 20 TFPDLESEF 493 97-105 A24 20 VAELVHFLL 494 113-121 B18 6 MEVDPIGHLY 495 167-176 B35 20 EVDPIGHLY 496 168-176 B37 3 REPVTKAEML 497 127-136 B40 6 AELVHFLLL 498 114-122 B44 21 MEVDPIGHLY 499 167-176 B52 5 WQYFFPVIF 500 143-151 Cw7 41 EGDCAPEEK 501 212-220 DP4 75 KKLLTQHFVQENYLEY 502 243-258 DP4 75 RKVAELVHFLLLKYR 503 111-125 DQ6 63 KKLLTQHFVQENYLEY 504 243-258 DR1 18 ACYEFLWGPRALVETS 505 267-282 DR4 24 RKVAELVHFLLLKYR 506 111-125 DR4 24 VIFSKASSSLQL 507 149-160 DR7 25 VIFSKASSSLQL 508 149-160 DR7 25 VFGIELMEVDPIGHL 509 161-175 DR11 25 GDNQIMPKAGLLIIV 510 191-205 DR11 25 TSYVKVLHHMVKISG 511 281-295 DR13 19 RKVAELVHFLLLKYRA 512 111-126 DR13 19 FLLLKYRAREPVTKAE 513 119-134 MAGE-A4 A1 26 EVDPASNTY 514 169-177 A2 44 GVYDGREHTV 515 230-239 A24 20 NYKRCFPVI 516 143-151 B37 3 SESLKMIF 517 156-163 MAGE-A6 A34 1 MVKISGGPR 518 290-298 B35 20 EVDPIGHVY 519 168-176 B37 3 REPVTKAEML 520 127-136 Cw7 41 EGDCAPEEK 521 212-220 Cw16 7 ISGGPRISY 522 293-301 DR13 19 LLKYRAREPVTKAE 523 121-134 MAGE-A9 A2 44 ALSVMGVYV 524 223-231 MAGE-A10 A2 44 GLYDGMEHLI 525 254-262 B53 2 DPARYEFLW 526 290-298 MAGE-A12 m A2g 44 FLWGPRALV 527 271-279 Cw7 41 VRIGHLYIL 528 170-178 Cw7 41 EGDCAPEEK 529 212-220 DP4 75 REPFTKAEMLGSVIR 530 127-141 DR13 19 AELVHFLLLKYRAR 531 114-127 MAGE-C1 A2 44 ILFGISLREV 532 959-968 A2 44 KVVEFLAML 533 1083-1091 DQ6 63 SSALLSIFQSSPE 534 137-149 DQ6 63

SFSYTLLSL 535 450-458 DR15 20 VSSFFSYTL 536 779-787 MAGE-C2 A2 44 LLFGLALIEV 537 191-200 A2 44 ALKDVEERV 538 336-344 B44 21 SESIKKKVL 539 307-315 B57 8 ASSTLYLVF 540 42-50 DR15 20 SSTLYLVFSPSSFST 541 43-57 mucink PDTRPAPGSTAPPAHGVTSA 542 NA88-A B13 6 QGQHFLQKV 543 A2 44 SLLMWITQC 544 157-165 NY-ESO-1/ A2 44 MLMAQEALAFL 545 alt. ORF LAGE-2 (1-11) A24 20 YLAMPFATPME 546 91-101 A31 5 ASGPGGGAPR 547 53-62 A31 5 LAAQERRVPR 548 alt. ORF (18-27) A68 8 TVSGNILTIR 549 127-136 B7 17 APRGPHGGAASGL 550 60-72 B35 20 MPFATPMEAEL 551 94-104 B49 KEFTVSGNILTI 552 124-135 B51 12 MPFATPMEA 553 94-102 B52 5 FATPMEAEL 554 96-104 C12 12 FATPMEAELAR 555 96-106 Cw3 17 LAMPFATPM 556 92-100 Cw6 18 ARGPESRLL 557 80-88 DP4 75 SLLMWITQCFLPVF 558 157-170 DP4 75 LLEFYLAMPFATPMEAELARRSLAQ 559 87-111 DR1 18 LLEFYLAMPFATPMEAELARRSLAQ 560 87-111 DR1 18 EFYLAMPFATPM 561 89-100 DR1 18 PGVLLKEFTVSGNILTIRLTAADHR 562 119-143 DR2 25 RLLEFYLAMPFA 563 86-97 DR3 21 QGAMLAAQERRVPRAAEVPR 564 alt. ORF (14-33) DR4 24 PFATPMEAELARR 565 95-107 DR4 24 PGVLLKEFTVSGNILTIRLT 566 119-138 DR4 24 VLLKEFTVSG 567 121-130 DR4 24 AADHRQLQLSISSCLQQL 568 139-156 DR4 24 LLEFYLAMPFATPMEAELARRSLAQ 569 87-111 DR52b 25 LKEFTVSGNILTIRL 570 123-137 DR7 25 PGVLLKEFTVSGNILTIRLTAADHR 571 119-143 DR7 25 LLEFYLAMPFATPMEAELARRSLAQ 572 87-111 DR8 4 KEFTVSGNILT 573 124-134 DR9 3 LLEFYLAMPFATPM 574 87-100 DR15 20 AGATGGRGPRGAGA 575 37-50 SAGE A24 20 LYATVIHDI 576 715-723 Sp17 A1 26 ILDSSEEDK 577 103-111 SSX-2 A2 44 KASEKIFYV 578 41-49 DP1 14 EKIQKAFDDIAKYFSK 579 19-34 DR1 18 FGRLQGISPKI 580 101-111 DR3 21 WEKMKASEKIFYVYMKRK 581 37-54 DR4 24 KIFYVYMKRKYEAMT 582 45-59 DR11 25 KIFYVYMKRKYEAM 583 45-58 SSX-4 DP10 2 INKTSGPKRGKHAWTHRLRE 584 151-170 DR3 21 YFSKKEWEKMKSSEKIVYVY 585 31-50 DR8 4 MKLNYEVMTKLGFKVTLPPF 586 51-70 DR8 4 KHAWTHRLRERKQLVVYEEI 587 161-180 DR11 25 LGFKVTLPPFMRSKRAADFH 588 61-80 DR15 20 KSSEKIVYVYMKLNYEVMTK 589 41-60 DR52 41 KHAWTHRLRERKQLVVYEEI 590 161-180 survivin/ A2 44 ELTLGEFLKL 591 96-106 BIRC5 A24 20 AYACNTSTL 592 intron B2 TAG-1 A2 44 SLGWLFLLL 593 78-86 B8 14 LSRLSNRLL 594 42-50 TAG-2 B8 14 LSRLSNRLL 595 42-50 TRAG-3 DR1 18 CEFHACWPAFTVLGE 596 34-48 DR4 24 CEFHACWPAFTVLGE 597 34-48 DR7 25 CEFHACWPAFTVLGE 598 34-48 TRP2-INT2g A68 8 EVISCKLIKR 599 intron 2 XAGE-1b/ A2 44 RQKKIRIQL 600 21-29 GAGED2a DR4 24 HLGSRQKKIRIQLRSQ 601 17-32 DR9 3 CATWKVICKSCISQTPG 602 33-49 BCR-ABL A2 44 SSKALQRPV 603 926-934 (b3a2) B8 14 GFKQSSKAL 604 922-930 DR4 24 ATGFKQSSKALQRPVAS 605 920-936 DR9 3 ATGFKQSSKALQRPVAS 606 920-936

(90) TABLE-US-00007 TABLE 3 Overexpressed tumor specific antigen HLA SEQ Normal tissue Freq ID Gene/Protein expression HLAa (%) Peptide NO Position adipophilin adipocytes, macrophages A2 44 SVASTITGV 607 129-137 AIM-2 ubiquitous (low level) A1 26 RSDSGQQARY 608 intron ALDH1A1 mucosa, keratinocytes A2 44 LLYKLADLI 609 88-96 BCLX (L) ubiquitous (low level) A2 44 YLNDHLEPWI 610 173-182 BING-4 ubiquitous (low level) A2 44 CQWGRLWQL 611 ORF2 CALCA thyroid A2 44 VLLQAGSLHA 612 16-25 CD45 proliferating cells, A24 20 KFLDALISL 613 556-564 testis, multiple tissues (low level) CD274 multiple tissues A2 44 LLNAFTVTV 614 15-23 (lung, heart, dendritic cells, etc.) and induced by IFN-γ CPSF ubiquitous (low level) A2 44 KVHPVIWSL 615 250-258 A2 44 LMLQNALTTM 616 1360-1369 cyclin D1 ubiquitous (low level) A2 44 LLGATCMFV 617 101-109 DR4 24 NPPSMVAAGSVVAAV 618 198-212 DKK1 testis, prostate, A2 44 ALGGHPLLGV 619 20-29 mesenchymal stem cells ENAH (hMen a) breast, prostate stroma A2 44 TMNGSKSPV 620 502-510 and epithelium of colon-rectum, pancreas, endometrium EpCAM epithelial cells A24 20 RYQLDPKFI 621 173-181 EphA3 many DR11 25 DVTFNIICKKCG 622 356-367 EZH2 ubiquitous (low level) A2 44 FMVEDETVL 623 120-128 A2 44 FINDEIFVEL 624 165-174 A24 20 KYDCFLHPF 625 291-299 A24 20 KYVGIEREM 626 735-743 FGF5 brain, kidney A3 22 NTYASPRFKF 627 172-176 and 217-220 glypican-3 placental and A2 44 FVGEFFTDV 628 144-152 multiple tissues A24 20 EYILSLEEL 629 298-306 G250/MN/CAIX stomach, liver, A2 44 HLSTAFARV 630 254-262 pancreas HER-2/neu ubiquitous (low level) A2 44 KIFGSLAFL 631 369-377 A2 44 IISAVVGIL 632 654-662 A2 44 ALCRWGLLL 633 5-13 A2 44 ILHNGAYSL 634 435-443 A2 44 RLLQETELV 635 689-697 A2 44 VVLGVVFGI 636 665-673 A2 44 YMIMVKCWMI 637 952-961 A2 44 HLYQGCQVV 638 48-56 A2 44 YLVPQQGFFC 639 1023-1032 A2 44 PLQPEQLQV 640 391-399 A2 44 TLEEITGYL 641 402-410 A2 44 ALIHHNTHL 642 466-474 A2 44 PLTSIISAV 643 650-658 A3 22 VLRENTSPK 644 754-762 A24 20 TYLPTNASL 645 63-71 HLA-DOB B lymphocytes, A2 44 FLLGLIFLL 646 232-240 monocytes, blood cells, adrenals, . . . Hepsin kidney, liver, skin, A2 44 SLLSGDWVL 647 191-199 . . . A2 44 GLQLGVQAV 648 229-237 A2 44 PLTEYIQPV 649 268-276 IDO1 lymph nodes, placenta, A2 44 ALLEIASCL 650 199-207 and many cell types in the course of inflammatory response IGF2B3 ubiquitous (low level) A2 44 NLSSAEVVV 651 515-523 A3 44 RLLVPTQFV 652 199-207 IL13Ralpha2 A2 44 WLPFGFILI 653 345-353 Intestinal liver, intestine, B7 17 SPRWWPTCL 654 alt. ORF carboxyl kidney esterase alpha- liver A2 44 GVALQTMKQ 655 542-550 foetoprotein A2 44 FMNKFIYEI 656 158-166 DR13 19 QLAVSVILRV 657 364-373 Kallikrein 4 prostate and ovarian A2 44 FLGYLILGV 658 11-19 cancer DP4 75 SVSESDTIRSISIAS 659 125-139 cancer DR4 24 LLANGRMPTVLQCVN 660 155-169 DR7 25 RMPTVLQCVNVSVVS 661 160-174 KIF20A ubiquitous (low level) A2 44 LLSDDDVVV 662 12-20 A2 44 AQPDTAPLPV 663 284-293 A2 44 CIAEQYHTV 664 809-817 Lengsin eye lens and low level A2 44 FLPEFGISSA 665 270-279 in multiple tissues M-CSF liver, kidney B35 20

LPAVVGLSPGEQEY 666 alt. ORF MCSP endothelial cells, DR11 25 VGQDVSVLFRVTGALQ 667 693-708 chondrocytes, smooth muscle cells mdm-2 ubiquitous (brain, A2 44 VLFYLGQY 668 53-60 muscle, lung) Meloe ubiquitous (low level) A2 44 TLNDECWPA 669 36-44 DQ2 41 ERISSTLNDECWPA 670 31-44 DQ6 63 FGRLQGISPKI 671 32-44 DR1 18 TSREQFLPSEGAA 672 11-23 DR11 25 CPPWHPSERISSTL 673 24-37 Midkine ubiquitous (low level) A2 44 ALLALTSAV 674 13-21 A2 44 AQCQETIRV 675 114-122 DR4 24 LTLLALLALTSAVAK 676 9-23 MMP-2 ubiquitous A2 44 GLPPDVQRVH 677 560-568 MMP-7 ubiquitous (low level) A3 22 SLFPNSPKWTSK 678 96-107 MUC1 glandular epithelia A2 44 STAPPVHNV 679 950-958 A2 44 LLLLTVLTV 680 12-20 DR3 21 PGSTAPPAHGVT 681 repeated region MUC5AC surface mucosal A24 20 TCQPTCRSL 682 716-724 cells, respiratory tract, and stomach epithelia p53 ubiquitous (low level) A2 44 LLGRNSFEV 683 264-272 A2 44 RMPEAAPPV 684 65-73 B46 0.1 SQKTYQGSY 685 99-107 DP5 3 PGTRVRAMAIYKQ 686 153-165 DR14 6 HLIRVEGNLRVE 687 193-204 PAX5 hemopoietic system A2 44 TLPGYPPHV 688 311-319 PBF ovary, pancreas, spleen, B55 4 CTACRWKKACQR 689 499-510 liver PRAME testis, ovary, A2 44 VLDGLDVLL 690 100-108 endometrium, A2 44 SLYSFPEPEA 691 142-151 adrenals A2 44 ALYVDSLFFL 692 300-309 A2 44 SLLQHLIGL 693 425-433 A24 20 LYVDSLFFLC 694 301-309 PSMA prostate, CNS, liver A24 20 NYARTEDFF 695 178-186 RAGE-1 retina A2 44 LKLSGVVRL 696 352-360 A2 44 PLPPARNGGLG 697 32-40 B7 17 SPSSNRIRNT 698 11-20 RGS5 heart, skeletal A2 44 LAALPHSCL 699 5-13 muscle, pericytes A3 22 GLASFKSFLK 700 74-83 RhoC ubiquitous (low level) A3 22 RAGLQVRKNK 701 176-185 RNF43 A2 44 ALWPWLLMA(T) 702 11-19(20) A24 20 NSQPVWLCL 703 721-729 RU2AS testis, kidney, bladder B7 17 LPRWPPPQL 704 antisense secernin 1 ubiquitous A2 44 KMDAEHPEL 705 196-204 SOX10 ubiquitous (low level) A2 44 AWISKPPGV 706 332-340 A2 44 SAWISKPPGV 707 331-340 STEAP1 prostate A2 44 MIAVFLPIV 708 292-300 A2 44 HQQYFYKIPILVINK 709 102-116 survivin ubiquitous A2 44 ELTLGEFLKL 710 95-104 ubiquitous DR1 18 TLGEFLKLDRERAKN 711 97-111 Telomerase testis, thymus, A2 44 ILAKFLHWLE 712 540-548 bone marrow, A2 44 RLVDDFLLV 713 865-873 lymph nodes DR7 25 RPGLLGASVLGLDDI 714 672-686 DR11 25 LTDLQPYMRQFVAHL 715 766-780 hTERT WLFFYRKSV(R) 716 572-581 (572) TPBG multiple tissues A2 44 RLARLALVL 717 17-25 (esophagus, bladder, etc.) VEGF ubiquitous (low level) B27 7 SRFGGAVVR 718 -i WT1 testis, ovary, bone A1 26 TSEKRPFMCAY 719 317-327 marrow, spleen A24 20 CMTWNQMNL 720 235-243 DP5 3 LSHLQMHSRKH 721 337-347 DP5 3 KRYFKLSHLQMHSRKH 722 332-347 DR4 24 KRYFKLSHLQMHSRKH 723 332-347

(91) The identification of heteroclitic peptides are described in the art. For example, in previous studies (Selby, et al., *J. Immunol.*, 162(2):669 (1999), Skipper, et al., *J. Exp. Med.* 183:527 (1996), the entire contents of each of which are incorporated herein by reference), heteroclitic epitopes were fortuitously identified by eluting naturally occurring mutant peptides from melanoma cells, or by systematically screening a large number of epitopes consisting of substitutions at almost every position in the epitope (Zaremba, et al., *Cancer Research,* 57:4570 (1997), Loftus, et al., *Cancer Research* 58:2433 (1998), Blake, et al., *J. Exp. Med.* 18:121 (1996), the entire contents of each of which are incorporated herein by reference). Alternatively, heteroclitic epitopes were identified by screening random combinatorial peptide libraries which also has required the arduous synthesis and screening of large numbers of peptides (Pinilla, et al., *Current Opinion in Immunology* 11:193-202 (1999), the entire contents of each of which are incorporated herein by reference). Genetic approaches, such as screening of DNA expression libraries, have provided another method for generating CTL epitopes and analogs (Boon, et al., *Annu. Rev. Immunol.* 12:337-65 (1994), Gavin, et al., *Eur. J. Immunol.* 24(9):2124-33 (1994), the entire contents of each of which are incorporated herein by reference).

(92) Generating Cancer Vaccine in Tumor Cells

(93) Some aspects of the present disclosure provide systems, compositions, and methods of editing genes encoding tumor specific antigens in vivo (e.g., in tumor cells in a subject) or ex vivo (e.g., in isolated tumor cells) to introduce mutations in the genes encoding tumor specific antigens. In some embodiments, such mutations lead to the production of heteroclitic peptides that are more immunogenic than native peptides of the tumor-specific antigen. In some embodiments, such mutations lead to the translation of a non-coding region of the tumor specific antigen, which results in cryptic peptides that are more immunogenic than any native peptides from the tumor specific antigen.

(94) The gene editing methods described herein, rely on nucleobase editors as described in., in U.S. Pat. No. 9,068,179, US Patent Application Publications US 2015/0166980, US 2015/0166981, US 2015/0166982, US20150166984, and US20150165054, and US Provisional Applications, U.S. Ser. No. 62/245,828, filed Oct. 23, 2015; 62/279,346, filed Jan. 15, 2016; 62/311,763, filed Mar. 22, 2016; 62/322,178, filed Apr. 13, 2016, 62/357,352, filed Jun. 30, 2016, U.S. Pat. No. 62,370,700, filed Aug. 3, 2016; 62/398,490, filed Sep. 22, 2016; 62/408,686, filed Oct. 14, 2016; PCT Application PCT/US2016/058344, filed Oct. 22, 2016, U.S. patent application Ser. No. 15/311,852, filed Oct. 22, 2016; and in Komor et al., *Nature*, Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage, 533, 420-424 (2016), the entire contents of each of which are incorporated herein by reference.

(95) The nucleobase editors are highly efficient at precisely editing a target base in any of the tumor associated antigen genes described herein, and a DNA double stand break is not necessary for the gene editing, thus reducing genome instability and preventing possible oncogenic modifications that may be caused by other genome editing methods. The nucleobase editors described herein may be programmed to target and modify a single base. In some embodiments, the target base is a cytosine (C) base and may be converted to a thymine (T) base via deamination by the nucleobase editor.

(96) To edit the polynucleotide encoding a tumor associated antigen, the polynucleotide is contacted with a nucleobase

editor as described herein. In some embodiments, the tumor-associated antigen encoding polynucleotide is contacted with a nucleobase editor and a guide nucleotide sequence, wherein the guide nucleotide sequence targets the nucleobase editor the target base (e.g., a C base) in the tumor-associated antigen encoding polynucleotide.

(97) In some embodiments, the tumor-associated antigen encoding polynucleotide is the tumor-associated antigen gene locus in the genomic DNA of a cell (e.g., a tumor cell). In some embodiments, the tumor cell is a cultured cell. In some embodiments, the tumor cell is in vivo. In some embodiments, the tumor cell is ex vivo. In some embodiments, the tumor cell is from a mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a rodent. In some embodiments, the rodent is a mouse. In some embodiments, the rodent is a rat.

(98) In some embodiments, the tumor-associated antigen encoding polynucleotide may be a DNA molecule comprising a coding strand and a complementary strand, e.g., the tumor-associated antigen gene locus in the genome of a tumor cell. In some embodiments, the tumor-associated antigen encoding polynucleotide may also include coding regions (e.g., exons) and non-coding regions (e.g., introns or splicing sites). In some embodiments, the target base (e.g., a C base) is located in the coding region (e.g., an exon) of the tumor-associated antigen encoding polynucleotide. As such, the conversion of a base in the coding region may result in an amino acid change in the tumor-associated antigen protein sequence, i.e., a mutation. Tumor associated antigens comprising the desired mutation(s), once degraded (e.g., via any of the protein degradation pathways, such as degradation by the proteasome) results in immunogenic heteroclitic epitopes.

(99) In some embodiments, the target base is located in a non-coding region of the tumor-associated antigen gene, e.g., in an intron or a splice site. In some embodiments, a target base is located in a splice site, and the editing of such target base causes alternative splicing of the tumor-associated antigen mRNA. In some embodiments, the alternative splicing leads to translation of a non-coding region of the tumor-associated antigen gene, generating cryptic epitopes. The immunogenic epitopes (e.g., heteroclitic epitopes or cryptic epitopes) may be presented by the tumor cell, or a professional antigen presenting cell, and be recognized by the immune system, thus eliciting a tumor-specific immune response (e.g., T-cell response or B-cell response).

(100) To edit a tumor-associated antigen gene, the tumor-associated antigen gene (a polynucleotide molecule) may be contacted with the nucleobase editor, wherein the nucleobase editor binds to its target sequence and edits the desired base. For example, the nucleobase editor may be expressed in a cell where editing is desired (e.g., a tumor), allowing editing of the tumor-associated antigen gene by the nucleobase editor. In some embodiments, the binding of the nucleobase editor to its target sequence in the tumor-associated antigen gene is mediated by a guide nucleotide sequence, e.g., a nucleotide molecule comprising a nucleotide sequence that is complementary to one of the strands of the target sequence in the tumor-associated antigen gene. Thus, by designing the guide nucleotide sequence, the nucleobase editor may be programmed to edit any target base in any tumor associated antigen gene. In some embodiments, the guide nucleotide sequence is co-expressed with the nucleobase editor in a tumor cell where editing is desired. In some embodiments, a nucleobase editor/gRNA complex is delivered to the cell where editing is desired (e.g., a tumor cell).

(101) Provided herein are non-limiting, exemplary heteroclitic epitopes and cryptic epitopes that may be produced via base editing and strategies for making them.

(102) Codon Change

(103) Using the nucleobase editors described herein, several amino acid codons may be converted to a different codon via deamination of a target base within the codon. For example, in some embodiments, a cytosine (C) base is converted to a thymine (T) base via deamination by a nucleobase editor comprising a cytosine deaminase domain (e.g., APOBEC1 or AID). It is worth noting that during a C to T change via deamination (e.g., by a cytosine deaminase such as APOBEC1 or AID), the cytosine is first converted to a uridine (U), leading to a G:U mismatch. The G:U mismatch is then converted by DNA repair and replication pathways to T:A pair, thus introducing the thymine at the position of the original cytosine. As such, deamination of a C base results in a C-G base pair being replaced by a T-A base pair.

(104) As is familiar to one skilled in the art, conversion of a base in an amino acid codon may lead to a change of the amino acid the codon encodes. Cytosine deaminases are capable of converting a cytosine (C) base to a thymine (T) base via deamination. Thus, it is envisioned that, for amino acid codons containing a C base, the C base may be directly converted to T. For example, codon for leucine (CTC) may be changed to a TTC (phenylalanine) codon via the deamination of the first C on the coding strand. For amino acid codons that contain a guanine (G) base, a C base is present on the complementary strand; and the G base may be converted to an adenosine (A) via the deamination of the C on the complementary strand. For example, an ATG (Met/M) codon may be converted to a ATA (Ile/I) codon via the deamination of the third C on the complementary strand. In some embodiments, two C to T changes are required to convert a codon to a different codon. Non-limiting examples of possible mutations that may be made in any tumor associated antigens by the nucleobase editors of the present disclosure are summarized in Table 4.

(105) TABLE-US-00008 TABLE 4 Exemplary Codon Changes via Base Editing Target codon Base-editing reaction (s) Edited codon CTT (Leu/L) 1st base C to T on coding strand TTT (Phe/F) CTC (Leu/L) 1st base C to T on coding strand TTC (Phe/F) ATG (Met/M) 3rd base C to T on complementary strand ATA (Ile/I) GTT (Val/V) 1st base C to T on complementary stand ATT (Ile/I) GTA (Val/V) 1st base C to T on complementary stand ATA (Ile/I) GTC (Val/V) 1st base C to T on complementary strand ATC (Ile/I) GTG (Val/V) 1st base C to T on complementary strand ATG (Met/M) TCT (Ser/S) 2nd base C to T on coding strand TTT (Phe/F) TCC (Ser/S) 2nd base C to T on coding strand TTC (Phe/F) TCA (Ser/S) 2nd base C to T on coding strand TTA (Leu/L) TCG (Ser/S) 2nd base C to T on coding strand TTG (Leu/L) AGT (Ser/S) 2nd base C to T on complementary strand AAT (Asp/N) AGC (Ser/S) 2nd base C to T on complementary strand

AAC (Aps/N) CCT (Pro/P) 1st base C to T on coding strand TCT (Ser/S) CCC (Pro/P) 1st base C to T on coding strand TCC (Ser/S) CCA (Pro/P) 1st base C to T on coding strand TCA (Ser/S) CCG (Pro/P) 1st base C to T on coding strand TCG (Ser/S) CCT (Pro/P) 2nd base C to T on coding strand CTT (Leu/L) CCC (Pro/P) 2nd base C to T on coding strand CTC (Leu/L) CCA (Pro/P) 2nd base C to T on coding strand CTA (Leu/L) CCG (Pro/P) 2nd base C to T on coding strand CTG (Leu/L) ACT (Thr/T) 2nd base C to T on coding strand ATT (Leu/L) ACC (Thr/T) 2nd base C to T on coding strand ATC (Leu/L) ACA (Thr/T) 2nd base C to T on coding strand ATA (Leu/L) ACG (Thr/T) 2nd base C to T on coding strand ATG (Met/M) GCT (Ala/A) 2nd base C to T on coding strand GTT (Val/V) GCC (Ala/A) 2nd base C to T on coding strand GTC (Val/V) GCA (Ala/A) 2nd base C to T on coding strand GTA (Val/V) GCG (Ala/A) 2nd base C to T on coding strand GTG (Val/V) GCT (Ala/A) 1st base C to T on complementary stand ACT (Thr/T) GCC (Ala/A) 1st base C to T on complementary stand ACC (Thr/T) GCA (Ala/A) 1st base C to T on complementary stand ACA (Thr/T) GCG (Ala/A) 1st base C to T on complementary stand ACG (Thr/T) CAT (His/H) 1st base C to T on complementary stand TAT (Tyr/Y) CAC (His/H) 1st base C to T on complementary stand TAC (Tyr/Y) GAT (Asp/D) 1st base C to T on complementary stand AAT (Asp/N) GAC (Asp/D) 1st base C to T on complementary stand AAC (Asp/N) GAA (Glu/E) 1st base C to T on complementary stand AAA (Lys/K) GAG (Glu/E) 1st base C to T on complementary stand AAG (Lys/K) TGT (Cys/C) 2nd base C to T on complementary stand TAT (Tyr/Y) TGC (Cys/C) 2nd base C to T on complementary stand TAC (Tyr/Y) CGT (Arg/R) 1st base C to T on coding strand TGT (Cys/C) CGC (Arg/R) 1st base C to T on coding strand TGC (Cys/C) AGA (Arg/R) 2nd base C to T on complementary stand AAA (Lys/K) AGG (Arg/R) 2nd base C to T on complementary stand AAG (Lys/K) CGG (Arg/R) 2nd base C to T on complementary stand CAG (Gln/Q) CGG (Arg/R) 1st base C to T on coding strand TGG (Trp/W) GGT (Gly/G) 2nd base C to T on complementary stand GAT (Asp/D) GGC (Gly/G) 2nd base C to T on complementary stand GAC (Asp/D) GGA (Gly/G) 2nd base C to T on complementary stand GAA (Glu/E) GGG (Gly/G) 2nd base C to T on complementary stand GAG (Glu/E) GGT (Gly/G) 1st base C to T on complementary stand AGT (Ser/S) GGC (Gly/G) 1st base C to T on complementary stand AGC (Ser/S) GGA (Gly/G) 1st base C to T on complementary stand AGA (Arg/R) GGG (Gly/G) 1st base C to T on complementary stand AGG (Arg/R)

(106) Such amino acid substitutions introduced via base editing generate heteroclitic epitopes. Non-limiting examples of heteroclitic epitopes that may be generated from tumor associated antigens by nucleobase editors are summarized in Table 5.

(107) In some embodiments, to bind to its target sequence and edit the desired base, the nucleobase editor depends on its guide nucleotide sequence (e.g., a guide RNA). In some embodiments, the guide nucleotide sequence is a gRNA sequence. A gRNA typically comprises a tracrRNA framework allowing for Cas9 binding, and a guide sequence, which confers sequence specificity to fusion proteins disclosed herein. In some embodiments, the guide RNA comprises the structure 5′-[guide sequence]-guuuuagagcuagaaauagcaaguuaaaauaaaggcuaguccguuaucaacuugaaaaaguggcaccgagucggugcuu uuu-3′ (SEQ ID NO: 336), wherein the guide sequence comprises a sequence that is complementary to the target sequence. Other suitable tracrRNA framework sequences are provided in Table 11. The guide sequence is typically about 20 nucleotides long. In certain embodiments, the guide sequence may be 15-25 nucleotides long. In some embodiments, the guide sequence is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides long. Such suitable guide RNA sequences typically comprise guide sequences that are complementary to a nucleic sequence within 50 (e.g., within 50, 45, 40, 35, 30, 35, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, or 10) nucleotides upstream or downstream of the target nucleotide to be edited.

(108) Guide sequences that may be used to target the nucleobase editor to its target sequence to induce specific mutations in tumor associated antigen genes are provided in Table 5. It is to be understood that the mutations and guide sequences presented herein are for illustration purpose only and are not meant to be limiting.

(109) TABLE-US-00009 TABLE 5 Heteroclitic epitopes Antigen Name/Epitope Heteroclitic amino acid epitope position (mutation), Programmable SEQ Genome (Exemplary Genomic guide-RNA ID gRNA size Editor condition) target region sequence NO (PAM) (C-edited) type.sup.a gp100/209-217 IIDQVPFSV GCCUUCACCAUUACUGGUAA 724 (GGG) 20 (C14) SpBE3 (melanoma) (T2101) CACCAUUACUGGUAAGGGUU 870 (TAG) 20 (C9) SpBE3 (SEQ ID ACCAUUACUGGUAAGGGUUU 871 (AGG) 20 (C8) SpBE3 NO: 786) CCAUUACUGGUAAGGGUUUA 872 (GGAA) 20 (C7) VQR-SpBE3 ttcaccattaCt AUUACUGGUAAGGGUUUAGG 873 (AAG) 20 (C5) SpBE3 ggtaagggttta UUACUGGUAAGGGUUUAGGA 874 (AGG) 20 (C4) SpBE3 ggaaggggca UACUGGUAAGGGUUUAGGAA 875 (GGG) 20 (C3) SpBE3 (SEQ ID ACUGGUAAGGGUUUAGGAAG 876 (GGG) 20 (C2) SpBE3 NO: 831) CAGCCUUCACCAUUACUGGU 877 (AAGGGT) 20 (C16) SaBE3 UUACUGGUAAGGGUUUAGGA 888 (AGGGG) 20 (C5) St3BE3 gp100/280-288 YLEPGPVT UCACUGCCCAGGUGGUCCUG 725 (CAG) 20 (C7) SpBE3 (melanoma) V (A288V) CACUGCCCAGGUGGUCCUGC 889 (AGG) 20 (C6) SpBE3 (SEQ ID NO: 818) agtca**c**tg**C**c**c** aggtggtcctg caggctgccatt cc (SEQ ID NO: 832) gp100/154-162 KIWGQYW AUGUCUGGAAGACCUGGGGU 726 (GAG) 20 (C13) SpBE3 (melanoma) QV (T1551) UGUCUGGAAGACCUGGGGUG 890 (AGG) 20 (C12) SpBE3 (SEQ ID GUCUGGAAGACCUGGGGUGA 891 (GGG) 20 (C11) SpBE3 NO: 787) UCUGGAAGACCUGGGGUGAG 892 (GGAC) 20 (C10) VQR-SpBE3 tatgtctggaag aCctggggtg agggactccctt ct (SEQ ID NO: 833) MART-1/26-35 EVAGIGILT GGCCGCAGGGAUCGGCAUCC 727 (TGAT) 20 (C6) VQR-SpBE3 (melanoma) V (A27V) GCAGGGAUCGGCAUCCUGAU 893 (CGTG) 20 (C2) VQR-SpBE3 (SEQ ID UGGUCCAGGGCCGCAGGGAU

894 (CGG) 20 (C14) SpBE3 NO: 819) AGGGCCGCAGGGAUCGGCAU 895 (CCTGAT) 20 (C8) KKH-SaBE3 tggtccagggc GCAGGGAUCGGCAUCCUGAU 896 (CGTGGT) 20 (C2) KKH-SaBE3 **c**g**C**agggat**c** ggcatcctgatc gtggtcctggg ga (SEQ ID NO: 834) NY-ESO-1/157- SLLMWITQ ACUGCGUGAUCCACAUCAAC 728 (AGG) 20 (C-1) SpBE3 165 Y (C165Y) CACUGCGUGAUCCACAUCAA 897 (CAG) 20 (C1) SpBE3 (multiple (SEQ ID tumors, e.g., NO: 788) melanoma and ctttccctgttgat breast cancer) gtggatcac**g**c agt**G**ctttctgc cc (SEQ ID NO: 835) TYR/369-377 YMNGIMSQ AUGGAACAAUGUCCCAGGUA 729 (CAG) 20 (C7) SpBE3 (melanoma) V (T3731) UGGAACAAUGUCCCAGGUAC 898 (AGG) 20 (C6) SpBE3 (SEQ ID GGAACAAUGUCCCAGGUACA 899 (GGG) 20 (C5) SpBE3 NO: 789) GAACAAUGUCCCAGGUACAG 900 (GGAT) 20 (C4) VQR-SpBE3 tatgaatggaa UGGAACAAUGUCCCAGGUAC 901 (AGGGAT) 20 (C6) SaBE3 Caatgtcccag gtacagggatc tgcc (SEQ ID NO: 836) TyRP-1/240- DAEKYDIC CACACUUUUCUGCAUCCCGC 730 (CAG) 20 (C3) SpBE3 251 TDEY GUCACACUUUUCUGCAUCCC 902 (GCCAGT) 20 (C5) KKH-SaBE3 (melanoma) (C244Y) (SEQ ID NO: 790) tgggactggcg ggatgcagaa aa**gt**G**t**gacat ttgcacagatg agtacatggga (SEQ ID NO: 837) Survivin/95-102 ELILGEFLK AUUAACCCUUGGUGAAUUUU 731 (TGAA) 20 (C6) VQR-SpBE3 (multiple L (T971) CCUUGGUGAAUUUUUGAAAC 903 (TGG) 20 (C-1) SpBE3 tumors, e.g., (SEQ ID melanoma, NO: 791) breast cancer, tttgaagaatta and leukemia) a**C**ccttggtga atttttgaaactg gac (SEQ ID NO: 838) HER2/657-666 AMVGILLVV CGCAGAGAUGAUGGACGUCA 732 (GAG) 20 (C-1) VQR-SpBE3 (breast cancer) V (V658M) ACCGCAGAGAUGAUGGACGU 904 (CAG) 20 (C2) SpBE3 (SEQ ID CCAACCACCGCAGAGAUGAU 905 (GGAC) 20 (C8) VQR-SpBE3 NO: 793) GCCAACCACCGCAGAGAUGA 906 (TGG) 20 (C9) SpBE3 gcttccgccccc AAUGCCAACCACCGCAGAGA 907 (TGAT) 20 (C12) VQR-SpBE3 agccctctgac AGAAUGCCAACCACCGCAGA 908 (GATGAT) 20 (C14) KKH-SaBE3 gtccatcatctct CCGCAGAGAUGAUGGACGUC 909 (AGAG) 20 (C1) EQR-SpBE3 gcgGtggttgg cattctgctggtc (SEQ ID NO: 839) HER2/911-920 IIWELMTFG AGGUGUGACUGUGUGGGAGC 733 (TGAT) 20 (C9) VQR-SpBE3 (breast cancer) A (T9121) UGUGACUGUGUGGGAGCUGA 910 (TGAC) 20 (C6) VQR-SpBE3 (SEQ ID UUAGGUGUGACUGUGUGGGA 911 (GCTGAT) 20 (C11) KKH-SaBE3 NO: 794) GUGUGGGAGCUGAUGACUUU 912 (TGGGG) 20 (C-2) St3BE3 aggtgtgaCtg tgtgggagctg atgacttttggg gCcaaacctta cgatgggatcc cagcccggga gatccct (SEQ ID NO: 840) HER2/911-920 ITWELMTF ACUUUUGGGGCCAAACCUUA 734 (CGAT) 20 (C11) VQR-SpBE3 (breast cancer) GV (A920V) UUUGGGGCCAAACCUUACGA 913 (TGG) 20 (C8) SpBE3 (SEQ ID UUGGGGCCAAACCUUACGAU 914 (GGG) 20 (C7) SpBE3 NO: 795) UUUGGGGCCAAACCUUACGA 915 (TGGGAT) 20 (C8) SaBE3 gacttttgggg **C**caaaccttac gatgggatccc agcccggg (SEQ ID NO: 841) hTERT/540- ILAKFLHWL CAUCAGCCAGUGCAGGAACU 735 (TGG) 20 (C1) SpBE3 549 I (M5491) CACACUCAUCAGCCAGUGCA 916 (GGAA) 20 (C7) VQR-SpBE3 (breast cancer) (SEQ ID ACACACUCAUCAGCCAGUGC 917 (AGG) 20 (C8) SpBE3 NO: 792) UACACACUCAUCAGCCAGUG 918 (CAG) 20 (C9) SpBE3 cgtgaggagat GACGUACACACUCAUCAGCC 919 (AGTG) 20 (C12) VQR-SpBE3 cctggccaagtt GACGACGUACACACUCAUCA 920 (GCCAGT) 20 (C11) KKH-SaBE3 cctgcactggct gat**G**agtgtgt acgtcgtcgag ctg (SEQ ID NO: 842) hTERT/572- WLFFYRKS UUCUGAUGCUCGGCUCUUCU 736 (TGG) 20 (C11) SpBE3 580 V (R572W) (breast cancer) (SEQ ID NO: 716) cccaagcctat cttttctgatgct **C**ggctcttcttg gtcacctctccg ttcca (SEQ ID NO: 843) SSX2/41-49 KVSEKIFYV GAAAAGAUGAAAGCCUCGGA 737 (GAAAAT) 20 (C14) KKH-SaBE3 (multiple (A42V) GCCUCGGAGAAAAUCUUCUA 921 (TGTG) 20 (C2) VQR-SpBE3 tumors) (SEQ ID NO: 797) ggaaaagatg aaag**C**c**t**c**g**g agaaaatcttct atgtgtatatga agagaaagtat gaggctatgac t (SEQ ID NO: 844) WT1/235-243 YMTWNQM CAGGUCAUGCAUUCAAGCUG 738 (GGAT) 20 (C10) VQR-SpBE3 (Leukemia) NL (C235Y) CCAGGUCAUGCAUUCAAGCU 922 (GGG) 20 (C11) SpBE3 (SEQ ID UCCAGGUCAUGCAUUCAAGC 923 (TGG) 20 (C12) SpBE3 NO: 798) GCAUUCAAGCUGGGAUGUCA 924 (TTTGGT) 20 (C2) KKH-SaBE3 atttataccaaa UCCAGGUCAUGCAUUCAAGC 925 (TGGGAT) 20 (C12) SaBE3 tgacatcccag cttgaat**G**catg acctgga (SEQ ID NO: 845) WT1/235-243 CITWNQMN UGAUUCCAGGUCAUGCAUUC 739 (AAG) 20 (C12) SpBE3 (Leukemia) L (M2361) UCCAGGUCAUGCAUUCAAGC 926 (TGGGAT) 20 (C8) SaBE3 (SEQ ID CAGGUCAUGCAUUCAAGCUG 927 (GGAT) 20 (C6) VQR-SpBE3 NO: 799) CCAGGUCAUGCAUUCAAGCU 928 (GGG) 20 (C7) SpBE3 atttataccaaa UCCAGGUCAUGCAUUCAAGC 929 (TGG) 20 (C8) SpBE3 tgacatcccag cttgaatgcat**G** acctggaatca gat (SEQ ID NO: 846) CD33/65-73 VIISGDSPV GGGAAGGAGCCAUUAUAUCC 740 (AGG) 20 (C10) SpBE3 (Leukemia) (A65V) GGAAGGAGCCAUUAUAUCCA 930 (GGG) 20 (C9) SpBE3 (SEQ ID GAAGGAGCCAUUAUAUCCAG 931 (GGAC) 20 (C8) VQR-SpBE3 NO: 796) GCCAUUAUAUCCAGGGACUC 932 (TCCAGT) 20 (C2) KKH-SaBE3 ctggttccggg aaggag**C**c**c**at tatatccaggg actctccagtg (SEQ ID NO: 847) EpCAM/184- ILYENNVII UAAUGUUAUCACUAUUGAUC 741 (TGG) 20 (C12) SpBE3 192 (T1921) UUAUCACUAUUGAUCUGGUU 933 (CAAAAT) 20 (C7) KKH-SaBE3 (multiple (SEQ ID AAUAAUGUUAUCACUAUUGA 934 (TCTGGT) 20 (C14) KKH-SaBE3 tumors) NO: 800) atgagaataat gttatca**C**tattg atctggttcaaa attcttctc (SEQ ID NO: 848) CEA-CAM/24- LLTFWNPPI ACCACUGCCAAGCUCACUAU 742 (TGA) 20 (C2) SpBE3 31 (T3141) GGAACCCGCCCACCACUGCC 935 (AAG) 20 (C13) SpBE3 (multiple (SEQ ID ACCACUGCCAAGCUCACUAU 936 (TGAA) 20 (C2) VQR-SpBE3 tumors, e.g., NO: 801) colorectal taaccttctgga cancer, lung acccgcc**c**a**C** cancer, breast **c**actgccaagc cancer) tcactattgaatc cacgccgt (SEQ ID NO: 849) CEA-CAM/310- RITVTTITV CCUCAAUAGGACCACAGUCA 743 (CGAC) 20 (C12) VQR-SpBE3 318 (T3111) CAAUAGGACCACAGUCACGA 937 (CGAT) 20 (C9) VQR-SpBE3 (multiple (SEQ ID

