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(54) **CAS VARIANTS FOR GENE EDITING**

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(Continued)

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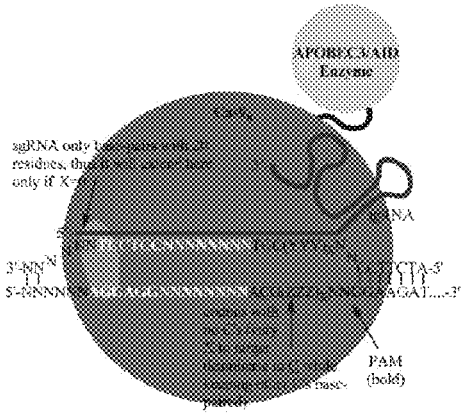
(57) **ABSTRACT**

Some aspects of this disclosure provide strategies, systems, reagents, methods, and kits that are useful for the targeted editing of nucleic acids, including editing a single site within the genome of a cell or subject, e.g., within the human genome. In some embodiments, fusion proteins of Cas9 and nucleic acid editing enzymes or enzyme domains, e.g., deaminase domains, are provided. In some embodiments, methods for targeted nucleic acid editing are provided. In some embodiments, reagents and kits for the generation of targeted nucleic acid editing proteins, e.g., fusion proteins of Cas9 and nucleic acid editing enzymes or domains, are provided.

Specification includes a Sequence Listing.



Related U.S. Application Data

(60) Provisional application No. 61/980,333, filed on Apr. 16, 2014, provisional application No. 61/915,386, filed on Dec. 12, 2013, provisional application No. 61/980,333, filed on Apr. 16, 2014, provisional application No. 61/915,386, filed on Dec. 12, 2013, provisional application No. 61/980,333, filed on Apr. 16, 2014, provisional application No. 61/915,386, filed on Dec. 12, 2013, provisional application No. 61/980,333, filed on Apr. 16, 2014, provisional application No. 61/915,386, filed on Dec. 12, 2013, provisional application No. 61/980,333, filed on Apr. 16, 2014, provisional application No. 61/915,386, filed on Dec. 12, 2013, provisional application No. 61/980,333, filed on Apr. 16, 2014, provisional application No. 61/915,386, filed on Dec. 12, 2013, provisional application No. 61/980,333, filed on Apr. 16, 2014, provisional application No. 61/915,386, filed on Dec. 12, 2013, provisional application No. 61/980,333, filed on Apr. 16, 2014, provisional application No. 61/915,386, filed on Dec. 12, 2013.

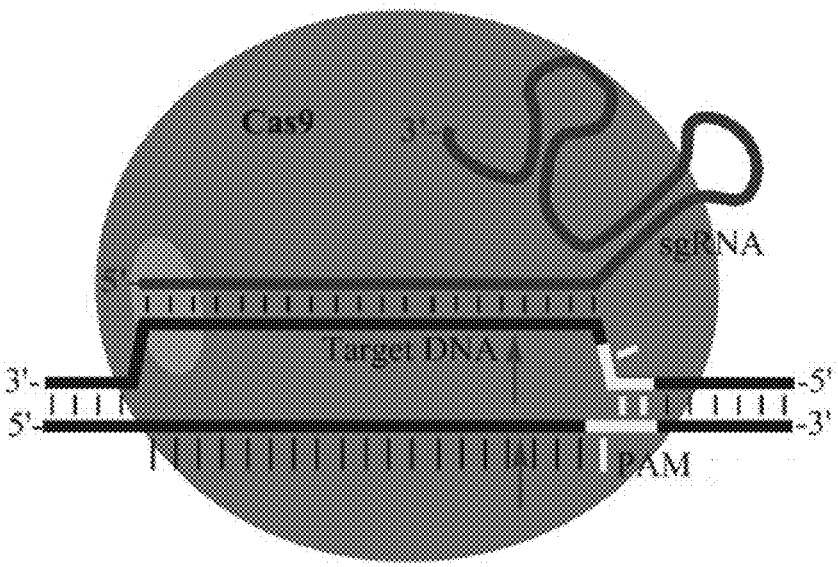


FIGURE 1

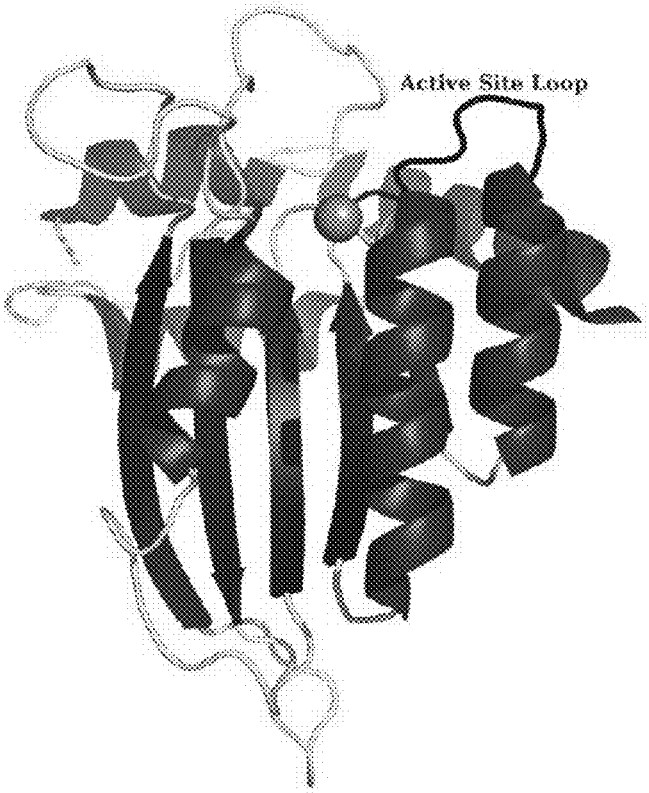


FIGURE 2

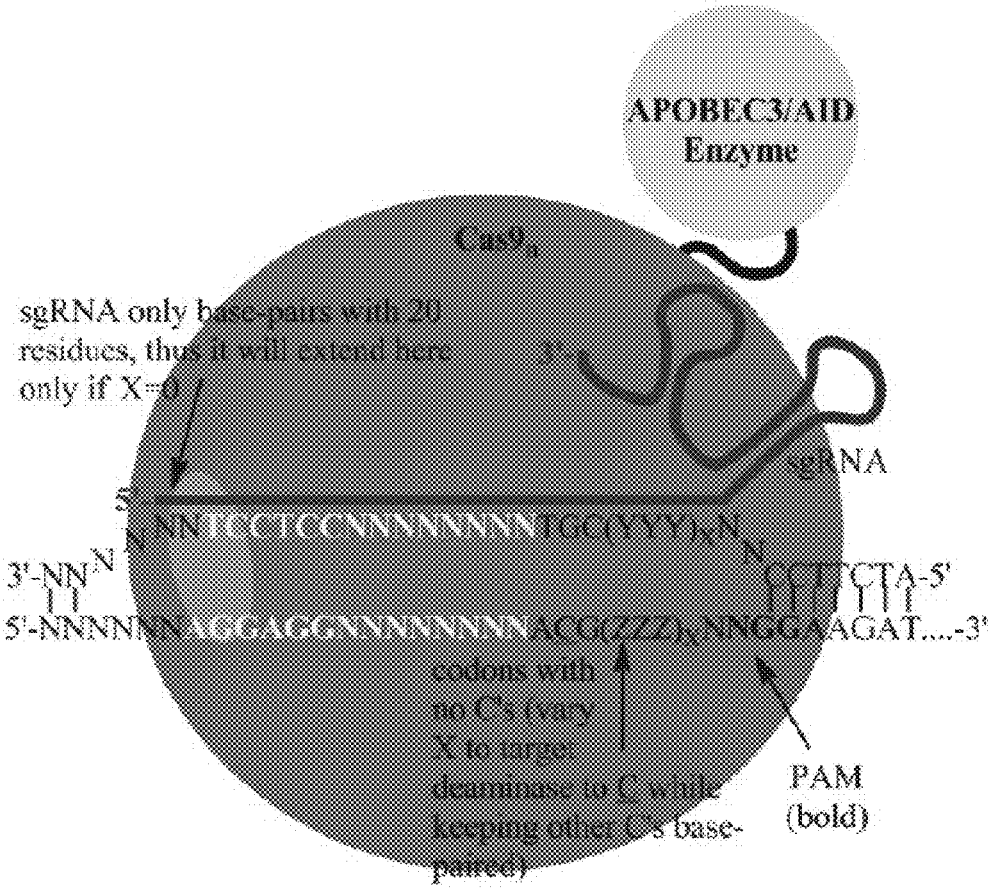

APOBEC3/AID
Enzyme
Cas9n
sgRNA only base-pairs with 20
residues, thus it will extend here
only if X=0
3'-
sgRNA
5'
N
NNTCCTCCNNNNNNNTGCYYYY)xN
N
3'-NN
N
CCTTCTA-5'
5'-NNNNNNAGGAGGNNNNNNNACGZZZ)xNNGGAAGAT....-3'
codons with
no C's (vary
X to target
deaminase to C while
keeping other C's base-
paired)
PAM
(bold)

FIGURE 3

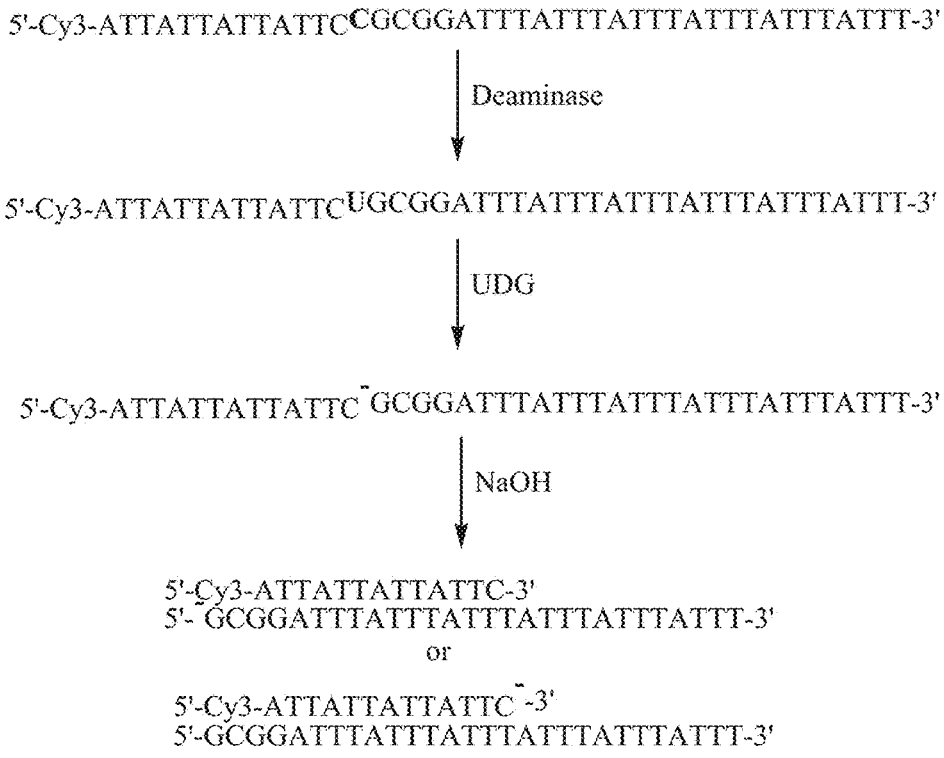

5'-Cy3-ATTATTATTATTCCGCGGATTTATTTATTTATTTATTTATTT-3'
Deaminase
5'-Cy3-ATTATTATTATTCUGCGGATTTATTTATTTATTTATTTATTT-3'
UDG
5'-Cy3-ATTATTATTATTC GCGGATTTATTTATTTATTTATTTATTT-3'
NaOH
5'-Cy3-ATTATTATTATTC-3'
5'- GCGGATTTATTTATTTATTTATTTATTT-3'
or
5'-Cy3-ATTATTATTATTC -3'
5'-GCGGATTTATTTATTTATTTATTTATTT-3'

FIGURE 4

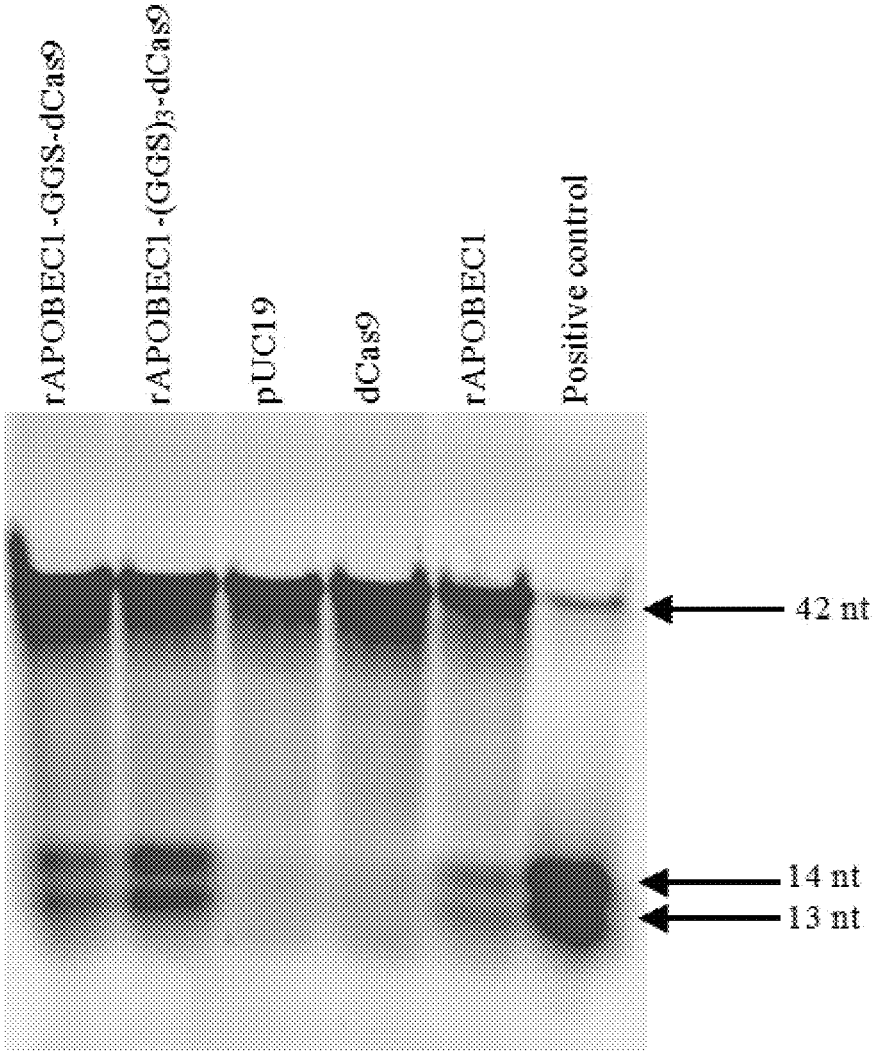

rAPOBEC1-GGS-dCas9
rAPOBEC1-(GGS)3-dCas9
pUC19
dCas9
rAPOBEC1
Positive control
42 nt
14 nt
13 nt

FIGURE 5

CAS VARIANTS FOR GENE EDITING

RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S. Ser. No. 61/915,386 filed Dec. 12, 2013, and U.S. provisional patent application, U.S. Ser. No. 61/980,333 filed Apr. 16, 2014; and also claims priority under 35 U.S.C. § 120 to U.S. patent application Ser. Nos. 14/325,815, 14/326,109, 14/326,140, 14/326,269, 14/326,290, 14/326,318, and 14/326,303, all filed on Jul. 8, 2014; each of which is incorporated herein by reference.

GOVERNMENT SUPPORT

[0002] This invention was made with U.S. Government support under grant HR0011-11-2-0003 awarded by the Defense Advanced Research Projects Agency (DARPA), grant GM095501 awarded by the National Institutes of Health (NIH), and grant N66001-12-C-4207 awarded by the Space and Naval Warfare Systems Center (SPAWAR). The Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

[0003] Targeted editing of nucleic acid sequences, for example, the introduction of a specific modification into genomic DNA, is a highly promising approach for the study of gene function and also has the potential to provide new therapies for human genetic diseases.[1] An ideal nucleic acid editing technology possesses three characteristics: (1) high efficiency of installing the desired modification; (2) minimal off-target activity; and (3) the ability to be programmed to edit precisely any site in a given nucleic acid, e.g., any site within the human genome.[2] Current genome engineering tools, including engineered zinc finger nucleases (ZFNs),[3] transcription activator like effector nucleases (TALENs),[4] and most recently, the RNA-guided DNA endonuclease Cas9,[5] effect sequence-specific DNA cleavage in a genome. This programmable cleavage can result in mutation of the DNA at the cleavage site via non-homologous end joining (NHEJ) or replacement of the DNA surrounding the cleavage site via homology-directed repair (HDR).[6,7]

[0004] One drawback to the current technologies is that both NHEJ and HDR are stochastic processes that typically result in modest gene editing efficiencies as well as unwanted gene alterations that can compete with the desired alteration.[8] Since many genetic diseases in principle can be treated by effecting a specific nucleotide change at a specific location in the genome (for example, a C to T change in a specific codon of a gene associated with a disease),[9] the development of a programmable way to achieve such precision gene editing would represent both a powerful new research tool, as well as a potential new approach to gene editing-based human therapeutics.

SUMMARY OF THE INVENTION

[0005] The clustered regularly interspaced short palindromic repeat (CRISPR) system is a recently discovered prokaryotic adaptive immune system[10] that has been modified to enable robust and general genome engineering in a variety of organisms and cell lines.[11] CRISPR-Cas (CRISPR associated) systems are protein-RNA complexes that use an RNA molecule (sgRNA) as a guide to localize the complex to a target DNA sequence via base-pairing.[12] In the natural systems, a Cas protein then acts as an endonuclease to cleave the targeted DNA sequence.[13] The target DNA sequence must be both complementary to the sgRNA, and also contain a "protospacer-adjacent motif" (PAM) dinucleotide at the 3'-end of the complementary region in order for the system to function (FIG. **1**).[14] Among the known Cas proteins, *S. pyogenes* Cas9 has been mostly widely used as a tool for genome engineering.[15] This Cas9 protein is a large, multi-domain protein containing two distinct nuclease domains. Point mutations can be introduced into Cas9 to abolish nuclease activity, resulting in a dead Cas9 (dCas9) that still retains its ability to bind DNA in a sgRNA-programmed manner.[16] In principle, when fused to another protein or domain, dCas9 can target that protein to virtually any DNA sequence simply by co-expression with an appropriate sgRNA.

[0006] The potential of the dCas9 complex for genome engineering purposes is immense. Its unique ability to bring proteins to specific sites in a genome programmed by the sgRNA in theory can be developed into a variety of site-specific genome engineering tools beyond nucleases, including transcriptional activators, transcriptional repressors, histone-modifying proteins, integrases, and recombinases.[11] Some of these potential applications have recently been implemented through dCas9 fusions with transcriptional activators to afford RNA-guided transcriptional activators,[17,18] transcriptional repressors,[16,19,20] and chromatin modification enzymes.[21] Simple co-expression of these fusions with a variety of sgRNAs results in specific expression of the target genes. These seminal studies have paved the way for the design and construction of readily programmable sequence-specific effectors for the precise manipulation of genomes.