GACCACAGUCACGACGAUCA 938 (CAG) 20 (C3) SpBE3 tumors, e.g., NO: 802) CUCAAUAGGACCACAGUCAC 939 (GACGAT) 20 (C11) KKH-SaBE3 colorectal gacactggcct AGGACCACAGUCACGACGAU 940 (CACAGT) 20 (C5) KKH-SaBE3 cancer, lung caataggaCc cancer, breast acagtcacgac cancer) gatcacagtct atggtaagtgg atccacgaa (SEQ ID NO: 850) CEA-CAM/687- AVVGIMIGV UGGGGCCACUGUCGGCAUCA 744 (TGAT) 20 (C9) VQR-SpBE3 695 (T688V) GCCACUGUCGGCAUCAUGAU 941 (TGG) 20 (C5) SpBE3 (multiple (SEQ ID CCACUGUCGGCAUCAUGAUU 942 (GGAG) 20 (C4) EQR-SpBE3 tumors, e.g., NO: 803) CACUGUCGGCAUCAUGAUUG 943 (GAG) 20 (C3) SpBE3 colorectal tctcctggtctct ACUGUCGGCAUCAUGAUUGG 944 (AGTG) 20 (C2) VQR-SpBE3 cancer, lung cagctggggcc GCUGGGGCCACUGUCGGCAU 945 (CATGAT) 20 (C11) KKH-SaBE3 cancer, breast aCtgtcggcat GCCACUGUCGGCAUCAUGAU 946 (TGGAGT) 20 (C5) SaBE3 cancer) catgattggagt GCCACUGUCGGCAUCAUGAU 947 (TGGAG) 20 (C5) St3BE3 gctggttggggt t (SEQ ID NO: 851) CEA-CAM/691- IMIGMLVGV UCCAAUCAUGAUGCCGACAG 745 (TGG) 20 (C-1) SpBE3 699 (V695M) ACUCCAAUCAUGAUGCCGAC 948 (AGTG) 20 (C2) VQR-SpBE3 (multiple (SEQ ID CACUCCAAUCAUGAUGCCGA 949 (CAG) 20 (C3) SpBE3 tumors, e.g., NO: 804) CAGCACUCCAAUCAUGAUGC 950 (CGAC) 20 (C6) VQR-SpBE3 colorectal tctcagctggg CCCAACCAGCACUCCAAUCA 951 (TGAT) 20 (C12) VQR-SpBE3 cancer, lung gccactgtcgg AGCACUCCAAUCAUGAUGCC 952 (GACAGT) 20 (C5) KKH-SaBE3 cancer, breast catcatgattgg ACCCCAACCAGCACUCCAAU 953 (CATGAT) 20 (C14) KKH-SaBE3 cancer) aGtgctggttg gggtt (SEQ ID NO: 852) MAGEA3/112- KVAELVYF GUUGGUUCAUUUUCUGCUCC 746 (TCAAGT) 20 (C8) KKH-SaBE3 120 L (H118Y) UGGUUCAUUUUCUGCUCCUC 954 (AAG) 20 (C6) SpBE3 (multiple (SEQ ID tumors) NO: 805) aggtggccga gttggttCattttc tgctcctcaagt atcgagccag ggagccggtc ac (SEQ ID NO: 853) MAGEA3/181- YLGLSYDG AGGUGACAAGGACAUAGGAG 747 (TGG) 20 (C-1) SpBE3 190 (also in LL (C181Y) GCAGGUGACAAGGACAUAGG 955 (AGTG) 20 (C2) VQR-SpBE3 MAGE A1 (SEQ ID GGCAGGUGACAAGGACAUAG 956 (GAG) 20 (C3) SpBE3 (multiple NO: 806) AGGCAGGUGACAAGGACAUA 957 (GGAG) 20 (C4) EQR-SpBE3 tumors) ctatgtccttgtc UAGGCAGGUGACAAGGACAU 958 (AGG) 20 (C5) SpBE3 acctGcctagg CUAGGCAGGUGACAAGGACA 959 (TAG) 20 (C6) SpBE3 tctctcctatgat GAGACCUAGGCAGGUGACAA 960 (GGAC) 20 (C11) VQR-SpBE3 (SEQ ID AGAGACCUAGGCAGGUGACA 961 (AGG) 20 (C13) SpBE3 NO: 854) UAGGCAGGUGACAAGGACAU 962 (AGGAGT) 20 (C5) SaBE3 20 (C-1) SpBE3 MAGEA3/181- YLGLSYDG AGGUGACAAGGAUGUACAAG 748 (TGG) 20 (C-1) SpBE3 190 (also in LL (C181Y) GCAGGUGACAAGGAUGUACA 963 (AGTG) 20 (C2) VQR-SpBE3 MAGE A2/A12 (SEQ ID GGCAGGUGACAAGGAUGUAC 964 (AAG) 20 (C3) SpBE3 (multiple NO: 806) GAGGCCCAGGCAGGUGACAA 965 (GGAT) 20 (C11) VQR-SpBE3 tumors) tacatccttgtca AGAGGCCCAGGCAGGUGACA 966 (AGG) 20 (C13) SpBE3 cctGcctgggc CAGGCAGGUGACAAGGAUGU 967 (ACAAGT) 20 (C5) KKH-SaBE3 ctctcctacgat GAGAGGCCCAGGCAGGUGAC 968 (AAGGAT) 20 (C14) SaBE3 (SEQ ID NO: 855) MAGEA3/181- YLGLSYDG AGGUGGCAAAGAUGUACAAG 749 (TGG) 20 (C-1) SpBE3 190 (also in LL (C181Y) GCAGGUGGCAAAGAUGUACA 969 (AGTG) 20 (C2) VQR-SpBE3 MAGE A3 (SEQ ID GGCAGGUGGCAAAGAUGUAC 970 (AAG) 20 (C3) SpBE3 (multiple NO: 806) GAGGCCCAGGCAGGUGGCAA 971 (AGAT) 20 (C11) VQR-SpBE3 tumors) gtacatctttgcc AGAGGCCCAGGCAGGUGGCA 972 (AAG) 20 (C13) SpBE3 acctGcctggg CAGGCAGGUGGCAAAGAUGU 973 (ACAAGT) 20 (C6) KKH-SaBE3 cctctcctacga GAGAGGCCCAGGCAGGUGGC 974 (AAAGAT) 20 (C12) KKH-SaBE3 (SEQ ID NO: 856) MAGEA3/181- YLGLSYDG AGGCAGGUGACAAGGGUGUA 750 (GGTG) 20 (C4) VQR-SpBE3 190 (also in LL (C181Y) CAGGCAGGUGACAAGGGUGU 975 (AGG) 20 (C5) SpBE3 MAGE A4 (SEQ ID CCAGGCAGGUGACAAGGGUG 976 (TAG) 20 (C6) SpBE3 (multiple NO: 806) AGGCCCAGGCAGGUGACAAG 977 (GGTG) 20 (C9) VQR-SpBE3 tumors) tacacccttgtc AAGGCCCAGGCAGGUGACAA 978 (GGG) 20 (C10) SpBE3 acctGcctggg AAAGGCCCAGGCAGGUGACA 979 (AGG) 20 (C11) SpBE3 cctttcctatgat GAAAGGCCCAGGCAGGUGAC 980 (AAG) 20 (C12) SpBE3 (SEQ ID CCCAGGCAGGUGACAAGGGU 981 (GTAGGT) 20 (C7) KKH-SaBE3 NO: 857) CAGGCAGGUGACAAGGGUGU 982 (AGGTG) 20 (C5) St3BE3 AAGGCCCAGGCAGGUGACAA 983 (GGGTG) 20 (C11) St3BE3 MUC-1/92-101 AIWGQDVT UCAGCUGCCACCUGGGGACA 751 (GGAT) 20 (C11) VQR-SpBE3 (multiple SV (T931) CUGGGGACAGGAUGUCACCU 984 (CGG) 20 (C-1) SpBE3 tumors) (SEQ ID ACCUGGGGACAGGAUGUCAC 985 (CTCGGT) 20 (C2) KKH-SaBE3 NO: 807) tcagctgccaC ctggggacag gatgtcacctcg gtcccagtcac caggcca (SEQ ID NO: 858) .sup.aGenome-editor types abbreviations: SpBE3 = APOBEC1—SpCas9n—UGI; VQR-SpBE3 = APOBEC1—VQR-SpCas9n—UGI; EQR-SpBE3 = APOBEC1—EQR-SpCas9n—UGI; VRER-SpBE3 = APOBEC1—VRER-SpCas9n—UGI; SaBE3 = APOBEC1—SaCas9n—UGI; KKH-SaBE3 = APOBEC1—KKH-SaCas9n—UGI; St3BE3 = APOBEC1—St3Cas9n—UGI; St1BE3 = APOBEC1—St1Cas9n—UGI. Guide sequences (the portion of the guide RNA that targets the nucleobase editor to the target sequence) are provided. The guide sequences may be used with any tracrRNA framework sequences known in the art to generate the full guide RNA sequence.

Cryptic Epitopes

(110) Some aspects of the present disclosure provide strategies for generating cryptic epitopes in tumor cells. In some embodiments, such strategies involve alterations of splicing sites in a tumor associated antigen gene. Altered splicing site

may lead to altered splicing of an mRNA that encodes a tumor associated antigen. One outcome of altered splicing is the translation of an otherwise non-coding region of the gene, leading to otherwise "hidden peptides," i.e., cryptic epitopes. The splicing site typically comprises an intron donor site, a Lariat branch point, and an intron acceptor site. The mechanism of splicing are familiar to those skilled in the art. The intron donor site has a consensus sequence of GGGTRAGT, and the C bases paired with the G bases in the intron donor site consensus sequence may be targeted by a nucleobase editor, thereby altering the intron donor site. The Lariat branch point also has a consensus sequence, e.g., YTRAC, wherein Y is a pyrimidine, and R is a purine. The C base in the Lariat branch point consensus sequence may be targeted by the nucleobase editors described herein, leading to skipping of the following exon. The intron acceptor site has a consensus sequence of YNCAGG, wherein Y is a pyrimidine, and N is any nucleotide. The C base of the consensus sequence of the intron acceptor site, and the C base paired with the G bases in the consensus sequence of the intron acceptor site may be targeted by the nucleobase editors described herein, thereby altering the intron acceptor site, in turn leading to skipping of an exon. General strategies of altering the splicing sites are described in Table 6.

(111) TABLE-US-00010 TABLE 6 Exemplary Alteration of Intron-Exon Junction via Base Editing Target Consensus Base-editing Edited site Sequence reaction (s) sequence Outcome Intron GGGTRAGT 2.sup.nd or 3.sup.rd base GAGTRAGT Intron sequence is donor (example) C to T on (example) translated as exon, in complementary frame premature STOP strand codon Lariat YTRAC 5.sup.th base C to T YTRAT The following exon is branch (example) on coding (example) skipped from the mature point strand mRNA, which may affect the coding frame Intron Y(rich)NCAGG 2.sup.nd to last base Y(rich)NCAAG The exon is skipped from acceptor (example) C to T on (example) the mature mRNA, which complementary may affect the coding strand frame Start ATG (Met/M) 3.sup.rd base C to T ATA (Ile/I) The next ATG is used as codon on start codon, which may complementary affect the coding frame strand

(112) Non-limiting, exemplary cryptic epitopes that may be produced using the base editing methods described herein are provided in Table 7.

(113) TABLE-US-00011 TABLE 7 Cryptic Epitopes Antigen Name Cryptic and epitope(s) and Programmable SEQ gRNA Genome Exemplary Genomic target guide-RNA ID size (C- Editor Condition(s) region sequence NO (PAM) edited) type.sup.a gp100 (PMEL VYFFLPDHL UCCCUCACCCCAGGUCUUCC 752 (AGAC) 20 (C9) VQR-SpBE3 gene) (SEQ ID NO: GUCCCUCACCCCAGGUCUUC 986 (CAG) 20 (C9/10) SpBE3 (melanoma) 808) AGAAGGGAGUCCCUCACCCC 987 (AGG) 20 (n.a.) WT Cas9 AAGCTTTGTTT UGUCUGGAAGACCUGGGGUG 988 (AGG) 20 (n.a.) WT Cas9 ATGTCTGGAAG GUCUGGAAGACCUGGGGUGA 989 (GGG) 20 (n.a.) WT Cas9 ACCTGG**Gg**tgag AUGUCUGGAAGACCUGGGGU 990 (GAG) 20 (n.a.) WT Cas9 ggactcccttctcagcc GAGAAGGGAGUCCCUCACCC 991 (CAG) 20 (n.a.) WT Cas9 tatcatccacac (SEQ ID NO: 859) intron 4, intron donor site gp100 (PMEL VYFFLPDHL CCUGAAGUUUUUGGAAUGAA 753 (AAG) 20 (C1/2) SpBE3 gene) (SEQ ID NO: UUGGCCUGAAGUUUUUGGAA 992 (TGAA) 20 (C4/5) VQR-SpBE3 (melanoma) 808) AGUAUUGGCCUGAAGUUUUU 993 (GGAA) 20 (C9/10) VQR-SpBE3 ccaaaaacttcagG CAGUAUUGGCCUGAAGUUUU 994 (TGG) 20 (C10/11) SpBE3 CCAATACTGGC CAGUAUUGGCCUGAAGUUUU 995 (TGGAAT) 20 (C10/11) SaBE3 AAGTTCT (SEQ CUUUUCAUUCCAAAAACUUC 996 (AGG) 20 (n.a.) WT Cas9 ID NO: 860) AACUUGCCAGUAUUGGCCUG 997 (AAG) 20 (n.a.) WT Cas9 intron 4, intron GCUUUUCAUUCCAAAAACUU 998 (CAG) 20 (n.a.) WT Cas9 acceptor site TYRP1 MSLQRQFLR (S CUCAUUCUGCUUGAAAUAAG 754 (AGTG) 20 (C3) VQR-SpBE3 (melanoma) EQ ID NO: 809) ACUCAUUCUGCUUGAAAUAA 999 (GAG) 20 (C4) SpBE3 gcactcttatttcaagc GCACUCAUUCUGCUUGAAAU 1000 (AAG) 20 (C6) SpBE3 agaat**G**agtgctccta UUAGGAGCACUCAUUCUGCU 1001 (TGAA) 20 (C11) VQR-SpBE3 a (SEQ ID NO: GCACUCAUUCUGCUUGAAAU 1002 (AAGAGT) 20 (C6) SaBE3 861) UUAGGAGCACUCAUUCUGCU 1003 (TGAAAT) 20 (C11) KKH-SaBE3 ORF1, target CACUCAUUCUGCUUGAAAUA 1004 (AGAG) 20 (C5) EQR-SpBE3 start codon ACUCUUAUUUCAAGCAGAAU 1005 (GAG) 20 (n.a.) WT Cas9 MGAT5 VLPDVFIRCV UGUAAGACAGAAAACCACAC 755 (AGCG) 20 (C-1) VRER-SpBE3 (melanoma) (SEQ ID NO: CUGUAAGACAGAAAACCACA 1006 (CAG) 20 (C1) SpBE3 810) CAAGUCCAACAAACAACUGU 1007 (AAG) 20 (n.a.) WT Cas9 tcatacgctgtgtggt UCUGUCUUACAGUUGUUUGU 1008 (TGG) 20 (n.a.) WT Cas9 tttctgtctt**acag**TT GTTTGTTGGACTT GGGTTC (SEQ ID NO: 862) target intron2- exon3 junction, last base of intron 2 LAGE-1 MLMAQEALAFL CUUCGGCCUGCAUGGCUCCG 756 (GAG) 20 (C11) SpBE3 (multiple (SEQ ID NO: AUGGCUCCGGAGCCUCUGCC 1009 (CGG) 20 (C -1) SpBE3 tumors, e.g., 811) GCCUUCGGCCUGCAUGGCUC 1010 (CGG) 20 (C13) SpBE3 melanoma LAAQERRVPR CCUUCGGCCUGCAUGGCUCC 1011 (GGAG) 20 (C12) EQR-SpBE3 and breast (SEQ ID NO: CAGAGGCUCCGGAGCCAUGC 1012 (AGG) 20 (n.a.) WT Cas9 cancer) 812) GCAGAGGCUCCGGAGCCAUG 1013 (CAG) 20 (n.a.) WT Cas9 APRGVRMAV GCCUUCGGCCUGCAUGGCUC 1014 (CGG) 20 (n.a.) WT Cas9 (SEQ ID NO: 813) QGAMLAAQERR VPRAAEVPR (SEQ ID NO: 814) CLSRRPWKRS WSAGSCPGMP HL (SEQ ID NO: 815) tctctgagagccgggc agaggctccggagcc at**G**caggccgaagg c (SEQ ID NO: 863) target OFR1 start site TRP-2 EVISCKLIKR CCUAAUAAUGUAUCUCUAAC 757 (AGAA) 20 (C1/2) VQR-SpBE3 (melanoma) (SEQ ID NO: ACCUAAUAAUGUAUCUCUAA 1015 (CAG) 20 (C2/3) SpBE3 816) ACCUAAUAAUGUAUCUCUAA 1016 (CAGAAT) 20 (C2/3) SaBE3 TATTCTGTTAG

CACCUAAUAAUGUAUCUCUA 1017 (ACAGAAT) 20 (C3/4) St1BE3 AGATACATTATT
UUAGAGAUACAUUAUUAGGU 1018 (GGG) 20 (n.a.) WT Cas9 A**G**gtgggttttttcc
GUUAGAGAUACAUUAUUAGG 1019 (TGG) 20 (n.a.) WT Cas9 (SEQ ID NO: 864) target intron 2 donor site TRP-2 EVISCKLIKR UCCUGGUCCUGAAACAAUUG 758 (GGAA) 20 (C8/9) VQR-SpBE3 (melanoma) (SEQ ID NO: GUCCUGGUCCUGAAACAAUU 1020 (GGG) 20 (C9/10) SpBE3 816)
CGUCCUGGUCCUGAAACAAU 1021 (TGG) 20 (C10/11) SpBE3 tatgtttcccaattgtttc
UUUCCCAAUUGUUUCAGGAC 1022 (CAG) 20 (n.a.) WT Cas9 a**g**GACCAGGAC
UUCCCAAUUGUUUCAGGACC 1023 (AGG) 20 (n.a.) WT Cas9 GCCCCT (SEQ ID NO: 865) target intron 2 acceptor site BIRC5/ AYACNTSTL AGCUGAAGGGAUUAAAGCGG 759 (CAG) 20 (C3) SpBE3 Survivin (SEQ ID NO: GGCAGCUGAAGGGAUUAAAG 1024 (CGG) 20 (C6) SpBE3 (multiple 817)
AAGGCAGCUGAAGGGAUUAA 1025 (AGCG) 20 (C8) VRER-SpBE3 tumors, e.g., agtggactgccgcttta
AAAGGCAGCUGAAGGGAUUA 1026 (AAG) 20 (C9) SpBE3 melanoma, atcccttCa**u**ctgcctt
GCAGCUGAAGGGAUUAAAGC 1027 (GGCAGT) 20 (C5) KKH-SaBE3 breast cancer, tccgctgtt (SEQ ID
GACUGCCGCUUUAAUCCCUU 1028 (CAG) 20 (n.a.) WT Cas9 and leukemia) NO: 866)
CUGCCGCUUUAAUCCCUUCA 1029 (GCT) 20 (n.a.) WT Cas9 target intron 2 spliceosome branch site BIRC5/ AYACNTSTL UCUAGAAAAAUCAAAACAAC 760 (AGCG) 20 (C2) VRER-SpBE3 Survivin (SEQ ID NO: CUCUAGAAAAAUCAAAACAA 1030 (CAG) 20 (C3) SpBE3 (multiple 817)
GAACAUAAAAAGCAUUCGUC 1031 (CGG) 20 (n.a.) WT Cas9 tumors, e.g., tccgctgttgttttgattttt melanoma, cta**g**AGAGGAAC breast cancer, ATAA (SEQ ID and leukemia) NO: 867) target intron 2 acceptor site Bcr-Abl-OOF SSKALQRPV UGGAAGAGAAAGGGGGGAAC 761 (AGAA) 20 (C-1) VQR-SpBE3 (Leukemia) (SEQ ID CUGGAAGAGAAAGGGGGGAA 1032 (CAG) 20 (C1) SpBE3 NO: GCUUCUGGAAGAGAAAGGGG 1033 (GGAA) 20 (C5) VQR-SpBE3 603) GGCUUCUGGAAGAGAAAGGG 1034 (GGG) 20 (C6) SpBE3 GFKQSSKAL GGGCUUCUGGAAGAGAAAGG 1035 (GGG) 20 (C7) SpBE3 (SEQ ID NO: AGGGCUUCUGGAAGAGAAAG 1036 (GGG) 20 (C8) SpBE3 604) AAGGGCUUCUGGAAGAGAAA 1037 (GGG) 20 (C9) SpBE3 ATGFKQSSKAL GAAGGGCUUCUGGAAGAGAA 1038 (AGG) 20 (C10) SpBE3 QRPVAS (SEQ
UGAAGGGCUUCUGGAAGAGA 1039 (AAG) 20 (C11) SpBE3 ID NO: 605) UCUGGAAGAGAAAGGGGGGA 1040 (ACAGAAA) 20 (C2) St1BE3 ATGFKQSSKAL AGGGCUUCUGGAAGAGAAAG 1041 (GGGGG) 20 (C8) St3BE3 QRPVAS (SEQ AAGGGCUUCUGGAAGAGAAA 1042 (GGGGG) 20 (C9) St3BE3 ID NO: 606)
GAAGGGCUUCUGGAAGAGAA 1043 (AGGGG) 20 (C10) St3BE3 tccccccttctcttcca
UUCCCCCCUUUCUCUUCCAG 1044 (AAG) 20 (n.a.) WT Cas9 **g**AAGCCCTTCA
CUGUUCCCCCCUUUCUCUUC 1045 (CAG) 20 (n.a.) WT Cas9 GC (SEQ ID NO: 868) target intron 1 acceptor site Bcr-Abl-OOF SSKALQRPV UGAGAAGAAAGGAACCAAAU 762 (CAG) 20 (C-1) SpBE3 (Leukemia) (SEQ ID NO: GCUUUUCACCUGAGAAGAAA 1046 (GGAA) 20 (C9/10) VQR-SpBE3 603) AGCUUUUCACCUGAGAAGAA 1047 (AGG) 20 (C10/11) SpBE3 GFKQSSKAL GAGCUUUUCACCUGAGAAGA 1048 (AAG) 20 (C11/12) SpBE3 (SEQ ID NO: UUCACCUGAGAAGAAAGGAA 1049 (CCAAAT) 20 (C5/6) KKH-SaBE3 604) CCGGAGCUUUUCACCUGAGA 1050 (AGA) 20 (C7/8) SpBE3 ATGFKQSSKAL CCCGGAGCUUUUCACCUGAG 1051 (AAG) 20 (C6/7) SpBE3 QRPVAS (SEQ ACCCGGAGCUUUUCACCUGA 1052 (GAAGAA) 20 (C8/9) KKH-SaBE3 ID NO: 605) CACCUGAGAAGAAAGGAACC 1053 (AAATC) 20 (C6/7) St3BE3 ATGFKQSSKAL GAUUUGGUUCCUUUCUUCUC 1054 (AGG) 20 (n.a.) WT Cas9 QRPVAS (SEQ UUCCUUUCUUCUCAGGUGAA 1055 (AAG) 20 (n.a.) WT Cas9 ID NO: 606)
UGAUUUGGUUCCUUUCUUCU 1056 (CAG) 20 (n.a.) WT Cas9 tcctttcttctca**g**GTG AAAAGCTCCGG GTCT (SEQ ID NO: 869) target intron 2 acceptor site .sup.aGenome-editor types abbreviations: SpBE3 = APOBEC1—SpCas9n—UGI; VQR-SpBE3 = APOBEC1—VQR-SpCas9n—UGI; EQR-SpBE3 = APOBEC1—EQR-SpCas9n—UGI; VRER-SpBE3 = APOBEC1—VRER-SpCas9n—UGI; SaBE3 = APOBEC1—SaCas9n—UGI; KKH-SaBE3 = APOBEC1—KKH-SaCas9n—UGI; St3BE3 = APOBEC1—St3Cas9n—UGI; St1BE3 = APOBEC1—St1Cas9n—UGI. Guide sequences (the portion of the guide RNA that targets the nucleobase editor to the target sequence) are provided. The guide sequences may be used with any tracrRNA framework sequences known in the art to generate the full guide RNA sequence.

(114) In some embodiments, the nucleobase editor may be used to introduce a premature stop codon (a stop codon that occurs upstream of the normal stop codon) into a tumor specific antigen gene (e.g., TAA, TAG, and TGA). In some embodiments, introduction of a premature stop codon destabilizes the tumor specific antigen. In some embodiments, destabilization of the tumor specific antigen leads to enhanced presentation of immunogenic epitopes (e.g., heteroclitic epitopes or cryptic epitopes).

(115) Premature stop codons are introduced by changing one or more bases in a target codon that encodes a target residue. For example, nucleobase editors including a cytosine deaminase domain are capable of converting a cytosine (C) base to a thymine (T) base via deamination. Thus, it is envisioned that, for amino acid codons containing a C base, the C base may be converted to T. For example, a CAG (Gln/Q) codon may be changed to a TAG (amber) codon via the deamination of the first C on the coding strand. For sense codons that contain a guanine (G) base, a C base is present on the complementary strand; and the G base may be converted to an adenosine (A) via the deamination of the C on the complementary strand. For example, a TGG (Trp/W) codon may be converted to a TAG (amber) codon via the deamination of the second C on the complementary strand. In some embodiments, two C to T changes are required to

convert a codon to a nonsense codon. For example, a CGG (R) codon is converted to a TAG (amber) codon via the deamination of the first C on the coding strand and the deamination of the second C on the complementary strand.

(116) In some embodiments, the target residue is located in a flexible loop region of the tumor specific antigen. In some embodiments, tandem premature stop codons are introduced. Non-limiting examples of codons that may be changed to stop codons via base editing are provided in Table 8.

(117) TABLE-US-00012 TABLE 8 Conversion to Stop Codon Target codon Base-editing process Edited codon CAG (Gln/Q) 1.sup.st base C to T on coding strand TAG (amber) TGG (Trp/W) 2.sup.nd base C to T on complementary strand TAG (amber) CGA (Arg/R) 1.sup.st base C to T on coding strand TGA (opal) CAA (Gln/Q) 1.sup.st base C to T on coding strand TAA (ochre) TGG (Trp/W) 3.sup.rd base C to T on complementary strand TGA (opal) CGG (Arg/R) 1.sup.st base C to T on coding strand and 2.sup.nd TAG (amber) base C to T on complementary strand CGA (Arg/R) 1.sup.st base C to T on coding strand and 2.sup.nd TAA (orchre) base C to T on complementary strand *single underline: changes on the coding strand double underline: changes on the complementary strand

(118) In some embodiments, cryptic epitopes are generated by shifting the coding frame of a tumor specific antigen gene. In some embodiments, the coding frame is shifted by changing a start codon (ATG) to a sense codon that cannot be used as a start codon. As such, translation will start at the next start codon in the coding region, and the coding frame may be shifted. In some embodiments, a normal sense codon may be edited to generate a start codon to allow translation to start at the newly generated start codon, which may also lead to shifting of the coding frame. Alterations of start codons and the resulting shift in the coding frame generate peptides that would not otherwise be generated from the tumor specific antigen gene (i.e., cryptic epitopes). Non-limiting, exemplary start codon alterations that may be achieved by the nucleobase editors described herein are provided in Table 9.

(119) TABLE-US-00013 TABLE 9 Alteration of Start Codons via Base Editing Target codon Base-editing process Edited codon Cognate Start 3.sup.rd base C to T on complementary strand ATA (Ile/I, next ATG is codon ATG used as start codon) (Met/M) ACG (Thr/T) 2.sup.nd base C to T on coding strand ATG (Met/M) GTG (Val/V) 1.sup.st base C to T on complementary strand ATG (Met/M) GCG (Ala/A) 1.sup.st base C to T on complimentary strand and 2.sup.nd ATG (Met/M) base C to T on coding strand

(120) The tumor associated antigens listed in Table 5 and Table 6 and their respective gene sequences and protein sequences are known in the art. The amino acid sequence of the listed tumor specific antigens are listed in Table 10.

(121) TABLE-US-00014 TABLE 10 Amino acid sequences of human tumor specific antigens

Name of tumor associated antigen	SEQ ID NO	Amino acid sequence
Melanocyte protein PMEL (gp100)	763	MDLVLKRCLLHLAVIGALLAVGATKVPRNQDWLGVSRQLRTKAWNRQLYPEW TEAQRLDCWRGGQVSLKVSNDGPTLIGANASFSIALNFPGSQKVLPDGQVIW VNNTIINGSQVWGGQPVYPQETDDACIFPDGGPCPSGSWSQKRSFVYVWKTW GQYWQVLGGPVSGLSIGTGRAMLGTHTMEVTVYHRRGSRSYVPLAHSSSAFT ITDQVPFSVSVSQLRALDGGNKHFLRNQPLTFALQLHDPSGYLAEADLSYTW DFGDSSGTLISRALVVTHTYLEPGPVTAQVVLQAAIPLTSCGSSPVPGTTDG HRPTAEAPNTTAGQVPTTEVVGTTPGQAPTAEPSGTTSVQVPTTEVISTAPV QMPTAESTGMTPEKVPVSEVMGTTLAEMSTPEATGMTPAEVSIVVLSGTTAA QVTTTEWVETTARELPIPEPEGPDASSIMSTESITGSLGPLLDGTATLRLVK RQVPLDCVLYRYGSFSVTLDIVQGIESAEILQAVPSGEGDAFELTVSCQGGL PKEACMEISSPGCQPPAQRLCQPVLPSPACQLVLHQILKGGSGTYCLNVSLA DTNSLAVVSTQLIMPGQEAGLGQVPLIVGILLVLMAVVLASLIYRRRLMKQD FSVPQLPHSSSHWLRLPRIFCSCPIGENSPLLSGQQV	Melanoma antigen recognized by T-cells 1 (MLANA/M ART-1)
5,6-dihydroxyindole-2-carboxylic acid oxidase (TYRP1)	764	MPREDAHFIYGYPKKGHGHSYTTAEEAAGIGILTVILGVLLLIGCWYCRRRN GYRALMDKSLHVGTQCALTRRCPQEGFDHRDSKVSLQEKNCEPVVPNAPPAY EKLSAEQSPPPYSP
6-N-acetylglucosaminyltransferase	765	MSAPKLLSLGCIFFPLLLFQQARAQFPRQCATVEALRSGMCCPDLSPVSGPG TDRCGSSSGRGRCEAVTADSRPHSPQYPHDGRDDREVWPLRFFNRTCHCNGN FSGHNCGTCRPGWRGAACDQRVLIVRRNLLDLSKEEKNHFVRALDMAKRTTH PLFVIATRRSEEILGPDGNTPQFENISIYNYFVWTHYYSVKKTFLGVGQESF GEVDFSHEGPAFLTWHRYHLLRLEKDMQEMLQEPSFSLPYWNFATGKNVCDI CTDDLMGSRSNFDSTLISPNSVFSQWRVVCDSLEDYDTLGTLCNSTEDGPIR RNPAGNVARPMVQRLPEPQDVAQCLEVGLFDTPPFYSNSTNSFRNTVEGYSD PTGKYDPAVRSLHNLAHLFLNGTGGQTHLSPNDPIFVLLHTFTDAVEDEWLR RYNADISTFPLENAPIGHNRQYNMVPFWPPVTNTEMFVTAPDNLGYTYEIQW PSREFSVPEIIAIAVVGALLLVALIFGTASYLIRARRSMDEANQPLLTDQYQ CYAEEYEKLQNPNQSVV
Alpha-1,6-mannosyl-glycoprotein 6-beta-N-acetylglucos-aminyltransferase	766	MALFTPWKLSSQKLGFFLVTFGFIWGMMLLHFTIQQRTQPESSSMLREQILD LSKRYIKALAEENRNVVDGPYAGVMTAYDLKKTLAVLLDNILQRIGKLESKV DNLVVNGTGTNSTNSTTAVPSLVALEKINVADIINGAQEKCVLPPMDGYPHC EGKIKWMKDMWRSDPCYADYGVDGSTCSFFIYLSEVENWCPHLPWRAKNPYE EADHNSLAEIRTDFNILYSMMKKHEEFRWMRLRIRRMADAWIQAIKSLAEKQ NLEKRKRKKVLVHLGLLTKESGFKIAETAFSGGPLGELVQWSDLITSLYLLG A

HDIRISASLAELKEIMKKVVGNRSGCPTVGDRIVELIYIDIVGLAQFKKTLG (MGAT5)
PSWVHYQCMLRVLDSFGTEPEFNHANYAQSKGHKTPWGKWNLNPQQFYTMFP
HTPDNSFLGFVVEQHLNSSDIHHINEIKRQNQSLVYGKVDSFWKNKKIYLDI
IHTYMEVHATVYGSSTKNIPSYVKNHGILSGRDLQFLLRETKLFVGLGFPYE
GPAPLEAIANGCAFLNPKFNPPKSSKNTDFFIGKPTLRELTSQHPYAEVFIG
RPHVWTVDLNNQEEVEDAVKAILNQKIEPYMPYEFTCEGMLQRINAFIEKQD
FCHGQVMWPPLSALQVKLAEPGQSCKQVCQESQLICEPSFFQHLNKDKDMLK
YKVTCQSSELAKDILVPSFDPKNKHCVFQGDLLLFSCAGAHPRHQRVCPCRD FIKGQVALCKDCL Cancer/testis
MQAEGRGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGAAR 767 antigen 1
ASGPGGGAPRGPHGGAASGLNGCCRCGARGPESRLLEFYLAMPFATPMEAEL (CTAG1;
ARRSLAQDAPPLPVPGVLLKEFTVSGNILTIRLTAADHRQLQLSISSCLQQL LAGE2/NY-
SLLMWITQCFLPVFLAQPPSGQRR ESO-1) CTL-
MLMAQEALAFLMAQGAMLAAQERRVPRAAEVPGAQGQQGPRGREEAPRGVRM 768 recognized
AVPLLRRMEGAPAGPGGRTAACFSCTSRCLSRRPWKRSWSAGSCPGMPHLSP antigen on DQGRF melanoma
(CAMEL) L- MSPLWWGFLLSCLGCKILPGAQGQFPRVCMTVDSLVNKECCPRLGAESANVC 769 dopachrome
GSQQGRGQCTEVRADTRPWSGPYILRNQDDRELWPRKFFHRTCKCTGNFAGY tautomerase
NCGDCKFGWTGPNCERKKPPVIRQNIHSLSPQEREQFLGALDLAKKRVHPDY (DCT)
VITTQHWLGLLGPNGTQPQFANCSVYDFFVWLHYYSVRDTLLGPGRPYRAID
FSHQGPAFVTWHRYHLLCLERDLQRLIGNESFALPYWNFATGRNECDVCTDQ
LFGAARPDDPTLISRNSRFSSWETVCDSLDDYNHLVTLCNGTYEGLLRRNQM
GRNSMKLPTLKDIRDCLSLQKFDNPPFFQNSTFSFRNALEGEDKADGTLDSQ
VMSLHNLVHSFLNGTNALPHSAANDPIFVVLHSFTDAIFDEWMKRFNPPADA
WPQELAPIGHNRMYNMVPFFPPVTNEELFLTSDQLGYSYAIDLPVSVEETPG
WPTTLLVVMGTLVALVGLFVLLAFLQYRRLRKGYTPLMETHLSSKRYTEEA Tyrosinase
MLLAVLYCLLWSFQTSAGHFPRACVSSKNLMEKECCPPWSGDRSPCGQLSGR 770 (TYR)
GSCQNILLSNAPLGPQFPFTGVDDRESWPSVFYNRTCQCSGNFMGFNCGNCK
FGFWGPNCTERRLLVRRNIFDLSAPEKDKFFAYLTLAKHTISSDYVIPIGTY
GQMKNGSTPMENDINIYDLFVWMHYYVSMDALLGGSEIWRDIDFAHEAPAFL
PWHRLFLLRWEQEIQKLTGDENFTIPYWDWRDAEKCDICTDEYMGGQHPTNP
NLLSPASFFSSWQIVCSRLEEYNSHQSLCNGTPEGPLRRNPGNHDKSRTPRL
PSSADVEFCLSLTQYESGSMDKAANFSFRNTLEGFASPLTGIADASQSSMHN
ALHIYMNGTMSQVQGSANDPIFLLHHAFVDSIFEQWLRRHRPLQEVYPEANA
PIGHNRESYMVPFIPLYRNGDFFISSKDLGYDYSYLQDSDPDSFQDYIKSYL
EQASRIWSWLLGAAMVGAVLTALLAGLVSLLCRHKRKQLPEEKQPLLMEKED YHSLYQSHL Baculoviral
MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFIHCPTENEP 771 IAP repeat-
DLAQCFFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFLKL containing
DRERAKNKIAKETNNKKKEFEETAKKVRRAIEQLAAMD protein 5 (BIRC5) Receptor
MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQG 772 tyrosine-
CQVVQGNLELTYLPTNASLSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRG protein kinase
TQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTEILKGGVLIQ erbB-2
RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGES (ERBB2/HER
SEDCQSLTRTVCAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLHENH 2)
SGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCT
LVCPLHNQEVTAEDGTQRCEKCSKPCARVCYGLGMEHLREVRAVTSANIQEF
AGCKKIFGSLAFLPESEDGDPASNTAPLQPEQLQVFETLEEITGYLYISAWP
DSLPDLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLALI
HHNTHLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGEGLACHQLCARGHC
WGPGPTQCVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNG
SVTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQ
PCPINCTHSCVDLDDKGCPAEQRASPLTSIISAVVGILLVVVLGVVFGILIK
RRQQKIRKYTMRRLLQETELVEPLTPSGAMPNQAQMRILKETELRKVKVLGS
GAFGTVYKGIWIPDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGVGSP
YVSRLLGICLTSTVQLVTQLMPYGCLLDHVRENRGRLGSQDLLNWCMQIAKG
MSYLEDVRLVHRDLAARNVLVKSPNHVKITDFGLARLLDIDETEYHADGGKV
PIKWMALESILRRRFTHQSDVWSYGVTVWELMTFGAKPYDGIPAREIPDLLE
KGERLPQPPICTIDVYMIMVKCWMIDSECRPRFRELVSEFSRMARDPQRFVV
IQNEDLGPASPLDSTFYRSLLEDDDMGDLVDAEEYLVPQQGFFCPDPAPGAG
GMVHHRHRSSSTRSGGGDLTLGLEPSEEEAPRSPLAPSEGAGSDVEDGDLGM
GAAKGLQSLPTHDPSPLQRYSEDPTVPLPSETDGYVAPLTCSPQPEYVNQPD
VRPQPPSPREGPLPAARPAGATLERPKTLSPGKNGVVKDVFAFGGAVENPEY
LTPQGGAAPQPHPPPAFSPAFDNLYYWDQDPPERGAPPSTFKGTPTAENPEY LGLDVPV Myeloid cell