[0007] Significantly, 80-90% of protein mutations responsible for human disease arise from the substitution, deletion, or insertion of only a single nucleotide.[6] No genome engineering tools, however, have yet been developed that enable the manipulation of a single nucleotide in a general and direct manner. Current strategies for single-base gene correction include engineered nucleases (which rely on the creation of double-strand breaks, DSBs, followed by stochastic, inefficient homology-directed repair, HDR), and DNA-RNA chimeric oligonucleotides.[22] The latter strategy involves the design of a RNA/DNA sequence to base pair with a specific sequence in genomic DNA except at the nucleotide to be edited. The resulting mismatch is recognized by the cell's endogenous repair system and fixed, leading to a change in the sequence of either the chimera or the genome. Both of these strategies suffer from low gene editing efficiencies and unwanted gene alterations, as they are subject to both the stochasticity of HDR and the competition between HDR and non-homologous end-joining, NHEJ.[23-25] HDR efficiencies vary according to the location of the target gene within the genome,[26] the state of the cell cycle,[27] and the type of cell/tissue.[28] The development of a direct, programmable way to install a specific type of base modification at a precise location in genomic DNA with enzyme-like efficiency and no stochasticity would therefore represent a powerful new approach to gene editing-based research tools and human therapeutics.

[0008] Some aspects of this disclosure provide strategies, systems, reagents, methods, and kits that are useful for the targeted editing of nucleic acids, including editing a single site within a subject's genome, e.g., the human genome. In

some embodiments, fusion proteins of Cas9 and nucleic acid editing enzymes or enzyme domains, e.g., deaminase domains, are provided. In some embodiments, methods for targeted nucleic acid editing are provided. In some embodiments, reagents and kits for the generation of targeted nucleic acid editing proteins, e.g., fusion proteins of Cas9 and nucleic acid editing enzymes or domains, are provided.

[0009] Some aspects of this disclosure provide fusion proteins comprising (i) a nuclease-inactive CAS9 domain; and (ii) a nucleic acid-editing domain. In some embodiments, the nucleic acid-editing domain is a DNA-editing domain. In some embodiments, the nucleic-acid-editing domain is a deaminase domain. In some embodiments, the deaminase is a cytidine deaminase. In some embodiments, the deaminase is an apolipoprotein B mRNA-editing complex (APOBEC) family deaminase. In some embodiments, the deaminase is an APOBEC1 family deaminase. In some embodiments, the deaminase is an activation-induced cytidine deaminase (AID). In some embodiments, the deaminase is an ACF1/ASE deaminase. In some embodiments, the deaminase is an adenosine deaminase. In some embodiments, the deaminase is an ADAT family deaminase. In some embodiments, the nucleic-acid-editing domain is fused to the N-terminus of the CAS9 domain. In some embodiments, the nucleic-acid-editing domain is fused to the C-terminus of the CAS9 domain. In some embodiments, the CAS9 domain and the nucleic-acid-editing domain are fused via a linker. In some embodiments, the linker comprises a $(GGGGS)_n$ (SEQ ID NO: 91), a $(G)_n$, an $(EAAAK)_n$(SEQ ID NO: 5), a $(GGS)_n$, an SGSETPGTSESATPES (SEQ ID NO: 93) motif (see, e.g., Guilinger J P, Thompson D B, Liu D R. Fusion of catalytically inactive Cas9 to FokI nuclease improves the specificity of genome modification. *Nat. Biotechnol.* 2014; 32(6): 577-82; the entire contents are incorporated herein by reference), or an $(XP)_n$ motif, or a combination of any of these, wherein n is independently an integer between 1 and 30.

[0010] Some aspects of this disclosure provide methods for DNA editing. In some embodiments, the methods comprise contacting a DNA molecule with (a) a fusion protein comprising a nuclease-inactive Cas9 domain and a deaminase domain; and (b) an sgRNA targeting the fusion protein of (a) to a target nucleotide sequence of the DNA strand; wherein the DNA molecule is contacted with the fusion protein and the sgRNA in an amount effective and under conditions suitable for the deamination of a nucleotide base. In some embodiments, the target DNA sequence comprises a sequence associated with a disease or disorder, and wherein the deamination of the nucleotide base results in a sequence that is not associated with a disease or disorder. In some embodiments, the DNA sequence comprises a T>C or A>G point mutation associated with a disease or disorder, and wherein the deamination of the mutant C or G base results in a sequence that is not associated with a disease or disorder. In some embodiments, the deamination corrects a point mutation in the sequence associated with the disease or disorder. In some embodiments, the sequence associated with the disease or disorder encodes a protein, and wherein the deamination introduces a stop codon into the sequence associated with the disease or disorder, resulting in a truncation of the encoded protein. In some embodiments, the deamination corrects a point mutation in the PI3KCA gene, thus correcting an H1047R and/or a A3140G mutation. In some embodiments, the contacting is performed in vivo in a subject susceptible to having, having, or diagnosed with the disease or disorder. In some embodiments, the disease or disorder is a disease associated with a point mutation, or a single-base mutation, in the genome. In some embodiments, the disease is a genetic disease, a cancer, a metabolic disease, or a lysosomal storage disease.

[0011] Some aspects of this disclosure provide a reporter construct for detecting nucleic-acid-editing activity of a Cas9:DNA-editing domain fusion protein. In some embodiments, the construct comprises (a) a reporter gene comprising a target site for the Cas9 DNA-editing protein, wherein targeted DNA editing results in an increase in expression of the reporter gene; and (b) a promoter sequence that controls expression of the reporter gene. In some embodiments, the construct further comprises (c) a sequence encoding an sgRNA targeting the Cas9 DNA-editing protein to the target site of the reporter gene, wherein expression of the sgRNA is independent of the expression of the reporter gene. In some embodiments, the target site of the reporter gene comprises a premature stop codon, and wherein targeted DNA editing of the template strand by the Cas9 DNA-editing protein results in a conversion of the premature stop codon to a codon encoding an amino acid residue. In some embodiments, the reporter gene encodes a luciferase, a fluorescent protein, or an antibiotic resistance marker.

[0012] Some aspects of this disclosure provide kits comprising a nucleic acid construct that comprises a sequence encoding a nuclease-inactive Cas9 sequence, a sequence comprising a cloning site positioned to allow cloning of a sequence encoding a nucleic acid-editing enzyme or enzyme domain in-frame with the Cas9-encoding sequence, and, optionally, a sequence encoding a linker positioned between the Cas9 encoding sequence and the cloning site. In addition, in some embodiments, the kit comprises suitable reagents, buffers, and/or instructions for in-frame cloning of a sequence encoding a nucleic acid-editing enzyme or enzyme domain into the nucleic acid construct to generate a Cas9 nucleic acid editing fusion protein. In some embodiments, the sequence comprising the cloning site is N-terminal of the Cas9 sequence. In some embodiments, the sequence comprising the cloning site is C-terminal of the Cas9 sequence. In some embodiments, the encoded linker comprises a $(GGGGS)_n$ (SEQ ID NO: 91), a $(G)_n$, an $(EAAAK)_n$ (SEQ ID NO: 5), a $(GGS)_n$, an SGSETPGTSESATPES (SEQ ID NO: 93) motif (see, e.g., Guilinger J P, Thompson D B, Liu D R. Fusion of catalytically inactive Cas9 to FokI nuclease improves the specificity of genome modification. *Nat. Biotechnol.* 2014; 32(6): 577-82; the entire contents are incorporated herein by reference), or an $(XP)_n$ motif, or a combination of any of these, wherein n is independently an integer between 1 and 30.

[0013] Some aspects of this disclosure provide kits comprising a fusion protein comprising a nuclease-inactive Cas9 domain and a nucleic acid-editing enzyme or enzyme domain, and, optionally, a linker positioned between the Cas9 domain and the nucleic acid-editing enzyme or enzyme domain. In addition, in some embodiments, the kit comprises suitable reagents, buffers, and/or instructions for using the fusion protein, e.g., for in vitro or in vivo DNA or RNA editing. In some embodiments, the kit comprises instructions regarding the design and use of suitable sgRNAs for targeted editing of a nucleic acid sequence.

[0014] The summary above is meant to illustrate, in a non-limiting manner, some of the embodiments, advantages,

features, and uses of the technology disclosed herein. Other embodiments, advantages, features, and uses of the technology disclosed herein will be apparent from the Detailed Description, the Drawings, the Examples, and the Claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. **1**. The Cas9/sgRNA-DNA complex. The 3' end of the sgRNA forms a ribonucleoprotein complex with the Cas9 nuclease, while the 20 nt 5' end of the sgRNA recognizes its complementary stretch of DNA. DNA binding requires the 3-nt PAM sequence 5' to the target DNA. In the case of wtCas9, double-strand DNA cleavage occurs 3 nt from the PAM to produce blunt ends (shown by the arrows). It should be noted that the size of the bubble is unknown.

[0016] FIG. **2**. Crystal structure of the catalytic domain of APOBEC3G (PDB ID 3E1U). The core secondary structure, which is believed to be conserved among the entire family, consists of a five-stranded β-sheet (arrows) flanked by six α-helices. The active center loop (active site loop), is believed to be responsible for determining deamination specificity. The Zn^{2+} responsible for catalytic activity is shown as a sphere. Sequences correspond, from top to bottom, to SEQ ID NOs: 97-98.

[0017] FIG. **3**. Design of luciferase-based reporter assay. The sgRNA will be varied to target numerous sequences that correspond to regions prior to and including the luciferase gene in order to target the mutated start codon (C residue underlined). A "buffer" region will be added between the start codon and the luciferase gene to include codons of only A's and T's (shown as $(ZZZ)_X$). The Shine-Dalgarno sequence is indicated. In some embodiments, it is preferable to keep all C's base-paired to prevent off-target effects.

[0018] FIG. **4**. Deaminase assay. Sequences correspond, from top to bottom, to SEQ ID NOs: 99-105.

[0019] FIG. **5**. SDS PAGE gel of ssDNA edited by Cas9-APOBEC1 fusion proteins.

DEFINITIONS

[0020] 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.

[0021] The term "Cas9" or "Cas9 nuclease" refers to an RNA-guided nuclease comprising a Cas9 protein, or a fragment thereof (e.g., a protein comprising an active or inactive DNA cleavage domain of Cas9, and/or the gRNA binding domain of Cas9). A Cas9 nuclease is also referred to sometimes as a casn1 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 (rnc) 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 M., Chylinski K., Fonfara I., Hauer M., Doudna J. A., Charpentier E. *Science* 337:816-821 (2012), the entire contents of which is hereby incorporated by reference. Cas9 recognizes a short motif in the CRISPR repeat sequences (the PAM or protospacer adjacent motif) to help distinguish self versus non-self. Cas9 nuclease sequences and structures are well known to those of skill in the art (see, e.g., "Complete genome sequence of an M1 strain of *Streptococcus pyogenes*." Ferretti et al., J. J., McShan W. M., Ajdic D. J., Savic D. J., Savic G., Lyon K., Primeaux C., Sezate S., Suvorov A. N., Kenton S., Lai H. S., Lin S. P., Qian Y., Jia H. G., Najar F. Z., Ren Q., Zhu H., Song L., White J., Yuan X., Clifton S. W., Roe B. A., McLaughlin R. E., Proc. Natl. Acad. Sci. U.S.A. 98:4658-4663(2001); "CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III." Deltcheva E., Chylinski K., Sharma C. M., Gonzales K., Chao Y., Pirzada Z. A., Eckert M. R., Vogel J., Charpentier E., Nature 471:602-607(2011); and "A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity." Jinek M., Chylinski K., Fonfara I., Hauer M., Doudna J. A., Charpentier E. 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, Rhun, and Charpentier, "The tracrRNA and Cas9 families of type II CRISPR-Cas immunity systems" (2013) RNA Biology 10:5, 726-737; the entire contents of which are incorporated herein by reference. In some embodiments, a Cas9 nuclease has an inactive (e.g., an inactivated) DNA cleavage domain.

[0022] A nuclease-inactivated 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., "Repurposing CRISPR as an RNA-Guided Platform for Sequence-Specific Control of Gene Expression" (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 H841A 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). In some embodiments, proteins comprising fragments of Cas9 are provided. For example, in some embodiments, a protein comprises one of two Cas9 domains: (1) the gRNA binding domain of Cas9; or (2) the DNA cleavage domain of Cas9. In some embodiments, proteins comprising Cas9 or fragments

thereof are referred to as "Cas9 variants." A Cas9 variant shares homology to Cas9, or a fragment thereof. For example a Cas9 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 wild type Cas9. In some embodiments, the Cas9 variant comprises a fragment of Cas9 (e.g., a gRNA binding domain or a DNA-cleavage domain), 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 Cas9. In some embodiments, wild type Cas9 corresponds to Cas9 from *Streptococcus pyogenes* (NCBI Reference Sequence: NC_017053.1, SEQ ID NO:1 (nucleotide); SEQ ID NO:2 (amino acid)).

(SEQ ID NO: 1)

ATGGATAAGAAATACTCAATAGGCTTAGATATCGGCACAAATAGCGTCGGATGGGCGGTGATCACTGATGATTAT

AAGGTTCCGTCTAAAAAGTTCAAGGTTCTGGGAAATACAGACCGCCACAGTATCAAAAAAAATCTTATAGGGGCT

CTTTTATTTGGCAGTGGAGAGACAGCGGAAGCGACTCGTCTCAAACGGACAGCTCGTAGAAGGTATACACGTCGG

AAGAATCGTATTTGTTATCTACAGGAGATTTTTTCAAATGAGATGGCGAAAGTAGATGATAGTTTCTTTCATCGA

CTTGAAGAGTCTTTTTTGGTGGAAGAAGACAAGAAGCATGAACGTCATCCTATTTTTGGAAATATAGTAGATGAA

GTTGCTTATCATGAGAAATATCCAACTATCTATCATCTGCGAAAAAAATTGGCAGATTCTACTGATAAAGCGGAT

TTGCGCTTAATCTATTTGGCCTTAGCGCATATGATTAAGTTTCGTGGTCATTTTTTGATTGAGGGAGATTTAAAT

CCTGATAATAGTGATGTGGACAAACTATTTATCCAGTTGGTACAAATCTACAATCAATTATTTGAAGAAAACCCT

ATTAACGCAAGTAGAGTAGATGCTAAAGCGATTCTTTCTGCACGATTGAGTAAATCAAGACGATTAGAAAATCTC

ATTGCTCAGCTCCCCGGTGAGAAGAGAAATGGCTTGTTTGGGAATCTCATTGCTTTGTCATTGGGATTGACCCCT

AATTTTAAATCAAATTTTGATTTGGCAGAAGATGCTAAATTACAGCTTTCAAAAGATACTTACGATGATGATTTA

GATAATTTATTGGCGCAAATTGGAGATCAATATGCTGATTTGTTTTTGGCAGCTAAGAATTTATCAGATGCTATT

TTACTTTCAGATATCCTAAGAGTAAATAGTGAAATAACTAAGGCTCCCCTATCAGCTTCAATGATTAAGCGCTAC

GATGAACATCATCAAGACTTGACTCTTTTAAAAGCTTTAGTTCGACAACAACTTCCAGAAAAGTATAAAGAAATC

TTTTTTGATCAATCAAAAAACGGATATGCAGGTTATATTGATGGGGGAGCTAGCCAAGAAGAATTTTATAAATTT

ATCAAACCAATTTTAGAAAAAATGGATGGTACTGAGGAATTATTGGTGAAACTAAATCGTGAAGATTTGCTGCGC

AAGCAACGGACCTTTGACAACGGCTCTATTCCCCATCAAATTCACTTGGGTGAGCTGCATGCTATTTTGAGAAGA

CAAGAAGACTTTTATCCATTTTTAAAAGACAATCGTGAGAAGATTGAAAAAATCTTGACTTTTCGAATTCCTTAT

TATGTTGGTCCATTGGCGCGTGGCAATAGTCGTTTTGCATGGATGACTCGGAAGTCTGAAGAAACAATTACCCCA

TGGAATTTTGAAGAAGTTGTCGATAAAGGTGCTTCAGCTCAATCATTTATTGAACGCATGACAAACTTTGATAAA

AATCTTCCAAATGAAAAAGTACTACCAAAACATAGTTTGCTTTATGAGTATTTTACGGTTTATAACGAATTGACA

AAGGTCAAATATGTTACTGAGGGAATGCGAAAACCAGCATTTCTTTCAGGTGAACAGAAGAAAGCCATTGTTGAT

TTACTCTTCAAAACAAATCGAAAAGTAACCGTTAAGCAATTAAAAGAAGATTATTTCAAAAAAATAGAATGTTTT

GATAGTGTTGAAATTTCAGGAGTTGAAGATAGATTTAATGCTTCATTAGGCGCCTACCATGATTTGCTAAAAATT

ATTAAAGATAAAGATTTTTTGGATAATGAAGAAAATGAAGATATCTTAGAGGATATTGTTTTAACATTGACCTTA

TTTGAAGATAGGGGGATGATTGAGGAAAGACTTAAAACATATGCTCACCTCTTTGATGATAAGGTGATGAAACAG

CTTAAACGTCGCCGTTATACTGGTTGGGGACGTTTGTCTCGAAAATTGATTAATGGTATTAGGGATAAGCAATCT

GGCAAAACAATATTAGATTTTTTGAAATCAGATGGTTTTGCCAATCGCAATTTTATGCAGCTGATCCATGATGAT

AGTTTGACATTTAAAGAAGATATTCAAAAAGCACAGGTGTCTGGACAAGGCCATAGTTTACATGAACAGATTGCT

AACTTAGCTGGCAGTCCTGCTATTAAAAAAGGTATTTTACAGACTGTAAAAATTGTTGATGAACTGGTCAAAGTA

ATGGGGCATAAGCCAGAAAATATCGTTATTGAAATGGCACGTGAAAATCAGACAACTCAAAAGGGCCAGAAAAAT

TCGCGAGAGCGTATGAAACGAATCGAAGAAGGTATCAAAGAATTAGGAAGTCAGATTCTTAAAGAGCATCCTGTT

-continued

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GAATTAGATATTAATCGTTTAAGTGATTATGATGTCGATCACATTGTTCCACAAAGTTTCATTAAAGACGATTCA