MPLLLLLPLLWAGALAMDPNFWLQVQESVTVQEGLCVLVPCTFFHPIPYYDK 773 surface
NSPVHGYWFREGAIISRDSPVATNKLDQEVQEETQGRFRLLGDPSRNNCSLS antigen CD33
IVDARRRDNGSYFFRMERGSTKYSYKSPQLSVHVTDLTHRPKILIPGTLEPG
HSKNLTCSVSWACEQGTPPIFSWLSAAPTSLGPRITHSSVLIITPRPQDHGT
NLTCQVKFAGAGVTTERTIQLNVTYVPQNPTTGIFPGDGSGKQETRAGVVHG
AIGGAGVTALLALCLCLIFFIVKTHRRKAARTAVGRNDTHPTTGSASPKHQK
KSKLHGPTETSSCSGAAPTVEMDEELHYASLNFHGMNPSKDTSTEYSEVRTQ Telomerase
MPRAPRCRAVRSLLRSHYREVLPLATFVRRLGPQGWRLVQRGDPAAFRALVA 774 reverse
QCLVCVPWDARPPPAAPSFRQVSCLKELVARVLQRLCERGAKNVLAFGFALL transcriptase
DGARGGPPEAFTTSVRSYLPNTVTDALRGSGAWGLLLRRVGDDVLVHLLARC (TERT)
ALFVLVAPSCAYQVCGPPLYQLGAATQARPPPHASGPRRRLGCERAWNHSVR
EAGVPLGLPAPGARRRGGSASRSLPLPKRPRRGAAPEPERTPVGQGSWAHPG
RTRGPSDRGFCVVSPARPAEEATSLEGALSGTRHSHPSVGRQHHAGPPSTSR
PPRPWDTPCPPVYAETKHFLYSSGDKEQLRPSFLLSSLRPSLTGARRIVETI
FLGSRPWMPGTPRRLPRLPQRYWQMRPLFLELLGNHAQCPYGVLLKTHCPLR
AAVTPAAGVCAREKPQGSVAAPEEEDTDPRRLVQLLRQHSSPWQVYGFVRAC
LRRLVPPGLWGSRHNERRFLRNTKKFISLGKHAKLSLQELTWKMSVRDCAWL
RRSPGVGCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTETTFQKNR
LFFYRKSVWSKLQSIGIRQHLKRVQLRELSEAEVRQHREARPALLTSRLRFI
PKPDGLRPIVNMDYVVGARTFRREKRAERLTSRVKALFSVLNYERARRPGLL
GASVLGLDDIHRAWRTFVLRVRAQDPPPELYFVKVDVTGAYDTIPQDRLTEV
IASIIKPQNTYCVRRYAVVQKAAHGHVRKAFKSHVSTLTDLQPYMRQFVAHL
QETSPLRDAVVIEQSSSLNEASSGLEDVFLRFMCHHAVRIRGKSYVQCQGIP
QGSILSTLLCSLCYGDMENKLFAGIRRDGLLLRLVDDFLLVTPHLTHAKTFL
RTLVRGVPEYGCVVNLRKTVVNFPVEDEALGGTAFVQMPAHGLFPWCGLLLD
TRTLEVQSDYSSYARTSIRASLTFNRGFKAGRNMRRKLFGVLRLKCHSLFLD
LQVNSLQTVCTNIYKILLLQAYRFHACVLQLPFHQQVWKNPTFFLRVISDTA
SLCYSILKAKNAGMSLGAKGAAGPLPSEAVQWLCHQAFLLKLTRHRVTYVPL
LGSLRTAQTQLSRKLPGTTLTALEAAANPALPSDFKTILD Protein SSX2
MNGDDAFARRPTVGAQIPEKIQKAFDDIAKYFSKEEWEKMKASEKIFYVYMK 775
RKYEAMTKLGFKATLPPFMCNKRAEDFQGNDLDNDPNRGNQVERPQMTFGRL
QGISPKIMPKKPAEEGNDSEEVPEASGPQNDGKELCPPGKPTTSEKIHERSG
PKRGEHAWTHRLRERKQLVIYEEISDPEEDDE Wilms tumor
MGSDVRDLNALLPAVPSLGGGGGCALPVSGAAQWAPVLDFAPPGASAYGSLG 776 protein (WT1)
GPAPPPAPPPPPPPPPHSFIKQEPSWGGAEPHEEQCLSAFTVHFSGQFTGTA
GACRYGPFGPPPPSQASSGQARMFPNAPYLPSCLESQPAIRNQGYSTVTEDG
TPSYGHTPSHHAAQFPNHSFKHEDPMGQQGSLGEQQYSVPPPVYGCHTPTDS
CTGSQALLLRTPYSSDNLYQMTSQLECMTWNQMNLGATLKGVAAGSSSSVKW
TEGQSNHSTGYESDNHTTPILCGAQYRIHTHGVERGIQDVRRVPGVAPTLVR
SASETSEKRPFMCAYPGCNKRYFKLSHLQMHSRKHTGEKPYQCDFKDCERRF
SRSDQLKRHQRRHTGVKPFQCKTCQRKFSRSDHLKTHTRTHTGKTSEKPFSC
RWPSCQKKFARSDELVRHHNMHQRNMTKLQLAL Sperm-
MRQRLLPSVTSLLLVALLFPGSSQARHVNHSATEALGELRERAPGQGINGFQ 777 associated
LLRHAVKRDLLPPRTPPYQVHISHQEARGPSFKICVGFLGPRWARGCSTGNE antigen 11A
KYHLPYAARDLQTFFLPFW (SPAG11A) BCR/ABL
MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERCKASIRRLEQEVNQE 778 fusion protein
RFRMIYLQTLLAKEKKSYDRQRWGFRRAAQAPDGASEPRASASRPQPAPADG isoform X3
ADPPPAEEPEARPDGEGSPGKARPGTARRPGAAASGERDDRGPPASVAALRS
NFERIRKGHGQPGADAEKPFYVNVEFHHERGLVKVNDKEVSDRISSLGSQAM
QMERKKSQHGAGSSVGDASRPPYRGRSSESSCGVDGDYEDAELNPRFLKDNL
IDANGGSRPPWPPLEYQPYQSIYVGGMMEGEGKGPLLRSQSTSEQEKRLTWP
RRSYSPRSFEDCGGGYTPDCSSNENLTSSEEDFSSGQSSRVSPSPTTYRMER
DKSRSPSQNSQQSFDSSSPPTPQCHKRHRHCPVVVSEATIVGVRKTGQIWPN
DGEGAFHGDADGSFGTPPGYGCAADRAEEQRRHQDGLPYIDDSPSSSPHLSS
KGRGSRDALVSGALESTKASELDLEKGLEMRKWVLSGILASEETYLSHLEAL
LLPMKPLKAAATTSQPVLTSQQIETIFFKVPELYEIHKEFYDGLFPRVQQWS
HQQRVGDLFQKLASQLGVYRVLGYNHNGEWCEAQTKNGQGWVPSNYITPVNS
LEKHSWYHGPVSRNAAEYLLSSGINGSFLVRESESSPGQRSISLRYEGRVYH
YRINTASDGKLYVSSESRENTLAELVHHHSTVADGLITTLHYPAPKRNKPTV
YGVSPNYDKWEMERTDITMKHKLGGGQYGEVYEGVWKKYSLTVAVKTLKEDT
MEVEEFLKEAAVMKEIKHPNLVQLLGVCTREPPFYIITEFMTYGNLLDYLRE

CNRQEVNAVVLLYMATQISSAMEYLEKKNFIHRDLAARNCLVGENHLVKVAD
FGLSRLMTGDTYTAHAGAKFPIKWTAPESLAYNKFSIKSDVWAFGVLLWEIA
TYGMSPYPGIDLSQVYELLEKDYRMERPEGCPEKVYELMRACWQWNPSDRPS
FAEIHQAFETMFQESSISDEVEKELGKQGVRGAVSTLLQAPELPTKTRTSRR
AAEHRDTTDVPEMPHSKGQGESDPLDHEPAVSPLLPRKERGPPEGGLNEDER
LLPKDKKTNLFSALIKKKKKTAPTPPKRSSSFREMDGQPERRGAGEEEGRDI
SNGALAFTPLDTADPAKSPKPSNGAGVPNGALRESGGSGFRSPHLWKKSSTL Carcinoembry
TSSRLATGEEEGGGSSSKRFLRSCSASCVPHGAKDTEWRSVTLPRDLQSTGR 779 onic antigen-
QFDSSTFGGHKSEKPALPRKRAGENRSDQVTRGTVTPPPRLVKKNEEAADEV related cell
FKDIMESSPGSSPPNLTPKPLRRQVTVAPASGLPHKEEAGKGSALGTPAAAE adhesion
PVTPTSKAGSGAPGGTSKGPAEESRVRRHKHSSESPGRDKGKLSRLKPAPPP molecule 5
PPAASAGKAGGKPSQSPSQEAAGEAVLGAKTKATSLVDAVNSDAAKPSQPGE (CEACAM5)
GLKKPVLPATPKPQSAKPSGTPISPAPVPSTLPSASSALAGDQPSSTAFIPL
ISTRVSLRKTRQPPERIASGAITKGVVLDSTEALCLAISRNSEQMASHSAVL
EAGKNLYTFCVSYVDSIQQMRNKFAFREAINKLENNLRELQICPATAGSGPA ATQDFSKLLSSVKEISDIVQR
MESPSAPPHRWCIPWQRLLLTASLLTFWNPPTTAKLTIESTPENVAEGKEVL
LLVHNLPQHLFGYSWYKGERVDGNRQIIGYVIGTQQATPGPAYSGREIIYPN
ASLLIQNIIQNDTGFYTLHVIKSDLVNEEATGQFRVYPELPKPSISSNNSKP
VEDKDAVAFTCEPETQDATYLWWVNNQSLPVSPRLQLSNGNRTLTLENVTRN
DTASYKCETQNPVSARRSDSVILNVLYGPDAPTISPLNTSYRSGENLNLSCH
AASNPPAQYSWFVNGTFQQSTQELFIPNITVNNSGSYTCQAHNSDTGLNRTT
VTTITVYAEPPKPFITSNNSNPVEDEDAVALTCEPEIQNTTYLWWVNNQSLP
VSPRLQLSNDNRTLTLLSVTRNDVGPYECGIQNKLSVDHSDPVILNVLYGPD
DPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWLIDGNIQQHTQELFISNIT
EKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSNNSKPVEDKDAVA
FTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDARAYVCG
IQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQ
YSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVSA
SGTSPGLSAGATVGIMIGVLVGVALI Melanoma
MPLEQRSQHCKPEEGLEARGEALGLVGAQAPATEEQEAASSSSTLVEVTLGE 780 antigen,
VPAAESPDPPQSPQGASSLPTTMNYPLWSQSYEDSSNQEEEGPSTFPDLESE family A, 3
FQAALSRKVAELVHFLLLKYRAREPVTKAEMLGSVVGNWQYFFPVIFSKAFS variant
SLQLVFGIELMEVDPIGHLYIFATCLGLSYDGLLGDNQIMPKAGLLIIVLAI (MAGE-A3)
IAREGDCAPEEKIWEELSVLEVFEGREDSILGDPKKLLTQHFVQENYLEYRQ
VPGSDPACYEFLWGPRALVETSYVKVLHHMVKISGGPHISYPPLHEWVLREG EE Mucin-1
MTPGTQSPFFLLLLLTVLTVVTGSGHASSTPGGEKETSATQRSSVPSSTEKN 781 (MUC1)
AVSMTSSVLSSHSPGSGSSTTQGQDVTLAPATEPASGSAATWGQDVTSVPVT
RPALGSTTPPAHDVTSAPDNKPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAH
GVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAP
GSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTS
APDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTA
PPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDT
RPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAH
GVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAP
GSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTS
APDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTA
PPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDT
RPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAH
GVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAP
GSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTS
APDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTA
PPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDT
RPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAH
GVTSAPDNRPALGSTAPPVHNVISASGSASGSASTLVHNGTSARATTTPASK
STPFSIPSHHSDTPTTLASHSTKTDASSTHHSSVPPLTSSNHSTSPQLSTGV
SFFFLSFHISNLQFNSSLEDPSTDYYQELQRDISEMFLQIYKQGGFLGLSNI
KFRPGSVVVQLTLAFREGTINVHDVETQFNQYKTEAASRYNLTISDVSVSDV
PFPFSAQSGAGVPGWGIALLVLVCVLVALAIVYLIALAVCQCRRKNYGQLDI
FPARDTYHPMSEYPTYHTHGRYVPPSSTDRSPYEKVSAGNGGSSLSYTNPAV AATSANL Epithelial cell
MAPPQVLAFGLLLAAATATFAAAQEECVCENYKLAVNCFVNNNRQCQCTSVG 782 adhesion
AQNTVICSKLAAKCLVMKAEMNGSKLGRRAKPEGALQNNDGLYDPDCDESGL molecule

FKAKQCNGTSMCWCVNTAGVRRTDKDTEITCSERVRTYWIIIELKHKAREKP precursor
YDSKSLRTALQKEITTRYQLDPKFITSILYENNVITIDLVQNSSQKTQNDVD (EpCAM)
IADVAYYFEKDVKGESLFHSKKMDLTVNGEQLDLDPGQTLIYYVDEKAPEFS
MQGLKAGVIAVIVVVVIAVVAGIVVLVISRKKRMAKYEKAEIKEMGEMHREL NA

(122) In some embodiments, cancer vaccines containing immunogenic peptides from tumor specific antigens (e.g., heteroclitic epitopes and cryptic epitopes) are generated in vivo (e.g., in tumor cells in a subject) or ex vivo (e.g., in tumor cells isolated from a subject). In some embodiments, the tumor cells are treated with the nucleobase editors to generate the immunogenic peptides and are irradiated and administered to the subject as whole-cell cancer vaccines.

(123) To edit the genes encoding the tumor associated antigens, the nucleobase editor and/or the guide nucleotide sequence is introduced into the cell (e.g., a tumor cell) where the editing occurs. In some embodiments, nucleic acid molecules (e.g., expression vectors) encoding the nucleobase editors and/or the guide nucleotide sequences are delivered into the cell, resulting in co-expression of nucleobase editors and/or the guide nucleotide sequences in the cell. The nucleic acid molecules encoding the nucleobase editors and/or the guide nucleotide sequences may be delivered into the cell using any known methods in the art, e.g., transfection (e.g., transfection mediated by cationic liposomes), transduction (e.g., via viral infection) and electroporation. In some embodiments, an isolated nucleobase editor/gRNA complex is delivered. Methods of delivering an isolated protein to a cell is familiar to those skilled in the art. For example, the isolated nucleobase editor in complex with a gRNA be associated with a supercharged, cell-penetrating protein or peptide, which facilitates its entry into a cell (e.g., as described in PCT Application Publication WO2010129023 and US Patent Application Publication US20150071906, incorporated herein by reference). In some embodiments, the isolated nucleobase editor in complex with a gRNA may be delivered by a cationic transfection reagent, e.g., the Lipofectamine CRISPRMAX Cas9 Transfection Reagent from Thermofisher Scientific. In some embodiments, the nucleobase editor and the gRNA may be delivered separately. Other suitable delivery methods may also be used, e.g., AAV mediated gene transfer. Strategies for delivery a Cas9-based genome editing agent (e.g., the nucleobase editor described herein) using AAV have been described, e.g., in Zetsche et al., Nature Biotechnology 33, 139-142 (2015), incorporated herein by reference.

(124) In some embodiments, once generated, the immunogenic peptide is displayed on the surface of the tumor cell via the MHC class I antigen presentation pathway. In some embodiments, the immunogenic peptide is displayed on the surface of an antigen presenting cell (APC) via the MHC class II antigen presentation pathway. In some embodiments, the APC is selected from the group consisting of: tumor cells, dendritic cells, mononuclear phagocytes, thymic epithelial cells, and B cells. In some embodiments, the immunogenic peptide elicits an adaptive immune response against the tumor-specific antigen where the peptide is derived from. In some embodiments, the immunogenic peptide elicits an adaptive immune response against the tumor. In some embodiments, the adaptive immune response comprises promoting the maturation of dendritic cells, activation of CD4+ T lymphocytes, (T helper cells) activation of CD8+ T lymphocytes (cytotoxic T cells), activation and maturation of B lymphocytes, and/or production of tumor antigen-specific antibodies.

(125) T helper cells (TH cells) assist other white blood cells in immunologic processes, including maturation of B cells into plasma cells and memory B cells, and activation of cytotoxic T cells and macrophages. These cells are also known as CD4+ T cells because they express the CD4 glycoprotein on their surfaces. Helper T cells become activated when they are presented with peptide antigens by MHC class II molecules, which are expressed on the surface of antigen-presenting cells (APCs). Once activated, they divide rapidly and secrete small proteins called cytokines that regulate or assist in the active immune response. These cells can differentiate into one of several subtypes, including TH1, TH2, TH3, TH17, TH9, or TFH, which secrete different cytokines to facilitate different types of immune responses. Signaling from the APC directs T cells into particular subtypes.

(126) Cytotoxic T cells (e.g., TC cells, CTLs, T-killer cells, killer T cells) destroy virus-infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as CD8+ T cells since they express the CD8 glycoprotein at their surfaces. These cells recognize their targets by binding to antigen associated with MHC class I molecules, which are present on the surface of all nucleated cells. Through IL-10, adenosine, and other molecules secreted by regulatory T cells, the CD8+ cells can be inactivated to an anergic state, which prevents autoimmune diseases.

(127) Most cytotoxic T cells express T-cell receptors (TCRs) that can recognize a specific antigen. Antigens inside a cell are bound to class I MHC molecules, and brought to the surface of the cell by the class I MHC molecule, where they can be recognized by the T cell. If the TCR is specific for that antigen, it binds to the complex of the class I MHC molecule and the antigen, and the T cell destroys the cell, e.g., via inducing apoptosis. In order for the TCR to bind to the class I MHC molecule, the former must be accompanied by a glycoprotein called CD8, which binds to the constant portion of the class I MHC molecule. Therefore, these T cells are called CD8+ T cells.

(128) Natural killer T cells (NKT cells—not to be confused with natural killer cells of the innate immune system) bridge the adaptive immune system with the innate immune system. Unlike conventional T cells that recognize peptide antigens presented by major histocompatibility complex (MHC) molecules, NKT cells recognize glycolipid antigen presented by a molecule called CD1d. Once activated, these cells can perform functions ascribed to both Th and Tc cells (i.e., cytokine production and release of cytolytic/cell killing molecules). They are also able to recognize and eliminate some tumor cells and cells infected with microorganisms, e.g., bacteria or virus.

(129) Memory T cells are a subset of antigen-specific T cells that persist long-term after an initial T cell response. They quickly expand to large numbers of effector T cells upon re-exposure to their cognate antigen, thus providing the immune

system with “memory” against past antigens. The cancer vaccine described herein provides the immune system with “memory” against the tumor specific antigen, thereby eliciting strong immune response against newly emerged cancer cells or metastasized cancer cells.
(130) Regulatory T cells (suppressor T cells) are crucial for the maintenance of immunological tolerance. Their major role is to shut down T cell-mediated immunity toward the end of an immune reaction and to suppress autoreactive T cells that escaped the process of negative selection in the thymus. Suppressor T cells along with Helper T cells can collectively be called Regulatory T cells due to their regulatory functions.
(131) B cell activation occurs in the secondary lymphoid organs (SLOs), such as the spleen and lymph nodes. After B cells mature in the bone marrow, they migrate through the blood to SLOs, which receive a constant supply of antigen through circulating lymph. At the SLO, B cell activation begins when the B cell binds to an antigen via its BCR. The antigen can either be free-floating or presented by APCs such as macrophages or dendritic cells (DCs), and include proteins, glycoproteins, polysaccharides, whole virus particles, and whole bacterial cells. Some subtypes of B cell preferentially undergo T cell-dependent activation while other subtypes of cells preferentially undergo T cell-independent activation.
(132) Antigens that activate B cells with the help of T-cell are known as T cell-dependent (TD) antigens and include foreign proteins. They are named as such because they are unable to induce a humoral response in organisms that lack T cells. B cell response to these antigens takes multiple days, though antibodies generated have a higher affinity and are more functionally versatile than those generated from T cell-independent activation.
(133) Once a BCR binds a TD antigen, the antigen is taken up into the B cell through receptor-mediated endocytosis, degraded, and presented to T cells as peptide pieces in complex with MHC-II molecules on the cell membrane. T helper (TH) cells, typically follicular T helper (TFH) cells, that were activated with the same antigen recognize and bind these MHC-II-peptide complexes through their T cell receptor (TCR). Following TCR-MHC-II-peptide binding, T cells express the surface protein CD40L as well as cytokines such as IL-4 and IL-21. CD40L serves as a necessary co-stimulatory factor for B cell activation by binding the B cell surface receptor CD40, which promotes B cell proliferation, immunoglobulin class switching, and somatic hypermutation as well as sustains T cell growth and differentiation. T cell-derived cytokines bound by B cell cytokine receptors also promote B cell proliferation, immunoglobulin class switching, and somatic hypermutation as well as guide differentiation. After B cells receive these signals, they are considered activated.
(134) Activated B cells participate in a two-step differentiation process that yields both short-lived plasmablasts for immediate protection and long-lived plasma cells and memory B cells for persistent protection. The first step, known as the extrafollicular response, occurs outside of lymphoid follicles but still in the SLO. During this step activated B cells proliferate, may undergo immunoglobulin class switching, and differentiate into plasmablasts that produce early, weak antibodies mostly of class IgM. The second step consists of activated B cells entering a lymphoid follicle and forming a germinal center (GC), which is a specialized microenvironment where B cells undergo extensive proliferation, immunoglobulin class switching, and affinity maturation directed by somatic hypermutation. These processes are facilitated by TFH cells within the GC and generate both high-affinity memory B cells and long-lived plasma cells. Resultant plasma cells secrete large amounts of antibody and either stay within the SLO or, more preferentially, migrate to bone marrow.
(135) Antigens that activate B cells without T cell help are known as T cell-independent (TI) antigens and include foreign polysaccharides and unmethylated CpG DNA. They are named as such because they are able to induce a humoral response in organisms that lack T cells. B cell response to these antigens is rapid, though antibodies generated tend to have lower affinity and are less functionally versatile than those generated from T cell-dependent activation.
(136) As with TD antigens, B cells activated by TI antigens need additional signals to complete activation, but instead of receiving them from T cells, they are provided either by recognition and binding of a common microbial constituent to toll-like receptors (TLRs) or by extensive crosslinking of BCRs to repeated epitopes on a bacterial cell. B cells activated by TI antigens go on to proliferate outside of lymphoid follicles but still in SLOs (GCs do not form), possibly undergo immunoglobulin class switching, and differentiate into short-lived plasmablasts that produce early, weak antibodies mostly of class IgM, but also some populations of long-lived plasma cells.
(137) Memory B cell activation begins with the detection and binding of their target antigen, which is shared by their parent B cell. Some memory B cells can be activated without T cell help, such as certain virus-specific memory B cells, but others need T cell help. Upon antigen binding, the memory B cell takes up the antigen through receptor-mediated endocytosis, degrades it, and presents it to T cells as peptide pieces in complex with MHC-II molecules on the cell membrane. Memory T helper (TH) cells, typically memory follicular T helper (TFH) cells, that were derived from T cells activated with the same antigen recognize and bind these MHC-II-peptide complexes through their TCR. Following TCR-MHC-II-peptide binding and the relay of other signals from the memory TFH cell, the memory B cell is activated and differentiates either into plasmablasts and plasma cells via an extrafollicular response or enter a germinal center reaction where they generate plasma cells and more memory B cells.
(138) In some embodiments, the adaptive immune response results in the killing tumor cells, reducing tumor burden, reducing tumor size, and/or preventing metastasis. In some embodiments, the adaptive immune response is active against neo-epitopes associated with spontaneous somatic mutations. In some embodiments, the neo-epitope is specific to the lineage of tumor cells.

(139) In some embodiments, the adaptive immune response elicited by the heteroclitic or cryptic epitopes is cross-reactive with the native tumor-specific antigen. In some embodiments, the adaptive immune response elicited by the heteroclitic or cryptic epitopes is cross-reactive with neoepitopes arising from spontaneous mutations occurring in the tumor specific antigen.
(140) There are advantages associated with using heteroclitic epitopes in clinical applications. For example, heteroclitic epitopes have the ability to break/overcome tolerance by reversing a state of T cell anergy, activating non-tolerized cross-reactive clones of T cells, or by mediating "immune deviation," i.e., the type of CTL produced, such as Th1 or Th2. Recent studies indicate that heteroclitic epitopes are immunogenic (Zaremba, et al., *Cancer Research,* 57:4570 (1997); Rivoltoni, et al., *Cancer Research,* 59:301 (1999); Selby, et al., *The Journal of Immunology* 162(2):669 (1999), the entire contents of each of which are incorporated herein by reference) in that they are capable of inducing CTLs that recognize endogenously processed epitopes. This is confirmed by studies in different immunological systems (Zugel, et al., *J. Immunol.,* 161:1705 (1998), Wang, et al., *J. Exp. Med.,* 190:983 (1999), Men, et al., *J. Immunol.,* 162:3566, (1999), the entire contents of each of which are incorporated herein by reference). For example, studies by Zugel et al. have shown that T cell tolerance to an immunodominant T cell epitope in adult mice can be overcome by immunization with heteroclitic cross-reactive peptide analogs of that peptide.
(141) In some embodiments, heteroclitic epitopes or cryptic epitopes modulate cytokine production from T cells (Pfeiffer, et al., *J. Exp. Med.,* 181:1569 (1995), Tao, et al., *J. Immunol.,* 158:4237 (1997), Salazar, et al., *Int. J. Cancer* 85(6):829-38 (2000), Nicholson, et al., *Int. Immunol.* 12(2):205-13 (2000), the entire contents of each of which are incorporated herein by reference). The immune deviation induced by such analogs has implications in several disease states, where generation of a specific subset of Th cell responses correlate with tumor regression (Zitvogel, et al., *J. Exp. Med.,* 183:87 (1996), Celluzzi, et al., *J. Exp. Med.* 183:283 (1996), the entire contents of each of which are incorporated herein by reference) or affected the clinical outcome of autoimmune or infectious disease (Romagnani, et al., *Annu. Rev. Immunol.,* 12:227-57 (1994), the entire contents of which are incorporated herein by reference). Thus, immunization with heteroclitic epitopes offers the capacity to modulate cytokine production by induction of specific subsets of effector T cells, thereby altering the course of disease.
(142) In some embodiments, heteroclitic epitopes offer an advantage in drug development since significantly smaller amounts of peptide are needed for treatment doses, due to their strong biological potency. This feature overcomes certain manufacturing and toxicity concerns. In this regard, it has been shown that a heteroclitic analog of a MART-1 peptide (Rivoltini, et al., *Cancer Research* 59:301 (1999), the entire contents of which are incorporated herein by reference), which generated antigen specific T cells in melanoma patients, was active at much lower concentrations than the native epitope. Similar results were reported by Schlom and colleagues (Zaremba, et al., *Cancer Research* 57:4570 (1997), the entire contents of which are incorporated herein by reference) regarding heteroclitic analog of the CEA derived CAP1 epitope.
(143) Nucleobase Editors
(144) The methods of generating immunogenic peptides or epitopes from tumor associated antigens as cancer vaccines described herein, are enabled by the use of the nucleobase editors. As described herein, a nucleobase editor is a fusion protein comprising: (i) a programmable DNA binding protein domain; and (ii) a deaminase domain. It is to be understood that any programmable DNA binding domain may be used in the based editors.
(145) In some embodiments, the programmable DNA binding protein domain comprises the DNA binding domain of a zinc finger nuclease (ZFN) or a transcription activator-like effector domain (TALE). In some embodiments, the programmable DNA binding protein domain may be programmed by a guide nucleotide sequence, and is thus referred as a "guide nucleotide sequence-programmable DNA binding-protein domain." In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a nuclease inactive Cas9, or dCas9. A dCas9, as used herein, encompasses a Cas9 that is completely inactive in its nuclease activity, or partially inactive in its nuclease activity (e.g., a Cas9 nickase). Thus, in some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a Cas9 nickase. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a nuclease inactive Cpf1. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a nuclease inactive Argonaute. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a nuclease inactive CasX or CasY, e.g., as described in Burstein et al., New CRISPR-Cas systems from uncultivated microbes, Nature 542, 237-241, 2017, incorporated herein by reference.
(146) In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a dCas9 domain. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a Cas9 nickase. In some embodiments, the dCas9 domain comprises the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3. In some embodiments, the dCas9 domain comprises an amino acid sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to any one of the Cas9 domains provided herein (e.g., SEQ ID NOs: 11-260), and comprises mutations corresponding to D10X (X is any amino acid except for D) and/or H840X (X is any amino acid except for H) in SEQ ID NO: 1. In some embodiments, the dCas9 domain comprises an amino acid sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to any one of the Cas9 domains provided herein (e.g., SEQ ID NOs: 11-260), and

comprises mutations corresponding to D10A and/or H840A in SEQ ID NO: 1. In some embodiments, the Cas9 nickase comprises an amino acid sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to any one of the Cas9 domains provided herein (e.g., SEQ ID NOs: 11-260), and comprises mutations corresponding to D10X (X is any amino acid except for D) in SEQ ID NO: 1 and a histidine at a position correspond to position 840 in SEQ ID NO: 1. In some embodiments, the Cas9 nickase comprises an amino acid sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to any one of the Cas9 domains provided herein (e.g., SEQ ID NOs: 11-260), and comprises mutations corresponding to D10A in SEQ ID NO: 1 and a histidine at a position correspond to position 840 in SEQ ID NO: 1. In some embodiments, variants or homologues of dCas9 or Cas9 nickase (e.g., variants of SEQ ID NO: 2 or SEQ ID NO: 3, respectively) are provided which are at least about 70% identical, at least about 80% identical, at least about 90% identical, at least about 95% identical, at least about 98% identical, at least about 99% identical, at least about 99.5% identical, or at least about 99.9% to SEQ ID NO: 2 or SEQ ID NO: 3, respectively, and comprises mutations corresponding to D10A and/or H840A in SEQ ID NO: 1. In some embodiments, variants of Cas9 (e.g., variants of SEQ ID NO: 2) are provided having amino acid sequences which are shorter, or longer than SEQ ID NO: 2, by about 5 amino acids, by about 10 amino acids, by about 15 amino acids, by about 20 amino acids, by about 25 amino acids, by about 30 amino acids, by about 40 amino acids, by about 50 amino acids, by about 75 amino acids, by about 100 amino acids, or more, provided that the dCas9 variants comprise mutations corresponding to D10A and/or H840A in SEQ ID NO: 1. In some embodiments, variants of Cas9 nickase (e.g., variants of SEQ ID NO: 3) are provided having amino acid sequences which are shorter, or longer than SEQ ID NO: 3, by about 5 amino acids, by about 10 amino acids, by about 15 amino acids, by about 20 amino acids, by about 25 amino acids, by about 30 amino acids, by about 40 amino acids, by about 50 amino acids, by about 75 amino acids, by about 100 amino acids, or more, provided that the dCas9 variants comprise mutations corresponding to D10A and comprises a histidine at a position corresponding to position 840 in SEQ ID NO: 1.

(147) Additional suitable nuclease-inactive dCas9 domains will be apparent to those of skill in the art based on this disclosure and knowledge in the field, and are within the scope of this disclosure. Such additional exemplary suitable nuclease-inactive Cas9 domains include, but are not limited to, D10A/H840A, D10A/D839A/H840A, D10A/D839A/H840A/N863A mutant domains (See, e.g., Prashant et al., *Nature Biotechnology.* 2013; 31(9): 833-838, which are incorporated herein by reference), or K603R (See, e.g., Chavez et al., *Nature Methods* 12, 326-328, 2015, which is incorporated herein by reference.

(148) In some embodiments, the nucleobase editors utilized in the present invention comprise a Cas9 domain with decreased electrostatic interactions between the Cas9 domain and a sugar-phosphate backbone of a DNA, as compared to a wild-type Cas9 domain. In some embodiments, a Cas9 domain comprises one or more mutations that decreases the association between the Cas9 domain and a sugar-phosphate backbone of a DNA. In some embodiments, the nucleobase editors described herein comprises a dCas9 (e.g., with D10A and H840A mutations) or a Cas9 nickase (e.g., with D10A mutation), wherein the dCas9 or the Cas9 nickase further comprises one or more of a N497X, R661X, Q695X, and/or Q926X mutation of the amino acid sequence provided in SEQ ID NO: 1, or a corresponding mutation in any of the amino acid sequences provided in SEQ ID NOs: 11-260, wherein X is any amino acid. In some embodiments, the nucleobase editors described herein comprises a dCas9 (e.g., with D10A and H840A mutations) or a Cas9 nickase (e.g., with D10A mutation), wherein the dCas9 or the Cas9 nickase further comprises one or more of a N497A, R661A, Q695A, and/or Q926A mutation of the amino acid sequence provided in SEQ ID NO: 1, or a corresponding mutation in any of the amino acid sequences provided in SEQ ID NOs: 11-260. In some embodiments, the dCas9 domain (e.g., of any of the nucleobase editors provided herein) comprises the amino acid sequence as set forth in any one of SEQ ID NOs: 2-9. In some embodiments, the nucleobase editor comprises the amino acid sequence as set forth in any one of SEQ ID NOs: 293-302 and 321.

(149) TABLE-US-00015 Cas9 variant with decreased electrostatic interactions between the Cas9 and DNA backbone

DKKYSIGL**A**IGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARR
RYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRK
KLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAK
AILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLL
AQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYK
EIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGE
LHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASA
QSFIERMT**A**FDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTN
RKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFE
DREMIEERLKTYAHLFDDKVMKQLKRRRYTGWG**A**LSRKLINGIRDKQSGKTILDFLKSDGFANRNFM
ALIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEM
ARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDIN
RLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFD
NLTKAERGGLSELDKAGFIKRQLVETR**A**ITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFR

KDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATA
KYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTG
GFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERS
SFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASH
YEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIH
LFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGD (SEQ ID NO: 9, mutations relative to SEQ ID NO: 1 are bolded and underlined) High fidelity nucleobase editor (SEQ ID NO: 321)
MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKF
TTERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTI
QIMTEQESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTIALQ
SCHYQRLPPHILWATGLKSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLG
NTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFL
VEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLN
PDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALS
LGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITK
APLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKM
DGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGP
LARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTAFDKNLPNEKVLPKHSLLYEYFTVYN
ELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASL
GTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWG
ALSRKLINGIRDKQSGKTILDFLKSDGFANRNFMALIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGS
PAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEH
PVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKS
DNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRAITKHVAQIL
DSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPK
LESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIV
WDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVA
YSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGR
KRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKR
VILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIH
QSITGLYETRIDLSQLGGD

(150) In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a single effector of a microbial CRISPR-Cas system. Single effectors of microbial CRISPR-Cas systems include, without limitation, Cas9, Cpf1, C2c1, C2c2, and C2c3. Typically, microbial CRISPR-Cas systems are divided into Class 1 and Class 2 systems. Class 1 systems have multisubunit effector complexes, while Class 2 systems have a single protein effector. Cas9 and Cpf1 are Class 2 effectors. In addition to Cas9 and Cpf1, three distinct Class 2 CRISPR-Cas systems (C2c1, C2c2, and C2c3) have been described by Shmakov et al., "Discovery and Functional Characterization of Diverse Class 2 CRISPR Cas Systems", *Mol. Cell*, 2015 Nov. 5; 60(3): 385-397, the entire contents of which are herein incorporated by reference. Effectors of two of the systems, C2cl and C2c3, contain RuvC-like endonuclease domains related to Cpf1. A third system, C2c2 contains an effector with two predicted HEPN RNase domains. Production of mature CRISPR RNA is tracrRNA-independent, unlike production of CRISPR RNA by C2c1. C2c1 depends on both CRISPR RNA and tracrRNA for DNA cleavage. Bacterial C2c2 has been shown to possess a unique RNase activity for CRISPR RNA maturation distinct from its RNA-activated single-stranded RNA degradation activity. These RNase functions are different from each other and from the CRISPR RNA-processing behavior of Cpf1. See, e.g., East-Seletsky, et al., "Two distinct RNase activities of CRISPR-C2c2 enable guide-RNA processing and RNA detection", *Nature*, 2016 Oct. 13; 538(7624):270-273, the entire contents of which are hereby incorporated by reference. In vitro biochemical analysis of C2c2 in Leptotrichia shahii has shown that C2c2 is guided by a single CRISPR RNA and can be programmed to cleave ssRNA targets carrying complementary protospacers. Catalytic residues in the two conserved HEPN domains mediate cleavage. Mutations in the catalytic residues generate catalytically inactive RNA-binding proteins. See e.g., Abudayyeh et al., "C2c2 is a single-component programmable RNA-guided RNA-targeting CRISPR effector," *Science*, 2016 Aug. 5; 353(6299), the entire contents of which are hereby incorporated by reference.

(151) The crystal structure of *Alicyclobaccillus acidoterrastris* C2c1 (AacC2c1) has been reported in complex with a chimeric single-molecule guide RNA (sgRNA). See, e.g., Liu et al., "C2c1-sgRNA Complex Structure Reveals RNA-Guided DNA Cleavage Mechanism", Mol. Cell, 2017 Jan. 19; 65(2):310-322, incorporated herein by reference. The crystal structure has also been reported for *Alicyclobacillus acidoterrestris* C2c1 bound to target DNAs as ternary complexes. See, e.g., Yang et al., "PAM-dependent Target DNA Recognition and Cleavage by C2C1 CRISPR-Cas endonuclease", *Cell*, 2016 Dec. 15; 167(7):1814-1828, the entire contents of which are hereby incorporated by reference. Catalytically competent conformations of AacC2c1, both with target and non-target DNA strands, have been captured independently positioned within a single RuvC catalytic pocket, with C2c1-mediated cleavage resulting in a staggered seven-nucleotide break of target DNA. Structural comparisons between C2c1 ternary complexes and previously identified

Cas9 and Cpf1 counterparts demonstrate the diversity of mechanisms used by CRISPR-Cas9 systems.

(152) In some embodiments, the nucleobase editors described herein comprise a C2c1, a C2c2, or a C2c3 protein. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a C2c1 protein. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a C2c2 protein. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a C2c3 protein. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein comprises an amino acid sequence that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to a naturally-occurring C2c1, C2c2, or C2c3 protein. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a naturally-occurring C2c1, C2c2, or C2c3 protein. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein comprises an amino acid sequence that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to any one of SEQ ID NOs: 1057-1059. In some embodiments, the guide nucleotide sequence-programmable DNA binding protein comprises an amino acid sequence of any one SEQ ID NOs: 1057-1059. It should be appreciated that C2c1, C2c2, or C2c3 from other bacterial species may also be used in accordance with the present disclosure.

(153) C2c1 (uniprot.org/uniprot/TOD7A2 #) sp|T0D7A2|C2C1_ALIAG CRISPR-associated endonuclease C2c1 OS=*Alicyclobacillus acidoterrestris* (strain ATCC 49025/DSM 3922/CIP 106132/NCIMB 13137/GD3B) GN=c2c1 PE=1 SV=1

(154) TABLE-US-00016 C2c1 (uniprot.org/uniprot/T0D7A2#) sp|T0D7A2|C2C1_ALIAG CRISPR- associated endonuclease C2c1 OS = Alicyclobacillus acidoterrestris (strain ATCC 49025/DSM 3922/CIP 106132/MCIMB 13137/GD3B) GN = c2c1 PE = 1 SV = 1 (SEQ ID NO: 1057)

MAVKSIKVKLRLDDMPEIRAGLWKLHKEVNAGVRYYTEWLSLLRQENLYRRSPNGDGEQECDKTAE
ECKAELLERLRARQVENGHRGPAGSDDELLQLARQLYELLVPQAIGAKGDAQQIARKFLSPLADKDAV
GGLGIAKAGNKPRWVRMREAGEPGWEEEKEKAETRKSADRTADVLRALADFGLKPLMRVYTDSEMS
SVEWKPLRKGQAVRTWDRDMFQQAIERMMSWESWNQRVGQEYAKLVEQKNRFEQKNFVGQEHLV
HLVNQLQQDMKEASPGLESKEQTAHYVTGRALRGSDKVFEKWGKLAPDAPFDLYDAEIKNVQRRNT
RRFGSHDLFAKLAEPEYQALWREDASFLTRYAVYNSILRKLNHAKMFATFTLPDATAHPIWTRFDKLG
GNLHQYTFLFNEFGERRHAIRFHKLLKVENGVAREVDDVTVPISMSEQLDNLLPRDPNEPIALYFRDYG
AEQHFTGEFGGAKIQCRRDQLAHMHRRRGARDVYLNVSVRVQSQSEARGERRPPYAAVFRLVGDNH
RAFVHFDKLSDYLAEHPDDGKLGSEGLLSGLRVMSVDLGLRTSASISVFRVARKDELKPNSKGRVPFFF
PIKGNDNLVAVHERSQLLKLPGETESKDLRAIREERQRTLRQLRTQLAYLRLLVRCGSEDVGRRERSW
AKLIEQPVDAANHMTPDWREAFENELQKLKSLHGICSDKEWMDAVYESVRRVWRHMGKQVRDWRK
DVRSGERPKIRGYAKDVVGGNSIEQIEYLERQYKFLKSWSFFGKVSGQVIRAEKGSRFAITLREHIDHAK
EDRLKKLADRIIMEALGYVYALDERGKGKWVAKYPPCQLILLEELSEYQFNNDRPPSENNQLMQWSH
RGVFQELINQAQVHDLLVGTMYAAFSSRFDARTGAPGIRCRRVPARCTQEHNPEPFPWWLNKFVVEHT
LDACPLRADDLIPTGEGEIFVSPFSAEEGDFHQIHADLNAAQNLQQRLWSDFDISQIRLRCDWGEVDGE
LVLIPRLTGKRTADSYSNKVFYTNTGVTYYERERGKKRRKVFAQEKLSEEEAELLVEADEAREKSVVL
MRDPSGIINRGNWTRQKEFWSMVNQRIEGYLVKQIRSRVPLQDSACENTGDI C2c2 (uniprot.org/uniprot/P0DOC6) >sp|P0DOC6|C2C2_LEPSD CRISPR- associated endoribonuclease C2c2 OS = Leptotrichia shahii (strain DSM 19757/CCUG 47503/CIP 107916/JCM 16776/LB37) GN = c2c2 PE = 1 SV = 1 (SEQ ID NO: 1058)

MGNLFGHKRWYEVRDKKDFKIKRKVKVKRNYDGNKYILNINENNNKEKIDNNKFIRKYINYKKNDNI
LKEFTRKFHAGNILFKLKGKEGIIRIENNDDFLETEEVVLYIEAYGKSEKLKALGITKKKIIDEAIRQGITK
DDKKIEIKRQENEEEIEIDIRDEYTNKTLNDCSIILRIIENDELETKKSIYEIFKNINMSLYKIIEKIIENETEK
VFENRYYEEHLREKLLKDDKIDVILTNFMEIREKIKSNLEILGFVKFYLNVGGDKKKSKNKKMLVEKIL
NINVDLTVEDIADFVIKELEFWNITKRIEKVKKVNNEFLEKRRNRTYIKSYVLLDKHEKFKIERENKKDK
IVKFFVENIKNNSIKEKIEKILAEFKIDELIKKLEKELKKGNCDTEIFGIFKKHYKVNFDSKKFSKKSDEEK
ELYKIIYRYLKGRIEKILVNEQKVRLKKMEKIEIEKILNESILSEKILKRVKQYTLEHIMYLGKLRHNDID
MTTVNTDDFSRLHAKEELDLELITFFASTNMELNKIFSRENINNDENIDFFGGDREKNYVLDKKILNSKI
KIIRDLDFIDNKNNITNNFIRKFTKIGTNERNRILHAISKERDLQGTQDDYNKVINIIQNLKISDEEVSKAL
NLDVVFKDKKNIITKINDIKISEENNNDIKYLPSFSKVLPEILNLYRNNPKNEPFDTIETEKIVLNALIYVN
KELYKKLILEDDLEENESKNIFLQELKKTLGNIDEIDENIIENYYKNAQISASKGNNKAIKKYQKKVIECY
IGYLRKNYEELFDFSDFKMNIQEIKKQIKDINDNKTYERITVKTSDKTIVINDDFEYIISIFALLNSNAVIN
KIRNRFFATSVWLNTSEYQNIIDILDEIMQLNTLRNECITENWNLNLEEFIQKMKEIEKDFDDFKIQTKKE
IFNNYYEDIKNNILTEFKDDINGCDVLEKKLEKIVIFDDETKFEIDKKSNILQDEQRKLSNINKKDLKKKV
DQYIKDKDQEIKSKILCRIIFNSDFLKKYKKEIDNLIEDMESENENKFQEIYYPKERKNELYIYKKNLFLNI
GNPNFDKIYGLISNDIKMADAKFLFNIDGKNIRKNKISEIDAILKNLNDKLNGYSKEYKEKYIKKLKEND
DFFAKNIQNKNYKSFEKDYNRVSEYKKIRDLVEFNYLNKIESYLIDINWKLAIQMARFERDMHYIVNGL
RELGIIKLSGYNTGISRAYPKRNGSDGFYTTTAYYKFFDEESYKKFEKICYGFGIDLSENSEINKPENESIR
NYISHFYIVRNPFADYSIAEQIDRVSNLLSYSTRYNNSTYASVFEVFKKDVNLDYDELKKKFKLIGNNDI
LERLMKPKKVSVLELESYNSDYIKNLIIELLTKIENTNDTL C2c3, translated from >CEPX01008730.1

marine metagenome genome assembly TARA_037_MES_0.1-0.22, contig TARA_037_MES_0.1-0.22_scaffold22115_1, whole genome shotgun sequence. (SEQ ID NO: 1059)
MRSNYHGGRNARQWRKQISGLARRTKETVFTYKFPLETDAAEIDFDKAVQTYGIAEGVGHGSLIGLVC
AFHLSGFRLFSKAGEAMAFRNRSRYPTDAFAEKLSAIMGIQLPTLSPEGLDLIFQSPPRSRDGIAPVWSE
NEVRNRLYTNWTGRGPANKPDEHLLEIAGEIAKQVFPKFGGWDDLASDPDKALAAADKYFQSQGDFP
SIASLPAAIMLSPANSTVDFEGDYIAIDPAAETLLHQAVSRCAARLGRERPDLDQNKGPFVSSLQDALVS
SQNNGLSWLFGVGFQHWKEKSPKELIDEYKVPADQHGAVTQVKSFVDAIPLNPLFDTTHYGEFRASVA
GKVRSWVANYWKRLLDLKSLLATTEFTLPESISDPKAVSLFSGLLVDPQGLKKVADSLPARLVSAEEAI
DRLMGVGIPTAADIAQVERVADEIGAFIGQVQQFNNQVKQKLENLQDADDEEFLKGLKIELPSGDKEPP
AINRISGGAPDAAAEISELEEKLQRLLDARSEHFQTISEWAEENAVTLDPIAAMVELERLRLAERGATGD
PEEYALRLLLQRIGRLANRVSPVSAGSIRELLKPVFMEEREFNLFFHNRLGSLYRSPYSTSRHQPFSIDVG
KAKAIDWIAGLDQISSDIEKALSGAGEALGDQLRDWINLAGFAISQRLRGLPDTVPNALAQVRCPDDVR
IPPLLAMLLEEDDIARDVCLKAFNLYVSAINGCLFGALREGFIVRTRFQRIGTDQIHYVPKDKAWEYPDR
LNTAKGPINAAVSSDWIEKDGAVIKPVETVRNLSSTGFAGAGVSEYLVQAPHDWYTPLDLRDVAHLVT
GLPVEKNITKLKRLTNRTAFRMVGASSFKTHLDSVLLSDKIKLGDFTIIIDQHYRQSVTYGGKVKISYEP
ERLQVEAAVPVVDTRDRTVPEPDTLFDHIVAIDLGERSVGFAVFDIKSCLRTGEVKPIHDNNGNPVVGT
VAVPSIRRLMKAVRSHRRRRQPNQKVNQTYSTALQNYRENVIGDVCNRIDTLMERYNAFPVLEFQIKN
FQAGAKQLEIVYGS

(155) Cas9 recognizes a short motif (PAM motif) in the CRISPR repeat sequences in the target DNA sequence. A "PAM motif," or "protospacer adjacent motif," as used herein, refers a DNA sequence immediately following the DNA sequence targeted by the Cas9 nuclease in the CRISPR bacterial adaptive immune system. PAM is a component of the invading virus or plasmid, but is not a component of the bacterial CRISPR locus. Naturally, Cas9 will not successfully bind to or cleave the target DNA sequence if it is not followed by the PAM sequence. PAM is an essential targeting component (not found in the bacterial genome) which distinguishes bacterial self from non-self DNA, thereby preventing the CRISPR locus from being targeted and destroyed by nuclease.