ATAGACAATAAGGTACTAACGCGTTCTGATAAAAATCGTGGTAAATCGGATAACGTTCCAAGTGAAGAAGTAGTC

AAAAAGATGAAAAACTATTGGAGACAACTTCTAAACGCCAAGTTAATCACTCAACGTAAGTTTGATAATTTAACG

AAAGCTGAACGTGGAGGTTTGAGTGAACTTGATAAAGCTGGTTTTATCAAACGCCAATTGGTTGAAACTCGCCAA

ATCACTAAGCATGTGGCACAAATTTTGGATAGTCGCATGAATACTAAATACGATGAAAATGATAAACTTATTCGA

GAGGTTAAAGTGATTACCTTAAAATCTAAATTAGTTTCTGACTTCCGAAAAGATTTCCAATTCTATAAAGTACGT

GAGATTAACAATTACCATCATGCCCATGATGCGTATCTAAATGCCGTCGTTGGAACTGCTTTGATTAAGAAATAT

CCAAAACTTGAATCGGAGTTTGTCTATGGTGATTATAAAGTTTATGATGTTCGTAAAATGATTGCTAAGTCTGAG

CAAGAAATAGGCAAAGCAACCGCAAAATATTTCTTTTACTCTAATATCATGAACTTCTTCAAAACAGAAATTACA

CTTGCAAATGGAGAGATTCGCAAACGCCCTCTAATCGAAACTAATGGGGAAACTGGAGAAATTGTCTGGGATAAA

GGGCGAGATTTTGCCACAGTGCGCAAAGTATTGTCCATGCCCCAAGTCAATATTGTCAAGAAAACAGAAGTACAG

ACAGGCGGATTCTCCAAGGAGTCAATTTTACCAAAAAGAAATTCGGACAAGCTTATTGCTCGTAAAAAAGACTGG

GATCCAAAAAAATATGGTGGTTTTGATAGTCCAACGGTAGCTTATTCAGTCCTAGTGGTTGCTAAGGTGGAAAAA

GGGAAATCGAAGAAGTTAAAATCCGTTAAAGAGTTACTAGGGATCACAATTATGGAAAGAAGTTCCTTTGAAAAA

AATCCGATTGACTTTTTAGAAGCTAAAGGATATAAGGAAGTTAAAAAAGACTTAATCATTAAACTACCTAAATAT

AGTCTTTTTGAGTTAGAAAACGGTCGTAAACGGATGCTGGCTAGTGCCGGAGAATTACAAAAAGGAAATGAGCTG

GCTCTGCCAAGCAAATATGTGAATTTTTTATATTTAGCTAGTCATTATGAAAAGTTGAAGGGTAGTCCAGAAGAT

AACGAACAAAAACAATTGTTTGTGGAGCAGCATAAGCATTATTTAGATGAGATTATTGAGCAAATCAGTGAATTT

TCTAAGCGTGTTATTTTAGCAGATGCCAATTTAGATAAAGTTCTTAGTGCATATAACAAACATAGAGACAAACCA

ATACGTGAACAAGCAGAAAATATTATTCATTTATTTACGTTGACGAATCTTGGAGCTCCCGCTGCTTTTAAATAT

TTTGATACAACAATTGATCGTAAACGATATACGTCTACAAAAGAAGTTTTAGATGCCACTCTTATCCATCAATCC

ATCACTGGTCTTTATGAAACACGCATTGATTTGAGTCAGCTAGGAGGTGACTGA

(SEQ ID NO: 2)

MDKKYSIGLDIGTNSVGWAVITDDYKVPSKKFKVLGNTDRHSIKKNLIGALLFGSGETAEATRLKRTARRYTRR

KNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLADSTDKAD

LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQIYNQLFEENPINASRVDAKAILSARLSKSRRLENL

IAQLPGEKRNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAI

LLSDILRVNSEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKF

IKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPY

YVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELT

KVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGAYHDLLKI

IKDKDFLDNEENEDILEDIVLTLTLFEDRGMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQS

GKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGHSLHEQIANLAGSPAIKKGILQTVKIVDELVKV

MGHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQ

ELDINRLSDYDVDHIVPQSFIKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLT

KAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVR

EINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEIT

LANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDW

DPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKY

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SLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEF

SKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQS

ITGLYETRIDLSQLGGD
(single underline: HNH domain; double underline: RuvC domain)

[0023] In some embodiments, wild type Cas9 corresponds to, or comprises SEQ ID NO:3 (nucleotide) and/or SEQ ID NO: 4 (amino acid):

(SEQ ID NO: 3)

ATGGATAAAAAGTATTCTATTGGTTTAGACATCGGCACTAATTCCGTTGGATGGGCTGTCATAACCGATGAATAC

AAAGTACCTTCAAAGAAATTTAAGGTGTTGGGGAACACAGACCGTCATTCGATTAAAAAGAATCTTATCGGTGCC

CTCCTATTCGATAGTGGCGAAACGGCAGAGGCGACTCGCCTGAAACGAACCGCTCGGAGAAGGTATACACGTCGC

AAGAACCGAATATGTTACTTACAAGAAATTTTTAGCAATGAGATGGCCAAAGTTGACGATTCTTTCTTTCACCGT

TTGGAAGAGTCCTTCCTTGTCGAAGAGGACAAGAAACATGAACGGCACCCCATCTTTGGAAACATAGTAGATGAG

GTGGCATATCATGAAAAGTACCCAACGATTTATCACCTCAGAAAAAAGCTAGTTGACTCAACTGATAAAGCGGAC

CTGAGGTTAATCTACTTGGCTCTTGCCCATATGATAAAGTTCCGTGGGCACTTTCTCATTGAGGGTGATCTAAAT

CCGGACAACTCGGATGTCGACAAACTGTTCATCCAGTTAGTACAAACCTATAATCAGTTGTTTGAAGAGAACCCT

ATAAATGCAAGTGGCGTGGATGCGAAGGCTATTCTTAGCGCCCGCCTCTCTAAATCCCGACGGCTAGAAAACCTG

ATCGCACAATTACCCGGAGAGAAGAAAAATGGGTTGTTCGGTAACCTTATAGCGCTCTCACTAGGCCTGACACCA

AATTTTAAGTCGAACTTCGACTTAGCTGAAGATGCCAAATTGCAGCTTAGTAAGGACACGTACGATGACGATCTC

GACAATCTACTGGCACAAATTGGAGATCAGTATGCGGACTTATTTTTGGCTGCCAAAAACCTTAGCGATGCAATC

CTCCTATCTGACATACTGAGAGTTAATACTGAGATTACCAAGGCGCCGTTATCCGCTTCAATGATCAAAAGGTAC

GATGAACATCACCAAGACTTGACACTTCTCAAGGCCCTAGTCCGTCAGCAACTGCCTGAGAAATATAAGGAAATA

TTCTTTGATCAGTCGAAAAACGGGTACGCAGGTTATATTGACGGCGGAGCGAGTCAAGAGGAATTCTACAAGTTT

ATCAAACCCATATTAGAGAAGATGGATGGGACGGAAGAGTTGCTTGTAAAACTCAATCGCGAAGATCTACTGCGA

AAGCAGCGGACTTTCGACAACGGTAGCATTCCACATCAAATCCACTTAGGCGAATTGCATGCTATACTTAGAAGG

CAGGAGGATTTTTATCCGTTCCTCAAAGACAATCGTGAAAAGATTGAGAAAATCCTAACCTTTCGCATACCTTAC

TATGTGGGACCCCTGGCCCGAGGGAACTCTCGGTTCGCATGGATGACAAGAAAGTCCGAAGAAACGATTACTCCA

TGGAATTTTGAGGAAGTTGTCGATAAAGGTGCGTCAGCTCAATCGTTCATCGAGAGGATGACCAACTTTGACAAG

AATTTACCGAACGAAAAAGTATTGCCTAAGCACAGTTTACTTTACGAGTATTTCACAGTGTACAATGAACTCACG

AAAGTTAAGTATGTCACTGAGGGCATGCGTAAACCCGCCTTTCTAAGCGGAGAACAGAAGAAAGCAATAGTAGAT

CTGTTATTCAAGACCAACCGCAAAGTGACAGTTAAGCAATTGAAAGAGGACTACTTTAAGAAAATTGAATGCTTC

GATTCTGTCGAGATCTCCGGGGTAGAAGATCGATTTAATGCGTCACTTGGTACGTATCATGACCTCCTAAAGATA

ATTAAAGATAAGGACTTCCTGGATAACGAAGAGAATGAAGATATCTTAGAAGATATAGTGTTGACTCTTACCCTC

TTTGAAGATCGGGAAATGATTGAGGAAAGACTAAAAACATACGCTCACCTGTTCGACGATAAGGTTATGAAACAG

TTAAAGAGGCGTCGCTATACGGGCTGGGGACGATTGTCGCGGAAACTTATCAACGGGATAAGAGACAAGCAAAGT

GGTAAAACTATTCTCGATTTTCTAAAGAGCGACGGCTTCGCCAATAGGAACTTTATGCAGCTGATCCATGATGAC

TCTTTAACCTTCAAAGAGGATATACAAAAGGCACAGGTTTCCGGACAAGGGGACTCATTGCACGAACATATTGCG

AATCTTGCTGGTTCGCCAGCCATCAAAAAGGGCATACTCCAGACAGTCAAAGTAGTGGATGAGCTAGTTAAGGTC

ATGGGACGTCACAAACCGGAAAACATTGTAATCGAGATGGCACGCGAAAATCAAACGACTCAGAAGGGGCAAAAA

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AACAGTCGAGAGCGGATGAAGAGAATAGAAGAGGGTATTAAAGAACTGGGCAGCCAGATCTTAAAGGAGCATCCT

GTGGAAAATACCCAATTGCAGAACGAGAAACTTTACCTCTATTACCTACAAAATGGAAGGGACATGTATGTTGAT

CAGGAACTGGACATAAACCGTTTATCTGATTACGACGTCGATCACATTGTACCCCAATCCTTTTTGAAGGACGAT

TCAATCGACAATAAAGTGCTTACACGCTCGGATAAGAACCGAGGGAAAAGTGACAATGTTCCAAGCGAGGAAGTC

GTAAAGAAAATGAAGAACTATTGGCGGCAGCTCCTAAATGCGAAACTGATAACGCAAAGAAAGTTCGATAACTTA

ACTAAAGCTGAGAGGGGTGGCTTGTCTGAACTTGACAAGGCCGGATTTATTAAACGTCAGCTCGTGGAAACCCGC

CAAATCACAAAGCATGTTGCACAGATACTAGATTCCCGAATGAATACGAAATACGACGAGAACGATAAGCTGATT

CGGGAAGTCAAAGTAATCACTTTAAAGTCAAAATTGGTGTCGGACTTCAGAAAGGATTTTCAATTCTATAAAGTT

AGGGAGATAAATAACTACCACCATGCGCACGACGCTTATCTTAATGCCGTCGTAGGGACCGCACTCATTAAGAAA

TACCCGAAGCTAGAAAGTGAGTTTGTGTATGGTGATTACAAAGTTTATGACGTCCGTAAGATGATCGCGAAAAGC

GAACAGGAGATAGGCAAGGCTACAGCCAAATACTTCTTTTATTCTAACATTATGAATTTCTTTAAGACGGAAATC

ACTCTGGCAAACGGAGAGATACGCAAACGACCTTTAATTGAAACCAATGGGGAGACAGGTGAAATCGTATGGGAT

AAGGGCCGGGACTTCGCGACGGTGAGAAAAGTTTTGTCCATGCCCCAAGTCAACATAGTAAAGAAAACTGAGGTG

CAGACCGGAGGGTTTTCAAAGGAATCGATTCTTCCAAAAAGGAATAGTGATAAGCTCATCGCTCGTAAAAAGGAC

TGGGACCCGAAAAAGTACGGTGGCTTCGATAGCCCTACAGTTGCCTATTCTGTCCTAGTAGTGGCAAAAGTTGAG

AAGGGAAAATCCAAGAAACTGAAGTCAGTCAAAGAATTATTGGGGATAACGATTATGGAGCGCTCGTCTTTTGAA

AAGAACCCCATCGACTTCCTTGAGGCGAAAGGTTACAAGGAAGTAAAAAAGGATCTCATAATTAAACTACCAAAG

TATAGTCTGTTTGAGTTAGAAAATGGCCGAAAACGGATGTTGGCTAGCGCCGGAGAGCTTCAAAAGGGGAACGAA

CTCGCACTACCGTCTAAATACGTGAATTTCCTGTATTTAGCGTCCCATTACGAGAAGTTGAAAGGTTCACCTGAA

GATAACGAACAGAAGCAACTTTTTGTTGAGCAGCACAAACATTATCTCGACGAAATCATAGAGCAAATTTCGGAA

TTCAGTAAGAGAGTCATCCTAGCTGATGCCAATCTGGACAAAGTATTAAGCGCATACAACAAGCACAGGGATAAA

CCCATACGTGAGCAGGCGGAAAATATTATCCATTTGTTTACTCTTACCAACCTCGGCGCTCCAGCCGCATTCAAG

TATTTTGACACAACGATAGATCGCAAACGATACACTTCTACCAAGGAGGTGCTAGACGCGACACTGATTCACCAA

TCCATCACGGGATTATATGAAACTCGGATAGATTTGTCACAGCTTGGGGGTGACGGATCCCCCAAGAAGAAGAGG

AAAGTCTCGAGCGACTACAAAGACCATGACGGTGATTATAAAGATCATGACATCGATTACAAGGATGACGATGAC

AAGGCTGCAGGA

(SEQ ID NO: 4)

MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR

KNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD

LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENL

IAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAI

LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKF

IKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPY

YVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELT

KVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKI

IKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQS

GKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKV

MGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVD

QELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNL

TKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKV

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REINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEI

TLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKD

WDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPK

YSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISE

FSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQ

SITGLYETRIDLSQLGGD
(single underline: HNH domain; double underline: RuvC domain)

[0024] In some embodiments, dCas9 corresponds to, or comprises in part or in whole, a Cas9 amino acid sequence having one or more mutations that inactivate the Cas9 nuclease activity. For example, in some embodiments, a dCas9 domain comprises D10A and/or H820A mutation. dCas9 (D10A and H840A):

(SEQ ID NO: 34)
MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRR

KNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD

LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENL

IAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAI

LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKF

IKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPY

YVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELT

KVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKI

IKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQS

GKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKV

MGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVD

QELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNL

TKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKV

REINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEI

TLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKD

WDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPK

YSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISE

FSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQ

SITGLYETRIDLSQLGGD
(single underline: HNH domain; double underline: RuvC domain)

[0025] In other embodiments, dCas9 variants having mutations other than D10A and H820A are provided, which e.g., result in nuclease inactivated Cas9 (dCas9). Such mutations, by way of example, include other amino acid substitutions at D10 and H820, or other substitutions within the nuclease domains of Cas9 (e.g., substitutions in the HNH nuclease subdomain and/or the RuvC1 subdomain). In some embodiments, variants or homologues of dCas9 (e.g., variants of SEQ ID NO: 34) 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: 34. In some embodiments, variants of dCas9 (e.g., variants of SEQ ID NO: 34) are provided having amino acid sequences which are shorter, or longer than SEQ ID NO: 34, 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.

[0026] In some embodiments, Cas9 fusion proteins as provided herein comprise the full-length amino acid of a Cas9 protein, e.g., one of the sequences provided above. In other embodiments, however, fusion proteins as provided herein do not comprise a full-length Cas9 sequence, but only a fragment thereof. For example, in some embodiments, a Cas9 fusion protein provided herein comprises a Cas9

fragment, wherein the fragment binds crRNA and tracrRNA or sgRNA, but does not comprise a functional nuclease domain, e.g., in that it comprises only a truncated version of a nuclease domain or no nuclease domain at all. Exemplary amino acid sequences of suitable Cas9 domains and Cas9 fragments are provided herein, and additional suitable sequences of Cas9 domains and fragments will be apparent to those of skill in the art.

[0027] 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); *Streptococcus thermophilus* (NCBI Ref: YP_820832.1); *Listeria innocua* (NCBI Ref: NP_472073.1); *Campylobacter jejuni* (NCBI Ref: YP_002344900.1); or *Neisseria. meningitidis* (NCBI Ref: YP_002342100.1).

[0028] The term "deaminase" refers to an enzyme that catalyzes a deamination reaction. In some embodiments, the deaminase is a cytidine deaminase, catalyzing the hydrolytic deamination of cytidine or deoxycytidine to uracil or deoxyuracil, respectively.

[0029] The term "effective amount," as used herein, refers to an amount of a biologically active agent that is sufficient to elicit a desired biological response. For example, in some embodiments, an effective amount of a nuclease may refer to the amount of the nuclease that is sufficient to induce cleavage of a target site specifically bound and cleaved by the nuclease. In some embodiments, an effective amount of a fusion protein provided herein, e.g., of a fusion protein comprising a nuclease-inactive Cas9 domain and a nucleic acid-editing domain (e.g., a deaminase domain) may refer to the amount of the fusion protein that is sufficient to induce editing of a target site specifically bound and edited by the fusion protein. As will be appreciated by the skilled artisan, the effective amount of an agent, e.g., a fusion protein, a nuclease, a deaminase, a recombinase, a hybrid protein, a protein dimer, a complex of a protein (or protein dimer) and a polynucleotide, or a polynucleotide, may vary depending on various factors as, for example, on the desired biological response, e.g., on the specific allele, genome, or target site to be edited, on the cell or tissue being targeted, and on the agent being used.

[0030] 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). In some embodiments, a linker joins a gRNA binding domain of an RNA-programmable nuclease, including a Cas9 nuclease domain, and the catalytic domain of a nucleic-acid editing protein. In some embodiments, a linker joins a dCas9 and a nucleic-acid editing protein. 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.

[0031] 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^{th} ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2012)).

[0032] 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).

[0033] The term "proliferative disease," as used herein, refers to any disease in which cell or tissue homeostasis is disturbed in that a cell or cell population exhibits an abnormally elevated proliferation rate. Proliferative diseases include hyperproliferative diseases, such as pre-neoplastic hyperplastic conditions and neoplastic diseases. Neoplastic diseases are characterized by an abnormal proliferation of cells and include both benign and malignant neoplasias. Malignant neoplasia is also referred to as cancer.

[0034] 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^{th} ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2012)), the entire contents of which are incorporated herein by reference.

[0035] The term "RNA-programmable nuclease," and "RNA-guided nuclease" are used interchangeably herein and refer to a nuclease that forms a complex with (e.g., binds or associates with) one or more RNA that is not a target for cleavage. In some embodiments, an RNA-programmable nuclease, when in a complex with an RNA, may be referred to as a nuclease:RNA complex. Typically, the bound RNA(s) is referred to as a guide RNA (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 single RNA species comprise two domains: (1) a domain that shares homology to a target nucleic acid (e.g., and directs binding of a Cas9 complex to the target); and (2) a domain that binds a 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 homologous to a tracrRNA as depicted in FIG. 1E of 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 Ser. No. 61/874,682, filed Sep. 6, 2013, entitled "Switchable Cas9 Nucleases And Uses Thereof," and U.S. Provisional Patent Application 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. In some embodiments, a gRNA comprises two or more of domains (1) and (2), and may be referred to as an "extended gRNA." For example, an extended gRNA will, e.g., bind two or more Cas9 proteins and bind a target nucleic acid at two or more distinct regions, as described herein. 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. In some embodiments, the RNA-programmable nuclease is the (CRISPR-associated system) Cas9 endonuclease, for example Cas9 (Csn1) from *Streptococcus pyogenes* (see, e.g., "Complete genome sequence of an M1 strain of *Streptococcus pyogenes*." Ferretti J. J., McShan W. M., Ajdic D. J., Savic D. J., Savic G., Lyon K., Primeaux C., Sezate S., Suvorov A. N., Kenton S., Lai H. S., Lin S. P., Qian Y., Jia H. G., Najar F. Z., Ren Q., Zhu H., Song L., White J., Yuan X., Clifton S. W., Roe B. A., McLaughlin R. E., Proc. Natl. Acad. Sci. U.S.A. 98:4658-4663(2001); "CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III." Deltcheva E., Chylinski K., Sharma C. M., Gonzales K., Chao Y., Pirzada Z. A., Eckert M. R., Vogel J., Charpentier E., Nature 471:602-607(2011); and "A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity." Jinek M., Chylinski K., Fonfara I., Hauer M., Doudna J. A., Charpentier E. Science 337:816-821(2012), the entire contents of each of which are incorporated herein by reference.

[0036] Because RNA-programmable nucleases (e.g., Cas9) use RNA:DNA hybridization to target DNA cleavage sites, 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. Multiplex genome engineering using CRISPR/Cas systems. *Science* 339, 819-823 (2013);

Mali, P. et al. RNA-guided human genome engineering via Cas9. *Science* 339, 823-826 (2013); Hwang, W. Y. et al. Efficient genome editing in zebrafish using a CRISPR-Cas system. *Nature biotechnology* 31, 227-229 (2013); Jinek, M. et al. RNA-programmed genome editing in human cells. *eLife* 2, e00471 (2013); Dicarlo, J. E. et al. Genome engineering in *Saccharomyces cerevisiae* using CRISPR-Cas systems. *Nucleic acids research* (2013); Jiang, W. et al. RNA-guided editing of bacterial genomes using CRISPR-Cas systems. *Nature biotechnology* 31, 233-239 (2013); the entire contents of each of which are incorporated herein by reference).

[0037] 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.

[0038] The term "target site" refers to a sequence within a nucleic acid molecule that is deaminated by a deaminase or a fusion protein comprising a deaminase, (e.g., a dCas9-deaminase fusion protein provided herein).

[0039] The terms "treatment," "treat," and "treating," refer to a clinical intervention aimed to reverse, alleviate, delay the onset of, or inhibit the progress of a disease or disorder, or one or more symptoms thereof, as described herein. As used herein, the terms "treatment," "treat," and "treating" refer to a clinical intervention aimed to reverse, alleviate, delay the onset of, or inhibit the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed and/or after a disease has been diagnosed. In other embodiments, treatment may be administered in the absence of symptoms, e.g., to prevent or delay onset of a symptom or inhibit onset or progression of a disease. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to prevent or delay their recurrence.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

[0040] Some aspects of this disclosure provide fusion proteins that comprise a Cas9 domain that binds to a guide RNA (also referred to as gRNA or sgRNA), which, in turn, binds a target nucleic acid sequence via strand hybridization; and a DNA-editing domain, for example, a deaminase domain that can deaminate a nucleobase, such as, for example, cytidine. The deamination of a nucleobase by a deaminase can lead to a point mutation at the respective residue, which is referred to herein as nucleic acid editing. Fusion proteins comprising a Cas9 variant or domain and a DNA editing domain can thus be used for the targeted editing of nucleic acid sequences. Such fusion proteins are useful for targeted editing of DNA in vitro, e.g., for the generation of mutant cells or animals; for the introduction of targeted mutations, e.g., for the correction of genetic defects in cells ex vivo, e.g., in cells obtained from a subject that are subsequently re-introduced into the same or another subject; and for the introduction of targeted mutations, e.g., the correction of genetic defects or the introduction of deactivating mutations in disease-associated genes in a subject. Typically, the Cas9 domain of the fusion proteins described herein does not have any nuclease activity but instead is a Cas9 fragment or a dCas9 protein or domain. Methods for the use of Cas9 fusion proteins as described herein are also provided.

[0041] Non-limiting, exemplary nuclease-inactive Cas9 domains are provided herein. One exemplary suitable nuclease-inactive Cas9 domain is the D10A/H840A Cas9 domain mutant:

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MDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGA
LLFDSGETAEATRLKRTARRYTRRKNRICYLQEIFSNEMAKVDDSFFHR
LEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKAD
LRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENP
INASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTP
NFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAI
LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEI
FFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLR
KQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPY
YVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDK
NLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVD
LLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKI
IKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQ
LKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDD
SLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKV
MGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHP
VENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDD
SIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNL
TKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLI
REVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKK
YPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEI
TLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEV
QTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVE
KGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPK
YSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPE
DNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDK
PIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQ
SITGLYETRIDLSQLGGD
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(SEQ ID NO: 37; see, e.g., Qi et al., Repurposing CRISPR as an RNA-guided platform for sequence-specific control of

gene expression. Cell. 2013; 152(5):1173-83, the entire contents of which are incorporated herein by reference).

[0042] Additional suitable nuclease-inactive Cas9 domains will be apparent to those of skill in the art based on this disclosure. Such additional exemplary suitable nuclease-inactive Cas9 domains include, but are not limited to, D10A, D10A/D839A/H840A, and D10A/D839A/H840A/N863A mutant domains (See, e.g., Prashant et al., CAS9 transcriptional activators for target specificity screening and paired nickases for cooperative genome engineering. Nature Biotechnology. 2013; 31(9): 833-838, the entire contents of which are incorporated herein by reference).

Fusion Proteins Between Cas9 and Nucleic Acid Editing Enzymes or Domains

[0043] Some aspects of this disclosure provide fusion proteins comprising (i) a nuclease-inactive Cas9 enzyme or domain; and (ii) a nucleic acid-editing enzyme or domain. In some embodiments, the nucleic acid-editing enzyme or domain is a DNA-editing enzyme or domain. In some embodiments, the nucleic acid-editing enzyme possesses deaminase activity. In some embodiments, the nucleic acid-editing enzyme or domain comprises or is a deaminase domain. In some embodiments, the deaminase is a cytidine deaminase. In some embodiments, the deaminase is an apolipoprotein B mRNA-editing complex (APOBEC) family deaminase. In some embodiments, the deaminase is an APOBEC1 family deaminase. In some embodiments, the deaminase is an activation-induced cytidine deaminase (AID). In some embodiments, the deaminase is an ACF1/ASE deaminase. In some embodiments, the deaminase is an adenosine deaminase. In some embodiments, the deaminase is an ADAT family deaminase. Some nucleic-acid editing enzymes and domains as well as Cas9 fusion proteins including such enzymes or domains are described in detail herein. Additional suitable nucleic acid-editing enzymes or domains will be apparent to the skilled artisan based on this disclosure.

[0044] The instant disclosure provides Cas9:nucleic acid-editing enzyme/domain fusion proteins of various configurations. In some embodiments, the nucleic acid-editing enzyme or domain is fused to the N-terminus of the Cas9 domain. In some embodiments, the nucleic acid-editing enzyme or domain is fused to the C-terminus of the Cas9 domain. In some embodiments, the Cas9 domain and the nucleic acid-editing-editing enzyme or domain are fused via a linker. In some embodiments, the linker comprises a $(GGGGS)_n$(SEQ ID NO: 91), a $(G)_n$, an $(EAAAK)_n$(SEQ ID NO: 5), a $(GGS)_n$, an SGSETPGTSESATPES (SEQ ID NO: 93) motif (see, e.g., Guilinger J P, Thompson D B, Liu D R. Fusion of catalytically inactive Cas9 to FokI nuclease improves the specificity of genome modification. *Nat. Biotechnol.* 2014; 32(6): 577-82; the entire contents are incorporated herein by reference), or an $(XP)_n$ motif, or a combination of any of these, wherein n is independently an integer between 1 and 30. 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. Additional suitable linker motifs and linker configurations will be apparent to those of skill in the art. 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, the entire contents of which are incorporated herein by reference. Additional suitable linker sequences will be apparent to those of skill in the art based on the instant disclosure.

[0045] In some embodiments, the general architecture of exemplary Cas9 fusion proteins provided herein comprises the structure:

[0046] $[NH_2]$-[nucleic acid-editing enzyme or domain]-[Cas9]-[COOH] or

[0047] $[NH_2]$-[Cas9]-[nucleic acid-editing enzyme or domain]-[COOH],

wherein NH_2 is the N-terminus of the fusion protein, and COOH is the C-terminus of the fusion protein.

[0048] Additional features may be present, for example, one or more linker sequences between the NLS and the rest of the fusion protein and/or between the nucleic acid-editing enzyme or domain and the Cas9. Other exemplary features that may be present are localization sequences, such as nuclear localization sequences, cytoplasmic localization sequences, export sequences, such as nuclear export sequences, or other localization sequences, as well as sequence tags that are useful for solubilization, purification, or detection of the fusion proteins. Suitable localization signal sequences and sequences of protein tags are provided herein, and include, but are not limited to, biotin carboxylase carrier protein (BCCP) tags, myc-tags, calmodulin-tags, FLAG-tags, hemagglutinin (HA)-tags, polyhistidine tags, also referred to as histidine tags or His-tags, maltose binding protein (MBP)-tags, nus-tags, glutathione-S-transferase (GST)-tags, green fluorescent protein (GFP)-tags, thioredoxin-tags, S-tags, Softags (e.g., Softag 1, Softag 3), strep-tags, biotin ligase tags, FlAsH tags, V5 tags, and SBP-tags. Additional suitable sequences will be apparent to those of skill in the art.

[0049] In some embodiments, the nucleic acid-editing enzyme or domain is a deaminase. For example, in some embodiments, the general architecture of exemplary Cas9 fusion proteins with a deaminase enzyme or domain comprises the structure:

[0050] $[NH_2]$-[NLS]-[Cas9]-[deaminase]-[COOH],

[0051] $[NH_2]$-[NLS]-[deaminase]-[Cas9]- -[COOH],

[0052] $[NH_2]$-[Cas9]-[deaminase]-[COOH], or

[0053] $[NH_2]$-[deaminase]-[Cas9]-[COOH]

wherein NLS is a nuclear localization signal, NH_2 is the N-terminus of the fusion protein, and COOH is the C-terminus of the fusion protein. In some embodiments, a linker is inserted between the Cas9 and the deaminase. In some embodiments, the NLS is located C-terminal of the deaminase and/or the Cas9 domain. In some embodiments, the NLS is located between the deaminase and the Cas9 domain. Additional features, such as sequence tags, may also be present

[0054] One exemplary suitable type of nucleic acid-editing enzymes and domains are cytosine deaminases, for example, of the APOBEC family. The apolipoprotein B mRNA-editing complex (APOBEC) family of cytosine deaminase enzymes encompasses eleven proteins that serve to initiate mutagenesis in a controlled and beneficial manner.[29] One family member, activation-induced cytidine deaminase (AID), is responsible for the maturation of antibodies by converting cytosines in ssDNA to uracils in a transcription-dependent, strand-biased fashion.[30] 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.[31] These proteins all require a Zn^{2+}-coordinating motif (His-X-Glu-X_{23-26}-Pro-Cys-X_{2-4}-Cys) 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.[32] A recent crystal structure of the catalytic domain of APOBEC3G (FIG. **2**) revealed a secondary structure comprised of a five-stranded β-sheet core flanked by six α-helices, which is believed to be conserved across the entire family.[33] The active center loops have been shown to be responsible for both ssDNA binding and in determining "hotspot" identity.[34] Overexpression of these enzymes has been linked to genomic instability and cancer, thus highlighting the importance of sequence-specific targeting.[35]

[0055] Another exemplary suitable type of nucleic acid-editing enzymes and domains are adenosine deaminases. For example, an ADAT family adenosine deaminase can be fused to a Cas9 domain, e.g., a nuclease-inactive Cas9 domain, thus yielding a Cas9-ADAT fusion protein.

[0056] Some aspects of this disclosure provide a systematic series of fusions between Cas9 and deaminase enzymes, e.g., cytosine deaminase enzymes such as APOBEC enzymes, or adenosine deaminase enzymes such as ADAT enzymes, that has been generated in order to direct the enzymatic activities of these deaminases to a specific site in genomic DNA. The advantages of using Cas9 as the recognition agent are twofold: (1) the sequence specificity of Cas9 can be easily altered by simply changing the sgRNA sequence; and (2) Cas9 binds to its target sequence by denaturing the dsDNA, resulting in a stretch of DNA that is single-stranded and therefore a viable substrate for the deaminase. Successful fusion proteins have been generated with human and mouse deaminase domains, e.g., AID domains. A variety of other fusion proteins between the catalytic domains of human and mouse AID and Cas9 are also contemplated. It will be understood that other catalytic domains, or catalytic domains from other deaminases, can also be used to generate fusion proteins with Cas9, and that the disclosure is not limited in this regard.

[0057] In some embodiments, fusion proteins of Cas9 and AID are provided. In an effort to engineer Cas9 fusion proteins to increase mutation rates in ssDNA, both mouse and human AID were tethered to gene V of filamentous phage (a nonspecific ssDNA binding protein). The resulting fusion proteins exhibited enhanced mutagenic activities compared to the wild type enzymes in a cell-based assay. This work demonstrates that the enzymatic activity of these proteins is maintained in and can be successfully targeted to genetic sequences with fusion proteins.[36]

[0058] While several crystal structures of Cas9 (and even Cas9 in complex with its sgRNA and target DNA) have been reported, (see, e.g., Jinek M, Jiang F, Taylor D W, Sternberg S H, Kaya E, Ma E, Anders C, Hauer M, Zhou K, Lin S, Kaplan M, Iavarone A T, Charpentier E, Nogales E, Doudna J A. Structures of Cas9 endonucleases reveal RNA-mediated conformational activation. *Science.* 2014; 343(6176): 1247997. PMID: 24505130; and Nishimasu H, Ran F A, Hsu P D, Konermann S, Shehata S I, Dohmae N, Ishitani R, Zhang F, Nureki O. Crystal structure of Cas9 in complex with guide RNA and target DNA. *Cell.* 2014; 156(5):935-49. PMID: 24529477, the entire contents of each of which are incorporated herein by reference), the portion of DNA that is single stranded in the Cas9-DNA complex is unknown (the size of the Cas9-DNA bubble). However, it has been shown in a dCas9 system with a sgRNA specifically designed for the complex to interfere with transcription that transcriptional interference only occurs when the sgRNA binds to the non-template strand. This result suggests that certain portions of the DNA in the DNA-Cas9 complex are unguarded by Cas9, and could potentially be targeted by a deaminase in the fusion protein (see Qi L S, Larson M H, Gilbert L A, Doudna J A, Weissman J S, Arkin A P, Lim W A. Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. *Cell.* 2013; 152(5):1173-83. PMID: 23452860, the entire contents of which are incorporated herein by reference). Further supporting this notion, footprinting experiments with exonuclease III and nuclease P1 (which only acts on ssDNA as a substrate) have revealed that at least 26 bases on the non-template strand are susceptible to digestion by these enzymes (see Jinek M, Jiang F, Taylor D W, Sternberg S H, Kaya E, Ma E, Anders C, Hauer M, Zhou K, Lin S, Kaplan M, Iavarone A T, Charpentier E, Nogales E, Doudna J A. Structures of Cas9 endonucleases reveal RNA-mediated conformational activation. *Science.* 2014; 343(6176): 1247997. PMID: 24505130). It has also been reported that in certain cases, Cas9 induces single base-substitution mutations in this susceptible stretch of DNA at frequencies as high as 15% (see Tsai S Q, Wyvekens N, Khayter C, Foden J A, Thapar V, Reyon D, Goodwin M J, Aryee M J, Joung J K. Dimeric CRISPR RNA-guided FokI nucleases for highly specific genome editing. *Nat Biotechnol.* 2014; 32(6): 569-76. PMID: 24770325, the entire contents of which are incorporated herein by reference). While the mechanism of introduction of these mutations is unknown, in all cases, the base that is mutated is a cytosine, which could possibly indicate the involvement of a cytosine deaminase enzyme. Taken together, these data are clearly consistent with a portion of the target DNA being single stranded and susceptible to other enzymes. It has been shown in a dCas9 system with a sgRNA specifically designed for the complex to interfere with transcription that transcriptional interference only occurs when the sgRNA binds to the non-template strand. This result suggests that certain portions of the DNA in the DNA-Cas9 complex are unguarded by Cas9, and could potentially be targeted by AID in the fusion protein.[16] Accordingly, both N-terminal and C-terminal fusions of Cas9 with a deaminase domain are useful according to aspects of this disclosure.

[0059] In some embodiments, the 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., AID) and the Cas9 domain can be employed (e.g., ranging from very flexible linkers of the form $(GGGGS)_n$ (SEQ ID NO: 91), $(GGS)_n$, and $(G)_n$ to more rigid linkers of the form $(EAAAK)_n$ (SEQ ID NO: 5), SGSETPGTSESATPES (SEQ ID NO: 93) (see, e.g., Guilinger J P, Thompson D B, Liu D R. Fusion of catalytically inactive Cas9 to FokI nuclease improves the specificity of genome modification. *Nat. Biotechnol.* 2014; 32(6): 577-82; the entire contents are incorporated herein by reference) and $(XP)_n$)[37] in order to achieve the optimal length for deaminase activity for the specific application.

[0060] Some exemplary suitable nucleic-acid editing enzymes and domains, e.g., deaminases and deaminase domains, that can be fused to Cas9 domains according to aspects of this disclosure are provided below. It will be understood that, in some embodiments, the active domain of the respective sequence can be used, e.g., the domain without a localizing signal (nuclear localizing signal, without nuclear export signal, cytoplasmic localizing signal).

[0061] Human AID:

(SEQ ID NO: 6)
MDSLLMNRRKFLYQFKNVRWAKGRRETYLCYVVKRRDSATSFSLDFGYLR

NKNGCHVELLFLRYISDWDLDPGRCYRVTWFTSWSPCYDCARHVADFLRG

NPNLSLRIFTARLYFCEDRKAEPEGLRRLHRAGVQIAIMTFKDYFYCWNT

FVENHERTFKAWEGLHENSVRLSRQLRRILLPLYEVDDLRDAFRTLGL
(underline: nuclear localization signal; double underline: nuclear export signal)

[0062] Mouse AID:

(SEQ ID NO: 7)
MDSLLMKQKKFLYHFKNVRWAKGRHETYLCYVVKRRDSATSCSLDFGHLR

NKSGCHVELLFLRYISDWDLDPGRCYRVTWFTSWSPCYDCARHVAEFLRW

NPNLSLRIFTARLYFCEDRKAEPEGLRRLHRAGVQIGIMTFKDYFYCWNT

FVENRERTFKAWEGLHENSVRLTRQLRRILLPLYEVDDLRDAFRMLGF
(underline: nuclear localization signal; double underline: nuclear export signal)

[0063] Dog AID:

(SEQ ID NO: 8)
MDSLLMKQRKFLYHFKNVRWAKGRHETYLCYVVKRRDSATSFSLDFGHLR

NKSGCHVELLFLRYISDWDLDPGRCYRVTWFTSWSPCYDCARHVADFLRG

YPNLSLRIFAARLYFCEDRKAEPEGLRRLHRAGVQIAIMTFKDYFYCWNT

FVENREKTFKAWEGLHENSVRLSRQLRRILLPLYEVDDLRDAFRTLGL
(underline: nuclear localization signal; double underline: nuclear export signal)

[0064] Bovine AID:

(SEQ ID NO: 9)
MDSLLKKQRQFLYQFKNVRWAKGRHETYLCYVVKRRDSPTSFSLDFGHLR

NKAGCHVELLFLRYISDWDLDPGRCYRVTWFTSWSPCYDCARHVADFLRG

YPNLSLRIFTARLYFCDKERKAEPEGLRRLHRAGVQIAIMTFKDYFYCWN

TFVENHERTFKAWEGLHENSVRLSRQLRRILLPLYEVDDLRDAFRTLGL
(underline: nuclear localization signal; double underline: nuclear export signal)

[0065] Mouse APOBEC-3:

(SEQ ID NO: 10)
MGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLGYAKGRKDTFLCYEVTR

KDCDSPVSLHHGVFKNKDNI*HAEICFLYWFHDKVLKVLSPREEFKITWYM*

*SWSPCFEC*AEQIVRFLATHHNLSLDIFSSRLYNVQDPETQQNLCRLVQEG

-continued

AQVAAMDLYEFKKCWKKFVDNGGRRFRPWKRLLTNFRYQDSKLQEILRPC

YIPVPSSSSSTLSNICLTKGLPETRFCVEGRRMDPLSEEEFYSQFYNQRV

KHLCYYHRMKPYLCYQLEQFNGQAPLKGCLLSEKGKQ*HAEILFLDKIRSM*

*ELSQVTITCYLTWSPCPNC*AWQLAAFKRDRPDLILHIYTSRLYFHWKRPF

QKGLCSLWQSGILVDVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQ

RRLRRIKESWGLQDLVNDFGNLQLGPPMS
(italic: nucleic acid editing domain)