(156) Wild-type *Streptococcus pyogenes* Cas9 recognizes a canonical PAM sequence (5′-NGG-3′). Other Cas9 nucleases (e.g., Cas9 from *Streptococcus thermophiles*, *Staphylococcus aureus*, *Neisseria meningitidis*, or *Treponema denticolaor*) and Cas9 variants thereof have been described in the art to have different, or more relaxed PAM requirements. For example, in Kleinstiver et al., *Nature* 523, 481-485, 2015; Klenstiver et al., *Nature* 529, 490-495, 2016; Ran et al., *Nature*, April 9; 520(7546): 186-191, 2015; Kleinstiver et al., *Nat Biotechnol*, 33(12):1293-1298, 2015; Hou et al., *Proc Natl Acad Sci USA*, 110(39):15644-9, 2014; Prykhozhij et al., *PLoS One*, 10(3): e0119372, 2015; Zetsche et al., *Cell* 163, 759-771, 2015; Gao et al., *Nature Biotechnology*, doi:10.1038/nbt.3547, 2016; Want et al., *Nature* 461, 754-761, 2009; Chavez et al., doi: dx.doi.org/10.1101/058974; Fagerlund et al., *Genome Biol.* 2015; 16: 25, 2015; Zetsche et al., *Cell*, 163, 759-771, 2015; and Swarts et al., *Nat Struct Mol Biol*, 21(9):743-53, 2014, each of which is incorporated herein by reference.

(157) Thus, the guide nucleotide sequence-programmable DNA-binding protein of the present disclosure may recognize a variety of PAM sequences including, without limitation: NGG, NGAN, NGNG, NGAG, NGCG, NNGRRT, NGRRN, NNNRRT, NNNGATT, NNAGAAW, NAAAC, TTN, TTTN, and YTN, wherein Y is a pyrimidine, and N is any nucleobase. In some embodiments, the PAM is located 5′ of the target base. In some embodiments, the PAM is located 3′ of the target base.

(158) One example of an RNA-programmable DNA-binding protein that has different PAM specificity is Clustered Regularly Interspaced Short Palindromic Repeats from *Prevotella* and *Francisella* 1 (Cpf1). Similar to Cas9, Cpf1 is also a class 2 CRISPR effector. It has been shown that Cpf1 mediates robust DNA interference with features distinct from Cas9. Cpf1 is a single RNA-guided endonuclease lacking tracrRNA, and it utilizes a T-rich protospacer-adjacent motif (TTN, TTTN, or YTN). Moreover, Cpf1 cleaves DNA via a staggered DNA double-stranded break. Out of 16 Cpf1-family proteins, two enzymes from *Acidaminococcus* and Lachnospiraceae are shown to have efficient genome-editing activity in human cells.

(159) Also useful in the present disclosure are nuclease-inactive Cpf1 (dCpf1) variants that may be used as a guide nucleotide sequence-programmable DNA-binding protein domain. The Cpf1 protein has a RuvC-like endonuclease domain that is similar to the RuvC domain of Cas9 but does not have a HNH endonuclease domain, and the N-terminal of Cpf1 does not have the alfa-helical recognition lobe of Cas9. It was shown in Zetsche et al., *Cell*, 163, 759-771, 2015 (which is incorporated herein by reference) that, the RuvC-like domain of Cpf1 is responsible for cleaving both DNA strands and inactivation of the RuvC-like domain inactivates Cpf1 nuclease activity. For example, mutations corresponding to D917A, E1006A, or D1255A in *Francisella novicida* Cpf1 (SEQ ID NO: 10) inactivates Cpf1 nuclease activity. In some embodiments, the dCpf1 of the present disclosure comprises mutations corresponding to D917A, E1006A, D1255A, D917A/E1006A, D917A/D1255A, E1006A/D1255A, or D917A/E1006A/D1255A in SEQ ID NO: 10. It is to be understood that any mutations, e.g., substitution mutations, deletions, or insertions that inactivates the RuvC domain of Cpf1 may be used in accordance with the present disclosure.

(160) Thus, in some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a nuclease inactive Cpf1 (dCpf1). In some embodiments, the dCpf1 comprises the amino acid sequence of any one SEQ ID NOs: 261-267. In some embodiments, the dCpf1 comprises an amino acid sequence that is at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at

ease 99.5% identical to SEQ ID NO: 10, and comprises mutations corresponding to D917A, E1006A, D1255A, D917A/E1006A, D917A/D1255A, E1006A/D1255A, or D917A/E1006A/D1255A in SEQ ID NO: 10. Cpf1 from other bacterial species may also be used in accordance with the present disclosure.

(161) Wild type *Francisella novicida* Cpf1 (SEQ ID NO: 10) (D917, E1006, and D1255 are bolded and underlined)

(162) TABLE-US-00017 Wild type *Francisella novicida* Cpf1 (SEQ ID NO: 10) (D917, E1006, and D1255 are bolded and underlined)

MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILDDEKRAKDYKKAKQIIDKYHQFFIEEILSSVCIS
EDLLQNYSDVYFKLKKSDDDNLQKDFKSAKDTIKKQISEYIKDSEKFKNLFNQNLIDAKKGQESDLILW
LKQSKDNGIELFKANSDITDIDEALEIIKSFKGWTTYFKGFHENRKNVYSSNDIPTSIIYRIVDDNLPKFLE
NKAKYESLKDKAPEAINYEQIKKDLAEELTFDIDYKTSEVNQRVFSLDEVFEIANFNNYLNQSGITKENT
IIGGKFVNGENTKRKGINEYINLYSQQINDKTLKKYKMSVLFKQILSDTESKSFVIDKLEDDSDVVTTMQ
SFYEQIAAFKTVEEKSIKETLSLLFDDLKAQKLDLSKIYFKNDKSLTDLSQQVEDDYSVIGTAVLEYITQ
QIAPKNLDNPSKKEQELIAKKTEKAKYLSLETIKLALEEFNKHRDIDKQCRFEEILANFAAIPMIFDEIAQ
NKDNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQTNNLLHKLKIFHISQSEDKANILDKDEHFYL
VFEECYFELANIVPLYNKIRNYITQKPYSDEKFKLNFENSTLANGWDKNKEPDNTAILFIKDDKYYLGV
MNKKNNKIFDDKAIKENKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYNPSEDILRIRNHSTHTKNG
SPQKGYEKFEFNIEDCRKFIDFYKQSISKHPEWKDFGFRFSDTQRYNSIDEFYREVENQGYKLTFENISES
YIDSVVNQGKLYLFQIYNKDFSAYSKGRPNLHTLYWKALFDERNLQDVVYKLNGEAELFYRKQSIPKK
ITHPAKEAIANKNKDNPKKESVFEYDLIKDKRFTEDKFFFHCPITINFKSSGANKENDEINLLLKEKAND
VHILSI**D**RGERHLAYYTLVDGKGNIIKQDTFNIIGNDRMKTNYHDKLAAIEKDRDSARKDWKKINNIKE
MKEGYLSQVVHEIAKLVIEYNAIVVF**E**DLNFGFKRGRFKVEKQVYQKLEKMLIEKLNYLVFKDNEFDK
TGGVLRAYQLTAPFETFKKMGKQTGIIYYVPAGFTSKICPVTGFVNQLYPKYESVSKSQEFFSKFDKICY
NLDKGYFEFSFDYKNFGDKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVYPTKELEKLLKDYSIEY
GHGECIKAAICGESDKKFFAKLTSVLNTILQMRNSKTGTELDYLISPVADVNGNFFDSRQAPKNMPQDA
DANGAYHIGLKGLMLLGRIKNNQEGKKLNLVIKNEEYFEFVQNRNN *Francisella novicida* Cpf1 D917A (SEQ ID NO: 261) (A917, E1006, and D1255 are bolded and underlined)

MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILDDEKRAKDYKKAKQIIDKYHQFFIEEILSSVCIS
EDLLQNYSDVYFKLKKSDDDNLQKDFKSAKDTIKKQISEYIKDSEKFKNLFNQNLIDAKKGQESDLILW
LKQSKDNGIELFKANSDITDIDEALEIIKSFKGWTTYFKGFHENRKNVYSSNDIPTSIIYRIVDDNLPKFLE
NKAKYESLKDKAPEAINYEQIKKDLAEELTFDIDYKTSEVNQRVFSLDEVFEIANFNNYLNQSGITKENT
IIGGKFVNGENTKRKGINEYINLYSQQINDKTLKKYKMSVLFKQILSDTESKSFVIDKLEDDSDVVTTMQ
SFYEQIAAFKTVEEKSIKETLSLLFDDLKAQKLDLSKIYFKNDKSLTDLSQQVEDDYSVIGTAVLEYITQ
QIAPKNLDNPSKKEQELIAKKTEKAKYLSLETIKLALEEFNKHRDIDKQCRFEEILANFAAIPMIFDEIAQ
NKDNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQTNNLLHKLKIFHISQSEDKANILDKDEHFYL
VFEECYFELANIVPLYNKIRNYITQKPYSDEKFKLNFENSTLANGWDKNKEPDNTAILFIKDDKYYLGV
MNKKNNKIFDDKAIKENKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYNPSEDILRIRNHSTHTKNG
SPQKGYEKFEFNIEDCRKFIDFYKQSISKHPEWKDFGFRFSDTQRYNSIDEFYREVENQGYKLTFENISES
YIDSVVNQGKLYLFQIYNKDFSAYSKGRPNLHTLYWKALFDERNLQDVVYKLNGEAELFYRKQSIPKK
ITHPAKEAIANKNKDNPKKESVFEYDLIKDKRFTEDKFFFHCPITINFKSSGANKENDEINLLLKEKAND
VHILSI**A**RGERHLAYYTLVDGKGNIIKQDTFNIIGNDRMKTNYHDKLAAIEKDRDSARKDWKKINNIKE
MKEGYLSQVVHEIAKLVIEYNAIVVF**E**DLNFGFKRGRFKVEKQVYQKLEKMLIEKLNYLVFKDNEFDK
TGGVLRAYQLTAPFETFKKMGKQTGIIYYVPAGFTSKICPVTGFVNQLYPKYESVSKSQEFFSKFDKICY
NLDKGYFEFSFDYKNFGDKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVYPTKELEKLLKDYSIEY
GHGECIKAAICGESDKKFFAKLTSVLNTILQMRNSKTGTELDYLISPVADVNGNFFDSRQAPKNMPQDA
DANGAYHIGLKGLMLLGRIKNNQEGKKLNLVIKNEEYFEFVQNRNN *Francisella novicida* Cpf1 E1006A (SEQ ID NO: 262) (D917, A1006, and D1255 are bolded and underlined)

MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILDDEKRAKDYKKAKQIIDKYHQFFIEEILSSVCIS
EDLLQNYSDVYFKLKKSDDDNLQKDFKSAKDTIKKQISEYIKDSEKFKNLFNQNLIDAKKGQESDLILW
LKQSKDNGIELFKANSDITDIDEALEIIKSFKGWTTYFKGFHENRKNVYSSNDIPTSIIYRIVDDNLPKFLE
NKAKYESLKDKAPEAINYEQIKKDLAEELTFDIDYKTSEVNQRVFSLDEVFEIANFNNYLNQSGITKENT
IIGGKFVNGENTKRKGINEYINLYSQQINDKTLKKYKMSVLFKQILSDTESKSFVIDKLEDDSDVVTTMQ
SFYEQIAAFKTVEEKSIKETLSLLFDDLKAQKLDLSKIYFKNDKSLTDLSQQVFDDYSVIGTAVLEYITQ
QIAPKNLDNPSKKEQELIAKKTEKAKYLSLETIKLALEEFNKHRDIDKQCRFEEILANFAAIPMIFDEIAQ
NKDNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQTNNLLHKLKIFHISQSEDKANILDKDEHFYL
VFEECYFELANIVPLYNKIRNYITQKPYSDEKFKLNFENSTLANGWDKNKEPDNTAILFIKDDKYYLGV
MNKKNNKIFDDKAIKENKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYNPSEDILRIRNHSTHTKNG
SPQKGYEKFEFNIEDCRKFIDFYKQSISKHPEWKDFGFRFSDTQRYNSIDEFYREVENQGYKLTFENISES
YIDSVVNQGKLYLFQIYNKDFSAYSKGRPNLHTLYWKALFDERNLQDVVYKLNGEAELFYRKQSIPKK
ITHPAKEAIANKNKDNPKKESVFEYDLIKDKRFTEDKFFFHCPITINFKSSGANKENDEINLLLKEKAND
VHILSI**D**RGERHLAYYTLVDGKGNIIKQDTFNIIGNDRMKTNYHDKLAAIEKDRDSARKDWKKINNIKE
MKEGYLSQVVHEIAKLVIEYNAIVVF**A**DLNFGFKRGRFKVEKQVYQKLEKMLIEKLNYLVFKDNEFDK

TGGVLRAYQLTAPFETFKKMGKQTGIIYYVPAGFTSKICPVTGFVNQLYPKYESVSKSQEFFSKFDKICY
NLDKGYFEFSFDYKNFGDKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVYPTKELEKLLKDYSIEY
GHGECIKAAICGESDKKFFAKLTSVLNTILQMRNSKTGTELDYLISPVADVNGNFFDSRQAPKNMPQDA
DANGAYHIGLKGLMLLGRIKNNQEGKKLNLVIKNEEYFEFVQNRNN *Francisella novicida* Cpf1 D1255A (SEQ ID NO: 263) (D917, E1006, and A1255 are bolded and underlined)
MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILDDEKRAKDYKKAKQIIDKYHQFFIEEILSSVCIS
EDLLQNYSDVYFKLKKSDDDNLQKDFKSAKDTIKKQISEYIKDSEKFKNLFNQNLIDAKKGQESDLILW
LKQSKDNGIELFKANSDITDIDEALEIIKSFKGWTTYFKGFHENRKNVYSSNDIPTSIIYRIVDDNLPKFLE
NKAKYESLKDKAPEAINYEQIKKDLAEELTFDIDYKTSEVNQRVFSLDEVFEIANFNNYLNQSGITKENT
IIGGKFVNGENTKRKGINEYINLYSQQINDKTLKKYKMSVLFKQILSDTESKSFVIDKLEDDSDVVTTMQ
SFYEQIAAFKTVEEKSIKETLSLLFDDLKAQKLDLSKIYFKNDKSLTDLSQQVEDDYSVIGTAVLEYITQ
QIAPKNLDNPSKKEQELIAKKTEKAKYLSLETIKLALEEFNKHRDIDKQCRFEEILANFAAIPMIFDEIAQ
NKDNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQTNNLLHKLKIFHISQSEDKANILDKDEHFYL
VFEECYFELANIVPLYNKIRNYITQKPYSDEKFKLNFENSTLANGWDKNKEPDNTAILFIKDDKYYLGV
MNKKNNKIFDDKAIKENKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYNPSEDILRIRNHSTHTKNG
SPQKGYEKFEFNIEDCRKFIDFYKQSISKHPEWKDFGFRFSDTQRYNSIDEFYREVENQGYKLTFENISES
YIDSVVNQGKLYLFQIYNKDFSAYSKGRPNLHTLYWKALFDERNLQDVVYKLNGEAELFYRKQSIPKK
ITHPAKEAIANKNKDNPKKESVFEYDLIKDKRFTEDKFFFHCPITINFKSSGANKENDEINLLLKEKAND
VHILSI**D**RGERHLAYYTLVDGKGNIIKQDTFNIIGNDRMKTNYHDKLAAIEKDRDSARKDWKKINNIKE
MKEGYLSQVVHEIAKLVIEYNAIVVF**E**DLNFGFKRGRFKVEKQVYQKLEKMLIEKLNYLVFKDNEFDK
TGGVLRAYQLTAPFETFKKMGKQTGIIYYVPAGFTSKICPVTGFVNQLYPKYESVSKSQEFFSKFDKICY
NLDKGYFEFSFDYKNFGDKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVYPTKELEKLLKDYSIEY
GHGECIKAAICGESDKKFFAKLTSVLNTILQMRNSKTGTELDYLISPVADVNGNFFDSRQAPKNMPQDA
AANGAYHIGLKGLMLLGRIKNNQEGKKLNLVIKNEEYFEFVQNRNN Francisella novicida Cpf1 D917A/E1006A (SEQ ID NO: 264) (A917, A1006, and D1255 are bolded and underlined)
MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILDDEKRAKDYKKAKQIIDKYHQFFIEEILSSVCIS
EDLLQNYSDVYFKLKKSDDDNLQKDFKSAKDTIKKQISEYIKDSEKFKNLFNQNLIDAKKGQESDLILW
LKQSKDNGIELFKANSDITDIDEALEIIKSFKGWTTYFKGFHENRKNVYSSNDIPTSIIYRIVDDNLPKFLE
NKAKYESLKDKAPEAINYEQIKKDLAEELTFDIDYKTSEVNQRVFSLDEVFEIANFNNYLNQSGITKENT
IIGGKFVNGENTKRKGINEYINLYSQQINDKTLKKYKMSVLFKQILSDTESKSFVIDKLEDDSDVVTTMQ
SFYEQIAAFKTVEEKSIKETLSLLFDDLKAQKLDLSKIYFKNDKSLTDLSQQVFDDYSVIGTAVLEYITQ
QIAPKNLDNPSKKEQELIAKKTEKAKYLSLETIKLALEEFNKHRDIDKQCRFEEILANFAAIPMIFDEIAQ
NKDNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQTNNLLHKLKIFHISQSEDKANILDKDEHFYL
VFEECYFELANIVPLYNKIRNYITQKPYSDEKFKLNFENSTLANGWDKNKEPDNTAILFIKDDKYYLGV
MNKKNNKIFDDKAIKENKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYNPSEDILRIRNHSTHTKNG
SPQKGYEKFEFNIEDCRKFIDFYKQSISKHPEWKDFGFRFSDTQRYNSIDEFYREVENQGYKLTFENISES
YIDSVVNQGKLYLFQIYNKDFSAYSKGRPNLHTLYWKALFDERNLQDVVYKLNGEAELFYRKQSIPKK
ITHPAKEAIANKNKDNPKKESVFEYDLIKDKRFTEDKFFFHCPITINFKSSGANKENDEINLLLKEKAND
VHILSI**A**RGERHLAYYTLVDGKGNIIKQDTFNIIGNDRMKTNYHDKLAAIEKDRDSARKDWKKINNIKE
MKEGYLSQVVHEIAKLVIEYNAIVVF**A**DLNFGFKRGRFKVEKQVYQKLEKMLIEKLNYLVFKDNEFDK
TGGVLRAYQLTAPFETFKKMGKQTGIIYYVPAGFTSKICPVTGFVNQLYPKYESVSKSQEFFSKFDKICY
NLDKGYFEFSFDYKNFGDKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVYPTKELEKLLKDYSIEY
GHGECIKAAICGESDKKFFAKLTSVLNTILQMRNSKTGTELDYLISPVADVNGNFFDSRQAPKNMPQDA
DANGAYHIGLKGLMLLGRIKNNQEGKKLNLVIKNEEYFEFVQNRNN *Francisella novicida* Cpf1 D917A/D1255A (SEQ ID NO: 265) (A917, E1006, and A1255 are bolded and underlined)
MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILDDEKRAKDYKKAKQIIDKYHQFFIEEILSSVCIS
EDLLQNYSDVYFKLKKSDDDNLQKDFKSAKDTIKKQISEYIKDSEKFKNLFNQNLIDAKKGQESDLILW
LKQSKDNGIELFKANSDITDIDEALEIIKSFKGWTTYFKGFHENRKNVYSSNDIPTSIIYRIVDDNLPKFLE
NKAKYESLKDKAPEAINYEQIKKDLAEELTFDIDYKTSEVNQRVFSLDEVFEIANFNNYLNQSGITKENT
IIGGKFVNGENTKRKGINEYINLYSQQINDKTLKKYKMSVLFKQILSDTESKSFVIDKLEDDSDVVTTMQ
SFYEQIAAFKTVEEKSIKETLSLLFDDLKAQKLDLSKIYFKNDKSLTDLSQQVEDDYSVIGTAVLEYITQ
QIAPKNLDNPSKKEQELIAKKTEKAKYLSLETIKLALEEFNKHRDIDKQCRFEEILANFAAIPMIFDEIAQ
NKDNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQTNNLLHKLKIFHISQSEDKANILDKDEHFYL
VFEECYFELANIVPLYNKIRNYITQKPYSDEKFKLNFENSTLANGWDKNKEPDNTAILFIKDDKYYLGV
MNKKNNKIFDDKAIKENKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYNPSEDILRIRNHSTHTKNG
SPQKGYEKFEFNIEDCRKFIDFYKQSISKHPEWKDFGFRFSDTQRYNSIDEFYREVENQGYKLTFENISES
YIDSVVNQGKLYLFQIYNKDFSAYSKGRPNLHTLYWKALFDERNLQDVVYKLNGEAELFYRKQSIPKK
ITHPAKEAIANKNKDNPKKESVFEYDLIKDKRFTEDKFFFHCPITINFKSSGANKENDEINLLLKEKAND
VHILSI**A**RGERHLAYYTLVDGKGNIIKQDTFNIIGNDRMKTNYHDKLAAIEKDRDSARKDWKKINNIKE
MKEGYLSQVVHEIAKLVIEYNAIVVF**E**DLNFGFKRGRFKVEKQVYQKLEKMLIEKLNYLVFKDNEFDK
TGGVLRAYQLTAPFETFKKMGKQTGIIYYVPAGFTSKICPVTGFVNQLYPKYESVSKSQEFFSKFDKICY

NLDKGYFEFSFDYKNFGDKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVYPTKELEKLLKDYSIEY
GHGECIKAAICGESDKKFFAKLTSVLNTILQMRNSKTGTELDYLISPVADVNGNFFDSRQAPKNMPQDA
AANGAYHIGLKGLMLLGRIKNNQEGKKLNLVIKNEEYFEFVQNRNN *Francisella novicida* Cpf1 E1006A/D1255A (SEQ ID NO: 266) (D917, A1006, and A1255 are bolded and underlined)
MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILDDEKRAKDYKKAKQIIDKYHQFFIEEILSSVCIS
EDLLQNYSDVYFKLKKSDDDNLQKDFKSAKDTIKKQISEYIKDSEKFKNLFNQNLIDAKKGQESDLILW
LKQSKDNGIELFKANSDITDIDEALEIIKSFKGWTTYFKGFHENRKNVYSSNDIPTSIIYRIVDDNLPKFLE
NKAKYESLKDKAPEAINYEQIKKDLAEELTFDIDYKTSEVNQRVFSLDEVFEIANFNNYLNQSGITKENT
IIGGKFVNGENTKRKGINEYINLYSQQINDKTLKKYKMSVLFKQILSDTESKSFVIDKLEDDSDVVTTMQ
SFYEQIAAFKTVEEKSIKETLSLLFDDLKAQKLDLSKIYFKNDKSLTDLSQQVFDDYSVIGTAVLEYITQ
QIAPKNLDNPSKKEQELIAKKTEKAKYLSLETIKLALEEFNKHRDIDKQCRFEEILANFAAIPMIFDEIAQ
NKDNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQTNNLLHKLKIFHISQSEDKANILDKDEHFYL
VFEECYFELANIVPLYNKIRNYITQKPYSDEKFKLNFENSTLANGWDKNKEPDNTAILFIKDDKYYLGV
MNKKNNKIFDDKAIKENKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYNPSEDILRIRNHSTHTKNG
SPQKGYEKFEFNIEDCRKFIDFYKQSISKHPEWKDFGFRFSDTQRYNSIDEFYREVENQGYKLTFENISES
YIDSVVNQGKLYLFQIYNKDFSAYSKGRPNLHTLYWKALFDERNLQDVVYKLNGEAELFYRKQSIPKK
ITHPAKEAIANKNKDNPKKESVFEYDLIKDKRFTEDKFFFHCPITINFKSSGANKENDEINLLLKEKAND
VHILSI**D**RGERHLAYYTLVDGKGNIIKQDTFNIIGNDRMKTNYHDKLAAIEKDRDSARKDWKKINNIKE
MKEGYLSQVVHEIAKLVIEYNAIVVF**A**DLNFGFKRGRFKVEKQVYQKLEKMLIEKLNYLVFKDNEFDK
TGGVLRAYQLTAPFETFKKMGKQTGIIYYVPAGFTSKICPVTGFVNQLYPKYESVSKSQEFFSKFDKICY
NLDKGYFEFSFDYKNFGDKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVYPTKELEKLLKDYSIEY
GHGECIKAAICGESDKKFFAKLTSVLNTILQMRNSKTGTELDYLISPVADVNGNFFDSRQAPKNMPQDA
AANGAYHIGLKGLMLLGRIKNNQEGKKLNLVIKNEEYFEFVQNRNN Francisella novicida Cpf1 D917A/E1006A/D1255A (SEQ ID NO: 267) (A917, A1006, and A1255 are bolded and underlined)
MSIYQEFVNKYSLSKTLRFELIPQGKTLENIKARGLILDDEKRAKDYKKAKQIIDKYHQFFIEEILSSVCIS
EDLLQNYSDVYFKLKKSDDDNLQKDFKSAKDTIKKQISEYIKDSEKFKNLFNQNLIDAKKGQESDLILW
LKQSKDNGIELFKANSDITDIDEALEIIKSFKGWTTYFKGFHENRKNVYSSNDIPTSIIYRIVDDNLPKFLE
NKAKYESLKDKAPEAINYEQIKKDLAEELTFDIDYKTSEVNQRVFSLDEVFEIANFNNYLNQSGITKENT
IIGGKFVNGENTKRKGINEYINLYSQQINDKTLKKYKMSVLFKQILSDTESKSFVIDKLEDDSDVVTTMQ
SFYEQIAAFKTVEEKSIKETLSLLFDDLKAQKLDLSKIYFKNDKSLTDLSQQVFDDYSVIGTAVLEYITQ
QIAPKNLDNPSKKEQELIAKKTEKAKYLSLETIKLALEEFNKHRDIDKQCRFEEILANFAAIPMIFDEIAQ
NKDNLAQISIKYQNQGKKDLLQASAEDDVKAIKDLLDQTNNLLHKLKIFHISQSEDKANILDKDEHFYL
VFEECYFELANIVPLYNKIRNYITQKPYSDEKFKLNFENSTLANGWDKNKEPDNTAILFIKDDKYYLGV
MNKKNNKIFDDKAIKENKGEGYKKIVYKLLPGANKMLPKVFFSAKSIKFYNPSEDILRIRNHSTHTKNG
SPQKGYEKFEFNIEDCRKFIDFYKQSISKHPEWKDFGFRFSDTQRYNSIDEFYREVENQGYKLTFENISES
YIDSVVNQGKLYLFQIYNKDFSAYSKGRPNLHTLYWKALFDERNLQDVVYKLNGEAELFYRKQSIPKK
ITHPAKEAIANKNKDNPKKESVFEYDLIKDKRFTEDKFFFHCPITINFKSSGANKENDEINLLLKEKAND
VHILSI**A**RGERHLAYYTLVDGKGNIIKQDTFNIIGNDRMKTNYHDKLAAIEKDRDSARKDWKKINNIKE
MKEGYLSQVVHEIAKLVIEYNAIVVF**A**DLNFGFKRGRFKVEKQVYQKLEKMLIEKLNYLVFKDNEFDK
TGGVLRAYQLTAPFETFKKMGKQTGIIYYVPAGFTSKICPVTGFVNQLYPKYESVSKSQEFFSKFDKICY
NLDKGYFEFSFDYKNFGDKAAKGKWTIASFGSRLINFRNSDKNHNWDTREVYPTKELEKLLKDYSIEY
GHGECIKAAICGESDKKFFAKLTSVLNTILQMRNSKTGTELDYLISPVADVNGNFFDSRQAPKNMPQDA
AANGAYHIGLKGLMLLGRIKNNQEGKKLNLVIKNEEYFEFVQNRNN

(163) In some embodiments, the guide nucleotide sequence-programmable DNA binding protein is a Cpf1 protein from a *Acidaminococcus* species (AsCpf1). Cpf1 proteins form *Acidaminococcus* species have been described previously and would be apparent to the skilled artisan. Exemplary *Acidaminococcus* Cpf1 proteins (AsCpf1) include, without limitation, any of the AsCpf1 proteins provided herein.

(164) TABLE-US-00018 Wild-type AsCpf1 - Residue R912 is indicated in bold underlining and residues 661-667 are indicated in italics and underlining. (SEQ ID NQ: 1060)
TQFEGFTNLYQVSKTLRFELIPQGKTLKHIQEQGFIEEDKARNDHYKELKPIIDRIYKTYADQCLQLVQL
DWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHDYFIGRTDNLTDAINKRHAEIYKGLFKAELFNG
KVLKQLGTVTTTEHENALLRSFDKFTTYFSGFYENRKNVFSAEDISTAIPHRIVQDNFPKFKENCHIFTRL
ITAVPSLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAGTEKIKGLNEVLNL
AIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFKSDEEVIQSFCKYKTLLRNENVLETAEALFNEL
NSIDLTHIFISHKKLETISSALCDHWDTLRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEIISAAG
KELSEAFKQKTSEILSHAHAALDQPLPTTMLKKQEEKEILKSQLDSLLGLYHLLDWFAVDESNEVDPEF
SARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKFKLNFQMPTLASGWDVNKEKNNGAILFVKNGLY
YLGIMPKQKGRYKALSFEPTEKTSEGFDKMYYDYFPDAAKMIPKCSTQLKAVTAHFQTHTTPILLSNNF
IEPLEITKEIYDLNNPEKEPKKFQTAYAKKTGDQKGYREALCKWIDFTRDFLSKYTKTTSIDLSSLRPSSQ
YKDLGEYYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHGKPNLHTLYWTGLFSPE

NLAKTSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKKLKDQKTPIPDTLYQELYDYVNHRLSHDLS
DEARALLPNVITKEVSHEIIKDRRFTSDKFFFHVPITLNYQAANSPSKFNQRVNAYLKEHPETPIIGIDRGE
RNLIYITVIDSTGKILEQRSLNTIQQFDYQKKLDNREKERVAARQAWSVVGTIKDLKQGYLSQVIHEIVD
LMIHYQAVVVLENLNFGFKSKRTGIAEKAVYQQFEKMLIDKLNCLVLKDYPAEKVGGVLNPYQLTDQ
FTSFAKMGTQSGFLFYVPAPYTSKIDPLTGFVDPFVWKTIKNHESRKHFLEGFDFLHYDVKTGDFILHFK
MNRNLSFQRGLPGFMPAWDIVFEKNETQFDAKGTPFIAGKRIVPVIENHRFTGRYRDLYPANELIALLE
EKGIVFRDGSNILPKLLENDDSHAIDTMVALIRSVLQMRNSNAATGEDYINSPVRDLNGVCFDSRFQNP
EWPMDADANGAYHIALKGQLLLNHLKESKDLKLQNGISNQDWLAYIQELRN AsCpf1(R912A)- Residue A912 is indicated in bold underlining and residues 661- 667 are indicated in italics and underlining. (SEQ ID NO: 1061)
TQFEGFTNLYQVSKTLRFELIPQGKTLKHIQEQGFIEEDKARNDHYKELKPIIDRIYKTYADQCLQLVQL
DWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHDYFIGRTDNLTDAINKRHAEIYKGLFKAELFNG
KVLKQLGTVTTTEHENALLRSFDKFTTYFSGFYENRKNVFSAEDISTAIPHRIVQDNFPKFKENCHIFTRL
ITAVPSLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAGTEKIKGLNEVLNL
AIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFKSDEEVIQSFCKYKTLLRNENVLETAEALFNEL
NSIDLTHIFISHKKLETISSALCDHWDTLRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEIISAAG
KELSEAFKQKTSEILSHAHAALDQPLPTTMLKKQEEKEILKSQLDSLLGLYHLLDWFAVDESNEVDPEF
SARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKFKLNFQMPTLASGWDVNKEKNNGAILFVKNGLY
YLGIMPKQKGRYKALSFEPTEKTSEGFDKMYYDYFPDAAKMIPKCSTQLKAVTAHFQTHTTPILLSNNF
IEPLEITKEIYDLNNPEKEPKKFQTAYAKKTGDQKGYREALCKWIDFTRDFLSKYTKTTSIDLSSLRPSSQ
YKDLGEYYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHGKPNLHTLYWTGLFSPE
NLAKTSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKKLKDQKTPIPDTLYQELYDYVNHRLSHDLS
DEARALLPNVITKEVSHEIIKDRRFTSDKFFFHVPITLNYQAANSPSKFNQRVNAYLKEHPETPIIGIDRGE
ANLIYITVIDSTGKILEQRSLNTIQQFDYQKKLDNREKERVAARQAWSVVGTIKDLKQGYLSQVIHEIVD
LMIHYQAVVVLENLNFGFKSKRTGIAEKAVYQQFEKMLIDKLNCLVLKDYPAEKVGGVLNPYQLTDQ
FTSFAKMGTQSGFLFYVPAPYTSKIDPLTGFVDPFVWKTIKNHESRKHFLEGFDFLHYDVKTGDFILHFK
MNRNLSFQRGLPGFMPAWDIVFEKNETQFDAKGTPFIAGKRIVPVIENHRFTGRYRDLYPANELIALLE
EKGIVFRDGSNILPKLLENDDSHAIDTMVALIRSVLQMRNSNAATGEDYINSPVRDLNGVCFDSRFQNP
EWPMDADANGAYHIALKGQLLLNHLKESKDLKLQNGISNQDWLAYIQELRN
(165) In some embodiments, the nucleic acid programmable DNA binding protein is a Cpf1 protein from a Lachnospiraceae species (LbCpf1). Cpf1 proteins form Lachnospiraceae species have been described previously have been described previously and would be apparent to the skilled artisan. Exemplary Lachnospiraceae Cpf1 proteins (LbCpf1) include, without limitation, any of the LbCpf1 proteins provided herein.
(166) TABLE-US-00019 Wild-type LbCpf1 (SEQ ID NO: 1062)
MSKLEKFTNCYSLSKTLRFKAIPVGKTQENIDNKRLLVEDEKRAEDYKGVKKLLDRYYLSFINDVLHSI
KLKNLNNYISLFRKKTRTEKENKELENLEINLRKEIAKAFKGNEGYKSLFKKDIIETILPEFLDDKDEIAL
VNSFNGFTTAFTGFFDNRENMFSEEAKSTSIAFRCINENLTRYISNMDIFEKVDAIFDKHEVQEIKEKILN
SDYDVEDFFEGEFFNFVLTQEGIDVYNAIIGGFVTESGEKIKGLNEYINLYNQKTKQKLPKFKPLYKQVL
SDRESLSFYGEGYTSDEEVLEVFRNTLNKNSEIFSSIKKLEKLFKNFDEYSSAGIFVKNGPAISTISKDIFG
EWNVIRDKWNAEYDDIHLKKKAVVTEKYEDDRRKSFKKIGSFSLEQLQEYADADLSVVEKLKEIIIQK
VDEIYKVYGSSEKLFDADFVLEKSLKKNDAVVAIMKDLLDSVKSFENYIKAFFGEGKETNRDESFYGD
FVLAYDILLKVDHIYDAIRNYVTQKPYSKDKFKLYFQNPQFMGGWDKDKETDYRATILRYGSKYYLAI
MDKKYAKCLQKIDKDDVNGNYEKINYKLLPGPNKMLPKVFFSKKWMAYYNPSEDIQKIYKNGTFKK
GDMFNLNDCHKLIDFFKDSISRYPKWSNAYDFNFSETEKYKDIAGFYREVEEQGYKVSFESASKKEVD
KLVEEGKLYMFQIYNKDFSDKSHGTPNLHTMYFKLLFDENNHGQIRLSGGAELFMRRASLKKEELVVH
PANSPIANKNPDNPKKTTTLSYDVYKDKRFSEDQYELHIPIAINKCPKNIFKINTEVRVLLKHDDNPYVI
GIDRGERNLLYIVVVDGKGNIVEQYSLNEIINNFNGIRIKTDYHSLLDKKEKERFEARQNWTSIENIKELK
AGYISQVVHKICELVEKYDAVIALEDLNSGFKNSRVKVEKQVYQKFEKMLIDKLNYMVDKKSNPCAT
GGALKGYQITNKFESFKSMSTQNGFIFYIPAWLTSKIDPSTGFVNLLKTKYTSIADSKKFISSFDRIMYVP
EEDLFEFALDYKNFSRTDADYIKKWKLYSYGNRIRIFRNPKKNNVFDWEEVCLTSAYKELFNKYGINY
QQGDIRALLCEQSDKAFYSSFMALMSLMLQMRNSITGRTDVDFLISPVKNSDGIFYDSRNYEAQENAIL
PKNADANGAYNIARKVLWAIGQFKKAEDEKLDKVKIAISNKEWLEYAQTSVKH LbCpf1 (R836A) (SEQ ID NO: 1063)
MSKLEKFTNCYSLSKTLRFKAIPVGKTQENIDNKRLLVEDEKRAEDYKGVKKLLDRYYLSFINDVLHSI
KLKNLNNYISLFRKKTRTEKENKELENLEINLRKEIAKAFKGNEGYKSLFKKDIIETILPEFLDDKDEIAL
VNSFNGFTTAFTGFFDNRENMFSEEAKSTSIAFRCINENLTRYISNMDIFEKVDAIFDKHEVQEIKEKILN
SDYDVEDFFEGEFFNFVLTQEGIDVYNAIIGGFVTESGEKIKGLNEYINLYNQKTKQKLPKFKPLYKQVL
SDRESLSFYGEGYTSDEEVLEVFRNTLNKNSEIFSSIKKLEKLFKNFDEYSSAGIFVKNGPAISTISKDIFG
EWNVIRDKWNAEYDDIHLKKKAVVTEKYEDDRRKSFKKIGSFSLEQLQEYADADLSVVEKLKEIIIQK
VDEIYKVYGSSEKLFDADFVLEKSLKKNDAVVAIMKDLLDSVKSFENYIKAFFGEGKETNRDESFYGD
FVLAYDILLKVDHIYDAIRNYVTQKPYSKDKFKLYFQNPQFMGGWDKDKETDYRATILRYGSKYYLAI

MDKKYAKCLQKIDKDDVNGNYEKINYKLLPGPNKMLPKVFFSKKWMAYYNPSEDIQKIYKNGTFKK
GDMFNLNDCHKLIDFFKDSISRYPKWSNAYDFNFSETEKYKDIAGFYREVEEQGYKVSFESASKKEVD
KLVEEGKLYMFQIYNKDFSDKSHGTPNLHTMYFKLLFDENNHGQIRLSGGAELFMRRASLKKEELVVH
PANSPIANKNPDNPKKTTTLSYDVYKDKRFSEDQYELHIPIAINKCPKNIFKINTEVRVLLKHDDNPYVI
GIDRGEANLLYIVVVDGKGNIVEQYSLNEIINNFNGIRIKTDYHSLLDKKEKERFEARQNWTSIENIKEL
KAGYISQVVHKICELVEKYDAVIALEDLNSGFKNSRVKVEKQVYQKFEKMLIDKLNYMVDKKSNPCA
TGGALKGYQITNKFESFKSMSTQNGFIFYIPAWLTSKIDPSTGFVNLLKTKYTSIADSKKFISSFDRIMYV
PEEDLFEFALDYKNFSRTDADYIKKWKLYSYGNRIRIFRNPKKNNVFDWEEVCLTSAYKELFNKYGIN
YQQGDIRALLCEQSDKAFYSSFMALMSLMLQMRNSITGRTDVDFLISPVKNSDGIFYDSRNYEAQENAI
LPKNADANGAYNIARKVLWAIGQFKKAEDEKLDKVKIAISNKEWLEYAQTSVKH LbCpf1 (R1138A) (SEQ
ID NO: 1064)
MSKLEKFTNCYSLSKTLRFKAIPVGKTQENIDNKRLLVEDEKRAEDYKGVKKLLDRYYLSFINDVLHSI
KLKNLNNYISLFRKKTRTEKENKELENLEINLRKEIAKAFKGNEGYKSLFKKDIIETILPEFLDDKDEIAL
VNSFNGFTTAFTGFFDNRENMFSEEAKSTSIAFRCINENLTRYISNMDIFEKVDAIFDKHEVQEIKEKILN
SDYDVEDFFEGEFFNFVLTQEGIDVYNAIIGGFVTESGEKIKGLNEYINLYNQKTKQKLPKFKPLYKQVL
SDRESLSFYGEGYTSDEEVLEVFRNTLNKNSEIFSSIKKLEKLFKNFDEYSSAGIFVKNGPAISTISKDIFG
EWNVIRDKWNAEYDDIHLKKKAVVTEKYEDDRRKSFKKIGSFSLEQLQEYADADLSVVEKLKEIIIQK
VDEIYKVYGSSEKLFDADFVLEKSLKKNDAVVAIMKDLLDSVKSFENYIKAFFGEGKETNRDESFYGD
FVLAYDILLKVDHIYDAIRNYVTQKPYSKDKFKLYFQNPQFMGGWDKDKETDYRATILRYGSKYYLAI
MDKKYAKCLQKIDKDDVNGNYEKINYKLLPGPNKMLPKVFFSKKWMAYYNPSEDIQKIYKNGTFKK
GDMFNLNDCHKLIDFFKDSISRYPKWSNAYDFNFSETEKYKDIAGFYREVEEQGYKVSFESASKKEVD
KLVEEGKLYMFQIYNKDFSDKSHGTPNLHTMYFKLLFDENNHGQIRLSGGAELFMRRASLKKEELVVH
PANSPIANKNPDNPKKTTTLSYDVYKDKRFSEDQYELHIPIAINKCPKNIFKINTEVRVLLKHDDNPYVI
GIDRGERNLLYIVVVDGKGNIVEQYSLNEIINNFNGIRIKTDYHSLLDKKEKERFEARQNWTSIENIKELK
AGYISQVVHKICELVEKYDAVIALEDLNSGFKNSRVKVEKQVYQKFEKMLIDKLNYMVDKKSNPCAT
GGALKGYQITNKFESFKSMSTQNGFIFYIPAWLTSKIDPSTGFVNLLKTKYTSIADSKKFISSFDRIMYVP
EEDLFEFALDYKNFSRTDADYIKKWKLYSYGNRIRIFRNPKKNNVFDWEEVCLTSAYKELFNKYGINY
QQGDIRALLCEQSDKAFYSSFMALMSLMLQMANSITGRTDVDFLISPVKNSDGIFYDSRNYEAQENAIL
PKNADANGAYNIARKVLWAIGQFKKAEDEKLDKVKIAISNKEWLEYAQTSVKH

(167) In some embodiments, the Cpf1 protein is a crippled Cpf1 protein. As used herein a “crippled Cpf1” protein is a Cpf1 protein having diminished nuclease activity as compared to a wild-type Cpf1 protein. In some embodiments, the crippled Cpf1 protein preferentially cuts the target strand more efficiently than the non-target strand. For example, the Cpf1 protein preferentially cuts the strand of a duplexed nucleic acid molecule in which a nucleotide to be edited resides. In some embodiments, the crippled Cpf1 protein preferentially cuts the non-target strand more efficiently than the target strand. For example, the Cpf1 protein preferentially cuts the strand of a duplexed nucleic acid molecule in which a nucleotide to be edited does not reside. In some embodiments, the crippled Cpf1 protein preferentially cuts the target strand at least 5% more efficiently than it cuts the non-target strand. In some embodiments, the crippled Cpf1 protein preferentially cuts the target strand at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, or at least 100% more efficiently than it cuts the non-target strand.