[0066] Rat APOBEC-3:

(SEQ ID NO: 11)
MGPFCLGCSHRKCYSPIRNLISQETFKFHFKNLRYAIDRKDTFLCYEVTR

KDCDSPVSLHHGVFKNKDNI*HAEICFLYWFHDKVLKVLSPREEFKITWYM*

*SWSPCFEC*AEQVLRFLATHHNLSLDIFSSRLYNIRDPENQQNLCRLVQEG

AQVAAMDLYEFKKCWKKFVDNGGRRFRPWKKLLTNFRYQDSKLQEILRPC

YIPVPSSSSSTLSNICLTKGLPETRFCVERRRVHLLSEEEFYSQFYNQRV

KHLCYYHGVKPYLCYQLEQFNGQAPLKGCLLSEKGKQ*HAEILFLDKIRSM*

*ELSQVIITCYLTWSPCPNC*AWQLAAFKRDRPDLILHIYTSRLYFHWKRPF

QKGLCSLWQSGILVDVMDLPQFTDCWTNFVNPKRPFWPWKGLEIISRRTQ

RRLHRIKESWGLQDLVNDFGNLQLGPPMS
(italic: nucleic acid editing domain)

[0067] Rhesus Macaque APOBEC-3G:

(SEQ ID NO: 12)
MVEPMDPRTFVSNFNNRPILSGLNTVWLCCEVKTKDPSGPPLDAKIFQGK

VYSKAKY*HPEMRFLRWFHKWRQLHHDQEYKVTWYVSWSPCTRC*ANSVATF

LAKDPKVTLTIFVARLYYFWKPDYQQALRILCQKRGGPHATMKIMNYNEF

QDCWNKFVDGRGKPFKPRNNLPKHYTLLQATLGELLRHLMDPGTFTSNFN

NKPWVSGQHETYLCYKVERLHNDTWVPLNQHRGFLRNQAPNIHGFPKGR*H*

*AELCFLDLIPFWKLDGQQYRVTCFTSWSPCFSC*AQEMAKFISNNEHVSLC

IFAARIYDDQGRYQEGLRALHRDGAKIAMMNYSEFEYCWDTFVDRQGRPF

QPWDGLDEHSQALSGRLRAI
(italic: nucleic acid editing domain; underline: cytoplasmic localization signal)

[0068] Chimpanzee APOBEC-3G:

(SEQ ID NO: 13)
MKPHFRNPVERMYQDTFSDNFYNRPILSHRNTVWLCYEVKTKGPSRPPLD

AKIFRGQVYSKLKY*HPEMRFFHWFSKWRKLHRDQEYEVTWYISWSPCTKC*

TRDVATFLAEDPKVTLTIFVARLYYFWDPDYQEALRSLCQKRDGPRATMK

IMNYDEFQHCWSKFVYSQRELFEPWNNLPKYYILLHIMLGEILRHSMDPP

TFTSNFNNELWVRGRHETYLCYEVERLHNDTWVLLNQRRGFLCNQAPHKH

-continued

GFLEGR*HAELCFLDVIPFWKLDLHQDYRVTCFTSWSPCFSC*AQEMAKFIS

NNKHVSLCIFAARIYDDQGRCQEGLRTLAKAGAKISIMTYSEFKHCWDTF

VDHQGCPFQPWDGLEEHSQALSGRLRAILQNQGN
(italic: nucleic acid editing domain; underline: cytoplasmic localization signal)

[0069] Green Monkey APOBEC-3G:

(SEQ ID NO: 14)
MNPQIRNMVEQMEPDIFVYYFNNRPILSGRNTVWLCYEVKTKDPSGPPLD

ANIFQGKLYPEAKD*HPEMKFLHWFRKWRQLHRDQEYEVTWYVSWSPCTRC*

ANSVATFLAEDPKVTLTIFVARLYYFWKPDYQQALRILCQERGGPHATMK

IMNYNEFQHCWNEFVDGQGKPFKPRKNLPKHYTLLHATLGELLRHVMDPG

TFTSNFNNKPWVSGQRETYLCYKVERSHNDTWVLLNQHRGFLRNQAPDRH

GFPKGR*HAELCFLDLIPFWKLDDQQYRVTCFTSWSPCFSC*AQKMAKFISN

NKHVSLCIFAARIYDDQGRCQEGLRTLHRDGAKIAVMNYSEFEYCWDTFV

DRQGRPFQPWDGLDEHSQALSGRLRAI
(italic: nucleic acid editing domain; underline: cytoplasmic localization signal)

[0070] Human APOBEC-3G:

(SEQ ID NO: 15)
MKPHFRNTVERMYRDTFSYNFYNRPILSRRNTVWLCYEVKTKGPSRPPLD

AKIFRGQVYSELKY*HPEMRFFHWFSKWRKLHRDQEYEVTWYISWSPCTKC*

TRDMATFLAEDPKVTLTIFVARLYYFWDPDYQEALRSLCQKRDGPRATMK

IMNYDEFQHCWSKFVYSQRELFEPWNNLPKYYILLHIMLGEILRHSMDPP

TFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVLLNQRRGFLCNQAPHKH

GFLEGR*HAELCFLDVIPFWKLDLDQDYRVTCFTSWSPCFSC*AQEMAKFIS

KNKHVSLCIFTARIYDDQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTF

VDHQGCPFQPWDGLDEHSQDLSGRLRAILQNQEN
(italic: nucleic acid editing domain; underline: cytoplasmic localization signal)

[0071] Human APOBEC-3F:

(SEQ ID NO: 16)
MKPHFRNTVERMYRDTFSYNFYNRPILSRRNTVWLCYEVKTKGPSRPRLD

AKIFRGQVYSQPEH*HAEMCFLSWFCGNQLPAYKCFQITWFVSWTPCPDC*V

AKLAEFLAEHPNVTLTISAARLYYYWERDYRRALCRLSQAGARVKIMDDE

EFAYCWENFVYSEGQPFMPWYKFDDNYAFLHRTLKEILRNPMEAMYPHIF

YFHFKNLRKAYGRNESWLCFTMEVVKHHSPVSWKRGVFRNQVDPETH*CHA*

*ERCFLSWFCDDILSPNTNYEVTWYTSWSPCPEC*AGEVAEFLARHSNVNLT

IFTARLYYFWDTDYQEGLRSLSQEGASVEIMGYKDFKYCWENFVYNDDEP

FKPWKGLKYNFLFLDSKLQEILE
(italic: nucleic acid editing domain)

[0072] Human APOBEC-3B:

(SEQ ID NO: 17)
MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLCYEVKIKRGRSNLLW

DTGVFRGQVYFKPQY*HAEMCFLSWFCGNQLPAYKCFQITWFVSWTPCPDC*

VAKLAEFLSEHPNVTLTISAARLYYYWERDYRRALCRLSQAGARVTIMDY

EEFAYCWENFVYNEGQQFMPWYKFDENYAFLHRTLKEILRYLMDPDTFTF

NFNNDPLVLRRRQTYLCYEVERLDNGTWVLMDQHMGFLCNEAKNLLCGFY

*GRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGC*AGEVRAFLQENT

HVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMTYDEFEYCWDTFVYR

QGCPFQPWDGLEEHSQALSGRLRAILQNQGN
(italic: nucleic acid editing domain)

[0073] Human APOBEC-3C:

(SEQ ID NO: 18)
MNPQIRNPMKAMYPGTFYFQFKNLWEANDRNETWLCFTVEGIKRRSVVSW

KTGVFRNQVDSETH*CHAERCFLSWFCDDILSPNTKYQVTWYTSWSPCPDC*

AGEVAEFLARHSNVNLTIFTARLYYFQYPCYQEGLRSLSQEGVAVEIMDY

EDFKYCWENFVYNDNEPFKPWKGLKTNFRLLKRRLRESLQ
(italic: nucleic acid editing domain)

[0074] Human APOBEC-3A:

(SEQ ID NO: 19)
MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVERLDNGTSVKMDQ

HRGFLHNQAKNLLCGFYGR*HAELRFLDLVPSLQLDPAQIYRVTWFISWSP*

*CFSWGC*AGEVRAFLQENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQV

SIMTYDEFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLRAILQNQGN
(italic: nucleic acid editing domain)

[0075] Human APOBEC-3H:

(SEQ ID NO: 20)
MALLTAETFRLQFNNKRRLRRPYYPRKALLCYQLTPQNGSTPTRGYFENK

KK*CHAEICFINEIKSMGLDETQCYQVTCYLTWSPCSSC*AWELVDFIKAHD

HLNLGIFASRLYYHWCKPQQKGLRLLCGSQVPVEVMGFPKFADCWENFVD

HEKPLSFNPYKMLEELDKNSRAIKRRLERIKIPGVRAQGRYMDILCDAEV
(italic: nucleic acid editing domain)

[0076] Human APOBEC-3D:

(SEQ ID NO: 21)
MNPQIRNPMERMYRDTFYDNFENEPILYGRSYTWLCYEVKIKRGRSNLLW

DTGVFRGPVLPKRQSNHRQEVYFRFEN*HAEMCFLSWFCGNRLPANRRFQI*

*TWFVSWNPCLPC*VVKVTKFLAEHPNVTLTISAARLYYYRDRDWRWVLLRL

HKAGARVKIMDYEDFAYCWENFVCNEGQPFMPWYKFDDNYASLHRTLKEI

LRNPMEAMYPHIFYFHFKNLLKACGRNESWLCFTMEVTKHHSAVFRKRGV

FRNQVDPETH*CHAERCFLSWFCDDILSPNTNYEVTWYTSWSPCPEC*AGEV

-continued

AEFLARHSNVNLTIFTARLCYFWDTDYQEGLCSLSQEGASVKIMGYKDFV

SCWKNFVYSDDEPFKPWKGLQTNFRLLKRRLREILQ

(italic: nucleic acid editing domain)

[0077] Human APOBEC-1:

(SEQ ID NO: 22)

MTSEKGPSTGDPTLRRRIEPWEFDVFYDPRELRKEACLLYEIKWGMSRKI

WRSSGKNTTNHVEVNFIKKFTSERDFHPSMSCSITWFLSWSPCWECSQAI

REFLSRHPGVTLVIYVARLFWHMDQQNRQGLRDLVNSGVTIQIMRASEYY

HCWRNFVNYPPGDEAHWPQYPPLWMMLYALELHCIILSLPPCLKISRRWQ

NHLTFFRLHLQNCHYQTIPPHILLATGLIHPSVAWR

[0078] Mouse APOBEC-1:

(SEQ ID NO: 23)

MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSV

WRHTSQNTSNHVEVNFLEKFTTERYFRPNTRCSITWFLSWSPCGECSRAI

TEFLSRHPYVTLFIYIARLYHHTDQRNRQGLRDLISSGVTIQIMTEQEYC

YCWRNFVNYPPSNEAYWPRYPHLWVKLYVLELYCIILGLPPCLKILRRKQ

PQLTFFTITLQTCHYQRIPPHLLWATGLK

[0079] Rat APOBEC-1:

(SEQ ID NO: 24)

MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSI

WRHTSQNTNKHVEVNFIEKFTTERYFCPNTRCSITWFLSWSPCGECSRAI

TEFLSRYPHVTLFIYIARLYHHADPRNRQGLRDLISSGVTIQIMTEQESG

YCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCIILGLPPCLNILRRKQ

PQLTFFTIALQSCHYQRLPPHILWATGLK

[0080] Human ADAT-2:

(SEQ ID NO: 25)

MEAKAAPKPAASGACSVSAEETEKWMEEAMHMAKEALENTEVPVGCLMVY

NNEVVGKGRNEVNQTKNATRHAEMVAIDQVLDWCRQSGKSPSEVFEHTVL

YVTVEPCIMCAAALRLMKIPLVVYGCQNERFGGCGSVLNIASADLPNTGR

PFQCIPGYRAEEAVEMLKTFYKQENPNAPKSKVRKKECQKS

[0081] Mouse ADAT-2:

(SEQ ID NO: 26)

MEEKVESTTTPDGPCVVSVQETEKWMEEAMRMAKEALENIEVPVGCLMVY

NNEVVGKGRNEVNQTKNATRHAEMVAIDQVLDWCHQHGQSPSTVFEHTVL

YVTVEPCIMCAAALRLMKIPLVVYGCQNERFGGCGSVLNIASADLPNTGR

PFQCIPGYRAEEAVELLKTFYKQENPNAPKSKVRKKDCQKS

[0082] Mouse ADAT-1:

(SEQ ID NO: 27)

MWTADEIAQLCYAHYNVRLPKQGKPEPNREWTLLAAVVKIQASANQACDI

PEKEVQVTKEVV*SMGTGTKCIGQSKMRESGDILNDSHAEIIARRSFQRYL*

LHQLHLAAVLKEDSIFVPGTQRGLWRLRPDLSFVFFSSHTPCGDASIIPM

LEFEEQPCCPVIRSWANNSPVQETENLEDSKDKRNCEDPASPVAKKMRLG

TPARSLSNCVAHHGTQESGPVKPDVSSSDLTKEEPDAANGIASGSFRVVD

VYRTGAKCVPGETGDLREPGAAYHQVGLLRVKPGRGDRTCSMSCSDKMAR

WNVLGCQGALLMHFLEKPIYLSAVVIGKCPYSQEAMRRALTGRCEETLVL

PRGFGVQELEIQQSGLLFEQSRCAVHRKRGDSPGRLVPCGAAISWSAVPQ

QPLDVTANGFPQGTTKKEIGSPRARSRISKVELFRSFQKLLSSIADDEQP

DSIRVTKKLDTYQEYKDAASAYQEAWGALRRIQPFASWIRNPPDYHQFK
(italic: nucleic acid editing domain)

[0083] Human ADAT-1:

(SEQ ID NO: 28)

MWTADEIAQLCYEHYGIRLPKKGKPEPNHEWTLLAAVVKIQSPADKACDT

PDKPVQVTKEVV*SMGTGTKCIGQSKMRKNGDILNDSHAEVIARRSFQRYL*

LHQLQLAATLKEDSIFVPGTQKGVWKLRRDLIFVFFSSHTPCGDASIIPM

LEFEDQPCCPVFRNWAHNSSVEASSNLEAPGNERKCEDPDSPVTKKMRLE

PGTAAREVTNGAAHHQSFGKQKSGPISPGIHSCDLTVEGLATVTRIAPGS

AKVIDVYRTGAKCVPGEAGDSGKPGAAFHQVGLLRVKPGRGDRTRSMSCS

DKMARWNVLGCQGALLMHLLEEPIYLSAVVIGKCPYSQEAMQRALIGRCQ

NVSALPKGFGVQELKILQSDLLFEQSRSAVQAKRADSPGRLVPCGAAISW

SAVPEQPLDVTANGFPQGTTKKTIGSLQARSQISKVELFRSFQKLLSRIA

RDKWPHSLRVQKLDTYQEYKEAASSYQEAWSTLRKQVFGSWIRNPPDYHQ

FK
(italic: nucleic acid editing domain)

[0084] In some embodiments, fusion proteins as provided herein comprise the full-length amino acid of a nucleic acid-editing enzyme, e.g., one of the sequences provided above. In other embodiments, however, fusion proteins as provided herein do not comprise a full-length sequence of a nucleic acid-editing enzyme, but only a fragment thereof. For example, in some embodiments, a fusion protein provided herein comprises a Cas9 domain and a fragment of a nucleic acid-editing enzyme, e.g., wherein the fragment comprises a nucleic acid-editing domain. Exemplary amino acid sequences of nucleic acid-editing domains are shown in the sequences above as italicized letters, and additional suitable sequences of such domains will be apparent to those of skill in the art.

[0085] Additional suitable nucleic-acid editing enzyme sequences, e.g., deaminase enzyme and domain sequences, that can be used according to aspects of this invention, e.g., that can be fused to a nuclease-inactive Cas9 domain, will be apparent to those of skill in the art based on this disclosure. In some embodiments, such additional enzyme sequences include deaminase enzyme or deaminase domain sequences that are 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%, or at least 99% similar to the sequences provided herein. Additional suitable Cas9 domains, variants, and sequences will also be apparent to those of skill in the art. Examples of such additional suitable Cas9 domains include, but are not limited to, D10A, D10A/D839A/H840A, and D10A/D839A/H840A/N863A mutant domains (See, e.g., Prashant et al., CAS9 transcriptional activators for target specificity screening and paired nickases for cooperative genome engineering. Nature Biotechnology. 2013; 31(9): 833-838 the entire contents of which are incorporated herein by reference).

[0086] Additional suitable strategies for generating fusion proteins comprising a Cas9 domain and a deaminase domain will be apparent to those of skill in the art based on this disclosure in combination with the general knowledge in the art. Suitable strategies for generating fusion proteins according to aspects of this disclosure using linkers or without the use of linkers will also be apparent to those of skill in the art in view of the instant disclosure and the knowledge in the art. For example, Gilbert et al., CRISPR-mediated modular RNA-guided regulation of transcription in eukaryotes. *Cell.* 2013; 154(2):442-51, showed that C-terminal fusions of Cas9 with VP64 using 2 NLS's as a linker (SPKKKRK-VEAS, SEQ ID NO: 29), can be employed for transcriptional activation. Mali et al., CAS9 transcriptional activators for target specificity screening and paired nickases for cooperative genome engineering. *Nat Biotechnol.* 2013; 31(9):833-8, reported that C-terminal fusions with VP64 without linker can be employed for transcriptional activation. And Maeder et al., CRISPR RNA-guided activation of endogenous human genes. *Nat Methods.* 2013; 10: 977-979, reported that C-terminal fusions with VP64 using a Gly_4Ser (SEQ ID NO: 91) linker can be used as transcriptional activators. Recently, dCas9-FokI nuclease fusions have successfully been generated and exhibit improved enzymatic specificity as compared to the parental Cas9 enzyme (In Guilinger J P, Thompson D B, Liu D R. Fusion of catalytically inactive Cas9 to FokI nuclease improves the specificity of genome modification. *Nat. Biotechnol.* 2014; 32(6): 577-82, and in Tsai S Q, Wyvekens N, Khayter C, Foden J A, Thapar V, Reyon D, Goodwin M J, Aryee M J, Joung J K. Dimeric CRISPR RNA-guided FokI nucleases for highly specific genome editing. *Nat Biotechnol.* 2014; 32(6):569-76. PMID: 24770325 a SGSETPGTSESATPES (SEQ ID NO: 93) or a GGGGS (SEQ ID NO: 91) linker was used in FokI-dCas9 fusion proteins, respectively).

Use of Cas9 DNA Editing Fusion Proteins for Correcting Disease-Associated Mutations

[0087] Some embodiments provide methods for using the Cas9 DNA editing fusion proteins provided herein. In some embodiments, the fusion protein is used to introduce a point mutation into a nucleic acid by deaminating a target nucleobase, e.g., a C residue. In some embodiments, the deamination of the target nucleobase results in the correction of a genetic defect, e.g., in the correction of a point mutation that leads to a loss of function in a gene product. In some embodiments, the genetic defect is associated with a disease or disorder, e.g., a lysosomal storage disorder or a metabolic disease, such as, for example, type I diabetes. In some embodiments, the methods provided herein are used to introduce a deactivating point mutation into a gene or allele that encodes a gene product that is associated with a disease or disorder. For example, in some embodiments, methods are provided herein that employ a Cas9 DNA editing fusion protein to introduce a deactivating point mutation into an oncogene (e.g., in the treatment of a proliferative disease). A deactivating mutation may, in some embodiments, generate a premature stop codon in a coding sequence, which results in the expression of a truncated gene product, e.g., a truncated protein lacking the function of the full-length protein.