(168) In some embodiments, a crippled Cpf1 protein is a non-naturally occurring Cpf1 protein. In some embodiments, the crippled Cpf1 protein comprises one or more mutations relative to a wild-type Cpf1 protein. In some embodiments, the crippled Cpf1 protein comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mutations relative to a wild-type Cpf1 protein. In some embodiments, the crippled Cpf1 protein comprises an R836A mutation mutation as set forth in SEQ ID NO: 763, or in a corresponding amino acid in another Cpf1 protein. It should be appreciated that a Cpf1 comprising a homologous residue (e.g., a corresponding amino acid) to R836A of SEQ ID NO: 763 could also be mutated to achieve similar results. In some embodiments, the crippled Cpf1 protein comprises a R1138A mutation as set forth in SEQ ID NO: 763, or in a corresponding amino acid in another Cpf1 protein. In some embodiments, the crippled Cpf1 protein comprises an R912A mutation mutation as set forth in SEQ ID NO: 762, or in a corresponding amino acid in another Cpf1 protein. Without wishing to be bound by any particular theory, residue R838 of SEQ ID NO: 763 (LbCpf1) and residue R912 of SEQ ID NO: 762 (AsCpf1) are examples of corresponding (e.g., homologous) residues. For example, a portion of the alignment between SEQ ID NO: 762 and 763 shows that R912 and R838 are corresponding residues.

(169) In some embodiments, any of the Cpf1 proteins provided herein comprises one or more amino acid deletions. In some embodiments, any of the Cpf1 proteins provided herein comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acid deletions. Without wishing to be bound by any particular theory, there is a helical region in Cpf1, which includes residues 661-667 of AsCpf1 (SEQ ID NO: 762), that may obstruct the function of a deaminase (e.g., APOBEC) that is fused to the Cpf1. This region comprises the amino acid sequence KKTGDQK. Accordingly, aspects of the disclosure provide Cpf1 proteins comprising mutations (e.g., deletions) that disrupt this helical region in Cpf1. In some embodiments, the Cpf1 protein comprises one or more deletions of the following residues in SEQ ID NO: 762, or one or more corresponding deletions in another Cpf1 protein: K661, K662, T663, G664, D665, Q666, and K667. In some embodiments, the Cpf1 protein comprises a T663 and a D665 deletion in SEQ ID NO: 762, or corresponding deletions in another Cpf1 protein. In some embodiments, the Cpf1 protein comprises a K662, T663, D665, and Q666 deletion in SEQ

ID NO: 762, or corresponding deletions in another Cpf1 protein. In some embodiments, the Cpf1 protein comprises a K661, K662, T663, D665, Q666 and K667 deletion in SEQ ID NO: 762, or corresponding deletions in another Cpf1 protein.

(170) TABLE-US-00020 AsCpf1 (deleted T663 and D665) (SEQ ID NO: 1065)

TQFEGFTNLYQVSKTLRFELIPQGKTLKHIQEQGFIEEDKARNDHYKELKPIIDRIYKTYADQCLQLVQL
DWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHDYFIGRTDNLTDAINKRHAEIYKGLFKAELFNG
KVLKQLGTVTTTEHENALLRSFDKFTTYFSGFYENRKNVFSAEDISTAIPHRIVQDNFPKFKENCHIFTRL
ITAVPSLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAGTEKIKGLNEVLNL
AIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFKSDEEVIQSFCKYKTLLRNENVLETAEALFNEL
NSIDLTHIFISHKKLETISSALCDHWDTLRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEIISAAG
KELSEAFKQKTSEILSHAHAALDQPLPTTMLKKQEEKEILKSQLDSLLGLYHLLDWFAVDESNEVDPEF
SARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKFKLNFQMPTLASGWDVNKEKNNGAILFVKNGLY
YLGIMPKQKGRYKALSFEPTEKTSEGFDKMYYDYFPDAAKMIPKCSTQLKAVTAHFQTHTTPILLSNNF
IEPLEITKEIYDLNNPEKEPKKFQTAYAKKGQKGYREALCKWIDFTRDFLSKYTKTTSIDLSSLRPSSQY
KDLGEYYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHGKPNLHTLYWTGLFSPEN
LAKTSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKKLKDQKTPIPDTLYQELYDYVNHRLSHDLSD
EARALLPNVITKEVSHEIIKDRRFTSDKFFFHVPITLNYQAANSPSKFNQRVNAYLKEHPETPIIGIDRGER
NLIYITVIDSTGKILEQRSLNTIQQFDYQKKLDNREKERVAARQAWSVVGTIKDLKQGYLSQVIHEIVDL
MIHYQAVVVLENLNFGFKSKRTGIAEKAVYQQFEKMLIDKLNCLVLKDYPAEKVGGVLNPYQLTDQF
TSFAKMGTQSGFLFYVPAPYTSKIDPLTGFVDPFVWKTIKNHESRKHFLEGFDFLHYDVKTGDFILHFK
MNRNLSFQRGLPGFMPAWDIVFEKNETQFDAKGTPFIAGKRIVPVIENHRFTGRYRDLYPANELIALLE
EKGIVFRDGSNILPKLLENDDSHAIDTMVALIRSVLQMRNSNAATGEDYINSPVRDLNGVCFDSRFQNP
EWPMDADANGAYHIALKGQLLLNHLKESKDLKLQNGISNQDWLAYIQELRN AsCpf1 (deleted K662, T663, D665, and Q666) (SEQ ID NO: 1066)

TQFEGFTNLYQVSKTLRFELIPQGKTLKHIQEQGFIEEDKARNDHYKELKPIIDRIYKTYADQCLQLVQL
DWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHDYFIGRTDNLTDAINKRHAEIYKGLFKAELFNG
KVLKQLGTVTTTEHENALLRSFDKFTTYFSGFYENRKNVFSAEDISTAIPHRIVQDNFPKFKENCHIFTRL
ITAVPSLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAGTEKIKGLNEVLNL
AIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFKSDEEVIQSFCKYKTLLRNENVLETAEALFNEL
NSIDLTHIFISHKKLETISSALCDHWDTLRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEIISAAG
KELSEAFKQKTSEILSHAHAALDQPLPTTMLKKQEEKEILKSQLDSLLGLYHLLDWFAVDESNEVDPEF
SARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKFKLNFQMPTLASGWDVNKEKNNGAILFVKNGLY
YLGIMPKQKGRYKALSFEPTEKTSEGFDKMYYDYFPDAAKMIPKCSTQLKAVTAHFQTHTTPILLSNNF
IEPLEITKEIYDLNNPEKEPKKFQTAYAKGKGYREALCKWIDFTRDFLSKYTKTTSIDLSSLRPSSQYKDL
GEYYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHGKPNLHTLYWTGLFSPENLAK
TSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKKLKDQKTPIPDTLYQELYDYVNHRLSHDLSDEAR
ALLPNVITKEVSHEIIKDRRFTSDKFFFHVPITLNYQAANSPSKFNQRVNAYLKEHPETPIIGIDRGERNLI
YITVIDSTGKILEQRSLNTIQQFDYQKKLDNREKERVAARQAWSVVGTIKDLKQGYLSQVIHEIVDLMI
HYQAVVVLENLNFGFKSKRTGIAEKAVYQQFEKMLIDKLNCLVLKDYPAEKVGGVLNPYQLTDQFTS
FAKMGTQSGFLFYVPAPYTSKIDPLTGFVDPFVWKTIKNHESRKHFLEGFDFLHYDVKTGDFILHFKMN
RNLSFQRGLPGFMPAWDIVFEKNETQFDAKGTPFIAGKRIVPVIENHRFTGRYRDLYPANELIALLEEKG
IVFRDGSNILPKLLENDDSHAIDTMVALIRSVLQMRNSNAATGEDYINSPVRDLNGVCFDSRFQNPEWP
MDADANGAYHIALKGQLLLNHLKESKDLKLQNGISNQDWLAYIQELRN AsCpf1 (deleted K661, K662, T663,D665, Q666, and K667) (SEQ ID NO: 1067)

TQFEGFTNLYQVSKTLRFELIPQGKTLKHIQEQGFIEEDKARNDHYKELKPIIDRIYKTYADQCLQLVQL
DWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHDYFIGRTDNLTDAINKRHAEIYKGLFKAELFNG
KVLKQLGTVTTTEHENALLRSFDKFTTYFSGFYENRKNVFSAEDISTAIPHRIVQDNFPKFKENCHIFTRL
ITAVPSLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAGTEKIKGLNEVLNL
AIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFKSDEEVIQSFCKYKTLLRNENVLETAEALFNEL
NSIDLTHIFISHKKLETISSALCDHWDTLRNALYERRISELTGKITKSAKEKVQRSLKHEDINLQEIISAAG
KELSEAFKQKTSEILSHAHAALDQPLPTTMLKKQEEKEILKSQLDSLLGLYHLLDWFAVDESNEVDPEF
SARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKFKLNFQMPTLASGWDVNKEKNNGAILFVKNGLY
YLGIMPKQKGRYKALSFEPTEKTSEGFDKMYYDYFPDAAKMIPKCSTQLKAVTAHFQTHTTPILLSNNF
IEPLEITKEIYDLNNPEKEPKKFQTAYAGGYREALCKWIDFTRDFLSKYTKTTSIDLSSLRPSSQYKDLGE
YYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHHGKPNLHTLYWTGLFSPENLAKTS
IKLNGQAELFYRPKSRMKRMAHRLGEKMLNKKLKDQKTPIPDTLYQELYDYVNHRLSHDLSDEARAL
LPNVITKEVSHEIIKDRRFTSDKFFFHVPITLNYQAANSPSKFNQRVNAYLKEHPETPIIGIDRGERNLIYIT
VIDSTGKILEQRSLNTIQQFDYQKKLDNREKERVAARQAWSVVGTIKDLKQGYLSQVIHEIVDLMIHYQ
AVVVLENLNFGFKSKRTGIAEKAVYQQFEKMLIDKLNCLVLKDYPAEKVGGVLNPYQLTDQFTSFAK
MGTQSGFLFYVPAPYTSKIDPLTGFVDPFVWKTIKNHESRKHFLEGFDFLHYDVKTGDFILHFKMNRNL
SFQRGLPGFMPAWDIVFEKNETQFDAKGTPFIAGKRIVPVIENHRFTGRYRDLYPANELIALLEEKGIVF

RDGSNILPKLLENDDSHAIDTMVALIRSVLQMRNSNAATGEDYINSPVRDLNGVCFDSRFQNPEWPMD
ADANGAYHIALKGQLLLNHLKESKDLKLQNGISNQDWLAYIQELRN

(171) In some embodiments, the guide nucleotide sequence-programmable DNA-binding protein domain of the present disclosure has no requirements for a PAM sequence. One example of such guide nucleotide sequence-programmable DNA-binding protein may be an Argonaute protein from *Natronobacterium gregoryi* (NgAgo). NgAgo is a ssDNA-guided endonuclease. NgAgo binds 5′ phosphorylated ssDNA of ˜24 nucleotides (gDNA) to guide it to its target site and will make DNA double-strand breaks at gDNA site. In contrast to Cas9, the NgAgo-gDNA system does not require a protospacer-adjacent motif (PAM). Using a nuclease inactive NgAgo (dNgAgo) can greatly expand the codons that may be targeted. The characterization and use of NgAgo have been described in Gao et al., *Nat Biotechnol. Epub* 2016 May 2. PubMed PMID: 27136078; Swarts et al., *Nature.* 507(7491) (2014):258-61; and Swarts et al., *Nucleic Acids Res.* 43(10) (2015):5120-9, each of which are incorporated herein by reference. The sequence of *Natronobacterium gregoryi* Argonaute is provided in SEQ ID NO: 270.

(172) TABLE-US-00021 Wild type *Natronobacterium gregoryi* Argonaute (SEQ ID NO: 270)

MTVIDLDSTTTADELTSGHTYDISVTLTGVYDNTDEQHPRMSLAFEQDN
GERRYITLWKNTTPKDVFTYDYATGSTYIFTNIDYEVKDGYENLTATYQ
TTVENATAQEVGTTDEDETFAGGEPLDHHLDDALNETPDDAETESDSGH
VMTSFASRDQLPEWTLHTYTLTATDGAKTDTEYARRTLAYTVRQELYTD
HDAAPVATDGLMLLTPEPLGETPLDLDCGVRVEADETRTLDYTTAKDRL
LARELVEEGLKRSLWDDYLVRGIDEVLSKEPVLTCDEFDLHERYDLSVE
VGHSGRAYLHINFRHRFVPKLTLADIDDDNIYPGLRVKTTYRPRRGHIV
WGLRDECATDSLNTLGNQSVVAYHRNNQTPINTDLLDAIEAADRRVVET
RRQGHGDDAVSFPQELLAVEPNTHQIKQFASDGFHQQARSKTRLSASRC
SEKAQAFAERLDPVRLNGSTVEFSSEFFTGNNEQQLRLLYENGESVLTF
RDGARGAHPDETFSKGIVNPPESFEVAVVLPEQQADTCKAQWDTMADLL
NQAGAPPTRSETVQYDAFSSPESISLNVAGAIDPSEVDAAFVVLPPDQE
GFADLASPTETYDELKKALANMGIYSQMAYFDRFRDAKIFYTRNVALGL
LAAAGGVAFTTEHAMPGDADMFIGIDVSRSYPEDGASGQINIAATATAV
YKDGTILGHSSTRPQLGEKLQSTDVRDIMKNAILGYQQVTGESPTHIVI
HRDGFMNEDLDPATEFLNEQGVEYDIVEIRKQPQTRLLAVSDVQYDTPV
KSIAAINQNEPRATVATFGAPEYLATRDGGGLPRPIQIERVAGETDIET
LTRQVYLLSQSHIQVHNSTARLPITTAYADQASTHATKGYLVQTGAFES NVGFL

(173) Also provided herein are Cas9 variants that have relaxed PAM requirements (PAMless Cas9). PAMless Cas9 exhibits an increased activity on a target sequence that does not include a canonical PAM (e.g., NGG) at its 3′-end as compared to *Streptococcus pyogenes* Cas9 as provided by SEQ ID NO: 1, e.g., increased activity by at least 5-fold, at least 10-fold, at least 50-fold, at least 100-fold, at least 500-fold, at least 1,000-fold, at least 5,000-fold, at least 10,000-fold, at least 50,000-fold, at least 100,000-fold, at least 500,000-fold, or at least 1,000,000-fold. Such Cas9 variants that have relaxed PAM requirements are described in U.S. Provisional applications 62/245,828, 62/279,346, 62/311,763, 62/322,178, and 62/357,332, each of which is incorporated herein by reference. In some embodiments, the dCas9 or Cas9 nickase useful in the present disclosure may further comprise mutations that relax the PAM requirements, e.g., mutations that correspond to A262T, K294R, S409I, E480K, E543D, M694I, or E1219V in SEQ ID NO: 1.

(174) Other on-limiting, exemplary Cas9 variants (including dCas9, Cas9 nickase, and Cas9 variants with alternative PAM requirements) suitable for use in the nucleobase editors described herein and their respective sequence are provided below.

(175) TABLE-US-00022 VRER-nCas9 (D10A/D1135V/G1218R/R1335E/T1337R) *S. pyogenes* Cas9 Nickase (SEQ ID NO: 821)

MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTAR
RRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLR
KKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDA
KAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDN
LLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEK
YKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHL
GELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA
SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFK
TNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT
LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN
FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVI
EMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQEL
DINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRK
FDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSD
FRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKA
TAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQ

TGGFSKESILPKRNSDKLIARKKDWDPKKYGGFVSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME
RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASARELQKGNELALPSKYVNFLYLA
SHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENI
IHLFTLTNLGAPAAFKYFDTTIDRKEYRSTKEVLDATLIHQSITGLYETRIDLSQLGGD (single underline: HNH domain; double underline: RuvC domain) VQR-nCas9 (D10A/D1135V/R1335Q/T1337R) *S. pyogenes* Cas9 Nickase (SEQ ID NO: 822)
MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTAR
RRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLR
KKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDA
KAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDN
LLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEK
YKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHL
GELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA
SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFK
TNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT
LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN
FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVI
EMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQEL
DINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRK
FDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSD
FRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKA
TAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQ
TGGFSKESILPKRNSDKLIARKKDWDPKKYGGFVSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME
RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLA
SHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENI
IHLFTLTNLGAPAAFKYFDTTIDRKQYRSTKEVLDATLIHQSITGLYETRIDLSQLGGD (single underline: HNH domain; double underline: RuvC domain) EQR-nCas9 (D10A/D1135E/R1335Q/T1337R) *S. pyogenes* Cas9 Nickase (SEQ ID NO: 823)
MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLEDSGETAEATRLKRTAR
RRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLR
KKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDA
KAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDN
LLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEK
YKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHL
GELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA
SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFK
TNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT
LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN
FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVI
EMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQEL
DINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRK
FDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSD
FRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKA
TAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQ
TGGFSKESILPKRNSDKLIARKKDWDPKKYGGFESPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIME
RSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLA
SHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENI
IHLFTLTNLGAPAAFKYFDTTIDRKQYRSTKEVLDATLIHQSITGLYETRIDLSQLGGD (single underline: HNH domain; double underline: RuvC domain) KKH-nCas9 (D10A/E782K/N968K/R1015H) *S. aureus* Cas9 Nickase (SEQ ID NO: 268)
MKRNYILGLAIGITSVGYGIIDYETRDVIDAGVRLFKEANVENNEGRRSKRGARRLKRRRRHRIQRVKK
LLFDYNLLTDHSELSGINPYEARVKGLSQKLSEEEFSAALLHLAKRRGVHNVNEVEEDTGNELSTKEQI
SRNSKALEEKYVAELQLERLKKDGEVRGSINRFKTSDYVKEAKQLLKVQKAYHQLDQSFIDTYIDLLE
TRRTYYEGPGEGSPFGWKDIKEWYEMLMGHCTYFPEELRSVKYAYNADLYNALNDLNNLVITRDENE
KLEYYEKFQIIENVFKQKKKPTLKQIAKEILVNEEDIKGYRVTSTGKPEFTNLKVYHDIKDITARKEIIEN
AELLDQIAKILTIYQSSEDIQEELTNLNSELTQEEIEQISNLKGYTGTHNLSLKAINLILDELWHTNDNQIA
IFNRLKLVPKKVDLSQQKEIPTTLVDDFILSPVVKRSFIQSIKVINAIIKKYGLPNDIIIELAREKNSKDAQK
MINEMQKRNRQTNERIEEIIRTTGKENAKYLIEKIKLHDMQEGKCLYSLEAIPLEDLLNNPFNYEVDHIIP
RSVSFDNSFNNKVLVKQEENSKKGNRTPFQYLSSSDSKISYETFKKHILNLAKGKGRISKTKKEYLLEER
DINRFSVQKDFINRNLVDTRYATRGLMNLLRSYFRVNNLDVKVKSINGGFTSFLRRKWKFKKERNKGY
KHHAEDALIIANADFIFKEWKKLDKAKKVMENQMFEEKQAESMPEIETEQEYKEIFITPHQIKHIKDFK

DYKYSHRVDKKPNRKLINDTLYSTRKDDKGNTLIVNNLNGLYDKDNDKLKKLINKSPEKLLMYHHDP
QTYQKLKLIMEQYGDEKNPLYKYYEETGNYLTKYSKKDNGPVIKKIKYYGNKLNAHLDITDDYPNSR
NKVVKLSLKPYRFDVYLDNGVYKFVTVKNLDVIKKENYYEVNSKCYEEAKKLKKISNQAEFIASFYKN
DLIKINGELYRVIGVNNDLLNRIEVNMIDITYREYLENMNDKRPPHIIKTIASKTQSIKKYSTDILGNLYE
VKSKKHPQIIKKG *Streptococcus thermophilus* CRISPR1 Cas9 (St1Cas9) Nickase (D9A) (SEQ ID NO: 269) MSDLVLGLAIGIGSVGVGILNKVTGEIIHKNSRIFPAAQAENNLVRRTNRQGRRLTRRKKHRRVRLNRL
FEESGLITDFTKISINLNPYQLRVKGLTDELSNEELFIALKNMVKHRGISYLDDASDDGNSSIGDYAQIVK
ENSKQLETKTPGQIQLERYQTYGQLRGDFTVEKDGKKHRLINVFPTSAYRSEALRILQTQQEFNPQITDE
FINRYLEILTGKRKYYHGPGNEKSRTDYGRYRTSGETLDNIFGILIGKCTFYPDEFRAAKASYTAQEFNL
LNDLNNLTVPTETKKLSKEQKNQIINYVKNEKAMGPAKLFKYIAKLLSCDVADIKGYRIDKSGKAEIHT
FEAYRKMKTLETLDIEQMDRETLDKLAYVLTLNTEREGIQEALEHEFADGSFSQKQVDELVQFRKANS
SIFGKGWHNFSVKLMMELIPELYETSEEQMTILTRLGKQKTTSSSNKTKYIDEKLLTEEIYNPVVAKSVR
QAIKIVNAAIKEYGDFDNIVIEMARETNEDDEKKAIQKIQKANKDEKDAAMLKAANQYNGKAELPHSV
FHGHKQLATKIRLWHQQGERCLYTGKTISIHDLINNSNQFEVDHILPLSITFDDSLANKVLVYATANQE
KGQRTPYQALDSMDDAWSFRELKAFVRESKTLSNKKKEYLLTEEDISKFDVRKKFIERNLVDTRYASR
TLVSYSEDQLLDIETGELISDDEYKESVFKAPYQHFVDTLKSKEFEDSILFSYQVDSKFNRKISDATIYAT
RQAKVGKDKADETYVLGKIKDIYTQDGYDAFMKIYKKDKSKFLMYRHDPQTFEKVIEPILENYPNKQI
NEKGKEVPCNPFLKYKEEHGYIRKYSKKGNGPEIKSLKYYDSKLGNHIDITPKDSNNKVVLQSVSPWR
ADVYFNKTTGKYEILGLKYADLQFEKGTGTYKISQEKYNDIKKKEGVDSDSEFKFTLYKNDLLLVKDT
ETKEQQLFRFLSRTMPKQKHYVELKPYDKQKFEGGEALIKVLGNVANSGQCKKGLGKSNISIYKVRTD
VLGNQHIIKNEGDKPKLDF *Streptococcus thermophilus* CRISPR3Cas9 (St3Cas9) Nickase (D10A) (SEQ ID NO: 824)
MTKPYSIGLAIGTNSVGWAVITDNYKVPSKKMKVLGNTSKKYIKKNLLGVLLFDSGITAEGRRLKRTA
RRRYTRRRNRILYLQEIFSTEMATLDDAFFQRLDDSFLVPDDKRDSKYPIFGNLVEEKVYHDEFPTIYHL
RKYLADSTKKADLRLVYLALAHMIKYRGHFLIEGEFNSKNNDIQKNFQDFLDTYNAIFESDLSLENSKQ
LEEIVKDKISKLEKKDRILKLFPGEKNSGIFSEFLKLIVGNQADFRKCFNLDEKASLHFSKESYDEDLETL
LGYIGDDYSDVFLKAKKLYDAILLSGFLTVTDNETEAPLSSAMIKRYNEHKEDLALLKEYIRNISLKTYN
EVFKDDTKNGYAGYIDGKTNQEDFYVYLKNLLAEFEGADYFLEKIDREDFLRKQRTFDNGSIPYQIHLQ
EMRAILDKQAKFYPFLAKNKERIEKILTFRIPYYVGPLARGNSDFAWSIRKRNEKITPWNFEDVIDKESS
AEAFINRMTSFDLYLPEEKVLPKHSLLYETFNVYNELTKVRFIAESMRDYQFLDSKQKKDIVRLYFKDK
RKVTDKDIIEYLHAIYGYDGIELKGIEKQFNSSLSTYHDLLNIINDKEFLDDSSNEAIIEEIIHTLTIFEDRE
MIKQRLSKFENIFDKSVLKKLSRRHYTGWGKLSAKLINGIRDEKSGNTILDYLIDDGISNRNFMQLIHDD
ALSFKKKIQKAQIIGDEDKGNIKEVVKSLPGSPAIKKGILQSIKIVDELVKVMGGRKPESIVVEMARENQ
YTNQGKSNSQQRLKRLEKSLKELGSKILKENIPAKLSKIDNNALQNDRLYLYYLQNGKDMYTGDDLDI
DRLSNYDIDHIIPQAFLKDNSIDNKVLVSSASNRGKSDDFPSLEVVKKRKTFWYQLLKSKLISQRKFDNL
TKAERGGLLPEDKAGFIQRQLVETRQITKHVARLLDEKFNNKKDENNRAVRTVKIITLKSTLVSQFRKD
FELYKVREINDFHHAHDAYLNAVIASALLKKYPKLEPEFVYGDYPKYNSFRERKSATEKVYFYSNIMNI
FKKSISLADGRVIERPLIEVNEETGESVWNKESDLATVRRVLSYPQVNVVKKVEEQNHGLDRGKPKGL
FNANLSSKPKPNSNENLVGAKEYLDPKKYGGYAGISNSFAVLVKGTIEKGAKKKITNVLEFQGISILDRI
NYRKDKLNFLLEKGYKDIELIIELPKYSLFELSDGSRRMLASILSTNNKRGEIHKGNQIFLSQKFVKLLYH
AKRISNTINENHRKYVENHKKEFEELFYYILEFNENYVGAKKNGKLLNSAFQSWQNHSIDELCSSFIGPT
GSERKGLFELTSRGSAADFEFLGVKIPRYRDYTPSSLLKDATLIHQSVTGLYETRIDLAKLGEG
(176) In some embodiments, the nucleobase editors useful in the present disclosure comprises: (i) a guide nucleotide sequence-programmable DNA-binding protein domain; and (ii) a deaminase domain. In some embodiments, the deaminase domain of the fusion protein is a cytosine deaminase. In some embodiments, the deaminase is an APOBEC1 deaminase. In some embodiments, the deaminase is a rat APOBEC1. In some embodiments, the deaminase is a human APOBEC1. In some embodiments, the deaminase is an APOBEC2 deaminase. In some embodiments, the deaminase is an APOBEC3A deaminase. In some embodiments, the deaminase is an APOBEC3B deaminase. In some embodiments, the deaminase is an APOBEC3C deaminase. In some embodiments, the deaminase is an APOBEC3D deaminase. In some embodiments, is an APOBEC3F deaminase. In some embodiments, the deaminase is an APOBEC3G deaminase. In some embodiments, the deaminase is an APOBEC3H deaminase. In some embodiments, the deaminase is an APOBEC4 deaminase. In some embodiments, the deaminase is an activation-induced deaminase (AID). In some embodiments, the deaminase is a Lamprey CDA1 (pmCDA1). In some embodiments, the deaminase is a human APOBEC3G or a functional fragment thereof. In some embodiments, the deaminase is an APOBEC3G variant comprising mutations correspond to the D316R/D317R mutations in the human APOBEC3G. Exemplary, non-limiting cytosine deaminase sequences that may be used in accordance with the methods of the present disclosure are provided in Example 1 below.
(177) In some embodiments, the cytosine deaminase is a wild type deaminase or a deaminase as set forth in SEQ ID NOs: 271-292, 303, and 1072-1083. In some embodiments, the cytosine deaminase domains of the fusion proteins provided herein include fragments of deaminases and proteins homologous to a deaminase. For example, in some embodiments, a deaminase domain may comprise a fragment of the amino acid sequence set forth in any of SEQ ID NOs: 271-292, 303, and 1072-1083. In some embodiments, a deaminase domain comprises an amino acid sequence homologous to the amino

acid sequence set forth in any of SEQ ID NOs: 271-292, 303, and 1072-1083, or an amino acid sequence homologous to a fragment of the amino acid sequence set forth in any of SEQ ID NOs: 271-292, 303, and 1072-1083. In some embodiments, proteins comprising a deaminase, a fragments of a deaminase, or homologs of a deaminase or a deaminase are referred to as "deaminase variants." A deaminase variant shares homology to a deaminase, or a fragment thereof. For example a deaminase variant is at least about 70% identical, at least about 80% identical, at least about 90% identical, at least about 95% identical, at least about 96% identical, at least about 97% identical, at least about 98% identical, at least about 99% identical, at least about 99.5% identical, or at least about 99.9% to a wild type deaminase or a deaminase as set forth in any of SEQ ID NOs: 271-292, 303, and 1072-1083. In some embodiments, the deaminase variant comprises a fragment of the deaminase, such that the fragment is at least about 70% identical, at least about 80% identical, at least about 90% identical, at least about 95% identical, at least about 96% identical, at least about 97% identical, at least about 98% identical, at least about 99% identical, at least about 99.5% identical, or at least about 99.9% to the corresponding fragment of wild type deaminase or a deaminase as set forth in any of SEQ ID NOs: 271-292, 303, and 1072-1083. In some embodiments, the cytosine deaminase is at least at least about 70% identical, at least about 80% identical, at least about 90% identical, at least about 95% identical, at least about 96% identical, at least about 97% identical, at least about 98% identical, at least about 99% identical, at least about 99.5% identical, or at least about 99.9% identical to an APOBEC3G variant as set forth in SEQ ID NO: 291 or SEQ ID NO: 292, and comprises mutations corresponding to the D316E/D317R mutations in SEQ ID NO: 290.

(178) In some embodiments, the cytosine deaminase domain is fused to the N-terminus of the guide nucleotide sequence-programmable DNA-binding protein domain. For example, the fusion protein may have an architecture of NH.sub.2-[cytosine deaminase]-[guide nucleotide sequence-programmable DNA-binding protein domain]-COOH. The "]-[" used in the general architecture above indicates the presence of an optional linker sequence. The term "linker," as used herein, refers to a chemical group or a molecule linking two molecules or moieties, e.g., two domains of a fusion protein, such as, for example, a dCas9 domain and a cytosine deaminase domain. Typically, the linker is positioned between, or flanked by, two groups, molecules, or other moieties and connected to each one via a covalent bond, thus connecting the two. In some embodiments, the linker is an amino acid or a plurality of amino acids (e.g., a peptide or protein). In some embodiments, the linker is an organic molecule, group, polymer, or chemical moiety. In some embodiments, the linker is 5-100 amino acids in length, for example, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 30-35, 35-40, 40-45, 45-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-150, or 150-200 amino acids in length. Longer or shorter linkers are also contemplated.

(179) In some embodiments, the cytosine deaminase domain and the Cas9 domain are fused to each other via a linker. Various linker lengths and flexibilities between the deaminase domain (e.g., APOBEC1) and the Cas9 domain can be employed (e.g., ranging from very flexible linkers of the form (GGGS).sub.n (SEQ ID NO: 337), (GGGGS).sub.n (SEQ ID NO: 308), (GGS).sub.n(SEQ ID NO: 784), and (G).sub.n(SEQ ID NO: 783) to more rigid linkers of the form (EAAAK).sub.n (SEQ ID NO: 309), SGSETPGTSESATPES (SEQ ID NO: 310) (see, e.g., Guilinger et al., *Nat. Biotechnol.* 2014; 32(6): 577-82; the entire contents are incorporated herein by reference), (SGGS).sub.nSGSETPGTSESATPES(SGGS).sub.n (SEQ ID NO: 1068), (XP).sub.1 (SEQ ID NO: 785), or a combination of any of these, wherein X is any amino acid and n is independently an integer between 1 and 30, in order to achieve the optimal length for deaminase activity for the specific application. In some embodiments, n is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, or, if more than one linker or more than one linker motif is present, any combination thereof. In some embodiments, the linker comprises a (GGS).sub.n(SEQ ID NO: 784) motif, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15. In some embodiments, the linker comprises a (GGS).sub.n(SEQ ID NO: 784) motif, wherein n is 1, 3, or 7. In some embodiments, the linker comprises the amino acid sequence SGSETPGTSESATPES (SEQ ID NO: 310), also referred to as the XTEN linker. In some embodiments, the linker comprises an amino acid sequence chosen from the group including, but not limited to, AGVF (SEQ ID NO: 825), GFLG (SEQ ID NO: 826), FK, AL, ALAL (SEQ ID NO: 827), or ALALA (SEQ ID NO: 828). In some embodiments, suitable linker motifs and configurations include those described in Chen et al., Fusion protein linkers: property, design and functionality. Adv Drug Deliv Rev. 2013; 65(10):1357-69, which is incorporated herein by reference. In some embodiments, the linker may comprise any of the following amino acid sequences: VPFLLEPDNINGKTC (SEQ ID NO: 311), GSAGSAAGSGEF (SEQ ID NO: 312), SIVAQLSRPDPA (SEQ ID NO: 313), MKIIEQLPSA (SEQ ID NO: 314), VRHKLKRVGS (SEQ ID NO: 315), GHGTGSTGSGSS (SEQ ID NO: 316), MSRPDPA (SEQ ID NO: 317), GSAGSAAGSGEF (SEQ ID NO: 312), SGSETPGTSESA (SEQ ID NO: 318), SGSETPGTSESATPEGGSGGS (SEQ ID NO: 319), or GGSM (SEQ ID NO: 320). Additional suitable linker sequences will be apparent to those of skill in the art based on the instant disclosure.

(180) In some embodiments, the nucleobase editor comprises a guide nucleotide sequence-programmable DNA-binding protein domain and an apolipoprotein B mRNA-editing complex 1 (APOBEC1) deaminase domain, where the deaminase domain is fused to the N-terminus of the napDNAbp domain via a linker comprising the amino acid sequence SGSETPGTSESATPES (SEQ ID NO: 310). In some embodiments, the a guide nucleotide sequence-programmable DNA-binding protein domain comprises the amino acid sequence of any of the a guide nucleotide sequence-programmable DNA-binding protein domains provided herein. In some embodiments, the deaminase is rat APOBEC1 (SEQ ID NO: 288). In some embodiments, the deaminase is human APOBEC1 (SEQ ID NO: 286). In some embodiments, the deaminase is pmCDA1 (SEQ ID NO: 289). In some embodiments, the deaminase is human APOBEC3G (SEQ ID NO:

279). In some embodiments, the deaminase is a human APOBEC3G variant of any one of (SEQ ID NOs: 290-292). In some embodiments, the fusion protein comprises a guide nucleotide sequence-programmable DNA-binding protein domain and an apolipoprotein B mRNA-editing complex 1 catalytic polypeptide-like 3G (APOBEC3G) deaminase domain, wherein the deaminase domain is fused to the N-terminus of the a guide nucleotide sequence-programmable DNA-binding protein domain domain via a linker of any length or composition (e.g., an amino acid sequence, a peptide, a polymer, or a bond). In some embodiments, the linker comprises the amino acid sequence SGSETPGTSESATPES (SEQ ID NO: 310). In some embodiments, the linker comprises the amino acid sequence (SGGS).sub.2SGSETPGTSESATPES(SGGS).sub.2 (SEQ ID NO: 1069).

(181) In some embodiments, the fusion protein comprises a guide nucleotide sequence-programmable DNA-binding protein domain and a cytidine deaminase 1 (CDA1) deaminase domain, wherein the deaminase domain is fused to the N-terminus of the guide nucleotide sequence-programmable DNA-binding protein domain domain via a linker comprising the amino acid sequence SGSETPGTSESATPES (SEQ ID NO: 310). In some embodiments, the linker comprises the amino acid sequence (SGGS).sub.2SGSETPGTSESATPES(SGGS).sub.2 (SEQ ID NO: 1069). In some embodiments, the guide nucleotide sequence-programmable DNA-binding protein domain comprises the amino acid sequence of any of the guide nucleotide sequence-programmable DNA-binding protein domains provided herein.

(182) In some embodiments, the fusion protein comprises a guide nucleotide sequence-programmable DNA-binding protein and an activation-induced cytidine deaminase (AID) deaminase domain, where the deaminase domain is fused to the N-terminus of the guide nucleotide sequence-programmable DNA-binding protein domain via a linker comprising the amino acid sequence SGSETPGTSESATPES (SEQ ID NO: 310). In some embodiments, the linker comprises the amino acid sequence (SGGS).sub.2SGSETPGTSESATPES(SGGS).sub.2 (SEQ ID NO: 1069). In some embodiments, the guide nucleotide sequence-programmable DNA-binding protein comprises the amino acid sequence of any of the guide nucleotide sequence-programmable DNA-binding protein domains provided herein.

(183) Some aspects of the disclosure are based on the recognition that certain configurations of a guide nucleotide sequence-programmable DNA-binding protein, and a cytidine deaminase domain fused by a linker are useful for efficiently deaminating target cytidine residues. Other aspects of this disclosure relate to the recognition that a nucleobase editing fusion protein with an apolipoprotein B mRNA-editing complex 1 (APOBEC1) deaminase domain fused to the N-terminus of a guide nucleotide sequence-programmable DNA-binding protein via a linker comprising the amino acid sequence SGSETPGTSESATPES (SEQ ID NO: 310) was capable of efficiently deaminating target nucleic acids in a double stranded DNA target molecule. In some embodiments, the fusion protein comprises a guide nucleotide sequence-programmable DNA-binding protein domain and an apolipoprotein B mRNA-editing complex 1 (APOBEC1) deaminase domain, where the deaminase domain is fused to the N-terminus of the napDNAbp via a linker comprising the amino acid sequence SGSETPGTSESATPES (SEQ ID NO: 310). In some embodiments, the fusion protein comprises a guide nucleotide sequence-programmable DNA-binding protein domain and an apolipoprotein B mRNA-editing complex 1 (APOBEC1) deaminase domain, where the deaminase domain is fused to the N-terminus of the napDNAbp via a linker comprising the amino acid sequence SGGS).sub.2SGSETPGTSESATPES(SGGS).sub.2 (SEQ ID NO: 1069).