[0088] In some embodiments, the purpose of the methods provide herein is to restore the function of a dysfunctional gene via genome editing. The Cas9 deaminase fusion proteins provided herein can be validated for gene editing-based human therapeutics in vitro, e.g., by correcting a disease-associated mutation in human cell culture. It will be understood by the skilled artisan that the fusion proteins provided herein, e.g., the fusion proteins comprising a Cas9 domain and a nucleic acid deaminase domain can be used to correct any single point T->C or A->G mutation. In the first case, deamination of the mutant C back to U corrects the mutation, and in the latter case, deamination of the C that is base-paired with the mutant G, followed by a round of replication, corrects the mutation.

[0089] An exemplary disease-relevant mutation that can be corrected by the provided fusion proteins in vitro or in vivo is the H1047R (A3140G) polymorphism in the PI3KCA protein. The phosphoinositide-3-kinase, catalytic alpha subunit (PI3KCA) protein acts to phosphorylate the 3-OH group of the inositol ring of phosphatidylinositol. The PI3KCA gene has been found to be mutated in many different carcinomas, and thus it is considered to be a potent oncogene.[50] In fact, the A3140G mutation is present in several NCI-60 cancer cell lines, such as, for example, the HCT116, SKOV3, and T47D cell lines, which are readily available from the American Type Culture Collection (ATCC).[51]

[0090] In some embodiments, a cell carrying a mutation to be corrected, e.g., a cell carrying a point mutation, e.g., an A3140G point mutation in exon 20 of the PI3KCA gene, resulting in a H1047R substitution in the PI3KCA protein, is contacted with an expression construct encoding a Cas9 deaminase fusion protein and an appropriately designed sgRNA targeting the fusion protein to the respective mutation site in the encoding PI3KCA gene. Control experiments can be performed where the sgRNAs are designed to target the fusion enzymes to non-C residues that are within the PI3KCA gene. Genomic DNA of the treated cells can be extracted, and the relevant sequence of the PI3KCA genes PCR amplified and sequenced to assess the activities of the fusion proteins in human cell culture.

[0091] It will be understood that the example of correcting point mutations in PI3KCA is provided for illustration purposes and is not meant to limit the instant disclosure. The skilled artisan will understand that the instantly disclosed DNA-editing fusion proteins can be used to correct other point mutations and mutations associated with other cancers and with diseases other than cancer including other proliferative diseases.

[0092] The successful correction of point mutations in disease-associated genes and alleles opens up new strategies for gene correction with applications in therapeutics and basic research. Site-specific single-base modification systems like the disclosed fusions of Cas9 and deaminase enzymes or domains also have applications in "reverse" gene therapy, where certain gene functions are purposely

suppressed or abolished. In these cases, site-specifically mutating Trp (TGG), Gln (CAA and CAG), or Arg (CGA) residues to premature stop codons (TAA, TAG, TGA) can be used to abolish protein function in vitro, ex vivo, or in vivo.

[0093] The instant disclosure provides methods for the treatment of a subject diagnosed with a disease associated with or caused by a point mutation that can be corrected by a Cas9 DNA editing fusion protein provided herein. For example, in some embodiments, a method is provided that comprises administering to a subject having such a disease, e.g., a cancer associated with a PI3KCA point mutation as described above, an effective amount of a Cas9 deaminase fusion protein that corrects the point mutation or introduces a deactivating mutation into the disease-associated gene. In some embodiments, the disease is a proliferative disease. In some embodiments, the disease is a genetic disease. In some embodiments, the disease is a neoplastic disease. In some embodiments, the disease is a metabolic disease. In some embodiments, the disease is a lysosomal storage disease. Other diseases that can be treated by correcting a point mutation or introducing a deactivating mutation into a disease-associated gene will be known to those of skill in the art, and the disclosure is not limited in this respect.

[0094] The instant disclosure provides methods for the treatment of additional diseases or disorders, e.g., diseases or disorders that are associated or caused by a point mutation that can be corrected by deaminase-mediated gene editing. Some such diseases are described herein, and additional suitable diseases that can be treated with the strategies and fusion proteins provided herein will be apparent to those of skill in the art based on the instant disclosure. Exemplary suitable diseases and disorders are listed below. It will be understood that the numbering of the specific positions or residues in the respective sequences depends on the particular protein and numbering scheme used. Numbering might be different, e.g., in precursors of a mature protein and the mature protein itself, and differences in sequences from species to species may affect numbering. One of skill in the art will be able to identify the respective residue in any homologous protein and in the respective encoding nucleic acid by methods well known in the art, e.g., by sequence alignment and determination of homologous residues. Exemplary suitable diseases and disorders include, without limitation, cystic fibrosis (see, e.g., Schwank et al., Functional repair of CFTR by CRISPR/Cas9 in intestinal stem cell organoids of cystic fibrosis patients. *Cell stem cell.* 2013; 13: 653-658; and Wu et. al., Correction of a genetic disease in mouse via use of CRISPR-Cas9. *Cell stem cell.* 2013; 13: 659-662, neither of which uses a deaminase fusion protein to correct the genetic defect); phenylketonuria—e.g., phenylalanine to serine mutation at position 835 (mouse) or 240 (human) or a homologous residue in phenylalanine hydroxylase gene (T>C mutation)—see, e.g., McDonald et al., *Genomics.* 1997; 39:402-405; Bernard-Soulier syndrome (BSS)—e.g., phenylalanine to serine mutation at position 55 or a homologous residue, or cysteine to arginine at residue 24 or a homologous residue in the platelet membrane glycoprotein IX (T>C mutation)—see, e.g., Noris et al., *British Journal of Haematology.* 1997; 97: 312-320, and Ali et al., *Hematol.* 2014; 93: 381-384; epidermolytic hyperkeratosis (EHK)—e.g., leucine to proline mutation at position 160 or 161 (if counting the initiator methionine) or a homologous residue in keratin 1 (T>C mutation)—see, e.g., Chipev et al., *Cell.* 1992; 70: 821-828, see also accession number P04264 in the UNIPROT database at www[dot]uniprot[dot]org; chronic obstructive pulmonary disease (COPD)—e.g., leucine to proline mutation at position 54 or 55 (if counting the initiator methionine) or a homologous residue in the processed form of α_1-antitrypsin or residue 78 in the unprocessed form or a homologous residue (T>C mutation)—see, e.g., Poller et al., *Genomics.* 1993; 17: 740-743, see also accession number P01011 in the UNIPROT database; Charcot-Marie-Toot disease type 4J—e.g., isoleucine to threonine mutation at position 41 or a homologous residue in FIG. **4** (T>C mutation)—see, e.g., Lenk et al., PLoS Genetics. 2011; 7: e1002104; neuroblastoma (NB)—e.g., leucine to proline mutation at position 197 or a homologous residue in Caspase-9 (T>C mutation)—see, e.g., Kundu et al., 3 *Biotech.* 2013, 3:225-234; von Willebrand disease (vWD)—e.g., cysteine to arginine mutation at position 509 or a homologous residue in the processed form of von Willebrand factor, or at position 1272 or a homologous residue in the unprocessed form of von Willebrand factor (T>C mutation)—see, e.g., Lavergne et al., *Br. J. Haematol.* 1992, see also accession number P04275 in the UNIPROT database; 82: 66-72; myotonia congenital—e.g., cysteine to arginine mutation at position 277 or a homologous residue in the muscle chloride channel gene CLCN1 (T>C mutation)—see, e.g., Weinberger et al., *The J. of Physiology.* 2012; 590: 3449-3464; hereditary renal amyloidosis—e.g., stop codon to arginine mutation at position 78 or a homologous residue in the processed form of apolipoprotein AII or at position 101 or a homologous residue in the unprocessed form (T>C mutation)—see, e.g., Yazaki et al., *Kidney Int.* 2003; 64: 11-16; dilated cardiomyopathy (DCM)—e.g., tryptophan to Arginine mutation at position 148 or a homologous residue in the FOXD4 gene (T>C mutation), see, e.g., Minoretti et. al., *Int. J. of Mol. Med.* 2007; 19: 369-372; hereditary lymphedema—e.g., histidine to arginine mutation at position 1035 or a homologous residue in VEGFR3 tyrosine kinase (A>G mutation), see, e.g., Irrthum et al., *Am. J. Hum. Genet.* 2000; 67: 295-301; familial Alzheimer's disease—e.g., isoleucine to valine mutation at position 143 or a homologous residue in presenilin1 (A>G mutation), see, e.g., Gallo et. al., *J. Alzheimer's disease.* 2011; 25: 425-431; Prion disease—e.g., methionine to valine mutation at position 129 or a homologous residue in prion protein (A>G mutation)—see, e.g., Lewis et. al., *J. of General Virology.* 2006; 87: 2443-2449; chronic infantile neurologic cutaneous articular syndrome (CINCA)—e.g., Tyrosine to Cysteine mutation at position 570 or a homologous residue in cryopyrin (A>G mutation)—see, e.g., Fujisawa et. al. *Blood.* 2007; 109: 2903-2911; and desmin-related myopathy (DRM)—e.g., arginine to glycine mutation at position 120 or a homologous residue in αB crystallin (A>G mutation)—see, e.g., Kumar et al., *J. Biol. Chem.* 1999; 274: 24137-24141. The entire contents of all references and database entries is incorporated herein by reference.

[0095] It will be apparent to those of skill in the art that in order to target a Cas9:nucleic acid-editing enzyme/domain fusion protein as disclosed herein to a target site, e.g., a site comprising a point mutation to be edited, it is typically necessary to co-express the Cas9:nucleic acid-editing enzyme/domain fusion protein together with a guide RNA, e.g., an sgRNA. As explained in more detail elsewhere herein, a guide RNA typically comprises a tracrRNA framework allowing for Cas9 binding, and a guide sequence,

which confers sequence specificity to the Cas9:nucleic acid-editing enzyme/domain fusion protein. In some embodiments, the guide RNA comprises a structure 5'-[guide sequence]-guuuuagagcuagaaauagcaaguuaaaauaaaggcuagucc-cguuaucaacuugaaaaaguggcaccgagucggugcuu uuu-3' (SEQ ID NO: 38), wherein the guide sequence comprises a sequence that is complementary to the target sequence. The guide sequence is typically 20 nucleotides long. The sequences of suitable guide RNAs for targeting Cas9:nucleic acid-editing enzyme/domain fusion proteins to specific genomic target sites will be apparent to those of skill in the art based on the instant disclosure. 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. Some exemplary guide RNA sequences suitable for targeting Cas9:nucleic acid-editing enzyme/domain fusion proteins to specific target sequences are provided below.

[0096] H1047R (A3140G) polymorphism in the phosphoinositide-3-kinase catalytic alpha subunit (PI3KCA or PIK3CA) (the position of the mutated nucleotide and the respective codon are underlined):

```
gatgacattgcatacattcgaaagaccctagccttagataaaactgagca
 D  D  I  A  Y  I  R  K  T  L  A  L  D  K  T  E  Q

agaggctttggagtatttcatgaaacaaatgaatgatgcacgtcatggtg
  E  A  L  E  Y  F  M  K  Q  M  N  D  A  R  H  G

gctggacaacaaaaatggattggatcttccacacaattaaacagcatgca
G  W  T  T  K  M  D  W  I  F  H  T  I  K  Q  H  A

ttgaactgaaagataactgagaaaatgaaa
 L  N  -  K  I  T  E  K  M  K
(Nucleotide sequence - SEQ ID NO: 39; protein
sequence - SEQ ID NO: 40).
```

[0097] Exemplary suitable guide sequences for targeting a Cas9:nucleic acid-editing enzyme/domain fusion proteins to the mutant A3140G residue include, without limitation: 5'-aucggaauctauuuugacuc-3' (SEQ ID NO: 41); 5'-ucg-gaaucuauuuugacucg-3' (SEQ ID NO: 42); 5'-cuua-gauaaaacugagcaag-3' (SEQ ID NO: 43); 5'-aucuauuuuga-cucguucuc-3' (SEQ ID NO: 44); 5'-uaaaacugagcaagaggcuu-3' (SEQ ID NO: 45); 5'-ugguggcuggacaacaaaaa-3' (SEQ ID NO: 46); 5'-gcuggacaacaaaaauggau-3' (SEQ ID NO: 47); 5'-guguuaauuugucguacgua-3' (SEQ ID NO: 48). Additional suitable guide sequences for targeting a Cas9:nucleic acid-editing enzyme/domain fusion protein to a mutant PI3KCA sequence, to any of the additional sequences provided below, or to additional mutant sequences associated with a disease will be apparent to those of skill in the art based on the instant disclosure.

[0098] Phenylketonuria phenylalanine to serine mutation at residue 240 in phenylalanine hydroxylase gene (T>C mutation) (the position of the mutated nucleotide and the respective codon are underlined):

```
aatcacatttttccacttcttgaaaagtactgtggcttccatgaagataa
 N  H  I  F  P  L  L  E  K  Y  C  G  F  H  E  D  N

cattccccagctggaagacgtttctcaattcctgcagacttgcactggtc
  I  P  Q  L  E  D  V  S  Q  F  L  Q  T  C  T  G

tccgcctccgacctgtggctggcctgctttcctctcgggatttcttgggt
S  R  L  R  P  V  A  G  L  L  S  S  R  D  F  L  G
```

-continued

```
ggcctggccttccgagtcttccactgcaca
 G  L  A  F  R  V  F  H  C  T
(Nucleotide sequence - SEQ ID NO: 49; protein
sequence - SEQ ID NO: 50).
```

[0099] Bernard-Soulier syndrome (BSS)—cysteine to arginine at residue 24 in the platelet membrane glycoprotein IX (T>C mutation):

```
atgcctgcctggggagccctgttcctgctctgggccacagcagaggccac
 M  P  A  W  G  A  L  F  L  L  W  A  T  A  E  A  T

caaggactgccccagcccacggtacctgccgcgccctggaaaccatggggc
  K  D  C  P  S  P  R  T  C  R  A  L  E  T  M  G

tgtgggtggactgcaggggccacggactcacggccctgcctgccctgccg
L  W  V  D  C  R  G  H  G  L  T  A  L  P  A  L  P

gcccgcacccgccaccttctgctggccaac
 A  R  T  R  H  L  L  L  A  N
(Nucleotide sequence - SEQ ID NO: 51; protein
sequence - SEQ ID NO: 52).
```

[0100] Epidermolytic hyperkeratosis (EHK)—leucine to proline mutation at residue 161 in keratin 1 (T>C mutation):

```
ggttatggtcctgtctgccctcctggtggcatacaagaagtcactatcaa
 G  Y  G  P  V  C  P  P  G  G  I  Q  E  V  T  I  N

ccagagccctcttcagcccctcaatgtggagattgaccctgagatccaaa
  Q  S  P  L  Q  P  L  N  V  E  I  D  P  E  I  Q

aggtgaagtctcgagaaagg
K  V  K  S  R  E  R
(Nucleotide sequence - SEQ ID NO: 53; protein
sequence - SEQ ID NO: 54).
```

[0101] Chronic obstructive pulmonary disease (COPD)—leucine to proline mutation at residue 54 in α_1-antitrypsin (T>C mutation):

```
gtctccctggctgaggatccccagggagatgctgcccagaagacagatac
 V  S  L  A  E  D  P  Q  G  D  A  A  Q  K  T  D  T

atcccaccatgatcaggatcacccaaccttcaacaagatcacccccaacc
  S  H  H  D  Q  D  H  P  T  F  N  K  I  T  P  N

cggctgagttcgccttcagcctataccgccagctggcacaccagtccaac
P  A  E  F  A  F  S  L  Y  R  Q  L  A  H  Q  S  N

agcaccaatatcttcttctccccagtgagc
 S  T  N  I  F  F  S  P  V  S
(Nucleotide sequence - SEQ ID NO: 55; protein
sequence - SEQ ID NO: 56).
```

[0102] Chronic obstructive pulmonary disease (COPD)—leucine to proline mutation at residue 78 in α_1-antichymotrypsin (T>C mutation):

```
gcctccgccaacgtggacttcgctttcagcctgtacaagcagttagtcct
 A  S  A  N  V  D  F  A  F  S  L  Y  K  Q  L  V  L

gaaggcccctgataagaatgtcatcttctccccaccgagcatctccaccg
  K  A  P  D  K  N  V  I  F  S  P  P  S  I  S  T
```

-continued

```
ccttggccttcctgtctctgggggcccataataccaccctgacagagatt
A  L  A  F  L  S  L  G  A  H  N  T  T  L  T  E  I

ctcaaaggcctcaagttctacctcacggag
 L  K  G  L  K  F  Y  L  T  E
```

(Nucleotide sequence - SEQ ID NO: 89; protein sequence - SEQ ID NO: 90).

[0103] Neuroblastoma (NB)—leucine to proline mutation at residue 197 in Caspase-9 (T>C mutation):

```
ggccactgcctcattatcaacaatgtgaacttctgccgtgagtccgggct
 G  H  C  L  I  I  N  N  V  N  F  C  R  E  S  G  L

ccgcacccgcactggctccaacatcgactgtgagaagttgcggcgtcgct
  R  T  R  T  G  S  N  I  D  C  E  K  L  R  R  R

tctcctcgccgcatttcatggtggaggtgaagggcgacctgactgccaag
F  S  S  P  H  F  M  V  E  V  K  G  D  L  T  A  K

aaaatggtgctggctttgctggagctggcg
 K  M  V  L  A  L  L  E  L  A
```

(Nucleotide sequence - SEQ ID NO: 57; protein sequence - SEQ ID NO: 58).

[0104] Charcot-Marie-Tooth disease type 4J—isoleucine to threonine mutation at residue 41 in FIG. **4** (T>C mutation):

```
actagagctagatactttctagttgggagcaataatgcagaaacgaaata
 T  R  A  R  Y  F  L  V  G  S  N  N  A  E  T  K  Y

tcgtgtcttgaagactgatagaacagaaccaaaagatttggtcataattg
  R  V  L  K  T  D  R  T  E  P  K  D  L  V  I  I

atgacaggcatgtctatactcaacaagaagtaagggaacttcttggccgc
D  D  R  H  V  Y  T  Q  Q  E  V  R  E  L  L  G  R

ttggatcttggaaatagaacaaagatggga
 L  D  L  G  N  R  T  K  M  G
```

(Nucleotide sequence - SEQ ID NO: 59; protein sequence - SEQ ID NO: 60).

[0105] von Willebrand disease (vWD)—cysteine to arginine mutation at residue 1272 in von Willebrand factor (T>C mutation):

```
acagatgccccggtgagccccaccactctgtatgtggaggacatctcgga
 T  D  A  P  V  S  P  T  T  L  Y  V  E  D  I  S  E

accgccgttgcacgatttctaccgcagcaggctactggacctggtcttcc
  P  P  L  H  D  F  Y  R  S  R  L  L  D  L  V  F

tgctggatggctcctccaggctgtccgaggctgagtttgaagtgctgaag
L  L  D  G  S  S  R  L  S  E  A  E  F  E  V  L  K

gcctttgtggtggacatgatggagcggctg
 A  F  V  V  D  M  M  E  R  L
```

(Nucleotide sequence - SEQ ID NO: 61; protein sequence - SEQ ID NO: 62).

[0106] Myotonia congenital—cysteine to arginine mutation at position 277 in the muscle chloride channel gene CLCN1 (T>C mutation):

```
atctgtgctgctgtcctcagcaaattcatgtctgtgttctgcggggtata
 I  C  A  A  V  L  S  K  F  M  S  V  F  C  G  V  Y
```

-continued

```
tgagcagccatactactactctgatatcctgacggtgggctgtgctgtgg
  E  Q  P  Y  Y  Y  S  D  I  L  T  V  G  C  A  V

gagtcggccgttgttttgggacaccacttggaggagtgctatttagcatc
G  V  G  R  C  F  G  T  P  L  G  G  V  L  F  S  I

gaggtcacctccacctactttgctgttcgg
 E  V  T  S  T  Y  F  A  V  R
```

(Nucleotide sequence - SEQ ID NO: 63; protein sequence - SEQ ID NO: 64).

[0107] Hereditary renal amyloidosis—stop codon to arginine mutation at residue 111 in apolipoprotein All (T>C mutation):

```
tactttgaaaagtcaaaggagcagctgacacccctgatcaagaaggctgg
 Y  F  E  K  S  K  E  Q  L  T  P  L  I  K  K  A  G

aacggaactggttaacttcttgagctatttcgtggaacttggaacacagc
  T  E  L  V  N  F  L  S  Y  F  V  E  L  G  T  Q

ctgccacccagcgaagtgtccagcaccattgtcttccaaccccagctggc
P  A  T  Q  R  S  V  Q  H  H  C  L  P  T  P  A  G

ctctagaacacccactggccagtcctagag
 L  -  N  T  H  W  P  V  L  E
```

(Nucleotide sequence - SEQ ID NO: 65; protein sequence - SEQ ID NO: 66).

[0108] Dilated cardiomyopathy (DCM)—tryptophan to Arginine mutation at position 148 in the FOXD4 gene (T>C mutation):

```
ccgcacaagcgcctcacgctcagcggcatctgcgccttcattagtgaccg
 P  H  K  R  L  T  L  S  G  I  C  A  F  I  S  D  R

cttcccctactaccgccgcaagttccccgccgcggcagaacagcatccgcc
  F  P  Y  Y  R  R  K  F  P  A  R  Q  N  S  I  R

acaacctctcgctgaacgactgcttcgtcaagatcccccgcgagccgggc
H  N  L  S  L  N  D  C  F  V  K  I  P  R  E  P  G

cgcccaggcaagggcaactactggagcctg
 R  P  G  K  G  N  Y  W  S  L
```

(Nucleotide sequence - SEQ ID NO: 67; protein sequence - SEQ ID NO: 68).

[0109] Hereditary lymphedema—histidine to arginine mutation at residue 1035 in VEGFR3 tyrosine kinase (A>G mutation):

```
gctgaggacctgtggctgagcccgctgaccatggaagatcttgtctgcta
 A  E  D  L  W  L  S  P  L  T  M  E  D  L  V  C  Y

cagcttccaggtggccagagggatggagttcctggcttcccgaaagtgca
  S  F  Q  V  A  R  G  M  E  F  L  A  S  R  K  C

tccgcagagacctggctgctcggaacattctgctgtcggaaagcgacgtg
I  R  R  D  L  A  A  R  N  I  L  L  S  E  S  D  V

gtgaagatctgtgactttggccttgcccgg
 V  K  I  C  D  F  G  L  A  R
```

(Nucleotide sequence - SEQ ID NO: 69; protein sequence - SEQ ID NO: 70).

[0110] Familial Alzheimer's disease—isoleucine to valine mutation at residue 143 in presenilin1 (A>G mutation):

```
gataccgagactgtgggccagagagccctgcactcaattctgaatgctgccatcatgatc
 D  T  E  T  V  G  Q  R  A  L  H  S  I  L  N  A  A  I  M  I

agtgtcgttgttgtcatgactatcctcctggtggttctgtataaatacaggtgctataag
 S  V  V  V  V  M  T  I  L  L  V  V  L  Y  K  Y  R  C   Y  K

gtcatccatgcctggcttattatatcatctctattgttgctgttctttttttcattcatt
 V  I  H  A  W  L  I  I  S  S  L  L  L  L  F  F  F  S  F  I
```

(Nucleotide sequence - SEQ ID NO: 71; protein sequence - SEQ ID NO: 72).

[0111] Prion disease—methionine to valine mutation at residue 129 in prion protein (A>G mutation):

```
aagccgagtaagccaaaaaccaacatgaagcacatggctggtgctgcagcagctggggca
 K  P  S  K  P  K  T  N  M  K  H  M  A  G  A  A  A  A  G  A

gtggtgggggccttggcggctacgtgctgggaagtgccatgagcaggcccatcatacat
 V  V  G  G  L  G  G  Y  V  L  G  S  A  M  S  R  P  I  I  H

ttcggcagtgactatgaggaccgttactatcgtgaaaacatgcaccgttaccccaaccaa
 F  G  S  D  Y  E  D  R  Y  Y  R  E  N  M  H  R  Y  P  N  Q
```

(Nucleotide sequence - SEQ ID NO: 73; protein sequence - SEQ ID NO: 74).

[0112] Chronic infantile neurologic cutaneous articular syndrome (CINCA)—Tyrosine to Cysteine mutation at residue 570 in cryopyrin (A>G mutation):

```
cttcccagccgagacgtgacagtccttctggaaaactatggcaaattcgaaaaggggtgt
 L  P  S  R  D  V  T  V  L  L  E  N  Y  G  K  F  E  K  G  C

ttgatttttgttgtacgtttcctctttggcctggtaaaccaggagaggacctcctacttg
 L  I  F  V  V  R  F  L  F  G  L  V  N  Q  E  R  T  S  Y  L
```

(Nucleotide sequence - SEQ ID NO: 75; protein sequence - SEQ ID NO: 76).

[0113] Desmin-related myopathy (DRM)—arginine to glycine mutation at residue 120 in αB crystallin (A>G mutation):

```
gtgaagcacttctccccagaggaactcaaagttaaggtgttgggagatgtgattgaggtg
 V  K  H  F  S  P  E  E  L  K  V  K  V  L  G  D  V  I  E  V

catggaaaacatgaagagcgccaggatgaacatggtttcatctccagggagttccacggg
 H  G  K  H  E  E  R  Q  D  E  H  G  F  I  S  R  E  F  H  G

aaataccggatcccagctgatgtagaccctctcaccattacttcatccctgtcatctgat
 K  Y  R  I  P  A  D  V  D  P  L  T  I  T  S  S  L  S  S  D
```

(Nucleotide sequence - SEQ ID NO: 77; protein sequence - SEQ ID NO: 78).

[0114] Beta-thalassemia—one example is leucine to proline mutation at residue 115 in Hemoglobin B.

```
gagctgcactgtgacaagctgcacgtggatcctgagaacttcaggctcctgggcaacgtg
 E  L  H  C  D  K  L  H  V  D  P  E  N  F  R  L  L  G  N  V

ctggtctgtgtgccggcccatcactttggcaaagaattcaccccaccagtgcaggctgcc
 L  V  C  V  P  A  H  H  F  G  K  E  F  T  P  P  V  Q  A  A

tatcagaaagtggtggctggtgtggctaatgccctggcccacaagtatcactaagctcgc
 Y  Q  K  V  V  A  G  V  A  N  A  L  A  H  K  Y  H  -  A  R
```

(Nucleotide sequence - SEQ ID NO: 79; protein sequence - SEQ ID NO: 80).

It is to be understood that the sequences provided above are exemplary and not meant to be limiting the scope of the instant disclosure. Additional suitable sequences of point mutations that are associated with disease and amenable to correction by Cas9:nucleic acid-editing enzyme/domain fusion proteins as well as suitable guide RNA sequences will be apparent to those of skill in the art based on this disclosure.

Reporter Systems

[0115] Some aspects of this disclosure provide a reporter system that can be used for detecting deaminase activity of the fusion proteins described herein. In some embodiments, the reporter system is a luciferase-based assay in which deaminase activity leads to expression of luciferase. To minimize the impact of potential substrate promiscuity of the deaminase domain (e.g., the AID domain), the number of residues that could unintentionally be targeted for deamination (e.g., off-target C residues that could potentially reside on ssDNA within the reporter system) is minimized. In some embodiments, an intended target residue is be located in an ACG mutated start codon of the luciferase gene that is unable to initiate translation. Desired deaminase activity results in a ACG>AUG modification, thus enabling translation of luciferase and detection and quantification of the deaminase activity.

[0116] In some embodiments, in order to minimize single-stranded C residues, a leader sequence is inserted between the mutated start codon and the beginning of the luciferase gene which consists of a stretch of Lys (AAA), Asn (AAT), Leu (TTA), Ile (ATT, ATA), Tyr (TAT), or Phe (TTT) residues. The resulting mutants can be tested to ensure that the leader sequence does not adversely affect luciferase expression or activity. Background luciferase activity with the mutated start codon can be determined as well.

[0117] The reporter system can be used to test many different sgRNAs, e.g., in order to determine which residue (s) with respect to the target DNA sequence the respective deaminase (e.g., AID enzyme) will target (FIG. **3**). Because the size of the Cas9-DNA bubble is not known, sgRNAs that target non-template strand can also be tested in order to assess off-target effects of a specific Cas9 deaminase fusion protein. In some embodiments, such sgRNAs are designed such that the mutated start codon will not be base-paired with the sgRNA.

[0118] Once fusion proteins that are capable of programmable site-specific C to U modifications have been identified, their activities can be further characterized. The data from the luciferase assays can, for example, be integrated into heat maps that describe which nucleotides, with respect to the sgRNA target DNA, are being targeted for deamination by a specific fusion protein. In some embodiments, the position that results in the highest activity in the luciferase assay for each fusion is considered the "target" position, while all others are considered off-target positions.

[0119] In some embodiments, Cas9 fusions with various APOBEC3 enzymes, or deaminase domains thereof, are provided. In some embodiments, Cas9 fusion proteins with other nucleic acid editing enzymes or catalytic domains are provided, including, for example, ssRNA editing enzymes, such as the cytidine deaminases APOBEC1 and ACF1/ASF, as well as the ADAT family of adenosine deaminases,[38] that can be used for ssDNA editing activity when fused to Cas9. The activity of such fusion proteins can be tested using the same reporter systems and assays described above.

[0120] In some embodiments, a reporter system is provided herein that includes a reporter gene comprising a deactivated start codon, e.g., a mutation on the template strand from 3'-TAC-5' to 3'-CAC-5'. Upon successful deamination of the target C, the corresponding mRNA will be transcribed as 5'-AUG-3' instead of 5'-GUG-3', enabling the translation of the reporter gene. Suitable reporter genes will be apparent to those of skill in the art.

[0121] The description of exemplary embodiments of the reporter systems above is provided for illustration purposes only and not meant to be limiting. Additional reporter systems, e.g., variations of the exemplary systems described in detail above, are also embraced by this disclosure.

EXAMPLES

Example 1: Fusion Proteins

[0122] Exemplary Cas9:deaminase fusion proteins are provided below:

[0123] Cas9: Human AID Fusion (C-Terminal)

(SEQ ID NO: 30)

MDSLLMNRRKFLYQFKNVRWAKGRRETYLCDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFK

VLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDD

SFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLA

LAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKS

RRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQ

IGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQL

PEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTF

DNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTR

KSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKY

VTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASL

GTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKR

-continued

RRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSG

QGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNS

RERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVD

AIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLT

KAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLV

SDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKS

EQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVL

SMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKV

EKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRK

RMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQI

SEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKR

YTSTKEVLDATLIHQSITGLYETRIDLSQLGGD**GGGGSGGGGSGGGGS**YVVKRRDSATSFSL

DFGYLRNKNGCHVELLFLRYISDWDLDPGRCYRVTWFTSWSPCYDCARHVADFLRGNPNLSL

RIFTARLYFCEDRKAEPEGLRRLHRAGVQIAIMTFKDYFYCWNTFVENHERTFKAWEGLHEN

SVRLSRQLRRILLPLYEVDDLRDAFRTLGL

(underline: nuclear localization signal; double underline: nuclear export signal, bold: linker sequence)

[0124] Cas9: Human AID Fusion (N-Terminal)

(SEQ ID NO: 31)

MDSLLMNRRKFLYQFKNVRWAKGRRETYLCYVVKRRDSATSFSLDFGYLRNKNGCHVELLFL

RYISDWDLDPGRCYRVTWFTSWSPCYDCARHVADFLRGNPNLSLRIFTARLYFCEDRKAEPE

GLRRLHRAGVQIAIMTFKDYFYCWNTFVENHERTFKAWEGLHENSVRLSRQLRRILLP**GGGG**

SGGGGSGGGGSDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALL

FDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHE

RHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNP

DNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLF

GNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAI

LLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGY

IDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILR

RQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGA

SAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAI

VDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNE

ENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRD

KQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIK

KGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQIL

KEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLT

RSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQ

LVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYH

HAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMN

-continued

FFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFS

KESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITI

MERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPS

KYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLS

AYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITG

LYETRIDLSQLGGD

(underline: nuclear localization signal; bold: linker sequence)

[0125] Cas9:Mouse AID Fusion (C-Terminal)

(SEQ ID NO: 32)

MDSLLMNRRKFLYQFKNVRWAKGRRETYLCDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFK

VLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRYTRRKNRICYLQEIFSNEMAKVDD

SFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLA

LAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKS

RRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQ

IGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQL

PEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTF

DNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTR

KSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKY

VTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASL

GTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKR

RRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSG

QGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNS

RERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVD

AIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLT

KAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLV

SDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKS

EQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVL

SMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKV

EKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRK

RMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQI

SEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKR

YTSTKEVLDATLIHQSITGLYETRIDLSQLGGD**GGGGSGGGGSGGGGS**YVVKRRDSATSCSL

DFGHLRNKSGCHVELLFLRYISDWDLDPGRCYRVTWFTSWSPCYDCARHVAEFLRWNPNLSL

RIFTARLYFCEDRKAEPEGLRRLHRAGVQIGIMTFKDYFYCWNTFVENRERTFKAWEGLHEN

SVRLTRQLRRILLPLYEVDDLRDAFRMLGF

(underline: nuclear localization signal; bod: linker sequence;
double underline: nuclear export signal)

[0126] Cas9: Human APOBEC-3G Fusion (N-Terminal)

(SEQ ID NO: 33)

SPKKKRKVEASMELKYHPEMRFFHWFSKWRKLHRDQEYEVTWYISWSPCTKCTRDMATFLAE

DPKVTLTIFVARLYYFWDPDYQEALRSLCQKRDGPRATMKIMNYDEFQHCWSKFVYSQRELF

EPWNNLPKYYILLHIMLGEILRHSMDPPTFTFNFNNEPWVRGRHETYLCYEVERMHNDTWVL

LNQRRGFLCNQAPHKHGFLEGRHAELCFLDVIPFWKLDLDQDYRVTCFTSWSPCFSCAQEMA

KFISKNKHVSLCIFTARIYDDQGRCQEGLRTLAEAGAKISIMTYSEFKHCWDTFVDHQGCPF

QPWDGLDEHSQDLSGRLRAILQNQEN**SPKKKRKVEASSPKKKRKVEAS**KKYSIGLAIGTNSV

GWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNR

ICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRK

KLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPIN

ASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKL

QLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYD

EHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEE

LLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPY

YVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHS

LLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIEC

FDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERL

KTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIH

DDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIV

IEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDM

YVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWR

QLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDEN

DKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEF

VYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETG

EIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYG

GFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDL

IIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQ

LFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNL

GAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGD

(underline: nuclear localization signal; bold: linker (1 NLS),

[0127] Cas9: Human APOBEC-1 Fusion (N-Terminal)

(SEQ ID NO: 92)

SPKKKRKVEASMTSEKGPSTGDPTLRRRIEPWEFDVFYDPRELRKEACLLYEIKWGMSRKIW

RSSGKNTTNHVEVNFIKKFTSERDFHPSMSCSITWFLSWSPCWECSQAIREFLSRHPGVTLV

IYVARLFWHMDQQNRQGLRDLVNSGVTIQIMRASEYYHCWRNFVNYPPGDEAHWPQYPPLWM

MLYALELHCIILSLPPCLKISRRWQNHLTFFRLHLQNCHYQTIPPHILLATGLIHPSVAWR**S**

PKKKRKVEASSPKKKRKVEASDKKYSIGLAIGINSVGWAVITDEYKVPSKKFKVLGNTDRHS

IKKNLIGALLFDSGETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEES

-continued

FLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRG

HFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKSRRLENLIAQ

LPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLF

LAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFF

DQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQI

HLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITPW

NFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKYVTEGMRKPA

FLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASLGTYHDLLKI

IKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKRRRYTGWGRL

SRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHI

ANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIEE

GIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDAIVPQSFLK

DDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLTKAERGGLSE

LDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLVSDFRKDFQF

YKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKATA

KYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVNIVK

KTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLK

SVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLASAGEL

QKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQISEFSKRVIL

ADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLD

ATLIHQSITGLYETRIDLSQLGGD

(underline: nuclear localization signal; bold: linker (1 NLS),

[0128] Cas9: Human ADAT1 Fusion (N-Terminal)

(SEQ ID NO: 35)

MDSLLMNRRKFLYQFKNVRWAKGRRETYLC*SMGTGTKCIGQSKMRKNGDILNDSHAEVIARR*

SFQRYLLHQLQLAATLKEDSIFVPGTQKGVWKLRRDLIFVFFSSHTPCGDASIIPMLEFEDQ

PCCPVFRNWAHNSSVEASSNLEAPGNERKCEDPDSPVTKKMRLEPGTAAREVTNGAAHHQSF

GKQKSGPISPGIHSCDLTVEGLATVTRIAPGSAKVIDVYRTGAKCVPGEAGDSGKPGAAFHQ

VGLLRVKPGRGDRTRSMSCSDKMARWNVLGCQGALLMHLLEEPIYLSAVVIGKCPYSQEAMQ

RALIGRCQNVSALPKGFGVQELKILQSDLLFEQSRSAVQAKRADSPGRLVPCGAAISWSAVP

EQPLDVTANGFPQGTTKKTIGSLQARSQISKVELFRSFQKLLSRIARDKWPHSLRVQKLDTY

*QEYKEAASSYQEAWSTLRKQVFGSWIRNPPDYHQF***GGGGSGGGGSGGGGS**DKKYSIGLAIGT

NSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRYTRR

KNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYH

LRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEEN

PINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAED

AKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIK

RYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDG

TEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFR

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IPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLP

KHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKK

IECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIE

ERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQ

LIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPE

NIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNG

RDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKN

YWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKY

DENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLE

SEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNG

ETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPK

KYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVK

KDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNE

QKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTL

TNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGD

(underline: nuclear localization signal; bold: linker sequence)

[0129] Cas9: Human ADAT1 Fusion (-Terminal)

(SEQ ID NO: 36)

MDSLLMNRRKFLYQFKNVRWAKGRRETYLCDKKYSIGLAIGTNSVGWAVITDEYKVPSKKFK

VLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRYTRRKNRICYLQEIFSNEMAKVDD

SFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLA

LAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSARLSKS

RRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQ

IGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQL

PEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTF

DNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTR

KSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKY

VTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNASL

GTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLKR

RRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDIQKAQVSG

QGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMARENQTTQKGQKNS

RERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVD

AIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDNLT

KAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVITLKSKLV

SDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKVYDVRKMIAKS

EQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVWDKGRDFATVRKVL

SMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKV

EKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRK

-continued

RMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDEIIEQI

SEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDTTIDRKR

YTSTKEVLDATLIHQSITGLYETRIDLSQLGGD**GGGGSGGGGS***SMGTGTKCIGQSKMRKNGD*

ILNDSHAEVIARRSFORYLLHOLQLAATLKEDSIFVPGTQKGVWKLRRDLIFVFFSSHTPCG

DASIIPMLEFEDQPCCPVFRNWAHNSSVEASSNLEAPGNERKCEDPDSPVTKKMRLEPGTAA

REVTNGAAHHQSFGKQKSGPISPGIHSCDLTVEGLATVTRIAPGSAKVIDVYRTGAKCVPGE

AGDSGKPGAAFHQVGLLRVKPGRGDRTRSMSCSDKMARWNVLGCQGALLMHLLEEPIYLSAV

VIGKCPYSQEAMQRALIGRCQNVSALPKGFGVQELKILQSDLLFEQSRSAVQAKRADSPGRL

VPCGAAISWSAVPEQPLDVTANGFPQGTTKKTIGSLQARSQISKVELFRSFQKLLSRIARDK

WPHSLRVQKLDTYQEYKEAASSYQEAWSTLRKQVFGSWIRNPPDYHQF

(underline: nuclear localization signal; bold: linker sequence)

Example 2: Correction of a PI3K Point Mutation by a Cas9 Fusion Protein

[0130] An A3140G point mutation in exon 20 of the PI3KCA gene, resulting in an H1047R amino acid substitution in the PI3K protein is corrected by contacting a nucleic acid encoding the mutant protein with a Cas9:AID (SEQ ID NO: 30) or a Cas9:APOBEC1 (SEQ ID NO: 92) fusion protein and an appropriately designed sgRNA targeting the fusion protein to the mutation site in the encoding PI3KCA gene. The A3140G point mutation is confirmed via genomic PCR of the respective exon 20 sequence, e.g., generation of a PCR amplicon of nucleotides 3000-3250, and subsequent sequencing of the PCT amplicon.