(184) To successfully edit the desired target C base, the linker between Cas9 and APOBEC may be optimized, as described in Komor et al., *Nature*, 533, 420-424 (2016), which is incorporated herein by reference. The numbering scheme for base editing is based on the predicted location of the target C within the single stranded stretch of DNA (R-loop) displaced by a programmable guide RNA sequence occurring when a DNA-binding domain (e.g. Cas9, nCas9, dCas9) binds a genomic site (see FIG. **6**). Conveniently, the sequence immediately surrounding the target C also matches the sequence of the guide RNA. The numbering scheme for base editing is based on a standard 20-mer programmable sequence, and defines position “21” as the first DNA base of the PAM sequence, resulting in position “1” assigned to the first DNA base matching the 5′-end of the 20-mer programmable guide RNA sequence. Therefore, for all Cas9 variants, position “21” is defined as the first base of the PAM sequence (e.g. NGG, NGAN, NGNG, NGAG, NGCG, NNGRRT, NGRRN, NNNRRT, NNNGATT, NNAGAA, NAAAC). When a longer programmable guide RNA sequence is used (e.g. 21-mer) the 5′-end bases are assigned a decreasing negative number starting at “−1”. For other DNA-binding domains that differ in the position of the PAM sequence, or that require no PAM sequence, the programmable guide RNA sequence is used as a reference for numbering. A 3-aa linker gives a 2-5 base editing window (e.g., positions 2, 3, 4, or 5 relative to the PAM sequence at position 21). A 9-aa linker gives a 3-6 base editing window (e.g., positions 3, 4, 5, or 6 relative to the PAM sequence at position 21). A 16-aa linker (e.g., the SGSETPGTSESATPES (SEQ ID NO: 310) linker) gives a 4-7 base editing window (e.g., positions 4, 5, 6, or 7 relative to the PAM sequence at position 21). A 21-aa linker gives a 5-8 base editing window (e.g., positions 5, 6, 7, 8 relative to the PAM sequence at position 21). Each of these windows can be useful for editing different targeted C bases. For example, the targeted C bases may be at different distances from the adjacent PAM sequence, and by varying the linker length, the precise editing of the desired C base is ensured. One skilled in the art, based on the teachings of CRISPR/Cas9 technology, in particular the teachings of U.S. Provisional applications 62/245,828, 62/279,346, 62/311,763, 62/322,178, 62/357352, 62/370,700, and 62/398,490, and in Komor et al., Nature, Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage, 533, 420-424 (2016), each of which is incorporated herein by reference, will be able to determine the window of editing for his/her purpose, and properly design the linker of the cytosine deaminase-dCas9 protein for the precise targeting of the desired C base.

(185) To successfully edit the desired target C base, appropriate Cas9 domain may be selected to attached to the deaminase domain (e.g., APOBEC1), since different Cas9 domains may lead to different editing windows, as described in

in U.S. Pat. No. 9,068,179, US Patent Application Publications US 2015/0166980, US 2015/0166981, US 2015/0166982, US20150166984, and US20150165054, and US Provisional Applications, U.S. Ser. No. 62/245,828, filed Oct. 23, 2015; 62/279,346, filed Jan. 15, 2016; 62/311,763, filed Mar. 22, 2016; 62/322,178, filed Apr. 13, 2016, 62/357,352, filed Jun. 30, 2016, U.S. Pat. No. 62,370,700, filed Aug. 3, 2016; 62/398,490, filed Sep. 22, 2016; 62/408,686, filed Oct. 14, 2016; PCT Application PCT/US2016/058344, filed Oct. 22, 2016, U.S. patent application Ser. No. 15/311,852, filed Oct. 22, 2016; and in Komor et al., *Nature*, Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage, 533, 420-424 (2016), the entire contents of each of which are incorporated herein by reference. For example, APOBEC1-XTEN-SaCas9n-UGI gives a 1-12 base editing window (e.g., positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 relative to the NNNRRT PAM sequence in positions 20-26). One skilled in the art, based on the teachings of CRISPR/Cas9 technology, will be able to determine the editing window for his/her purpose, and properly determine the required Cas9 homolog and linker attached to the cytosine deaminase for the precise targeting of the desired C base.

(186) In some embodiments, the fusion protein useful in the present disclosure further comprises a uracil glycosylase inhibitor (UGI) domain. A "uracil glycosylase inhibitor" refers to a protein that inhibits the activity of uracil-DNA glycosylase. The C to T base change induced by deamination results in a U:G heteroduplex, which triggers cellular DNA-repair response. Uracil DNA glycosylase (UDG) catalyzes removal of U from DNA in cells and initiates base excision repair, with reversion of the U:G pair to a C:G pair as the most common outcome. Thus, such cellular DNA-repair response may be responsible for the decrease in nucleobase editing efficiency in cells. Uracil DNA Glycosylase Inhibitor (UGI) is known in the art to potently blocks human UDG activity. As described in Komor et al., Nature (2016), fusing a UGI domain to the cytidine deaminase-dCas9 fusion protein reduced the activity of UDG and significantly enhanced editing efficiency.

(187) Suitable UGI protein and nucleotide sequences are provided herein and additional suitable UGI sequences are known to those in the art, and include, for example, those published in Wang et al., Uracil-DNA glycosylase inhibitor gene of bacteriophage PBS2 encodes a binding protein specific for uracil-DNA glycosylase. J. Biol. Chem. 264:1163-1171(1989); Lundquist et al., Site-directed mutagenesis and characterization of uracil-DNA glycosylase inhibitor protein. Role of specific carboxylic amino acids in complex formation with *Escherichia coli* uracil-DNA glycosylase. J. Biol. Chem. 272:21408-21419(1997); Ravishankar et al., X-ray analysis of a complex of *Escherichia coli* uracil DNA glycosylase (EcUDG) with a proteinaceous inhibitor. The structure elucidation of a prokaryotic UDG. Nucleic Acids Res. 26:4880-4887(1998); and Putnam et al., Protein mimicry of DNA from crystal structures of the uracil-DNA glycosylase inhibitor protein and its complex with *Escherichia coli* uracil-DNA glycosylase. J. Mol. Biol. 287:331-346(1999), each of which is incorporated herein by reference. In some embodiments, the UGI domain comprises the amino acid sequence of SEQ ID NO: 304 without the N-terminal methionine (M). In some embodiments, the UGI comprises the following amino acid sequence: *Bacillus* phage PBS2 (Bacteriophage PBS2)Uracil-DNA glycosylase inhibitor MTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWAL VIQDSNGENKIKML (SEQ ID NO: 304)

(188) In some embodiments, the UGI protein comprises a wild type UGI or a UGI as set forth in SEQ ID NO: 304. In some embodiments, the UGI proteins useful in the present disclosure include fragments of UGI and proteins homologous to a UGI or a UGI fragment. For example, in some embodiments, a UGI comprises a fragment of the amino acid sequence set forth in SEQ ID NO: 304. In some embodiments, a UGI comprises an amino acid sequence homologous to the amino acid sequence set forth in SEQ ID NO: 304 or an amino acid sequence homologous to a fragment of the amino acid sequence set forth in SEQ ID NO: 304. In some embodiments, proteins comprising UGI or fragments of UGI or homologs of UGI or UGI fragments are referred to as "UGI variants." A UGI variant shares homology to UGI, or a fragment thereof. For example a UGI variant is at least about 70% identical, at least about 80% identical, at least about 90% identical, at least about 95% identical, at least about 96% identical, at least about 97% identical, at least about 98% identical, at least about 99% identical, at least about 99.5% identical, or at least about 99.9% to a wild type UGI or a UGI as set forth in SEQ ID NO: 304. In some embodiments, the UGI variant comprises a fragment of UGI, such that the fragment is at least about 70% identical, at least about 80% identical, at least about 90% identical, at least about 95% identical, at least about 96% identical, at least about 97% identical, at least about 98% identical, at least about 99% identical, at least about 99.5% identical, or at least about 99.9% to the corresponding fragment of wild type UGI or a UGI as set forth in SEQ ID NO: 304.

(189) It should be appreciated that additional proteins may be uracil glycosylase inhibitors. For example, other proteins that are capable of inhibiting (e.g., sterically blocking) a uracil-DNA glycosylase base-excision repair enzyme are within the scope of this disclosure. In some embodiments, a uracil glycosylase inhibitor is a protein that binds DNA. In some embodiments, a uracil glycosylase inhibitor is a protein that binds single-stranded DNA. For example, a uracil glycosylase inhibitor may be a *Erwinia tasmaniensis* single-stranded binding protein. In some embodiments, the single-stranded binding protein comprises the amino acid sequence (SEQ ID NO: 305). In some embodiments, a uracil glycosylase inhibitor is a protein that binds uracil. In some embodiments, a uracil glycosylase inhibitor is a protein that binds uracil in DNA. In some embodiments, a uracil glycosylase inhibitor is a catalytically inactive uracil DNA-glycosylase protein. In some embodiments, a uracil glycosylase inhibitor is a catalytically inactive uracil DNA-glycosylase protein that does not excise uracil from the DNA. For example, a uracil glycosylase inhibitor is a UdgX. In some embodiments, the UdgX comprises the amino acid sequence (SEQ ID NO: 306). As another example, a uracil glycosylase inhibitor is a catalytically inactive UDG. In some embodiments, a catalytically inactive UDG comprises the amino acid sequence (SEQ

ID NO: 307). It should be appreciated that other uracil glycosylase inhibitors would be apparent to the skilled artisan and are within the scope of this disclosure.

(190) TABLE-US-00023 *Erwinia tasmaniensis* SSB (themostable single- stranded DNA binding protein) (SEQ ID NO: 305) MASRGVNKVILVGNLGQDPEVRYMPNGGAVANITLATSESWRDKQTGET
KEKTEWHRVVLFGKLAEVAGEYLRKGSQVYIEGALQTRKWTDQAGVEKY
TTEVVVNVGGTMQMLGGRSQGGGASAGGQNGGSNNGWGQPQQPQGGNQF
SGGAQQQARPQQQPQQNNAPANNEPPIDEDDDIP UdgX (binds to Uracil in DNA but does not excise) (SEQ ID NO: 306) MAGAQDFVPHTADLAELAAAAGECRGCGLYRDATQAVFGAGGRSARIMM
IGEQPGDKEDLAGLPFVGPAGRLLDRALEAADIDRDALYVTNAVKHFKF
TRAAGGKRRIHKTPSRTEVVACRPWLIAEMTSVEPDVVVLLGATAAKAL
LGNDFRVTQHRGEVLHVDDVPGDPALVATVHPSSLLRGPKEERESAFAG LVDDLRVAADVRP UDG (catalytically inactive human UDG, binds to Uracil in DNA but does not excise) (SEQ ID NO: 307) MIGQKTLYSFFSPSPARKRHAPSPEPAVQGTGVAGVPEESGDAAAIPAK
KAPAGQEEPGTPPSSPLSAEQLDRIQRNKAAALLRLAARNVPVGFGESW
KKHLSGEFGKPYFIKLMGFVAEERKHYTVYPPPHQVFTWTQMCDIKDVK
VVILGQEPYHGPNQAHGLCFSVQRPVPPPPSLENIYKELSTDIEDFVHP
GHGDLSGWAKQGVLLLNAVLTVRAHQANSHKERGWEQFTDAVVSWLNQN
SNGLVFLLWGSYAQKKGSAIDRKRHHVLQTAHPSPLSVYRGFFGCRHFS KTNELLQKSGKKPIDWKEL

(191) In some embodiments, the UGI domain is fused to the C-terminus of the dCas9 domain in the fusion protein. Thus, the fusion protein would have an architecture of NH.sub.2-[cytosine deaminase]-[guide nucleotide sequence-programmable DNA-binding protein domain]-[UGI]-COOH. In some embodiments, the UGI domain is fused to the N-terminus of the cytosine deaminase domain. As such, the fusion protein would have an architecture of NH.sub.2-[UGI]-[cytosine deaminase]-[guide nucleotide sequence-programmable DNA-binding protein domain]-COOH. In some embodiments, the UGI domain is fused between the guide nucleotide sequence-programmable DNA-binding protein domain and the cytosine deaminase domain. As such, the fusion protein would have an architecture of NH.sub.2-[cytosine deaminase]-[UGI]-[guide nucleotide sequence-programmable DNA-binding protein domain]-COOH. The linker sequences described herein may also be used for the fusion of the UGI domain to the cytosine deaminase-dCas9 fusion proteins.

(192) In some embodiments, the fusion protein comprises the structure: [cytosine deaminase]-[optional linker sequence]-[guide nucleotide sequence-programmable DNA binding protein]-[optional linker sequence]-[UGI]; [cytosine deaminase]-[optional linker sequence]-[UGI]-[optional linker sequence]-[guide nucleotide sequence-programmable DNA binding protein]; [UGI]-[optional linker sequence]-[cytosine deaminase]-[optional linker sequence]-[guide nucleotide sequence-programmable DNA binding protein]; [UGI]-[optional linker sequence]-[guide nucleotide sequence-programmable DNA binding protein]-[optional linker sequence]-[cytosine deaminase]; [guide nucleotide sequence-programmable DNA binding protein]-[optional linker sequence]-[cytosine deaminase]-[optional linker sequence]-[UGI]; or [guide nucleotide sequence-programmable DNA binding protein]-[optional linker sequence]-[UGI]-[optional linker sequence]-[cytosine deaminase].

(193) In some embodiments, the fusion protein comprises the structure: [cytosine deaminase]-[optional linker sequence]-[Cas9 nickase]-[optional linker sequence]-[UGI]; [cytosine deaminase]-[optional linker sequence]-[UGI]-[optional linker sequence]-[Cas9 nickase]; [UGI]-[optional linker sequence]-[cytosine deaminase]-[optional linker sequence]-[Cas9 nickase]; [UGI]-[optional linker sequence]-[Cas9 nickase]-[optional linker sequence]-[cytosine deaminase]; [Cas9 nickase]-[optional linker sequence]-[cytosine deaminase]-[optional linker sequence]-[UGI]; or [Cas9 nickase]-[optional linker sequence]-[UGI]-[optional linker sequence]-[cytosine deaminase].

(194) In some embodiments, fusion proteins provided herein further comprise a nuclear localization sequence (NLS). In some embodiments, the NLS is fused to the N-terminus of the fusion protein. In some embodiments, the NLS is fused to the C-terminus of the fusion protein. In some embodiments, the NLS is fused to the N-terminus of the UGI protein. In some embodiments, the NLS is fused to the C-terminus of the UGI protein. In some embodiments, the NLS is fused to the N-terminus of the guide nucleotide sequence-programmable DNA-binding protein domain. In some embodiments, the NLS is fused to the C-terminus of the guide nucleotide sequence-programmable DNA-binding protein domain. In some embodiments, the NLS is fused to the N-terminus of the cytosine deaminase. In some embodiments, the NLS is fused to the C-terminus of the deaminase. In some embodiments, the NLS is fused to the fusion protein via one or more linkers. In some embodiments, the NLS is fused to the fusion protein without a linker. Non-limiting, exemplary NLS sequences may be PKKKRKV (SEQ ID NO: 829) or MDSLLMNRRKFLYQFKNVRWAKGRRETYLC (SEQ ID NO: 830).

(195) In some embodiments, any of the fusion proteins provided herein comprise a second UGI domain. Fusion proteins comprising two UGI domains are described in U.S. Provisional Applications, U.S. Ser. No. 62/475,830, filed Mar. 23, 2017; 62/490,587; 62/511,934, filed May 26, 2017; 62/551,951, filed Aug. 30, 2017; and Komor et al. (2017) Improved Base Excision Repair Inhibition and Bacteriophage Mu Gam Protein Yields C:G-to-T:A base editors with higher efficiency and product purity. *Sci Adv,* 3: eaao4774; the entire contents of which is incorporated herein by reference. In some embodiments, the second UGI domain comprises a wild-type UGI or a UGI as set forth in SEQ ID NO: 304. In some embodiments, the UGI proteins provided herein include fragments of UGI and proteins homologous to a UGI or a UGI fragment. For example, in some embodiments, the second UGI domain comprises a fragment of the amino acid sequence

set forth in SEQ ID NO: 304. In some embodiments, a UGI fragment comprises an amino acid sequence that comprises at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% of the amino acid sequence as set forth in SEQ ID NO: 304. In some embodiments, the second UGI domain comprises an amino acid sequence homologous to the amino acid sequence set forth in SEQ ID NO: 304 or an amino acid sequence homologous to a fragment of the amino acid sequence set forth in SEQ ID NO: 304. In some embodiments, proteins comprising UGI or fragments of UGI or homologs of UGI or UGI fragments are referred to as "UGI variants." A UGI variant shares homology to UGI, or a fragment thereof. For example a UGI variant is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, at least 99% identical, at least 99.5% identical, or at least 99.9% identical to a wild type UGI or a UGI as set forth in SEQ ID NO: 304. In some embodiments, the UGI variant comprises a fragment of UGI, such that the fragment is at least 70% identical, at least 80% identical, at least 90% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, at least 99% identical, at least 99.5% identical, or at least 99.9% to the corresponding fragment of wild-type UGI or a UGI as set forth in SEQ ID NO: 304.

(196) In some embodiments, the fusion protein comprises the structure: [deaminase]-[optional linker sequence]-[dCas9]-[optional linker sequence]-[first UGI]-[optional linker sequence]-[second UGI]; [deaminase]-[optional linker sequence]-[Cas9 nickase]-[optional linker sequence]-[first UGI]-[optional linker sequence]-[second UGI]; or [deaminase]-[optional linker sequence]-[Cas9]-[optional linker sequence]-[first UGI]-[optional linker sequence]-[second UGI].

(197) In some embodiments, the nucleobase editor comprises a guide nucleotide sequence-programmable DNA-binding protein domain and an apolipoprotein B mRNA-editing complex 1 (APOBEC1) deaminase domain, wherein the deaminase domain is fused to the N-terminus of the guide nucleotide sequence-programmable DNA-binding protein domain via a linker comprising the amino acid sequence (SGGS).sub.2SGSETPGTSESATPES(SGGS).sub.2 (SEQ ID NO: 1069). In some embodiments, the a guide nucleotide sequence-programmable DNA-binding protein domain comprises the amino acid sequence of any of the a guide nucleotide sequence-programmable DNA-binding protein domains provided herein. In some embodiments, the deaminase is rat APOBEC1 (SEQ ID NO: 288). In some embodiments, the deaminase is human APOBEC1 (SEQ ID NO: 286). In some embodiments, the deaminase is a human APOBEC3G variant of any one of (SEQ ID NOs: 290-292). In some embodiments, the nucleobase editor comprises a first UGI domain fused to the C-terminus of a guide nucleotide sequence-programmable DNA-binding protein domain via a linker comprising the amino acid sequence (GGS).sub.n(SEQ ID NO: 784), wherein n is 3. In some embodiments, the nucleobase editor comprises a second UGI domain fused to the C-terminus of a first UGI domain via a linker comprising the amino acid sequence (GGS).sub.n (SEQ ID NO: 784), wherein n is 3.

(198) In some embodiments, the fusion protein comprises the amino acid sequence of SEQ ID NO: 1084. In some embodiments, the fusion protein comprises an amino acid sequence that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence as set forth in SEQ ID NO: 1084.

(199) In some embodiments, any of the fusion proteins provided herein may further comprise a Gam protein. The term "Gam protein," as used herein, refers generally to proteins capable of binding to one or more ends of a double strand break of a double stranded nucleic acid (e.g., double stranded DNA). In some embodiments, the Gam protein prevents or inhibits degradation of one or more strands of a nucleic acid at the site of the double strand break. In some embodiments, a Gam protein is a naturally-occurring Gam protein from bacteriophage Mu, or a non-naturally occurring variant thereof. Fusion proteins comprising Gam proteins are described in Komor et al. (2017) Improved Base Excision Repair Inhibition and Bateriophage Mu Gam Protein Yields C:G-to-T:A base editors with higher efficiency and product purity. *Sci Adv,* 3: eaao4774; the entire contents of which is incorporated by reference herein. In some embodiments, the Gam protein comprises an amino acid sequence that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence provided by SEQ ID NO: 3027. In some embodiments, the Gam protein comprises the amino acid sequence of SEQ ID NO: 3027. In some embodiments, the fusion protein (e.g., BE4-Gam of SEQ ID NO: 3028) comprises a Gam protein, wherein the Cas9 domain of BE4 is replaced with any of the Cas9 domains provided herein.

(200) TABLE-US-00024 Gam from bacteriophage Mu: (SEQ ID NO: 1070)
AKPAKRIKSAAAAYVPQNRDAVITDIKRIGDLQREASRLETEMNDAIAEITEKFAARIAPIKTDIETLSKGVQGW
CEANRDELTNGGKVKTANLVTGDVSWRVRPPSVSIRGMDAVMETLERLGLQRFIRTKQEINKEAILLEPKAVAGV
AGITVKSGIEDFSIIPFEQEAGI BE4-Gam: (SEQ ID NO: 1071)
MAKPAKRIKSAAAAYVPQNRDAVITDIKRIGDLQREASRLETEMNDAIAEITEKFAARIAPIKTDIETLSKGVQG
WCEANRDELTNGGKVKTANLVTGDVSWRVRPPSVSIRGMDAVMETLERLGLQRFIRTKQEINKEAILLEPKAVAG
VAGITVKSGIEDFSIIPFEQEAGISGSETPGTSESATPESSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKET
CLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTTERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVT
LFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTEQESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCII
LGLPPCLNILRRKQPQLTFFTIALQSCHYQRLPPHILWATGLKSGGSSGGSSGSETPGTSESATPESSGGSSGGS
DKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRK
NRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADL
RLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLI

AQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAIL
LSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFI
KPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYY
VGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTK
VKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRENASLGTYHDLLKII
KDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLEDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSG
KTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVM
GRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQ
ELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLT
KAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVR
EINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEIT
LANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDW
DPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKY
SLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEF
SKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQS
ITGLYETRIDLSQLGGDSGGSGGSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDE
STDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSGGSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEE
VIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRK

(201) Some aspects of the present disclosure provide nucleobase editors associated with a guide nucleotide sequence (e.g., a guide RNA or gRNA). gRNAs can exist as a complex of two or more RNAs, or as a single RNA molecule. gRNAs that exist as a single RNA molecule may be referred to as single-guide RNAs (sgRNAs), though "gRNA" is used interchangeably to refer to guide RNAs that exist as either single molecules or as a complex of two or more molecules. Typically, gRNAs that exist as a single RNA species comprise two domains: (1) a domain that shares homology to a target nucleic acid (e.g., and directs binding of the Cas9 complex to the target); and (2) a domain that binds the Cas9 protein. In some embodiments, domain (2) corresponds to a sequence known as a tracrRNA, and comprises a stem-loop structure. For example, in some embodiments, domain (2) is identical or homologous to a tracrRNA as provided in Jinek et al., *Science* 337:816-821(2012), which is incorporated herein by reference. Other examples of gRNAs (e.g., those including domain 2) can be found in U.S. Provisional Patent Application, U.S. Ser. No. 61/874,682, filed Sep. 6, 2013, entitled "Switchable Cas9 Nucleases And Uses Thereof," and U.S. Provisional Patent Application, U.S. Ser. No. 61/874,746, filed Sep. 6, 2013, entitled "Delivery System For Functional Nucleases," each of which isincorporated herein by reference in their entirety. The gRNA comprises a nucleotide sequence that complements a target site, which mediates binding of the nuclease/RNA complex to said target site, providing the sequence specificity of the nuclease:RNA complex. These proteins are able to be targeted, in principle, to any sequence specified by the guide RNA. Methods of using RNA-programmable nucleases, such as Cas9, for site-specific cleavage (e.g., to modify a genome) are known in the art (see e.g., Cong, L. et al. *Science* 339, 819-823 (2013); Mali, P. et al. *Science* 339, 823-826 (2013); Hwang, W. Y. et al. *Nature biotechnology* 31, 227-229 (2013); Jinek, M. et al. eLife 2, e00471 (2013); Dicarlo, J. E. et al. *Nucleic acids research* (2013); Jiang, W. et al. *Nature Biotechnology* 31, 233-239 (2013); each of which are incorporated herein by reference). In particular, examples of guide nucleotide sequences (e.g., sgRNAs) that may be used to target the fusion protein of the present disclosure to its target sequence to deaminate the targeted C bases are described in Komor et al., *Nature,* 533, 420-424 (2016), which is incorporated herein by reference.

(202) The specific structure of the guide nucleotide sequences (e.g., sgRNAs) depends on its target sequence and the relative distance of a PAM sequence downstream of the target sequence. One skilled in the art will understand, that no unifying structure of guide nucleotide sequence is given, for that he target sequences are different for each and every C targeted to be deaminated.

(203) However, the present disclosure provides guidance in how to design the guide nucleotide sequence, e.g., an sgRNA, so that one skilled in the art may use such teaching to a target sequence of interest. An gRNA typically comprises a tracrRNA framework allowing for Cas9 binding, and a guide sequence, which confers sequence specificity to fusion proteins disclosed herein. In some embodiments, the guide RNA comprises a structure 5′-[guide sequence]-tracrRNA-3′. Non-limiting, exemplary tracrRNA sequences are shown in Table 11.

(204) TABLE-US-00025 TABLE 11 TracrRNA orthologues and sequences SEQ Organism tracrRNA sequence ID NO *S. pyogenes* GUUUAAGAGCUAUGCUGGAAAGCCACGGUGAAAAA 322
GUUCAACUAUUGCCUGAUCGGAAUAAAUUUGAACG AUACGACAGUCGGUGCUUUUUUU S. *pyogenes*
GUUUAAGAGCUAGAAAUAGCAAGUUUAAAUAAGGC 323
UAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGU CGGUGCUUUUUU *S. thermophilus* CRISPR1
GUUUUUGUACUCUCAAGAUUCAAUAAUCUUGCAGA 324
AGCUACAAAGAUAAGGCUUCAUGCCGAAAUCAACA CCCUGUCAUUUUAUGGCAGGGUGUUUU *S. thermophilus* CRISPR3 GUUUUAGAGCUGUGUUGUUUGUUAAAACAACACAG 325
CGAGUUAAAAUAAGGCUUAGUCCGUACUCAACUUG AAAAGGUGGCACCGAUUCGGUGUUUUU *C. jejuni*
AAGAAAUUUAAAAAGGGACUAAAAUAAAGAGUUUG 326
CGGGACUCUGCGGGGUUACAAUCCCCUAAAACCGCU UUU *F. novicida*
AUCUAAAAUUAUAAAUGUACCAAAUAAUUAAUGCU 327

CUGUAAUCAUUUAAAAGUAUUUUGAACGGACCUCU GUUUGACACGUCUGAAUAACUAAAA *S. thermophilus2* UGUAAGGGACGCCUUACACAGUUACUUAAAUCUUG 328
CAGAAGCUACAAAGAUAAGGCUUCAUGCCGAAAUC
AACACCCUGUCAUUUUAUGGCAGGGUGUUUUCGUU AUUU *M. mobile*
UGUAUUUCGAAAUACAGAUGUACAGUUAAGAAUAC 329
AUAAGAAUGAUACAUCACUAAAAAAAGGCUUUAUG
CCGUAACUACUACUUAUUUUCAAAAUAAGUAGUUU UUUUU *L. innocua*
AUUGUUAGUAUUCAAAAUAACAUAGCAAGUUAAAA 330
UAAGGCUUUGUCCGUUAUCAACUUUUAAUUAAGUA GCGCUGUUUCGGCGCUUUUUUU *S. pyogenes*
GUUGGAACCAUUCAAAACAGCAUAGCAAGUUAAAA 331
UAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCA CCGAGUCGGUGCUUUUUUU *S. mutans*
GUUGGAAUCAUUCGAAACAACACAGCAAGUUAAAA 332
UAAGGCAGUGAUUUUUAAUCCAGUCCGUACACAAC
UUGAAAAAGUGCGCACCGAUUCGGUGCUUUUUUAU UU *S. thermophilus*
UUGUGGUUUGAAACCAUUCGAAACAACACAGCGAG 333
UUAAAAUAAGGCUUAGUCCGUACUCAACUUGAAAA GGUGGCACCGAUUCGGUGUUUUUUUU *N. meningitidis* ACAUAUUGUCGCACUGCGAAAUGAGAACCGUUGCU 334
ACAAUAAGGCCGUCUGAAAAGAUGUGCCGCAACGC UCUGCCCCUUAAAGCUUCUGCUUUAAGGGGCA *P. multocida* GCAUAUUGUUGCACUGCGAAAUGAGAGACGUUGCU 335
ACAAUAAGGCUUCUGAAAAGAAUGACCGUAACGCU
CUGCCCCUUGUGAUUCUUAAUUGCAAGGGGCAUCG UUUUU

(205) The guide sequence of the gRNA comprises a sequence that is complementary to the target sequence. The guide sequence is typically about 20 nucleotides long. For example, the guide sequence may be 15-25 nucleotides long. In some embodiments, the guide sequence is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides long. In some embodiments, the guide sequence is more than 25 nucleotides long. Such suitable guide RNA sequences typically comprise guide sequences that are complementary to a nucleic sequence within 50 nucleotides upstream or downstream of the target nucleotide to be edited.

(206) In some embodiments, the guide RNA is about 15-100 nucleotides long and comprises a sequence of at least 10 contiguous nucleotides that is complementary to a target sequence. In some embodiments, the guide RNA is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides long. In some embodiments, the guide RNA comprises a sequence of 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, or 40 contiguous nucleotides that is complementary to a target sequence.

(207) Compositions

(208) Some aspects of the present disclosure relate to compositions that may be used for generating cancer vaccines in vivo or ex vivo. In some embodiments, the composition comprises: (i) a nucleobase editor or a nucleic acid molecule encoding the nucleobase editor described herein; and (ii) a guide nucleotide sequence targeting the nucleobase editor to a tumor specific antigen-encoding polynucleotide. The guide nucleotide sequence that may be used to generate heteroclitic or cryptic epitopes may be selected from SEQ ID NOs: X-X. Guide nucleotide sequences for generating specific heteroclitic or cryptic epitopes may be found in Tables 5 and 6.

(209) In some embodiments, the composition described herein further comprises a pharmaceutically acceptable carrier.

(210) As used here, the term “pharmaceutically-acceptable carrier” means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the compound from one site (e.g., the delivery site) of the body, to another site (e.g., organ, tissue or portion of the body). A pharmaceutically acceptable carrier is “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the tissue of the subject (e.g., physiologically compatible, sterile, physiologic pH, etc.). Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, methylcellulose, ethyl cellulose, microcrystalline cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol (PEG); (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; (22) C2-C12 alcohols, such as ethanol; and (23) other non-toxic compatible substances employed in pharmaceutical formulations. Wetting agents, coloring agents, release agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservative and antioxidants can also be present in the formulation. The terms such as “excipient”, “carrier”, “pharmaceutically acceptable carrier” or the like are used

interchangeably herein.
(211) In some embodiments, the nucleobase editors and the guide nucleotides of the present disclosure in a composition is administered by injection, by means of a catheter, by means of a suppository, or by means of an implant, the implant being of a porous, non-porous, or gelatinous material, including a membrane, such as a sialastic membrane, or a fiber. In some embodiments, the injection is directed to the liver.
(212) In other embodiments, the nucleobase editors and the guide nucleotides are delivered in a controlled release system. In one embodiment, a pump may be used (see, e.g., Langer, 1990, *Science* 249:1527-1533; Sefton, 1989, *CRC Crit. Ref Biomed. Eng.* 14:201; Buchwald et al., 1980, *Surgery* 88:507; Saudek et al., 1989, *N. Engl. J. Med.* 321:574). In another embodiment, polymeric materials can be used. (See, e.g., Medical Applications of Controlled Release (Langer and Wise eds., CRC Press, Boca Raton, Fla., 1974); Controlled Drug Bioavailability, Drug Product Design and Performance (Smolen and Ball eds., Wiley, New York, 1984); Ranger and Peppas, 1983, *Macromol. Sci. Rev. Macromol. Chem.* 23:61. See also Levy et al., 1985, *Science* 228:190; During et al., 1989, *Ann. Neurol.* 25:351; Howard et al., 1989, *J. Neurosurg.* 71:105.) Other controlled release systems are discussed, for example, in Langer, supra.
(213) In typical embodiments, the pharmaceutical composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous or subcutaneous administration to a subject, e.g., a human. Typically, compositions for administration by injection are solutions in sterile isotonic aqueous buffer. Where necessary, the pharmaceutical can also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the pharmaceutical is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the pharmaceutical is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.
(214) A pharmaceutical composition for systemic administration may be a liquid, e.g., sterile saline, lactated Ringer's or Hank's solution. In addition, the pharmaceutical composition can be in solid forms and re-dissolved or suspended immediately prior to use. Lyophilized forms are also contemplated.
(215) The pharmaceutical composition can be contained within a lipid particle or vesicle, such as a liposome or microcrystal, which is also suitable for parenteral administration. The particles can be of any suitable structure, such as unilamellar or plurilamellar, so long as compositions are contained therein. Compounds can be entrapped in ‘stabilized plasmid-lipid particles’ (SPLP) containing the fusogenic lipid dioleoylphosphatidylethanolamine (DOPE), low levels (5-10 mol %) of cationic lipid, and stabilized by a polyethyleneglycol (PEG) coating (Zhang Y. P. et al., *Gene Ther.* 1999, 6:1438-47). Positively charged lipids such as N-[1-(2,3-dioleoyloxi)propyl]-N,N,N-trimethyl-amoniummethylsulfate, or “DOTAP,” are particularly preferred for such particles and vesicles. The preparation of such lipid particles is well known. See, e.g., U.S. Pat. Nos. 4,880,635; 4,906,477; 4,911,928; 4,917,951; 4,920,016; and 4,921,757.
(216) The pharmaceutical compositions of this disclosure may be administered or packaged as a unit dose, for example. The term “unit dose” when used in reference to a pharmaceutical composition of the present disclosure refers to physically discrete units suitable as unitary dosage for the subject, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required diluent; i.e., carrier, or vehicle.
(217) In some embodiments, the nucleobase editors or the guide nucleotides described herein may be conjugated to a therapeutic moiety, e.g., an anti-inflammatory agent. Techniques for conjugating such therapeutic moieties to polypeptides, including e.g., Fc domains, are well known; see, e.g., Amon et al., “Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy”, in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), 1985, pp. 243-56, Alan R. Liss, Inc.); Hellstrom et al., “Antibodies For Drug Delivery”, in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), 1987, pp. 623-53, Marcel Dekker, Inc.); Thorpe, “Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review”, in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), 1985, pp. 475-506); “Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy”, in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), 1985, pp. 303-16, Academic Press; and Thorpe et al. (1982) “The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates,” Immunol. Rev., 62:119-158.
(218) Further, the compositions of the present disclosure may be assembled into kits. In some embodiments, the kit comprises nucleic acid vectors for the expression of the nucleobase editors described herein. In some embodiments, the kit further comprises appropriate guide nucleotide sequences (e.g., gRNAs) or nucleic acid vectors for the expression of such guide nucleotide sequences, to target the nucleobase editors to the desired target sequences.
(219) The kit described herein may include one or more containers housing components for performing the methods described herein and optionally instructions of uses. Any of the kit described herein may further comprise components needed for performing the assay methods. Each component of the kits, where applicable, may be provided in liquid form (e.g., in solution), or in solid form, (e.g., a dry powder). In certain cases, some of the components may be reconstitutable or otherwise processible (e.g., to an active form), for example, by the addition of a suitable solvent or other species (for example, water or certain organic solvents), which may or may not be provided with the kit.
(220) In some embodiments, the kits may optionally include instructions and/or promotion for use of the components

provided. As used herein, “instructions” can define a component of instruction and/or promotion, and typically involve written instructions on or associated with packaging of the disclosure. Instructions also can include any oral or electronic instructions provided in any manner such that a user will clearly recognize that the instructions are to be associated with the kit, for example, audiovisual (e.g., videotape, DVD, etc.), Internet, and/or web-based communications, etc. The written instructions may be in a form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals or biological products, which can also reflect approval by the agency of manufacture, use or sale for animal administration. As used herein, “promoted” includes all methods of doing business including methods of education, hospital and other clinical instruction, scientific inquiry, drug discovery or development, academic research, pharmaceutical industry activity including pharmaceutical sales, and any advertising or other promotional activity including written, oral and electronic communication of any form, associated with the disclosure. Additionally, the kits may include other components depending on the specific application, as described herein.

(221) The kits may contain any one or more of the components described herein in one or more containers. The components may be prepared sterilely, packaged in a syringe and shipped refrigerated. Alternatively it may be housed in a vial or other container for storage. A second container may have other components prepared sterilely. Alternatively the kits may include the active agents premixed and shipped in a vial, tube, or other container.

(222) The kits may have a variety of forms, such as a blister pouch, a shrink wrapped pouch, a vacuum sealable pouch, a sealable thermoformed tray, or a similar pouch or tray form, with the accessories loosely packed within the pouch, one or more tubes, containers, a box or a bag. The kits may be sterilized after the accessories are added, thereby allowing the individual accessories in the container to be otherwise unwrapped. The kits can be sterilized using any appropriate sterilization techniques, such as radiation sterilization, heat sterilization, or other sterilization methods known in the art. The kits may also include other components, depending on the specific application, for example, containers, cell media, salts, buffers, reagents, syringes, needles, a fabric, such as gauze, for applying or removing a disinfecting agent, disposable gloves, a support for the agents prior to administration, etc.

(223) Therapeutics

(224) The compositions or cancer vaccines (e.g., a whole-cell vaccine comprising a modified tumor cell) described herein may be administered to a subject in need thereof, in a therapeutically effective amount, to treat cancer. The compositions and cancer vaccines described herein induce tumor-specific adaptive responses. It is known that cancer cells exploit immune checkpoints to evade immune surveillance. Thus, in some embodiments, in addition to the compositions or cancer vaccines described herein, agents that modulate the activities of immune checkpoints are also administered to boost the tumor-specific immune response elicited by the cancer vaccines.

(225) In some embodiments, the agents that modulate the activities of immune checkpoints are immune checkpoint inhibitors. “Immune checkpoints” are proteins in the immune system that either enhance an immune response signal (co-stimulatory molecules) or reduce an immune response signal. Many cancers protect themselves from the immune system by exploiting the inhibitory immune checkpoint proteins to inhibit the T cell signal. Such inhibitory checkpoint proteins include, without limitation, Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4), Programmed Death 1 receptor (PD-1), T-cell Immunoglobulin domain and Mucin domain 3 (TIM3), Lymphocyte Activation Gene-3 (LAG3), V-set domain-containing T-cell activation inhibitor 1 (VTVN1 or B7-H4), Cluster of Differentiation 276 (CD276 or B7-H3), B and T Lymphocyte Attenuator (BTLA), Galectin-9 (GAL9), Checkpoint kinase 1 (Chk1), Adenosine A2A receptor (A2aR), Indoleamine 2,3-dioxygenase (IDO), Killer-cell Immunoglobulin-like Receptor (KIR), Lymphocyte Activation Gene-3 (LAG3), and V-domain Ig suppressor of T cell activation (VISTA).

(226) Some of these immune checkpoint proteins need their cognate binding partners, or ligands, for their immune inhibitory activity. For example, A2AR is the receptor of adenosine A2A and binding of A2A to A2AR activates a negative immune feedback loop. As another example, PD-1 associates with its two ligands, PD-L1 and PD-L2, to down regulate the immune system by preventing the activation of T-cells. PD-1 promotes the programmed cell death of antigen specific T-cells in lymph nodes and simultaneously reduces programmed cell death of suppressor T cells, thus achieving its immune inhibitory function. As yet another example, CTLA4 is present on the surface of T cells, and when bound to its binding partner CD80 or CD86 on the surface of antigen-present cells (APCs), it transmits an inhibitory signal to T cells, thereby reducing the immune response.

(227) Cancer cells are known to exploit the immune checkpoint proteins to escape being attacked by the immune system. Therefore, the use of immune checkpoint inhibitors to enhance an immune response against cancer, and thus treating cancer, have been described. The immunotherapeutic agents in the compositions of the present disclosure may also be immune checkpoint inhibitors. In some embodiments, the immune checkpoint inhibits any one or more of Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4), Programmed Death 1 receptor (PD-1), T-cell Immunoglobulin domain and Mucin domain 3 (TIM3), Lymphocyte Activation Gene-3 (LAG3), V-set domain-containing T-cell activation inhibitor 1 (VTVN1 or B7-H4), Cluster of Differentiation 276 (CD276 or B7-H3), B and T Lymphocyte Attenuator (BTLA), Galectin-9 (GAL9), Checkpoint kinase 1 (Chk1), Adenosine A2A receptor (A2aR), Indoleamine 2,3-dioxygenase (IDO), Killer-cell Immunoglobulin-like Receptor (KIR), Lymphocyte Activation Gene-3 (LAG3) and V-domain Ig suppressor of T cell activation (VISTA).

(228) An “immune checkpoint inhibitor” is a molecule that prevents or weakens the activity of an immune checkpoint inhibitor, For example, an immune checkpoint inhibitor may inhibit the binding of the immune checkpoint protein to its cognate binding partner, e.g., PD-1, CTLA-4, or A2aR. In some embodiments, the immune checkpoint inhibitor is a small

molecule. In some embodiments, the immune checkpoint inhibitors is a nucleic acid aptamer (e.g., a siRNA targeting any one of the immune checkpoint proteins). In some embodiments, the immune checkpoint inhibitor is a recombinant protein. In some embodiments, the immune checkpoint inhibitor is an antibody. In some embodiments, the antibody comprises an anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-TIM3, anti-LAG3, anti-B7-H3, anti-B7-H4, anti-BTLA, anti-GAL9, anti-Chk, anti-A2aR, anti-IDO, anti-KIR, anti-LAG3, anti-VISTA antibody, or a combination of any two or more of the foregoing antibodies. In some embodiments, the immune checkpoint inhibitor is a monoclonal antibody. In some embodiments, the immune checkpoint inhibitor comprises anti-PD1, anti-PD-L1, anti-CTLA-4, or a combination of any two or more of the foregoing antibodies. For example, the anti-PD-1 antibody is pembrolizumab (Keytruda®) or nivolumab (Opdivo®) and the anti-CTLA-4 antibody is ipilimumab (Yervoy®). Thus, in some embodiments, the immune checkpoint inhibitor comprises pembrolizumab, nivolumab, ipilimumab, or any combination of two or more of the foregoing antibodies. The examples described herein are not meant to be limiting and that any immune checkpoint inhibitors known in the art and any combinations thereof may be used in accordance with the present disclosure.

(229) In some embodiments, the immune checkpoint may be inhibited by disrupting any one of the immune checkpoint genes (e.g., CTLA-4, PD-1, PD-L1, TIM3, LAG3, B7-H3, B7-H4, BTLA, GAL9, Chk1, or A2aR) using any of the gene editing methods known in the art (e.g., CRISPR/Cas9 mediated cleavage of any of the genes).

(230) In some embodiments, an adjuvant is futher administered to the subject. Adjuvants are substances which enhance the immune response when administered together with an immunogen or antigen. Adjuvants are thought to function in several ways, including by increasing the surface area of antigen, prolonging the retention of the antigen in the body thus allowing time for the lymphoid system to have access to the antigen, slowing the release of antigen, targeting antigen to macrophages, activating macrophages, or otherwise eliciting non-specific activation of the cells of the immune system see, e.g., H. S. Warren et al, Annu. Rev. immunol., 4:369 (1986). Currently, an essential role of adjuvants in vaccines is to direct CD4+ T cell subset differentiation, although how adjuvants perform this function is poorly understood.

(231) The ability of a adjuvant to induce and increase a specific type of immune response and the identification of that ability is thus a key factor in the selection of particular adjuvants for vaccine use against a particular pathogen. Typical adjuvants include water and oil emulsions, e.g., Freund's adjuvant, and chemical compounds such as aluminum hydroxide or alum. At present, alum is the only adjuvant approved in the United States for human vaccines; it has been determined that alum induces the production of TH 2 cells.

(232) Many of the most effective adjuvants include bacteria or their products, e.g., microorganisms such as the attenuated strain of *Mycobacterium bovis, bacillus* Calmette-Guerin (BCG); microorganism components, e.g., alum-precipitated diphtheria toxoid, bacterial lipopolysaccharide and endotoxins. However, the role that the bacteria play is ill-defined. Recently, it has been noted that many bacteria or their products, lipopolysaccharide, *Staphylococcus aureus, Mycobacterium tuberculosis*, and *C. parvum*, stimulate IL-12 production by macrophages A. D'Andrea et al, J. Exp. Med., 176:1387 (1992).

(233) Cancers or tumors include but are not limited to neoplasms, malignant tumors, metastases, or any disease or disorder characterized by uncontrolled cell growth such that it would be considered cancerous. The cancer may be a primary or metastatic cancer. Cancers include, but are not limited to, biliary tract cancer; bladder cancer; brain cancer including glioblastomas and medulloblastomas; breast cancer; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hematological neoplasms including acute lymphocytic and myelogenous leukemia; multiple myeloma; AIDS-associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms including Bowen's disease and Paget's disease; liver cancer; lung cancer; lymphomas including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; oral cancer including squamous cell carcinoma; ovarian cancer including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreatic cancer; prostate cancer; rectal cancer; sarcomas including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma, and osteosarcoma; skin cancer including melanoma, Kaposi's sarcoma, basocellular cancer, and squamous cell cancer; testicular cancer including germinal tumors such as seminoma, non-seminoma, teratomas, choriocarcinomas; stromal tumors and germ cell tumors; thyroid cancer including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms' tumor. Commonly encountered cancers include breast, prostate, lung, ovarian, colorectal, and brain cancer.

(234) “A therapeutically effective amount” as used herein refers to the amount of each base-editing agent of the present disclosure required to confer therapeutic effect on the subject, either alone or in combination with one or more other therapeutic agents. Effective amounts vary, as recognized by those skilled in the art, depending on the particular condition being treated, the severity of the condition, the individual subject parameters including age, physical condition, size, gender and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the individual components or combinations thereof be used, that is, the highest safe dose according to sound medical judgment. It will be understood by those of ordinary skill in the art, however, that a subject may insist upon a lower dose or tolerable dose for medical reasons, psychological reasons or for virtually any other reasons. Empirical considerations, such as the half-life, generally will contribute to the determination of the dosage. For example, therapeutic agents that are compatible with the human immune system, such as polypeptides comprising regions from humanized antibodies or fully human antibodies, may be used to prolong the half-life of the polypeptide.

(235) Frequency of administration may be determined and adjusted over the course of therapy, and is generally, but not necessarily, based on treatment and/or suppression and/or amelioration and/or delay of a disease. Alternatively, sustained continuous release formulations of a polypeptide or a polynucleotide may be appropriate. Various formulations and devices for achieving sustained release are known in the art. In some embodiments, dosage is daily, every other day, every three days, every four days, every five days, or every six days. In some embodiments, dosing frequency is once every week, every 2 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, every 8 weeks, every 9 weeks, or every 10 weeks; or once every month, every 2 months, or every 3 months, or longer. The progress of this therapy is easily monitored by conventional techniques and assays.
(236) The dosing regimen (including the polypeptide used) can vary over time. In some embodiments, for an adult subject of normal weight, doses ranging from about 0.01 to 1000 mg/kg may be administered. In some embodiments, the dose is between 1 to 200 mg. The particular dosage regimen, i.e., dose, timing and repetition, will depend on the particular subject and that subject's medical history, as well as the properties of the polypeptide or the polynucleotide (such as the half-life of the polypeptide or the polynucleotide, and other considerations well known in the art).
(237) For the purpose of the present disclosure, the appropriate dosage of a therapeutic agent as described herein will depend on the specific agent (or compositions thereof) employed, the formulation and route of administration, the type and severity of the disease, whether the polypeptide or the polynucleotide is administered for preventive or therapeutic purposes, previous therapy, the subject's clinical history and response to the antagonist, and the discretion of the attending physician. Typically the clinician will administer a polypeptide until a dosage is reached that achieves the desired result.
(238) Administration of one or more agents can be continuous or intermittent, depending, for example, upon the recipient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to skilled practitioners. The administration of an agent (e.g., cancer vaccine) may be essentially continuous over a preselected period of time or may be in a series of spaced dose, e.g., either before, during, or after developing a disease. “Treat,” as used herein, means to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease, the symptom of the disease, or the predisposition toward the disease. “Treating,” as used herein refers to the application or administration of a composition or a cancer vaccine described herein to a subject in need thereof.
(239) “A subject in need thereof”, refers to an individual who has a disease, a symptom of the disease, or a predisposition toward the disease. In some embodiments, the subject is a mammal. In some embodiments, the subject is a non-human primate. In some embodiments, the subject is human. Alleviating a disease includes delaying the development or progression of the disease, or reducing disease severity. Alleviating the disease does not necessarily require curative results.
(240) As used therein, “delaying” the development of a disease means to defer, hinder, slow, retard, stabilize, and/or postpone progression of the disease. This delay can be of varying lengths of time, depending on the history of the disease and/or individuals being treated. A method that “delays” or alleviates the development of a disease, or delays the onset of the disease, is a method that reduces probability of developing one or more symptoms of the disease in a given time frame and/or reduces extent of the symptoms in a given time frame, when compared to not using the method. Such comparisons are typically based on clinical studies, using a number of subjects sufficient to give a statistically significant result.
(241) “Development” or “progression” of a disease means initial manifestations and/or ensuing progression of the disease. Development of the disease can be detectable and assessed using standard clinical techniques as well known in the art. However, development also refers to progression that may be undetectable. For purpose of this disclosure, development or progression refers to the biological course of the symptoms. “Development” includes occurrence, recurrence, and onset.
(242) As used herein “onset” or “occurrence” of a disease includes initial onset and/or recurrence. Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the isolated polypeptide or pharmaceutical composition to the subject, depending upon the type of disease to be treated or the site of the disease. This composition can also be administered via other conventional routes, e.g., administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir.
(243) The term “parenteral” as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques. In addition, it can be administered to the subject via injectable depot routes of administration such as using 1-, 3-, or 6-month depot injectable or biodegradable materials and methods.
(244) Without further elaboration, it is believed that one skilled in the art can, based on the above description, utilize the present disclosure to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All publications cited herein are incorporated by reference for the purposes or subject matter referenced herein.

EXAMPLES

(245) In order that the disclosure described herein may be more fully understood, the following examples are set forth. The synthetic examples described in this application are offered to illustrate the compounds and methods provided herein and are not to be construed in any way as limiting their scope.

Example 1: Guide Nucleotide Sequence-Programmable DNA-Binding Protein Domains, Deaminases, and Base Editors

(246) Non-limiting examples of suitable guide nucleotide sequence-programmable DNA-binding protein domain s are provided. The disclosure provides Cas9 variants, for example, Cas9 proteins from one or more organisms, which may comprise one or more mutations (e.g., to generate dCas9 or Cas9 nickase). In some embodiments, one or more of the

amino acid residues, identified below by an asterek, of a Cas9 protein may be mutated. In some embodiments, the D10 and/or H840 residues of the amino acid sequence provided in SEQ ID NO: 1, or a corresponding mutation in any of the amino acid sequences provided in SEQ ID NOs: 11-260, are mutated. In some embodiments, the D10 residue of the amino acid sequence provided in SEQ ID NO: 1, or a corresponding mutation in any of the amino acid sequences provided in SEQ ID NOs: 11-260, is mutated to any amino acid residue, except for D. In some embodiments, the D10 residue of the amino acid sequence provided in SEQ ID NO: 1, or a corresponding mutation in any of the amino acid sequences provided in SEQ ID NOs: 11-260, is mutated to an A. In some embodiments, the H840 residue of the amino acid sequence provided in SEQ ID NO: 1, or a corresponding residue in any of the amino acid sequences provided in SEQ ID NOs: 11-260, is an H. In some embodiments, the H840 residue of the amino acid sequence provided in SEQ ID NO: 1, or a corresponding mutation in any of the amino acid sequences provided in SEQ ID NOs: 11-260, is mutated to any amino acid residue, except for H. In some embodiments, the H840 residue of the amino acid sequence provided in SEQ ID NO: 1, or a corresponding mutation in any of the amino acid sequences provided in SEQ ID NOs: 11-260, is mutated to an A. In some embodiments, the D10 residue of the amino acid sequence provided in SEQ ID NO: 1, or a corresponding residue in any of the amino acid sequences provided in SEQ ID NOs: 11-260, is a D.

(247) A number of Cas9 sequences from various species were aligned to determine whether corresponding homologous amino acid residues of D10 and H840 of SEQ ID NO: 1 or SEQ ID NO: 11 can be identified in other Cas9 proteins, allowing the generation of Cas9 variants with corresponding mutations of the homologous amino acid residues. The alignment was carried out using the NCBI Constraint-based Multiple Alignment Tool (COBALT (accessible at st-va.ncbi.nlm.nih.gov/tools/cobalt), with the following parameters. Alignment parameters: Gap penalties −11, −1; End-Gap penalties −5, −1. CDD Parameters: Use RPS BLAST on; Blast E-value 0.003; Find Conserved columns and Recompute on. Query Clustering Parameters: Use query clusters on; Word Size 4; Max cluster distance 0.8; Alphabet Regular.

(248) An exemplary alignment of four Cas9 sequences is provided below. The Cas9 sequences in the alignment are: Sequence 1 (S1): SEQ ID NO: 11 WP_0109222511 gi 4992247111 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*]; Sequence 2 (S2): SEQ ID NO: 12|WP_039695303|gi 746743737|type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus* gallolyticus]; Sequence 3 (S3): SEQ ID NO: 13|WP_045635197|gi 782887988|type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mitis*]; Sequence 4 (S4): SEQ ID NO: 14|5AXW_A|gi 924443546| *Staphylococcus Aureus* Cas9. The HNH domain (bold and underlined) and the RuvC domain (boxed) are identified for each of the four sequences. Amino acid residues 10 and 840 in S1 and the homologous amino acids in the aligned sequences are identified with an asterisk following the respective amino acid residue.

(249) TABLE-US-00026 S1 1 --MDKK-YSIGLD*IGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLI--GALLFDSG--ETAEATRLKRTARRRYT 73 S2 1 --MTKKNYSIGLD*IGTNSVGWAVITDDYKVPAKKMKVLGNTDKKYIKKNLL--GALLFDSG--ETAEATRLKRTARRRYT 74 S3 1 --M-KKGYSIGLD*IGTNSVGFAVITDDYKVPSKKMKVLGNTDKRFIKKNLI--GALLFDEG--TTAEARRLKRTARRRYT 73 S4 1 GSHMKRNYILGLD*IGITSVGYGII--DYET----------RDVIDAGVRLFKEANVENNEGRRSKRGARRLKR 61 S1 74 RRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRL 153 S2 75 RRKNRLRYLQEIFANEIAKVDESFFQRLDESFLTDDDKTFDSHPIFGNKAEEDAYHQKFPTIYHLRKHLADSSEKADLRL 154 S3 74 RRKNRLRYLQEIFSEEMSKVDSSFFHRLDDSFLIPEDKRESKYPIFATLTEEKEYHKQFPTIYHLRKQLADSKEKTDLRL 153 S4 62 RRRHRIQRVKKLL----------FDYNLLTD----------HSELSGINPYEARVKGLSQKLSEEE 107 S1 154 IYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEK 233 S2 155 VYLALAHMIKFRGHFLIEGELNAENTDVQKIFADFVGVYNRTFDDSHLSEITVDVASILTEKISKSRRLENLIKYYPTEK 234 S3 154 IYLALAHMIKYRGHFLYEEAFDIKNNDIQKIFNEFISIYDNTFEGSSLSGQNAQVEAIFTDKISKSAKRERVLKLFPDEK 233 S4 108 FSAALLHLAKRRG----------VHNVNEVEEDT---------- 131 S1 234 KNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEIT 313 S2 235 KNTLFGNLIALALGLQPNFKTNFKLSEDAKLQFSKDTYEEDLEELLGKIGDDYADLFTSAKNLYDAILLSGILTVDDNST 314 S3 234 STGLFSEFLKLIVGNQADFKKHFDLEDKAPLQFSKDTYDEDLENLLGQIGDDFTDLFVSAKKLYDAILLSGILTVTDPST 313 S4 132 -----GNELS----------TKEQISRN---------- 144 S1 314 KAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKM--DGTEELLV 391 S2 315 KAPLSASMIKRYVEHHEDLEKLKEFIKANKSELYHDIFKDKNKNGYAGYIENGVKQDEFYKYLKNILSKIKIDGSDYFLD 394 S3 314 KAPLSASMIERYENHQNDLAALKQFIKNNLPEKYDEVFSDQSKDGYAGYIDGKTTQETFYKYIKNLLSKF--EGTDYFLD 391 S4 145 ----SKALEEKYVAELQ----------LERLKKDG------ 165 S1 392 KLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEE

471 S2 395
KIEREDFLRKQRTFDNGSIPHQIHLQEMHAILRRQGDYYPFLKEKQDRIEKILTFRIPYYVGPLVRKDSRFAWAEYRSDE
474 S3 392
KIEREDFLRKQRTFDNGSIPHQIHLQEMNAILRRQGEYYPFLKDNKEKIEKILTFRIPYYVGPLARGNRDFAWLTRNSDE
471 S4 166 --EVRGSINRFKTSD--------YVKEAKQLLKVQKAYHQLDQSFIDTYIDLLETRRTYYEGP--GEGSPFGW-
-----K 227 S1 472
TITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVD
551 S2 475 KITPWNFDKVIDKEKSAEKFITRMTLNDLYLPEEKVLPKHSHVYETYAVYNELTKIKYVNEQGKE-
SFFDSNMKQEIFDH 553 S3 472
AIRPWNFEEIVDKASSAEDFINKMTNYDLYLPEEKVLPKHSLLYETFAVYNELTKVKFIAEGLRDYQFLDSGQKKQIVNQ
551 S4 228 DIKEW----------YEMLMGHCTYFPEELRSVKYAYNADLYNALNDLNNLVITRDENEK---
LEYYEKFQIIEN 289 S1 552 LFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDR---
FNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFED 628 S2 554
VFKENRKVTKEKLLNYLNKEFPEYRIKDLIGLDKENKSFNASLGTYHDLKKIL-
DKAFLDDKVNEEVIEDIIKTLTLFED 632 S3 552 LFKENRKVTEKDIIHYLHN-VDGYDGIELKGIEKQ---
FNASLSTYHDLLKIIKDKEFMDDAKNEAILENIVHTLTIFED 627 S4 290
VFKQKKKPTLKQIAKEILVNEEDIKGYRVTSTGKPEF---TNLKVYHDIKDITARKEII---ENAELLDQIAKILTIYQS
363 S1 629 REMIEERLKTYAHLFDDKVMKQLKR-
RRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKED 707 S2 633
KDMIHERLQKYSDIFTANQLKKLER-
RHYTGWGRLSYKLINGIRNKENNKTILDYLIDDGSANRNFMQLINDDTLPFKQI 711 S3 628
REMIKQRLAQYDSLFDEKVIKALTR-
RHYTGWGKLSAKLINGICDKQTGNTILDYLIDDGKINRNFMQLINDDGLSFKEI 706 S4 364
SEDIQEELTNLNSELTQEEIEQISNLKGYTGTHNLSLKAINLILDE------LWHTNDNQIAIFNRLKLVP--------- 428
S1 708 IQKAQVSGQG custom character RENQTT------QK**GQKNSRERM** 781 S2 712 IQKSQVVGDV
custom character RENQTT------NR**GRSQSQQRL** 784 S3 707 IQKAQVIGKT custom character RENQTT------
AR**GKKNSQQRY** 779 S4 429 -KKVDLSQQK custom character REKNSKDAQKMINE**MQKRNRQTN** 505 S1
782 **KRIEEGIKELGSQIL-------KEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSD----
YDVDH*IVPQSFLKDD** 850 S2 785
**KKLQNSLKELGSNILNEEKPSYIEDKVENSHLQNDQLFLYYIQNGKDMYTGDELDIDHLSD----
YDIDH*IIPQAFIKDD** 860 S3 780 **KRIEDSLKILASGL---
DSNILKENPTDNNQLQNDRLFLYYLQNGKDMYTGEALDINQLSS----YDIDH*IIPQAFIKDD** 852 S4 506
ERIEEIIRTTGK----------ENAKYLIEKIKLHDMQEGKCLYSLEAIPLEDLLNNPFNYEVDH*IIPRSVSFDN
570 S1 851 **SIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDN-LTK**AERG
custom character 922 S2 861 **SIDNRVLTSSAKNRGKSDDVPSLDIVRARKAEWVRLYKSGLISKRKFDN-
LTK**AERG custom character 932 S3 853
SLDNRVLTSSKDNRGKSDNVPSIEVVQKRKAFWQQLLDSKLISERKENN-LTKAERG custom character 924
S4 571 **SFNNKVLVKQEEASKKGNRTPFQYLSSSDSKISYETFKKHILNLAKGKGRISK**TKKE
custom character 650 S1 923 custom character 1002 S2 933 custom character 1012 S3 925 custom character
1004 S4 651 custom character 712 S1 1003 custom character 1077 S2 1013 custom character 1083 S3 1005
custom character 1081 S4 713 custom character 764 S1 1078 custom character
GGFSKESILPKRNSDKLIARKKD---WDPKKYGGFDSPTVAYSVLVVAKV 1149 S2 1084 custom character
GGFSKESILPKGDSDKLIPRKTKKVYWDTKKYGGFDSPTVAYSVFVVADV 1158 S3 1082 custom character
GGFSKESILPKGNSDKLIPRKTKDILLDTTKYGGFDSPVIAYSILLIADI 1156 S4 765 custom character
RKDDKGNTLIVNNLNGLYDKDNDKL----KKLIN-KSP----EKLLMYHH 835 S1 1078
EKGKSKKLKSVKELLGITIMERSSFEKNPI-DFLEAKG-----
YKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKG 1223 S2 1084
EKGKAKKLKTVKELVGISIMERSFFEENPV-EFLENKG-----
YHNIREDKLIKLPKYSLFEFEGGRRRLLASASELQKG 1232 S3 1157
EKGKAKKLKTVKTLVGITIMEKAAFEENPI-TFLENKG-----
YHNVRKENILCLPKYSLFELENGRRRLLASAKELQKG 1230 S4 836 DPQTYQKLK--------
LIMEQYGDEKNPLYKYYEETGNYLTKYSKKDNGPVIKKIKYYGNKLNAHLDITDDYPNSRNKV 907 S1 1224
NELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKH---
--- 1297 S2 1233 NEMVLPGYLVELLYHAHRADNF-----
NSTEYLNYVSEHKKEFEKVLSCVEDFANLYVDVEKNLSKIRAVADSM------ 1301 S3 1231
NEIVLPVYLTTLLYHSKNVHKL-----DEPGHLEYIQKHRNEFKDLLNLVSEFSQKYVLADANLEKIKSLYADN------
1299 S4 908 VKLSLKPYRFD-VYLDNGVYKFV-----TVKNLDVIK--
KENYYEVNSKAYEEAKKLKKISNQAEFIASFYNNDLIKING 979 S1 1298
RDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSIT--GLYETRI ---- DLSQL 1365
S2 1302 DNFSIEEISNSFINLLTLTALGAPADFNFLGEKIPRKRYTSTKECLNATLIHQSIT-GLYETRIDLSKL
1369 S3 1300 EQADIEILANSFINLLTFTALGAPAAFKFFGKDIDRKRYTTVSEILNATLIHQSIT-GLYETWI 1369

S4 980 ELYRVIGVNNDLLNRIEVNMIDITYR-EYLENMNDKRPPRIIKTIASKT --- QSIKKYSTDILGNLYEVKSKKHPQIIKK 1055 S1 1366 GGD 1368 S2 1370 GEE 1372 S3 1368 GED 1370 S4 4056 G-- 1056

(250) The alignment demonstrates that amino acid sequences and amino acid residues that are homologous to a reference Cas9 amino acid sequence or amino acid residue can be identified across Cas9 sequence variants, including, but not limited to Cas9 sequences from different species, by identifying the amino acid sequence or residue that aligns with the reference sequence or the reference residue using alignment programs and algorithms known in the art. This disclosure provides Cas9 variants in which one or more of the amino acid residues identified by an asterisk in SEQ ID NOs: 11-14 (e.g., S1, S2, S3, and S4, respectively) are mutated as described herein. The residues D10 and H840 in Cas9 of SEQ ID NO: 1 that correspond to the residues identified in SEQ ID NOs: 11-14 by an asterisk are referred to herein as "homologous" or "corresponding" residues. Such homologous residues can be identified by sequence alignment, e.g., as described above, and by identifying the sequence or residue that aligns with the reference sequence or residue. Similarly, mutations in Cas9 sequences that correspond to mutations identified in SEQ ID NO: 1 herein, e.g., mutations of residues 10, and 840 in SEQ ID NO: 1, are referred to herein as "homologous" or "corresponding" mutations. For example, the mutations corresponding to the D10A mutation in SEQ ID NO: 1 or S1 (SEQ ID NO: 11) for the four aligned sequences above are D11A for S2, D10A for S3, and D13A for S4; the corresponding mutations for H840A in SEQ ID NO: 1 or S1 (SEQ ID NO: 11) are H850A for S2, H842A for S3, and H560A for S4.

(251) A total of 250 Cas9 sequences (SEQ ID NOs: 11-260) from different species are provided. Amino acid residues homologous to residues 10, and 840 of SEQ ID NO: 1 may be identified in the same manner as outlined above. All of these Cas9 sequences may be used in accordance with the present disclosure.

(252) TABLE-US-00027 WP_039695303.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus gallolyticus*] SEQ ID NO: 12 WP_045635197.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mitis*] SEQ ID NO: 13 5AXW A Cas9, Chain A, Crystal Structure [Staphylococcus Aureus] SEQ ID NO: 14 WP_009880683.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 15 WP_010922251.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 16 WP_011054416.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 17 WP_011284745.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 18 WP_011285506.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 19 WP_011527619.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 20 WP_012560673.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 21 WP_014407541.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 22 WP_020905136.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 23 WP_023080005.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 24 WP_023610282.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 25 WP_030125963.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 26 WP_030126706.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 27 WP_031488318.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 28 WP_032460140.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 29 WP_032461047.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 30 WP_032462016.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 31 WP_032462936.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 32 WP_032464890.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 33 WP_033888930.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 34 WP_038431314.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 35 WP_038432938.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 36 WP_038434062.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pyogenes*] SEQ ID NO: 37 BAQ51233.1 CRISPR-associated protein, Csnl family [*Streptococcus pyogenes*] SEQ ID NO: 38 KGE60162.1 hypothetical protein MGAS2111_0903 [*Streptococcus pyogenes* MGAS2111] SEQ ID NO: 39 KGE60856.1 CRISPR-associated endonuclease protein [*Streptococcus pyogenes* SS1447] SEQ ID NO: 40 WP_002989955.1 MULTISPECIES: type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus*] SEQ ID NO: 41 WP_003030002.1 MULTISPECIES: type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus*] SEQ ID NO: 42 WP_003065552.1 MULTISPECIES: type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus*] SEQ ID NO: 43 WP_001040076.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 44 WP_001040078.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 45 WP_001040080.1 type

II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 46 WP_001040081.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 47 WP_001040083.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 48 WP_001040085.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 49 WP_001040087.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 50 WP_001040088.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 51 WP_001040089.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 52 WP_001040090.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 53 WP_001040091.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 54 WP_001040092.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 55 WP_001040094.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 56 WP_001040095.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 57 WP_001040096.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 58 WP_001040097.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 59 WP_001040098.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 60 WP_001040099.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 61 WP_001040100.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 62 WP_001040104.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 63 WP_001040105.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 64 WP_001040106.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 65 WP_001040107.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 66 WP_001040108.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 67 WP_001040109.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 68 WP_001040110.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 69 WP_015058523.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 70 WP_017643650.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 71 WP_017647151.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 72 WP_017648376.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 73 WP_017649527.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 74 WP_017771611.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 75 WP_017771984.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 76 CFQ25032.1 CRISPR-associated protein [*Streptococcus agalactiae*] SEQ ID NO: 77 CFV16040.1 CRISPR-associated protein [*Streptococcus agalactiae*] SEQ ID NO: 78 KLJ37842.1 CRISPR-associated protein Csn1 [*Streptococcus agalactiae*] SEQ ID NO: 79 KLJ72361.1 CRISPR-associated protein Csn1 [*Streptococcus agalactiae*] SEQ ID NO: 80 KLL20707.1 CRISPR-associated protein Csn1 [*Streptococcus agalactiae*] SEQ ID NO: 81 KLL42645.1 CRISPR-associated protein Csn1 [*Streptococcus agalactiae*] SEQ ID NO: 82 WP_047207273.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 83 WP_047209694.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 84 WP_050198062.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 85 WP_050201642.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 86 WP_050204027.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 87 WP_050881965.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 88 WP_050886065.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus agalactiae*] SEQ ID NO: 89 AHN30376.1 CRISPR-associated protein Csn1 [*Streptococcus agalactiae* 138P] SEQ ID NO: 90 EAO78426.1 reticulocyte binding protein [*Streptococcus agalactiae* H36B] SEQ ID NO: 91 CCW42055.1 CRISPR-associated protein, SAG0894 family [*Streptococcus agalactiae* ILRI112] SEQ ID NO: 92 WP_003041502.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus anginosus*] SEQ ID NO: 93 WP_037593752.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus anginosus*] SEQ ID NO: 94 WP_049516684.1 CRISPR-associated protein Csn1 [*Streptococcus anginosus*] SEQ ID NO: 95 GAD46167.1 hypothetical protein ANG6_0662 [*Streptococcus anginosus* T5] SEQ ID NO: 96 WP_018363470.1 type II

CRISPR RNA-guided endonuclease Cas9 [*Streptococcus caballi*] SEQ ID NO: 97 WP_003043819.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus canis*] SEQ ID NO: 98 WP_006269658.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus constellatus*] SEQ ID NO: 99 WP_048800889.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus constellatus*] SEQ ID NO: 100 WP 012767106.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus dysgalactiae*] SEQ ID NO: 101 WP_014612333.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus dysgalactiae*] SEQ ID NO: 102 WP_015017095.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus dysgalactiae*] SEQ ID NO: 103 WP_015057649.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus dysgalactiae*] SEQ ID NO: 104 WP_048327215.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus dysgalactiae*] SEQ ID NO: 105 WP_049519324.1 CRISPR-associated protein Csn1 [*Streptococcus dysgalactiae*] SEQ ID NO: 106 WP_012515931.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus equi*] SEQ ID NO: 107 WP_021320964.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus equi*] SEQ ID NO: 108 WP_037581760.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus equi*] SEQ ID NO: 109 WP_004232481.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus equinus*] SEQ ID NO: 110 WP_009854540.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus gallolyticus*] SEQ ID NO: 111 WP_012962174.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus gallolyticus*] SEQ ID NO: 112 WP_039695303.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus gallolyticus*] SEQ ID NO: 113 WP_014334983.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus infantarius*] SEQ ID NO: 114 WP_003099269.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus iniae*] SEQ ID NO: 115 AHY15608.1 CRISPR-associated protein Csn1 [*Streptococcus iniae*] SEQ ID NO: 116 AHY17476.1 CRISPR-associated protein Csn1 [*Streptococcus iniae*] SEQ ID NO: 117 ESR09100.1 hypothetical protein IUSA1_08595 [*Streptococcus iniae* IUSA1] SEQ ID NO: 118 AGM98575.1 CRISPR-associated protein Cas9/Csn1, subtype II/NMEMI [*Streptococcus iniae* SF1] SEQ ID NO: 119 ALF27331.1 CRISPR-associated protein Csn1 [*Streptococcus intermedius*] SEQ ID NO: 120 WP_018372492.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus massiliensis*] SEQ ID NO: 121 WP_045618028.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mitis*] SEQ ID NO: 122 WP_045635197.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mitis*] SEQ ID NO: 123 WP_002263549.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 124 WP_002263887.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 125 WP_002264920.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 126 WP_002269043.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 127 WP_002269448.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 128 WP_002271977.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 129 WP_002272766.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 130 WP_002273241.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 131 WP_002275430.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 132 WP_002276448.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 133 WP_002277050.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 134 WP_002277364.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 135 WP_002279025.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 136 WP_002279859.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 137 WP_002280230.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 138 WP_002281696.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 139 WP_002282247.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 140 WP_002282906.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 141 WP_002283846.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 142 WP_002287255.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 143 WP_002288990.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 144 WP_002289641.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 145 WP_002290427.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 146 WP_002295753.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 147 WP_002296423.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus*

mutans] SEQ ID NO: 148 WP_002304487.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 149 WP_002305844.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 150 WP_002307203.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 151 WP_002310390.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 152 WP_002352408.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 153 WP_012997688.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 154 WP_014677909.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 155 WP_019312892.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 156 WP_019313659.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 157 WP_019314093.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 158 WP_019315370.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 159 WP_019803776.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 160 WP_019805234.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 161 WP_024783594.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 162 WP_024784288.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 163 WP_024784666.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 164 WP_024784894.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 165 WP_024786433.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus mutans*] SEQ ID NO: 166 WP_049473442.1 CRISPR-associated protein Csn1 [*Streptococcus mutans*] SEQ ID NO: 167 WP_049474547.1 CRISPR-associated protein Csn1 [*Streptococcus mutans*] SEQ ID NO: 168 EMC03581.1 hypothetical protein SMU69_09359 [*Streptococcus mutans* NLML4] SEQ ID NO: 169 WP_000428612.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus oralis*] SEQ ID NO: 170 WP_000428613.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus oralis*] SEQ ID NO: 171 WP_049523028.1 CRISPR-associated protein Csn1 [*Streptococcus parasanguinis*] SEQ ID NO: 172 WP_003107102.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus parauberis*] SEQ ID NO: 173 WP_054279288.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus phocae*] SEQ ID NO: 174 WP_049531101.1 CRISPR-associated protein Csn1 [*Streptococcus pseudopneumoniae*] SEQ ID NO: 175 WP_049538452.1 CRISPR-associated protein Csn1 [*Streptococcus pseudopneumoniae*] SEQ ID NO: 176 WP_049549711.1 CRISPR-associated protein Csn1 [*Streptococcus pseudopneumoniae*] SEQ ID NO: 177 WP_007896501.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus pseudoporcinus*] SEQ ID NO: 178 EFR44625.1 CRISPR-associated protein, Csn1 family [*Streptococcus pseudoporcinus* SPIN 20026] SEQ ID NO: 179 WP_002897477.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus sanguinis*] SEQ ID NO: 180 WP_002906454.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus sanguinis*] SEQ ID NO: 181 WP_009729476.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus* sp. F0441] SEQ ID NO: 182 CQR24647.1 CRISPR-associated protein [*Streptococcus* sp. FF10] SEQ ID NO: 183 WP_000066813.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus* sp. M334] SEQ ID NO: 184 WP_009754323.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus* sp. *taxon* 056] SEQ ID NO: 185 WP_044674937.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus suis*] SEQ ID NO: 186 WP_044676715.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus suis*] SEQ ID NO: 187 WP_044680361.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus suis*] SEQ ID NO: 188 WP_044681799.1 type II CRISPR RNA-guided endonuclease Cas9 [*Streptococcus suis*] SEQ ID NO: 189 WP_049533112.1 CRISPR-associated protein Csn1 [*Streptococcus suis*] SEQ ID NO: 190 WP_029090905.1 type II CRISPR RNA-guided endonuclease Cas9 [*Brochothrix thermosphacta*] SEQ ID NO: 191 WP_006506696.1 type II CRISPR RNA-guided endonuclease Cas9 [*Catenibacterium mitsuokai*] SEQ ID NO: 192 AIT42264.1 Cas9hc:NLS:A [Cloning vector pYB196] SEQ ID NO: 193 WP_034440723.1 type II CRISPR endonuclease Cas9 [*Clostridiales bacterium* S5-A11] SEQ ID NO: 194 AKQ21048.1 Cas9 [CRISPR-mediated gene targeting vector p (bhsp68-Cas9)] SEQ ID NO: 195 WP_004636532.1 type II CRISPR RNA-guided endonuclease Cas9 [*Dolosigranulum pigrum*] SEQ ID NO: 196 WP_002364836.1 MULTISPECIES: type II CRISPR RNA-guided endonuclease Cas9 [Enterococcus] SEQ ID NO: 197 WP_016631044.1 MULTISPECIES: type II CRISPR RNA-guided endonuclease Cas9 [Enterococcus] SEQ ID NO: 198 EMS75795.1 hypothetical protein H318_06676 [*Enterococcus* durans IPLA 655] SEQ ID NO: 199 WP_002373311.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 200

WP_002378009.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 201 WP_002407324.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 202 WP_002413717.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 203 WP_010775580.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 204 WP_010818269.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 205 WP_010824395.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 206 WP_016622645.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 207 WP_033624816.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 208 WP_033625576.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 209 WP_033789179.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecalis*] SEQ ID NO: 210 WP_002310644.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecium*] SEQ ID NO: 211 WP_002312694.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecium*] SEQ ID NO: 212 WP_002314015.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecium*] SEQ ID NO: 213 WP_002320716.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecium*] SEQ ID NO: 214 WP_002330729.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecium*] SEQ ID NO: 215 WP_002335161.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecium*] SEQ ID NO: 216 WP_002345439.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecium*] SEQ ID NO: 217 WP_034867970.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecium*] SEQ ID NO: 218 WP_047937432.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus faecium*] SEQ ID NO: 219 WP_010720994.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus hirae*] SEQ ID NO: 220 WP_010737004.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus hirae*] SEQ ID NO: 221 WP_034700478.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus hirae*] SEQ ID NO: 222 WP_007209003.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus italicus*] SEQ ID NO: 223 WP_023519017.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus mundtii*] SEQ ID NO: 224 WP_010770040.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus phoeniculicola*] SEQ ID NO: 225 WP_048604708.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus* sp. AM1] SEQ ID NO: 226 WP_010750235.1 type II CRISPR RNA-guided endonuclease Cas9 [*Enterococcus villorum*] SEQ ID NO: 227 AII16583.1 Cas9 endonuclease [Expression vector pCas9] SEQ ID NO: 228 WP_029073316.1 type II CRISPR RNA-guided endonuclease Cas9 [*Kandleria vitulina*] SEQ ID NO: 229 WP_031589969.1 type II CRISPR RNA-guided endonuclease Cas9 [*Kandleria vitulina*] SEQ ID NO: 230 KDA45870.1 CRISPR-associated protein Cas9/Csn1, subtype II/NMEMI [*Lactobacillus animalis*] SEQ ID NO: 231 WP_039099354.1 type II CRISPR RNA-guided endonuclease Cas9 [*Lactobacillus curvatus*] SEQ ID NO: 232 AKP02966.1 hypothetical protein ABB45_04605 [*Lactobacillus farciminis*] SEQ ID NO: 233 WP_010991369.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria innocua*] SEQ ID NO: 234 WP_033838504.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria innocua*] SEQ ID NO: 235 EHN60060.1 CRISPR-associated protein, Csn1 family [*Listeria innocua* ATCC 33091] SEQ ID NO: 236 EFR89594.1 crispr-associated protein, Csn1 family [*Listeria innocua* FSL S4-378] SEQ ID NO: 237 WP_038409211.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria* ivanovii] SEQ ID NO: 238 EFR95520.1 crispr-associated protein Csnl [*Listeria ivanovii* FSL F6-596] SEQ ID NO: 239 WP_003723650.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria monocytogenes*] SEQ ID NO: 240 WP_003727705.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria monocytogenes*] SEQ ID NO: 241 WP_003730785.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria monocytogenes*] SEQ ID NO: 242 WP_003733029.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria monocytogenes*] SEQ ID NO: 243 WP_003739838.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria monocytogenes*] SEQ ID NO: 244 WP_014601172.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria monocytogenes*] SEQ ID NO: 245 WP_023548323.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria monocytogenes*] SEQ ID NO: 246 WP_031665337.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria monocytogenes*] SEQ ID NO: 247 WP_031669209.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria monocytogenes*] SEQ ID NO: 248 WP_033920898.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria monocytogenes*] SEQ ID NO: 249 AKI42028.1 CRISPR-associated protein [*Listeria monocytogenes*] SEQ ID NO: 250 AKI50529.1 CRISPR-associated protein [*Listeria monocytogenes*] SEQ ID NO: 251 EFR83390.1 crispr-associated protein Csn1 [*Listeria monocytogenes* FSL F2-208] SEQ ID NO: 252 WP_046323366.1 type II CRISPR RNA-guided endonuclease Cas9 [*Listeria seeligeri*] SEQ ID NO: 253 AKE81011.1 Cas9 [Plant multiplex genome editing vector

pYLCRISPR/Cas9Pubi-H] SEQ ID NO: 254 CUO82355.1 Uncharacterized protein conserved in bacteria [*Roseburia hominis*] SEQ ID NO: 255 WP_033162887.1 type II CRISPR RNA-guided endonuclease Cas9 [*Sharpea azabuensis*] SEQ ID NO: 256 AGZ01981.1 Cas9 endonuclease [synthetic construct] SEQ ID NO: 257 AKA60242.1 nuclease deficient Cas9 [synthetic construct] SEQ ID NO: 258 AKS40380.1 Cas9 [Synthetic plasmid pFC330] SEQ ID NO: 259 4UN5_B Cas9, Chain B, Crystal Structure SEQ ID NO: 260

(253) TABLE-US-00028 Non-limiting examples of suitable deaminase domains are provided. Human AID (SEQ ID NO: 303)

MDSLLMNRRKFLYQFKNVRWAKGRRETYLCYVVKRRDSATSFSLDFGYLRNKNGCHVELLFLRYISDWD
LDPGRCYRVTWFTSWSPCYDCARHVADFLRGNPNLSLRIFTARLYFCEDRKAEPEGLRRLHRAGVQIAIMT
FKDYFYCWNTFVENHERTFKAWEGLHENSVRLSRQLRRILLPLYEVDDLRDAFRTLGL (underline: nuclear localization signal; double underline: nuclear export signal) Mouse AID (SEQ ID NO: 271)

MDSLLMKQKKFLYHFKNVRWAKGRHETYLCYVVKRRDSATSCSLDFGHLRNKSGCHVELLFLRYISDWD
LDPGRCYRVTWFTSWSPCYDCARHVAEFLRWNPNLSLRIFTARLYFCEDRKAEPEGLRRLHRAGVQIGIMT
FKDYFYCWNTFVENRERTFKAWEGLHENSVRLTRQLRRILLPLYEVDDLRDAFRMLGF (underline: nuclear localization signal; double underline: nuclear export signal) Dog AID (SEQ ID NO: 272)

MDSLLMKQRKFLYHFKNVRWAKGRHETYLCYVVKRRDSATSFSLDFGHLRNKSGCHVELLFLRYISDWD
LDPGRCYRVTWFTSWSPCYDCARHVADFLRGYPNLSLRIFAARLYFCEDRKAEPEGLRRLHRAGVQIAIMT
FKDYFYCWNTFVENREKTFKAWEGLHENSVRLSRQLRRILLPLYEVDDLRDAFRTLGL (underline: nuclear localization signal; double underline: nuclear export signal) Bovine AID (SEQ ID NO: 273)

MDSLLKKQRQFLYQFKNVRWAKGRHETYLCYVVKRRDSPTSFSLDFGHLRNKAGCHVELLFLRYISDWD
LDPGRCYRVTWFTSWSPCYDCARHVADFLRGYPNLSLRIFTARLYFCDKERKAEPEGLRRLHRAGVQIAIM
TFKDYFYCWNTFVENHERTFKAWEGLHENSVRLSRQLRRILLPLYEVDDLRDAFRTLGL (underline: nuclear localization signal; double underline: nuclear export signal) Rat AID (SEQ ID NO: 1072)

MAVGSKPKAALVGPHWERERIWCFLCSTGLGTQQTGQTSRWLRPAATQDPVSPPRSLLMKQRKFLYHFK
NVRWAKGRHETYLCYVVKRRDSATSFSLDFGYLRNKSGCHVELLFLRYISDWDLDPGRCYRVTWFTSWS
PCYDCARHVADFLRGNPNLSLRIFTARLTGWGALPAGLMSPARPSDYFYCWNTFVENHERTFKAWEGLHE
NSVRLSRRLRRILLPLYEVDDLRDAFRTLGL Mouse APOBEC-3 (SEQ ID NO: 274)

MGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLGYAKGRKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNI*H*
*AEICFLYWFHDKVLKVLSPREEFKITWYMSWSPCFEC*AEQIVRFLATHHNLSLDIFSSRLYNVQDPETQQNLCR
LVQEGAQVAAMDLYEFKKCWKKFVDNGGRRFRPWKRLLTNFRYQDSKLQEILRPCYIPVPSSSSSTLSNIC
LTKGLPETRFCVEGRRMDPLSEEEFYSQFYNQRVKHLCYYHRMKPYLCYQLEQFNGQAPLKGCLLSEKGK
Q*HAEILFLDKIRSMELSQVTITCYLTWSPCPNC*AWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKGLCSLWQ
SGILVDVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQRRLRRIKESWGLQDLVNDFGNLQLGPPMS
(italic: nucleic acid editing domain) Rat APOBEC-3 (SEQ ID NO: 275)

MGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLRYAIDRKDTFLCYEVTRKDCDSPVSLHHGVFKNKDNI*HA*
EICFLYWFHDKVLKVLSPREEFKITWYMSWSPCFECAEQVLRFLATHHNLSLDIFSSRLYNIRDPENQQNLCRL
VOEGAQVAAMDLYEFKKCWKKFVDNGGRRFRPWKKLLTNFRYQDSKLQEILRPCYIPVPSSSSSTLSNICL
TKGLPETRFCVERRRVHLLSEEEFYSQFYNQRVKHLCYYHGVKPYLCYQLEQFNGQAPLKGCLLSEKGKQ
*HAEILFLDKIRSMELSQVIITCYLTWSPCPNC*AWQLAAFKRDRPDLILHIYTSRLYFHWKRPFQKGLCSLWQSG
ILVDVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQRRLHRIKESWGLQDLVNDFGNLQLGPPMS (italic:
nucleic acid editing domain) Rhesus macaque APOBEC-3G (SEQ ID NO: 276)

MVEPMDPRTFVSNFNNRPILSGLNTVWLCCEVKTKDPSGPPLDAKIFQGKVYSKAKY*HPEMRFLRWFHKW*
*RQLHHDQEYKVTWYVSWSPCTRC*ANSVATFLAKDPKVTLTIFVARLYYFWKPDYQQALRILCQKRGGPHAT
MKIMNYNEFQDCWNKFVDGRGKPFKPRNNLPKHYTLLQATLGELLRHLMDPGTFTSNFNNKPWVSGQHE
TYLCYKVERLHNDTWVPLNQHRGFLRNQAPNIHGFPKGR*HAELCFLDLIPFWKLDGQQYRVTCFTSWSPCFS*
*C*AQEMAKFISNNEHVSLCIFAARIYDDQGRYQEGLRALHRDGAKIAMMNYSEFEYCWDTFVDRQGRPFQP
WDGLDEHSQALSGRLRAI (italic: nucleic acid editing domain; underline: cytoplasmic localization signal) Chimpanzee APOBEC-3G (SEQ ID NO: 277)

MKPHFRNPVERMYQDTFSDNFYNRPILSHRNTVWLCYEVKTKGPSRPPLDAKIFRGQVYSKLKY*HPEMRF*
*FHWFSKWRKLHRDQEYEVTWYISWSPCTKC*TRDVATFLAEDPKVTLTIFVARLYYFWDPDYQEALRSLCQKR
DGPRATMKIMNYDEFQHCWSKFVYSQRELFEPWNNLPKYYILLHIMLGEILRHSMDPPTFTSNFNNELWVR
GRHETYLCYEVERLHNDTWVLLNQRRGFLCNQAPHKHGFLEGR*HAELCFLDVIPFWKLDLHQDYRVTCFTS*
*WSPCFSC*AQEMAKFISNNKHVSLCIFAARIYDDQGRCQEGLRTLAKAGAKISIMTYSEFKHCWDTFVDHQG
CPFQPWDGLEEHSQALSGRLRAILQNQGN (italic: nucleic acid editing domain; underline: cytoplasmic localization signal) Green monkey APOBEC-3G (SEQ ID NO: 278)

MNPQIRNMVEQMEPDIFVYYFNNRPILSGRNTVWLCYEVKTKDPSGPPLDANIFQGKLYPEAKD*HPEMKFL*
*HWFRKWRQLHRDQEYEVTWYVSWSPCTRC*ANSVATFLAEDPKVTLTIFVARLYYFWKPDYQQALRILCQER
GGPHATMKIMNYNEFQHCWNEFVDGQGKPFKPRKNLPKHYTLLHATLGELLRHVMDPGTFTSNFNNKPW
VSGQRETYLCYKVERSHNDTWVLLNQHRGFLRNQAPDRHGFPKGR*HAELCFLDLIPFWKLDDQQYRVTCFT*
*SWSPCFSC*AQKMAKFISNNKHVSLCIFAARIYDDQGRCQEGLRTLHRDGAKIAVMNYSEFEYCWDTFVDR

QGRPFQPWDGLDEHSQALSGRLRAI (italic: nucleic acid editing domain; underline: cytoplasmic localization signal) Human APOBEC-3G (SEQ ID NO: 279)
MKPHFRNTVERMYRDTESYNFYNRPILSRRNTVWLCYEVKTKGPSRPPLDAKIFRGQVYSELKY*HPEMRFF*
*HWFSKWRKLHRDQEYEVTWYISWSPCTKC*TRDMATFLAEDPKVTLTIFVARLYYFWDPDYQEALRSLCQKR
DGPRATMKIMNYDEFQHCWSKFVYSQRELFEPWNNLPKYYILLHIMLGEILRHSMDPPTFTFNFNNEPWVR
GRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFLEGR*HAELCFLDVIPFWKLDLDQDYRVTCFTS*
*WSPCFSC*AQEMAKFISKNKHVSLCIFTARIYDDQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTFVDHQG
CPFQPWDGLDEHSQDLSGRLRAILQNQEN (italic: nucleic acid editing domain; underline: cytoplasmic localization signal) Human APOBEC-3F (SEQ ID NO: 280)
MKPHFRNTVERMYRDTFSYNFYNRPILSRRNTVWLCYEVKTKGPSRPRLDAKIFRGQVYSQPEH*HAEMCFL*
*SWFCGNQLPAYKCFQITWFVSWTPCPDC*VAKLAEFLAEHPNVTLTISAARLYYYWERDYRRALCRLSQAGA
RVKIMDDEEFAYCWENFVYSEGQPFMPWYKFDDNYAFLHRTLKEILRNPMEAMYPHIFYFHFKNLRKAY
GRNESWLCFTMEVVKHHSPVSWKRGVFRNQVDPETHCHAERCFLSWFCDDILSPNTNYEVTWYTSWSPCPE
CAGEVAEFLARHSNVNLTIFTARLYYFWDTDYQEGLRSLSQEGASVEIMGYKDFKYCWENFVYNDDEPFK
PWKGLKYNFLFLDSKLQEILE (italic: nucleic acid editing domain) Human APOBEC-3B (SEQ ID NO: 281)
MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLCYEVKIKRGRSNLLWDTGVFRGQVYFKPQY*HAEM*
*CFLSWFCGNQLPAYKCFQITWFVSWTPCPDC*VAKLAEFLSEHPNVTLTISAARLYYYWERDYRRALCRLSQA
GARVTIMDYEEFAYCWENFVYNEGQQFMPWYKFDENYAFLHRTLKEILRYLMDPDTFTFNFNNDPL VLRR
RQTYLCYEVERLDNGTWVLMDQHMGFLCNEAKNLLCGFYG*RHAELRFLDLVPSLQLDPAQIYRVTWFISWS*
*PCFSWGC*AGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFEYCWDTFVYRQ
GCPFQPWDGLEEHSQALSGRLRAILQNQGN (italic: nucleic acid editing domain) Rat APOBEC-3B: (SEQ ID NO: 1073)
MQPQGLGPNAGMGPVCLGCSHRRPYSPIRNPLKKLYQQTFYFHFKNVRYAWGRKNNFLCYEVNGMDCAL
PVPLRQGVFRKQGHIHAELCFIYWFHDKVLRVLSPMEEFKVTWYMSWSPCSKCAEQVARFLAAHRNLSLA
IFSSRLYYYLRNPNYQQKLCRLIQEGVHVAAMDLPEFKKCWNKFVDNDGQPFRPWMRLRINFSFYDCKLQ
EIFSRMNLLREDVFYLQFNNSHRVKPVQNRYYRRKSYLCYQLERANGQEPLKGYLLYKKGEQHVEILFLE
KMRSMELSQVRITCYLTWSPCPNCARQLAAFKKDHPDLILRIYTSRLYFYWRKKFQKGLCTLWRSGIHVD
VMDLPQFADCWTNFVNPQRPFRPWNELEKNSWRIQRRLRRIKESWGL Bovine APOBEC-3B: (SEQ ID NO: 1074)
DGWEVAFRSGTVLKAGVLGVSMTEGWAGSGHPGQGACVWTPGTRNTMNLLREVLFKQQFGNQPRVPAP
YYRRKTYLCYQLKQRNDLTLDRGCFRNKKQRHAEIRFIDKINSLDLNPSQSYKIICYITWSPCPNCANELVN
FITRNNHLKLEIFASRLYFHWIKSFKMGLQDLQNAGISVAVMTHTEFEDCWEQFVDNQSRPFQPWDKLEQY
SASIRRRLQRILTAPI Chimpanzee APOBEC-3B: (SEQ ID NO: 1075)
MNPQIRNPMEWMYQRTFYYNFENEPILYGRSYTWLCYEVKIRRGHSNLLWDTGVFRGQMYSQPEHHAEM
CFLSWFCGNQLSAYKCFQITWFVSWTPCPDCVAKLAKFLAEHPNVTLTISAARLYYYWERDYRRALCRLS
QAGARVKIMDDEEFAYCWENFVYNEGQPFMPWYKFDDNYAFLHRTLKEIIRHLMDPDTFTFNFNNDPLVL
RRHQTYLCYEVERLDNGTWVLMDQHMGFLCNEAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYRVTWF
ISWSPCFSWGCAGQVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFEYCWDTF
VYRQGCPFQPWDGLEEHSQALSGRLRAILQVRASSLCMVPHRPPPPQSPGPCLPLCSEPPLGSLLPTGRPAP
SLPFLLTASFSFPPPASLPPLPSLSLSPGHLPVPSFHSLTSCSIQPPCSSRIRETEGWASVSKEGRDLG Human APOBEC-3C: (SEQ ID NO: 282)
MNPQIRNPMKAMYPGTFYFQFKNLWEANDRNETWLCFTVEGIKRRSVVSWKTGVFRNQVDSETH*CHAER*
*CFLSWFCDDILSPNTKYQVTWYTSWSPCPDC*AGEVAEFLARHSNVNLTIFTARLYYFQYPCYQEGLRSLSQEG
VAVEIMDYEDFKYCWENFVYNDNEPFKPWKGLKTNFRLLKRRLRESLQ (italic: nucleic acid editing domain) Gorilla APOBEC-3C: (SEQ ID NO: 1076)
MNPQIRNPMKAMYPGTFYFQFKNLWEANDRNETWLCFTVEGIKRRSVVSWKTGVFRNQVDSETHCHAER
CFLSWFCDDILSPNTNYQVTWYTSWSPCPECAGEVAEFLARHSNVNLTIFTARLYYFQDTDYQEGLRSLSQ
EGVAVKIMDYKDFKYCWENFVYNDDEPFKPWKGLKYNFRFLKRRLQEILE Human APOBEC-3A: (SEQ ID NO: 283)
MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQHRGFLHNQAKNLLCGFYGR*H*
*AELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGC*AGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQML
RDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGN (italic: nucleic acid editing domain) Rhesus macaque APOBEC-3A: (SEQ ID NO: 1077)
MDGSPASRPRHLMDPNTFTFNFNNDLSVRGRHQTYLCYEVERLDNGTWVPMDERRGFLCNKAKNVPCGD
YGCHVELRFLCEVPSWQLDPAQTYRVTWFISWSPCFRRGCAGQVRVFLQENKHVRLRIFAARIYDYDPLY
QEALRTLRDAGAQVSIMTYEEFKHCWDTFVDRQGRPFQPWDGLDEHSQALSGRLRAILQNQGN Bovine APOBEC-3A: (SEQ ID NO: 1078)
MDEYTFTENFNNQGWPSKTYLCYEMERLDGDATIPLDEYKGFVRNKGLDQPEKPCHAELYFLGKIHSWNL
DRNQHYRLTCFISWSPCYDCAQKLTTFLKENHHISLHILASRIYTHNRFGCHQSGLCELQAAGARITIMTFED
FKHCWETFVDHKGKPFQPWEGLNVKSQALCTELQAILKTQQN Human APOBEC-3H: (SEQ ID NO:

284) MALLTAETFRLQFNNKRRLRRPYYPRKALLCYQLTPQNGSTPTRGYFENKKKCHAEICFINEIKSMGLDETQ CYQVTCYLTWSPCSSCAWELVDFIKAHDHLNLGIFASRLYYHWCKPQQKGLRLLCGSQVPVEVMGFPKFAD CWENFVDHEKPLSFNPYKMLEELDKNSRAIKRRLERIKIPGVRAQGRYMDILCDAEV (italic: nucleic acid editing domain) Rhesus macaque APOBEC-3H: (SEQ ID NO: 1079) MALLTAKTFSLQFNNKRRVNKPYYPRKALLCYQLTPQNGSTPTRGHLKNKKKDHAEIRFINKIKSMGLDET QCYQVTCYLTWSPCPSCAGELVDFIKAHRHLNLRIFASRLYYHWRPNYQEGLLLLCGSQVPVEVMGLPEFT DCWENFVDHKEPPSFNPSEKLEELDKNSQAIKRRLERIKSRSVDVLENGLRSLQLGPVTPSSSIRNSR Human APOBEC-3D (SEQ ID NO: 285) MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLCYEVKIKRGRSNLLWDTGVFRGPVLPKRQSNHRQE VYFRFEN*HAEMCFLSWFCGNRLPANRRFQITWFVSWNPC*LPCVVKVTKFLAEHPNVTLTISAARLYYYRDRD WRWVLLRLHKAGARVKIMDYEDFAYCWENFVCNEGQPFMPWYKFDDNYASLHRTLKEILRNPMEAMYP HIFYFHFKNLLKACGRNESWLCFTMEVTKHHSAVFRKRGVFRNQVDPETHC*HAERCFLSWFCDDILSPNTN YEVTWYTSWSPCPEC*AGEVAEFLARHSNVNLTIFTARLCYFWDTDYQEGLCSLSQEGASVKIMGYKDFVSC WKNFVYSDDEPFKPWKGLQTNFRLLKRRLREILQ (italic: nucleic acid editing domain) Human APOBEC-1 (SEQ ID NO: 286) MTSEKGPSTGDPTLRRRIEPWEFDVFYDPRELRKEACLLYEIKWGMSRKIWRSSGKNTTNHVEVNFIKKFTS ERDFHPSMSCSITWFLSWSPCWECSQAIREFLSRHPGVTLVIYVARLFWHMDQQNRQGLRDLVNSGVTIQI MRASEYYHCWRNFVNYPPGDEAHWPQYPPLWMMLYALELHCIILSLPPCLKISRRWQNHLTFFRLHLQNC HYQTIPPHILLATGLIHPSVAWR Mouse APOBEC-1 (SEQ ID NO: 287) MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSVWRHTSQNTSNHVEVNFLEKFTT ERYFRPNTRCSITWFLSWSPCGECSRAITEFLSRHPYVTLFIYIARLYHHTDQRNRQGLRDLISSGVTIQIMTE QEYCYCWRNFVNYPPSNEAYWPRYPHLWVKLYVLELYCIILGLPPCLKILRRKQPQLTFFTITLQTCHYQRI PPHLLWATGLK Rat APOBEC-1 (SEQ ID NO: 288) MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTTE RYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTEQ ESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTIALQSCHYQRLP PHILWATGLK Human APOBEC-2: (SEQ ID NO: 1080) MAQKEEAAVATEAASQNGEDLENLDDPEKLKELIELPPFEIVTGERLPANFFKFQFRNVEYSSGRNKTFLCY VVEAQGKGGQVQASRGYLEDEHAAAHAEEAFFNTILPAFDPALRYNVTWYVSSSPCAACADRIIKTLSKTK NLRLLILVGRLFMWEEPEIQAALKKLKEAGCKLRIMKPQDFEYVWQNFVEQEEGESKAFQPWEDIQENFLY YEEKLADILK Mouse APOBEC-2: (SEQ ID NO: 1081) MAQKEEAAEAAAPASQNGDDLENLEDPEKLKELIDLPPFEIVTGVRLPVNFFKFQFRNVEYSSGRNKTFLC YVVEVQSKGGQAQATQGYLEDEHAGAHAEEAFFNTILPAFDPALKYNVTWYVSSSPCAACADRILKTLSK TKNLRLLILVSRLFMWEEPEVQAALKKLKEAGCKLRIMKPQDFEYIWQNFVEQEEGESKAFEPWEDIQENF LYYEEKLADILK Rat APOBEC-2: (SEQ ID NO: 1082) MAQKEEAAEAAAPASQNGDDLENLEDPEKLKELIDLPPFEIVTGVRLPVNFFKFQFRNVEYSSGRNKTFLC YVVEAQSKGGQVQATQGYLEDEHAGAHAEEAFFNTILPAFDPALKYNVTWYVSSSPCAACADRILKTLSK TKNLRLLILVSRLFMWEEPEVQAALKKLKEAGCKLRIMKPQDFEYLWQNFVEQEEGESKAFEPWEDIQENF LYYEEKLADILK Bovine APOBEC-2: (SEQ ID NO: 1083) MAQKEEAAAAAEPASQNGEEVENLEDPEKLKELIELPPFEIVTGERLPAHYFKFQFRNVEYSSGRNKTFLCY VVEAQSKGGQVQASRGYLEDEHATNHAEEAFFNSIMPTFDPALRYMVTWYVSSSPCAACADRIVKTLNKT KNLRLLILVGRLFMWEEPEIQAALRKLKEAGCRLRIMKPQDFEYIWQNFVEQEEGESKAFEPWEDIQENFL YYEEKLADILK Petromyzon marinus CDA1 (pmCDA1) (SEQ ID NO: 289) MTDAEYVRIHEKLDIYTFKKQFFNNKKSVSHRCYVLFELKRRGERRACFWGYAVNKPQSGTERGIHAEIFSI RKVEEYLRDNPGQFTINWYSSWSPCADCAEKILEWYNQELRGNGHTLKIWACKLYYEKNARNQIGLWNL RDNGVGLNVMVSEHYQCCRKIFIQSSHNQLNENRWLEKTLKRAEKRRSELSIMIQVKILHTTKSPAV Human APOBEC3G D316R_D317R (SEQ ID NO: 290) MKPHFRNTVERMYRDTFSYNFYNRPILSRRNTVWLCYEVKTKGPSRPPLDAKIFRGQVYSELKYHPEMRFF HWFSKWRKLHRDQEYEVTWYISWSPCTKCTRDMATFLAEDPKVTLTIFVARLYYFWDPDYQEALRSLCQ KRDGPRATMKIMNYDEFQHCWSKFVYSQRELFEPWNNLPKYYILLHIMLGEILRHSMDPPTFTFNFNNEPW VRGRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFLEGRHAELCFLDVIPFWKLDLDQDYRVT CFTSWSPCFSCAQEMAKFISKNKHVSLCIFTARIYRRQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTFVD HQGCPFQPWDGLDEHSQDLSGRLRAILQNQEN Human APOBEC3G chain A (SEQ ID NO: 291) MDPPTFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFLEGRHAELCFLDV IPFWKLDLDQDYRVTCFTSWSPCFSCAQEMAKFISKNKHVSLCIFTARIYDDQGRCQEGLRTLAEAGAKISI MTYSEFKHCWDTFVDHQGCPFQPWDGLDEHSQDLSGRLRAILQ Human APOBEC3G chain A D120R_D121R (SEQ ID NO: 292) MDPPTFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFLEGRHAELCFLDV IPFWKLDLDQDYRVTCFTSWSPCFSCAQEMAKFISKNKHVSLCIFTARIYRRQGRCQEGLRTLAEAGAKISI MTYSEFKHCWDTFVDHQGCPFQPWDGLDEHSQDLSGRLRAILQ Non-limiting examples of fusion proteins/nucleobase editors are provided. His6-rAPOBEC1-XTEN-dCas9 for Escherichia coli expression

(SEQ ID NO: 293)
MGSSHHHHHHMSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKH
VEVNFIEKFTTERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLI
SSGVTIQIMTEQESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTI
ALQSCHYQRLPPHILWATGLKSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLG
NTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVE
EDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSD
VDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFK
SNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRY
DEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNRE
DLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKS
EETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFL
SGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEEN
EDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLK
SDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRH
KPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVD
QELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQR
KFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFR
KDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYF
FYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESI
LPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDF
LEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDN
EQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFK
YFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSPKKKRKV rAPOBEC1-XTEN-dCas9-NLS
for Mammalian expression (SEQ ID NO: 294)
MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTT
ERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTE
QESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTIALQSCHYQRL
PPHILWATGLKSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKN
LIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIF
GNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQT
YNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKL
QLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLK
ALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDN
GSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEV
VDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDL
LFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT
LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFM
QLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARE
NQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDY
DVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERG
GLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREI
NNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKT
EITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIA
RKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVK
KDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQH
KHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRY
TSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSPKKKRKV hAPOBEC1-XTEN-dCas9-NLS for
Mammalian expression (SEQ ID NO: 295)
MTSEKGPSTGDPTLRRRIEPWEFDVFYDPRELRKEACLLYEIKWGMSRKIWRSSGKNTTNHVEVNFIKKFTSE
RDFHPSMSCSITWFLSWSPCWECSQAIREFLSRHPGVTLVIYVARLFWHMDQQNRQGLRDLVNSGVTIQI
MRASEYYHCWRNFVNYPPGDEAHWPQYPPLWMMLYALELHCIILSLPPCLKISRRWQNHLTFFRLHLQNC
HYQTIPPHILLATGLIHPSVAWRSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGN
TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKK
HERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQ
LVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDA
KLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKA
LVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPH
QIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA
SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVT
VKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLK

TYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQK
AQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERM
KRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNK
VLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQIT
KHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYP
KLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKG
RDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVE
KGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNEL
ALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPI
REQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSPKKKRK V
rAPOBEC1-XTEN-dCas9-UGI-NLS (SEQ ID NO: 296)
MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTT
ERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTE
QESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTIALQSCHYQRL
PPHILWATGLKSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKN
LIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIF
GNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQT
YNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKL
QLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLK
ALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDN
GSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEV
VDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDL
LFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLT
LFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFM
QLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARE
NQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDY
DVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERG
GLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREI
NNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKT
EITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIA
RKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVK
KDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQH
KHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRY
TSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESD
ILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV rAPOBEC1-XTEN-Cas9
nickase-UGI-NLS) (BE3, SEQ ID NO: 297
MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTT
ERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTE
QESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTIALQSCHYQRL
PPHILWATGLKSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKN
LIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIF
GNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQT
YNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKL
QLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLK
ALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDN
GSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEV
VDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDL
LFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTITL
FEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQ
LIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMAREN
QTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYD
VDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGG
LSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREIN
NYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTE
ITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIAR
KKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKK
DLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHK
HYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYT
STKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDI
LVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV pmCDA1-XTEN-dCas9-UGI
(bacteria) (SEQ ID NO: 298)

MTDAEYVRIHEKLDIYTFKKQFFNNKKSVSHRCYVLFELKRRGERRACFWGYAVNKPQ
SGTERGIHAEIFSIRKVEEYLRDNPGQFTINWYSSWSPCADCAEKILEWYNQELRGNGHT
LKIWACKLYYEKNARNQIGLWNLRDNGVGLNVMVSEHYQCCRKIFIQSSHNQLNENR
WLEKTLKRAEKRRSELSIMIQVKILHTTKSPAVSGSETPGTSESATPESDKKYSIGLAIGT
NSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRY
TRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKY
PTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTY
NQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFK
SNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEIT
KAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEF
YKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFL
KDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIE
RMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDL
LFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEE
NEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIR
DKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSP
AIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKE
LGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKD
DSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGG
LSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFR
KDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKS
EQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRK
VLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVL
VVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFE
LENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHK
HYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFK
YFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSMTNLSDIIEKETGK
QLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQD SNGENKIKML
pmCDA1-XTEN-nCas9-UGI-NLS (mammalian construct) (SEQ ID NO: 299):
MTDAEYVRIHEKLDIYTFKKQFFNNKKSVSHRCYVLFELKRRGERRACFWGYAVNKPQ
SGTERGIHAEIFSIRKVEEYLRDNPGQFTINWYSSWSPCADCAEKILEWYNQELRGNGHT
LKIWACKLYYEKNARNQIGLWNLRDNGVGLNVMVSEHYQCCRKIFIQSSHNQLNENR
WLEKTLKRAEKRRSELSIMIQVKILHTTKSPAVSGSETPGTSESATPESDKKYSIGLAIGT
NSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRY
TRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKY
PTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTY
NQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFK
SNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEIT
KAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEF
YKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFL
KDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIE
RMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDL
LFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEE
NEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIR
DKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSP
AIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKE
LGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKD
DSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGG
LSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFR
KDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKS
EQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRK
VLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVL
VVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFE
LENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHK
HYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFK
YFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQL
VIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSN
GENKIKMLSGGSPKKKRKV huAPOBEC3G-XTEN-dCas9-UGI (bacteria) (SEQ ID NO: 300)
MDPPTFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFL
EGRHAELCFLDVIPFWKLDLDQDYRVTCFTSWSPCFSCAQEMAKFISKNKHVSLCIFTAR
IYDDQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTFVDHQGCPFQPWDGLDEHSQDL

SGRLRAILQSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLG
NTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDS
FFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYL
ALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARL
SKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLD
NLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLK
ALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNRE
DLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLAR
GNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYE
YFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECF
DSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLK
TYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQ
LIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRH
KPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLY
YLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPS
EEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKH
VAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYL
NAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKT
EITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKE
SILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGIT
IMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELA
LPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANL
DKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLI
HQSITGLYETRIDLSQLGGDSGGSMTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPE
SDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKML huAPOBEC3G-XTEN-nCas9-UGI-NLS
(mammalian construct) (SEQ ID NO: 301)
MDPPTFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFL
EGRHAELCFLDVIPFWKLDLDQDYRVTCFTSWSPCFSCAQEMAKFISKNKHVSLCIFTAR
IYDDQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTFVDHQGCPFQPWDGLDEHSQDL
SGRLRAILQSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLG
NTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDS
FFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYL
ALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARL
SKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLD
NLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLK
ALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNRE
DLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLAR
GNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYE
YFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECF
DSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLK
TYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQ
LIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRH
KPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLY
YLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPS
EEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKH
VAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYL
NAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKT
EITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKE
SILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGIT
IMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELA
LPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANL
DKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLI
HQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPES
DILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV huAPOBEC3G
(D316R_D317R)-XTEN-nCas9-UGI-NLS (mammalian construct) (SEQ ID NO: 302)
MDPPTFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKHGFL
EGRHAELCFLDVIPFWKLDLDQDYRVTCFTSWSPCFSCAQEMAKFISKNKHVSLCIFTAR
IYRRQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTFVDHQGCPFQPWDGLDEHSQDLS
GRLRAILQSGSETPGTSESATPESDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGN
TDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSF
FHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLA

LAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLS
KSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLD
NLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLK
ALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNRE
DLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLAR
GNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYE
YFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECF
DSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLK
TYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQ
LIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRH
KPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLY
YLQNGRDMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPS
EEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKH
VAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYL
NAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKT
EITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKE
SILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGIT
IMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELA
LPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANL
DKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLI
HQSITGLYETRIDLSQLGGDSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPES DILVHTA
YDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGGSPKKKRKV Base Editor 4 (BE4; APOBEC1-linker(32 aa)-Cas9n(D10A)-linker(9 aa)- UGI-linker(9 aa)-UGI) (SEQ ID NO: 1084)
MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHVEVNFIEKFTT
ERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTE
QESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQPQLTFFTIALQSCHYQRL
PPHILWATGLKSGGSSGGSSGSETPGTSESATPESSGGSSGGSDKKYSIGLAIGTNSVGWAVITDEYKVPSKK
FKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEE
SFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLN
PDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGL
TPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSAS
MIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLV
KLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAW
MTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGM
RKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDF
LDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGK
TILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVK
VMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLONGR
DMYVDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNA
KLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSK
LVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGK
ATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTG
GFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFE
KNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLK
GSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLG
APAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDSGGSGGSGGSTNLSDIIEKETGKQ
LVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGENKIKMLSGG
SGGSGGSTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDAPEYKP
WALVIQDSNGENKIKMLSGGSPKKKRK

Example 2: Anti-Cancer Vaccination Using CRISPR-Cas9 Genome/Base-Editing Technologies

(254) Described herein are new methods to stimulate the immune system to treat tumors and prevent metastatic lesions. By turning the genome and proteome of the malignant cells into a personalized endogenous anti-cancer vaccine in vivo.

(255) Provided herein is a new immuno-oncology methodology to raise robust T-cell and B-cell mediated immune responses against tumor-specific proteins, which are otherwise tolerated as “self” by the immune system of a cancer patient.sup.1-3 (FIG. **1**, Tables 1-3). This methodology is uniquely suited for programmable CRISPR-Cas9 genome- and base-editing tools,.sup.4-10 exploited to alter the translated sequences of tumor specific genes.sup.11 to produce highly immunogenic heteroclitic and cryptic peptide epitopes in situ (Tables 5 and 7, FIG. **1**). Heteroclitic epitopes are altered versions of endogenous peptide sequences engineered to elicit potent immune reactions through the MHC-I and MHC-II antigen presentation pathways,.sup.12 which also produce cross-reactive responses towards the parent wild-type peptide sequences (FIG. **2**A).sup.2,13,14. For example, the peptide epitope EAAGIGILTV (SEQ ID NO: 388) from the melanocyte differentiation and melanoma marker MART-1.sup.26-36 is weakly immunogenic, whereas vaccination with a

similar peptide engineered with a hydrophobic residue.sup.15,16 on the MHC-anchor position MART-1 (27L) ELAGIGILTV (SEQ ID NO: 1085) promotes robust T-cell immune responses against melanoma (Table 5)..sup.17,18 Cryptic epitopes arise from non-translated genomic sequences through processes that are elevated in cancer cells, such as aberrant mRNA splicing, alternative open-reading frames (ORFs), and deglycosidation of proteins..sup.19 For example, LAGE-1 immunogenic antigens are expressed from ORF-2.sup.20,21 of the gene NY-ESO-122-24 (Table 7). Introduction of these immunogenic protein sequences using genome/base editing is designed to break "self"-tolerance to cancer-specific antigens,.sup.1-3 which is known drive the infiltration of immune cells into the tumor promoting the recognition of malignant cells as foreign through 3,827,234 multiple mechanisms (FIG. **3**)..sup.25,26 Anti-cancer vaccination using genome/base-editing is rendered cancer-specific by targeting genes that are preferentially or exclusively expressed by tumor cells to prevent autoimmunity side effects..sup.2,27 Anti-cancer vaccination strategies could be particularly useful for the treatment of melanoma (Table 1),.sup.28-30 as well as colorectal tumors, stomach cancer, and other highly mutagenized cancers that accumulate non-synonymous hitchhiker mutations with high frequencies (FIG. **4**)..sup.31 In such cases, spreading of the adaptive immune response towards translated "neo-epitopes" .sup.32,33 that are unique to the cell lineage facilitate remission.sub.34 and prevent metastatic lesions (abscopal effect) 35-39 (FIG. **3**). Importantly, the recently FDA-approved checkpoint inhibitors (anti-PD1 and anti-CTLA4 antibodies), which lower the threshold for T-cell stimulation,.sup.27,40 have shown promise for co-administration with anti-cancer vaccines,.sup.41-46 and could enhance the clinical effectiveness of immunization against a broader assortment of cancer types..sup.47,48

(256) The heteroclitic and cryptic epitopes programmed by genome/base-editing may be personalized to match each patient's malignancy and immune system, or alternatively a guide-RNA cocktail can be developed to engage the most frequent HLA allele supertypes that broadly cover the human population (FIG. **2**B). Recent advances for the delivery of genome editing tools are enabling for anti-cancer vaccination. These methods include intracellular delivery using electroporation,.sup.49-50 viral vectors,.sup.51,52 cell penetrating peptides,.sup.53,54 liposomes,.sup.55,56 polymers,.sup.57 membrane deformation,.sup.58 and nanoparticles.sup.59; and the types of cargo include RNA transcripts, DNA expression vectors, or Cas9 protein-guide RNA complexes purified,.sup.60 or within cationic lipid vesicles..sup.61,62 Therefore, the vaccination treatments could be potentially performed in vivo directly on tumor cells,.sup.63 the tissues that originated the tumor,.sup.64 or alternatively ex vivo for re-injection of irradiated whole-cell vaccines..sup.65-67

(257) Also provided herein are numerous specific examples of genomic target sites in tumor-associated genes (Tables 1-3), and the guide-RNAs designed to program the alteration of these translated sequences (Tables 5 and 7), in order to replicate or closely mimic known epitopes that have literature or pre-clinical precedent. The genome editing reactions were designed for one of the CRISPR/Cas9 tools: (i) "base editors" that catalyze chemical reactions on nucleobases (e.g. cytidine deaminase-Cas9 fusion4); or (ii) engineered nucleases with DNA cutting activity (e.g. WT Cas9,.sup.5-7 Cas9 nickases.sup.8 or Fok1-nuclease-dCas9 fusions.sup.9,10). Examples of other potentially useful genome-editing reactions to alter cancer-specific genes to produce heteroclitic/cryptic epitopes are shown in Tables 5 and 7. By extension, Cas9 tools and Homology-Directed Repair (HDR) pathways may also be exploited to introduce heteroclitic epitopes through DNA templates by lowering the rate of indels using several techniques..sup.68-70 finally, to expand the repertoire of heteroclitic and cryptic epitopes in an unbiased high-throughput manner, the aforementioned tools could be used to screen libraries of guide-RNAs targeting all PAM sites across a tumor-associated genes of interest, which can be replicated using the genome/base-editing reactions shown in Tables 5 and 7..sup.71,72

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EQUIVALENTS AND SCOPE

(259) In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

(260) Furthermore, the disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, e.g., in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the disclosure, or aspects of the disclosure, is/are referred to as comprising particular elements and/or features, certain embodiments of the disclosure or aspects of the disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth in haec verba herein.

(261) It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as

ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.
(262) This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.
(263) Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present disclosure, as defined in the following claims.

Claims

1. A method for producing a heteroclitic epitope in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a composition comprising: (i) a fusion protein comprising (a) a guide nucleotide sequence-programmable DNA-binding protein domain, and (b) a cytosine deaminase domain; and (ii) a guide nucleotide sequence, wherein the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 724-751, 870-877, 888-905, and 907-985; wherein the guide nucleotide sequence of (ii) targets the fusion protein of (i) to a polynucleotide encoding a tumor-specific antigen in a tumor cell; and wherein the fusion protein changes a target cytosine (C) base to a thymine (T) base via deamination.
2. The method of claim 1, wherein the polynucleotide encoding the tumor-specific antigen is located in the genome of the tumor cell.
3. The method of claim 1, wherein the guide nucleotide sequence-programmable DNA-binding protein domain is selected from the group consisting of nuclease inactive Cas9 (dCas9) domains, Cas9 nickase (nCas9) domains, nuclease inactive Cpf1 domains, and nuclease inactive Argonaute domains.
4. The method of claim 3, wherein the guide nucleotide sequence-programmable DNA-binding protein domain is a nuclease inactive Cas9 (dCas9) domain or a Cas9 nickase (nCas9) domain.
5. The method of claim 1, wherein the cytosine deaminase domain is selected from the group consisting of APOBEC1, APOBEC2, APOBEC3A, APOBEC3B, APOBEC3C, APOBEC3D, APOBEC3F, APOBEC3G, APOBEC3H, APOBEC4, and activation-induced deaminase (AID).
6. The method of claim 1, wherein the fusion protein of (i) further comprises a uracil glycosylase inhibitor (UGI) domain.
7. The method of claim 6, wherein the fusion protein comprises the structure: NH.sub.2-[cytosine deaminase domain]-[optional linker sequence]-[guide nucleotide sequence-programmable DNA-binding protein domain]-[optional linker sequence]-[UGI domain]-COOH; NH.sub.2-[UGI domain]-[optional linker sequence]-[cytosine deaminase domain]-[optional linker sequence]-[guide nucleotide sequence-programmable DNA-binding protein domain]-COOH; or NH.sub.2-[cytosine deaminase domain]-[optional linker sequence]-[guide nucleotide sequence-programmable DNA-binding protein domain]-COOH.
8. The method of claim 7, wherein the optional linker sequence comprises (GGGS).sub.n, (SEQ ID NO: 337), (GGGGS).sub.n (SEQ ID NO: 308), (G).sub.n(SEQ ID NO: 783), (EAAAK).sub.n (SEQ ID NO: 309), (GGS).sub.n(SEQ ID NO: 784), SGSETPGTSESATPES (SEQ ID NO: 310), (XP).sub.n (SEQ ID NO: 785), or a combination of any of these, wherein n is independently an integer between 1 and 30, and wherein X is any amino acid.
9. The method of claim 1, wherein the fusion protein comprises the amino acid sequence of any one of SEQ ID NOs: 293-302, 1071, and 1084.
10. The method of claim 1, wherein the tumor-specific antigen is selected from the group consisting of: gp100; MART-1; hTERT; TyRP1; HER2; CEA-CAM; tyrosinase (TYR); CD33; MAGE-A3; MAGE-A4; NY-ESO-1; SSX-2; survivin; EpCAM; and MUC1.
11. The method of claim 1, wherein the target C base is in a target codon in a coding region of the polynucleotide encoding the tumor-specific antigen, and wherein the target codon is any one of the following target codons: CTT (Leu/L), CTC (Leu/L), ATG (Met/M), GTT (Val/V), GTA (Val/V), GTC (Val/V), GTG (Val/V), TCT (Ser/S), TCC (Ser/S), TCA (Ser/S), TCG (Ser/S), AGT (Ser/S), AGC (Ser/S), CCT (Pro/P), CCC (Pro/P), CCA (Pro/P), CCG (Pro/P), ACT (Thr/T), ACC (Thr/T), ACA (Thr/T), ACG (Thr/T), GCT (Ala/A), GCC (Ala/A), GCA (Ala/A), GCG (Ala/A), CAT (His/H), CAC (His/H), GAT (Asp/D), GAC (Asp/D), GAA (Glu/E), GAG (Glu/E), TGT (Cys/C), TGC (Cys/C), CGT (Arg/R), CGC (Arg/R), AGA (Arg/R), AGG (Arg/R), CGG (Arg/R), GGT (Gly/G), GGC (Gly/G), GGA (Gly/G), GGG (Gly/G), CAG (Gln/Q), TGG (Trp/W), CGA (Arg/R), CAA (Gln/Q), TGG (Trp/W), and CGA (Arg/R).
12. The method of claim 11, wherein the target codon is converted to a modified codon selected from any one of the following modified codons: ATA (Ile/I), ATT (Ile/I), ATC (Ile/I), ATG (Met/M), TTT (Phe/F), TTC (Phe/F), TTA (Leu/L), TTG (Leu/L), AAT (Asp/N), AAC (Aps/N), TCT (Ser/S), TCC (Ser/S), TCA (Ser/S), TCG (Ser/S), CTT (Leu/L), CTC

(Leu/L), CTA (Leu/L), CTG (Leu/L), GTT (Val/V), GTC (Val/V), GTA (Val/V), GTG (Val/V), ACT (Thr/T), ACC (Thr/T), ACA (Thr/T), ACG (Thr/T), TAT (Tyr/Y), TAC (Tyr/Y), AAA (Lys/K), AAG (Lys/K), TGT (Cys/C), TGC (Cys/C), CAG (Gln/Q), TGG (Trp/W), GAT (Asp/D), GAC (Asp/D), GAA (Glu/E), GAG (Glu/E), AGT (Ser/S), AGC (Ser/S), AGA (Arg/R), AGG (Arg/R), TAG (amber), TGA (opal), and TAA (ochre).

13. The method of claim 1, wherein the target C base is located in a non-coding region of the polynucleotide encoding the tumor-specific antigen.

14. The method of claim 1, wherein the heteroclitic epitope is at least 5-fold more immunogenic than a native epitope from the tumor-specific antigen.

15. The method of claim 1, wherein the heteroclitic epitope is displayed on the surface of the tumor cell via the MHC class I antigen presentation pathway.

16. The method of claim 1, wherein the method is carried out in vivo.

17. The method of claim 1, wherein the tumor-specific antigen is gp100.

18. The method of claim 17, wherein the deamination of the target C base: (a) in codon T210 of gp100 results in a T210I mutation (SEQ ID NO: 786); (b) in codon A288 of gp100 results in a A288V mutation (SEQ ID NO: 818); or (c) in codon T155 of gp100 results in a T155I mutation (SEQ ID NO: 787).

19. The method of claim 18, wherein; (a) a heteroclitic epitope comprising the amino acid sequence of IIDQVPFSV (SEQ ID NO: 786) is generated, and wherein the I at position 2 corresponds to the T210I mutation; (b) a heteroclitic epitope comprising the amino acid sequence of YLEPGPVTV (SEQ ID NO: 818) is generated, and wherein the V at position 7 corresponds to the A288V mutation; or (c) a heteroclitic epitope comprising the amino acid sequence of KIWGQYWQV (SEQ ID NO: 787) is generated, and wherein the I at position 2 corresponds to the T155I mutation.

20. The method of claim 19, wherein the guide nucleotide sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 724, 725, 870-877, 888, and 889.

21. The method of claim 1, the method further comprising administering to the subject a therapeutically effective amount of an immune checkpoint inhibitor.

22. The method of claim 1, wherein the target C base is in a target codon in a coding region of the polynucleotide encoding the tumor-specific antigen.

23. The method of claim 1, wherein the heteroclitic epitope is displayed on the surface of an antigen presenting cell (APC) via the MHC class II antigen presentation pathway.