[0131] Cells expressing a mutant PI3K protein comprising an A3140G point mutation in exon 20 are contacted with an expression construct encoding the Cas9:AID (SEQ ID NO: 30) or a Cas9:APOBEC1 (SEQ ID NO: 92) fusion protein and an appropriately designed sgRNA targeting the fusion protein to the mutation site in the antisense strand of the encoding PI3KCA gene. The sgRNA is of the sequence

(SEQ ID NO: 81)
5'-aucggaauctauuuugacucguuuuagagcuagaaauagcaaguuaa

aauaaaggcuaguccguuaucaacuugaaaaaguggcaccgagucggugc

uuuuu 3';

(SEQ ID NO: 82)
5'-ucggaaucuauuuugacucgguuuuagagcuagaaauagcaaguuaa

aauaaaggcuaguccguuaucaacuugaaaaaguggcaccgagucggugc

uuuuu-3';

(SEQ ID NO: 83)
5'-cuuagauaaaaacugagcaaggguuuuagagcuagaaauagcaaguuaa

aauaaaggcuaguccguuaucaacuugaaaaaguggcaccgagucggugc

uuuuu-3';

(SEQ ID NO: 84)
5'-aucuauuuugacucguucucguuuuagagcuagaaauagcaaguuaa

aauaaaggcuaguccguuaucaacuugaaaaaguggcaccgagucggugc

uuuuu-3';

-continued

(SEQ ID NO: 85)
5'-uaaaacugagcaagaggcuuguuuuagagcuagaaauagcaaguuaa

aauaaaggcuaguccguuaucaacuugaaaaaguggcaccgagucggugc

uuuuu-3';

(SEQ ID NO: 86)
5'-ugguggcuggacaacaaaaaguuuuagagcuagaaauagcaaguuaa

aauaaaggcuaguccguuaucaacuugaaaaaguggcaccgagucggugc

uuuuu-3';

(SEQ ID NO: 87)
5'-gcuggacaacaaaaauggauguuuuagagcuagaaauagcaaguuaa

aauaaaggcuaguccguuaucaacuugaaaaaguggcaccgagucggugc

uuuuu-3';
or

(SEQ ID NO: 88)
5'-guguuaauuugucguacguaguuuuagagcuagaaauagcaaguuaa

aauaaaggcuaguccguuaucaacuugaaaaaguggcaccgagucggugc

uuuuu.

[0132] The cytosine deaminase activity of the Cas9:AID or the Cas9:APOBEC1 fusion protein results in deamination of the cytosine that is base-paired with the mutant G3140 to uridine. After one round of replication, the wild type A3140 is restored. Genomic DNA of the treated cells is extracted and a PCR amplicon of nucleotides 3000-3250 is amplified with suitable PCR primers. The correction of the A3140G point mutation after treatment of the cells with the fusion protein is confirmed by sequencing the PCR amplicon.

Example 3: Correction of a Presenilin 1 Point Mutation by a Cas9 Fusion Protein

[0133] An A->G point mutation in codon 143 of the presenilin1 (PSEN1) gene, resulting in an I143V amino acid substitution in the PSEN1 protein is corrected by contacting a nucleic acid encoding the mutant PSEN1 protein with a Cas9:AID (SEQ ID NO: 30) or a Cas9:APOBEC1 (SEQ ID NO: 92) fusion protein and an appropriately designed sgRNA targeting the fusion protein to the mutation site in the

encoding PSEN1 gene. See, e.g., Gallo et. al., *J. Alzheimer's disease.* 2011; 25: 425-431 for a description of an exemplary PSEN1 I143V mutation associated with familial Alzheimer's Disease. The A->G point mutation is confirmed via genomic PCR of the respective PSEN1 sequence, e.g., generation of a PCR amplicon of about 100-250 nucleotides around exon 143, and subsequent sequencing of the PCT amplicon.

[0134] Cells expressing the mutant PSEN1 protein are contacted with an expression construct encoding the Cas9:AID (SEQ ID NO: 30) or a Cas9:APOBEC1 (SEQ ID NO: 92) fusion protein and an appropriately designed sgRNA targeting the fusion protein to the mutation site in the antisense strand of the encoding PSEN1 gene. The cytosine deaminase activity of the Cas9:AID or the Cas9:APOBEC1 fusion protein results in deamination of the cytosine that is base-paired with the mutant G in codon 143 to uridine. After one round of replication, the wild type A is restored. Genomic DNA of the treated cells is extracted and a PCR amplicon of 100-250 nucleotides is amplified with suitable PCR primers. The correction of the A->G point mutation after treatment of the cells with the fusion protein is confirmed by sequencing the PCR amplicon.

Example 4: Correction of an α_1-Antitrypsin Point Mutation by a Cas9 Fusion Protein

[0135] A T->C point mutation in codon 55 of the α_1-antitrypsin gene, resulting in an L55P amino acid substitution in the α_1-antitrypsin protein is corrected by contacting a nucleic acid encoding the mutant α_1-antitrypsin protein with a Cas9:ADAT1 fusion protein (SEQ ID NO: 35 or 36) and an appropriately designed sgRNA targeting the fusion protein to the mutation site in the encoding α_1-antitrypsin gene. See, e.g., Poller et al., Genomics. 1993; 17: 740-743 for a more detailed description of an exemplary codon 55 T->C mutation associated with chronic obstructive pulmonary disease (COPD). The T->C point mutation is confirmed via genomic PCR of the respective α_1-antitrypsin sequence encoding codon 55, e.g., generation of a PCR amplicon of about 100-250 nucleotides, and subsequent sequencing of the PCT amplicon.

[0136] Cells expressing the mutant α_1-antitrypsin protein are contacted with an expression construct encoding the Cas9:AID (SEQ ID NO: 30) or a Cas9:APOBEC1 (SEQ ID NO: 92) fusion protein and an appropriately designed sgRNA targeting the fusion protein to the mutated nucleotide in codon 55 on the sense strand in the encoding α_1-antitrypsin gene. The cytosine deaminase activity of the Cas9:ADAT1 fusion protein results in deamination of the mutant cytosine to uridine thus correcting the mutation. Genomic DNA of the treated cells is extracted and a PCR amplicon of 100-250 nucleotides is amplified with suitable PCR primers. The correction of the T->C point mutation in codon 55 of the α_1-antitrypsin gene after treatment of the cells with the fusion protein is confirmed by sequencing the PCR amplicon

Example 5: Correction of a Von Willebrand Factor Point Mutation by a Cas9 Fusion Protein

[0137] A T->C point mutation in codon 509 of the von Willebrand factor gene, resulting in a C509A amino acid substitution in the von Willebrand factor protein is corrected by contacting a nucleic acid encoding the mutant von Willebrand factor protein with a Cas9:ADAT1 fusion protein (SEQ ID NO: 35 or 36) and an appropriately designed sgRNA targeting the fusion protein to the mutation site in the sense strand of the encoding von Willebrand factor gene. See, e.g., Lavergne et al., *Br. J. Haematol.* 1992; 82: 66-7, for a description of an exemplary von Willebrand factor C509A mutation associated with von Willebrand disease (vWD). The T->C point mutation is confirmed via genomic PCR of the respective von Willebrand factor genomic sequence, e.g., generation of a PCR amplicon of about 100-250 nucleotides around exon 509, and subsequent sequencing of the PCT amplicon.

[0138] Cells expressing the mutant von Willebrand factor protein are contacted with an expression construct encoding the Cas9:ADAT1 fusion protein (SEQ ID NO: 35 or 36) and an appropriately designed sgRNA targeting the fusion protein to the mutation site in the sense strand of the encoding von Willebrand factor gene. The cytosine deaminase activity of the Cas9:ADAT1 fusion protein results in deamination of the mutant cytosine in codon 509 to uridine, thus correcting the mutation. Genomic DNA of the treated cells is extracted and a PCR amplicon of 100-250 nucleotides is amplified with suitable PCR primers. The correction of the T->C point mutation in codon 509 of the von Willebrand factor gene after treatment of the cells with the fusion protein is confirmed by sequencing the PCR amplicon.

Example 6: Correction of a Caspase 9 Point Mutation by a Cas9 Fusion Protein-Neuroblastoma

[0139] A T->C point mutation in codon 197 of the Caspase-9 gene, resulting in an L197P amino acid substitution in the Caspase-9 protein is corrected by contacting a nucleic acid encoding the mutant Caspase-9 protein with a Cas9:ADAT1 fusion protein (SEQ ID NO: 35 or 36) and an appropriately designed sgRNA targeting the fusion protein to the mutation site in the sense strand of the encoding Caspase-9 gene. See, e.g., Lenk et al., *PLoS Genetics.* 2011; 7: e1002104, for a description of an exemplary Caspase-9 L197P mutation associated with neuroblastoma (NB). The T->C point mutation is confirmed via genomic PCR of the respective Caspase-9 genomic sequence, e.g., generation of a PCR amplicon of about 100-250 nucleotides around exon 197, and subsequent sequencing of the PCT amplicon.

[0140] Cells expressing the mutant Caspase-9 protein are contacted with an expression construct encoding the Cas9:ADAT1 fusion protein (SEQ ID NO: 35 or 36) and an appropriately designed sgRNA targeting the fusion protein to the mutation site in the sense strand of the encoding Caspase-9 gene. The cytosine deaminase activity of the Cas9:ADAT1 fusion protein results in deamination of the mutant cytosine in codon 197 to uridine, thus correcting the mutation. Genomic DNA of the treated cells is extracted and a PCR amplicon of 100-250 nucleotides is amplified with suitable PCR primers. The correction of the T->C point mutation in codon 197 of the Caspase-9 gene after treatment of the cells with the fusion protein is confirmed by sequencing the PCR amplicon.

Example 7: Deaminase Activity of Two dCas9-APOBEC1 Fusion Proteins

[0141] Two dCas9-APOBEC1 fusion proteins with different linkers were generated:

[0142] rAPOBEC1_GGS_dCas9:

(SEQ ID NO: 94)

MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHV
EVNFIEKFTTERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHAD
PRNRQGLRDLISSGVTIQIMTEQESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCII
LGLPPCLNILRRKQPQLTFFTIALQSCHYQRLPPHILWATGLKGGSMDKKYSIGLAIGTNSV
GWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRYTRRKNR
ICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTIYHLRK
KLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLFEENPIN
ASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDLAEDAKL
QLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSASMIKRYD
EHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEE
LLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPY
YVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHS
LLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIEC
FDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERL
KTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRNFMQLIH
DDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIV
IEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDM
YVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKMKNYWR
QLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMNTKYDEN
DKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYPKLESEF
VYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETG
EIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYG
GFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVKKDL
IIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPEDNEQKQ
LFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHLFTLTNL
GAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGD;

underline = rAPOBEC1; double underline = dCas9.

[0143] rAPOBEC1_$(GGS)_3$_dCas9:

(SEQ ID NO: 95)

MSSETGPVAVDPTLRRRIEPHEFEVFFDPRELRKETCLLYEINWGGRHSIWRHTSQNTNKHV
EVNFIEKFTTERYFCPNTRCSITWFLSWSPCGECSRAITEFLSRYPHVTLFIYIARLYHHAD
PRNRQGLRDLISSGVTIQIMTEQESGYCWRNFVNYSPSNEAHWPRYPHLWVRLYVLELYCII
LGLPPCLNILRRKQPQLTFFTIALQSCHYQRLPPHILWATGLKGGSGGSGGSMDKKYSIGLA
IGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEATRLKRTARRRY

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TRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPT

IYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLF

EENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKSNFDL

AEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKAPLSAS

MIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEEFYKFIKPILEK

MDGTEELLVKLNREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFLKDNREKIEKIL

TFRIPYYVGPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQSFIERMTNFDKNLPNEK

VLPKHSLLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDY

FKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDRE

MIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSDGFANRN

FMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDELVKVMGRH

KPENIVIEMARENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVENTQLQNEKLYLYYL

QNGRDMYVDQELDINRLSDYDVDAIVPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKK

MKNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSRMN

TKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVGTALIKKYP

KLESEFVYGDYKVYDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLANGEIRKRPLIE

TNGETGEIVWDKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPKRNSDKLIARKKDW

DPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYK

EVKKDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSPE

DNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENIIHL

FTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGD;

underline = rAPOBEC1; double underline = dCas9.

[0144] Deaminase activity of both fusion proteins were examined. A deaminase assay was adapted from Nuc. Acids Res. 2014, 42, p. 1095; J. Biol. Chem. 2004, 279, p 53379; J. Virology 2014, 88, p. 3850; and J. Virology 2006, 80, p. 5992, the entire contents of each of which are incorporated by reference.

[0145] Expression constructs encoding the fusion proteins were inserted into a CMV backbone plasmid (Addgene plasmid 52970; see Guilinger J P, Thompson D B, Liu D R. Fusion of catalytically inactive Cas9 to FokI nuclease improves the specificity of genome modification. *Nat. Biotechnol.* 2014; 32(6): 577-82). The fusion proteins were expressed using a TNT Quick Coupled Transcription/Translation System (Promega). After 90 min, 5 μL of lysate was incubated with 5'-labeled ssDNA substrate (Cy3-ATTATT-ATTATTCCGCGGATTTATTTATTTATTTATTTATTT, SEQ ID NO: 96) and UDG (Uracil DNA Glycosylase) at 37° C. for 3 hr. A 1M solution of NaOH (10 μL) was then added to cleave the DNA at the abasic site. See FIG. **4**. The DNA was resolved on a 10% TBE PAGE gel (FIG. **5**). A negative control, where pUC19 was incubated in the TNT system, and a positive control, where the DNA has been synthesized with a "U" in place of the target C, were also included. FIG. **5** illustrates that both fusion proteins exhibit cytosine deaminase activity.

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[0198] All publications, patents, patent applications, publication, and database entries (e.g., sequence database entries) mentioned herein, e.g., in the Background, Summary, Detailed Description, Examples, and/or References sections, are hereby incorporated by reference in their entirety as if each individual publication, patent, patent application, publication, and database entry was specifically and individually incorporated herein by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS AND SCOPE

[0199] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents of the embodiments described herein. The scope of the present disclosure is not intended to be limited to the above description, but rather is as set forth in the appended claims.

[0200] 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 two or more members of a group are considered satisfied if one, more than one, or all of the group members are present, unless indicated to the contrary or otherwise evident from the context. The disclosure of a group that includes "or" between two or more group members provides embodiments in which exactly one member of the group is present, embodiments in which more than one members of the group are present, and embodiments in which all of the group members are present. For purposes of brevity those embodiments have not been individually spelled out herein, but it will be understood that each of these embodiments is provided herein and may be specifically claimed or disclaimed.

[0201] It is to be understood that the invention encompasses all variations, combinations, and permutations in which one or more limitation, element, clause, or descriptive term, from one or more of the claims or from one or more relevant portion of the description, is introduced into another claim. For example, a claim that is dependent on another claim can be modified to include one or more of the limitations found in any other claim that is dependent on the same base claim. Furthermore, where the claims recite a composition, it is to be understood that methods of making or using the composition according to any of the methods of making or using disclosed herein or according to methods known in the art, if any, are included, unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise.

[0202] Where elements are presented as lists, e.g., in Markush group format, it is to be understood that every possible subgroup of the elements is also disclosed, and that any element or subgroup of elements can be removed from the group. It is also noted that the term "comprising" is intended to be open and permits the inclusion of additional elements or steps. It should be understood that, in general, where an embodiment, product, or method is referred to as comprising particular elements, features, or steps, embodiments, products, or methods that consist, or consist essentially of, such elements, features, or steps, are provided as well. For purposes of brevity those embodiments have not been individually spelled out herein, but it will be understood that each of these embodiments is provided herein and may be specifically claimed or disclaimed.

[0203] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and/or the understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value within the stated ranges in some embodiments, to the tenth of the

unit of the lower limit of the range, unless the context clearly dictates otherwise. For purposes of brevity, the values in each range have not been individually spelled out herein, but it will be understood that each of these values is provided herein and may be specifically claimed or disclaimed. It is also to be understood that unless otherwise indicated or otherwise evident from the context and/or the understanding of one of ordinary skill in the art, values expressed as ranges can assume any subrange within the given range, wherein the endpoints of the subrange are expressed to the same degree of accuracy as the tenth of the unit of the lower limit of the range.

[0204] In addition, it is to be understood that any particular embodiment of the present invention may be explicitly excluded from any one or more of the claims. Where ranges are given, any value within the range may explicitly be excluded from any one or more of the claims. Any embodiment, element, feature, application, or aspect of the compositions and/or methods of the invention, can be excluded from any one or more claims. For purposes of brevity, all of the embodiments in which one or more elements, features, purposes, or aspects is excluded are not set forth explicitly herein.

SEQUENCE LISTING

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cggctagaaa acctgatcgc acaattaccc ggagagaaga aaaatgggtt gttcggtaac 720

cttatagcgc tctcactagg cctgacacca aattttaagt cgaacttcga cttagctgaa 780

gatgccaaat tgcagcttag taaggacacg tacgatgacg atctcgacaa tctactggca 840

caaattggag atcagtatgc ggacttattt ttggctgcca aaaaccttag cgatgcaatc 900

ctcctatctg acatactgag agttaatact gagattacca aggcgccgtt atccgcttca 960

atgatcaaaa ggtacgatga acatcaccaa gacttgacac ttctcaaggc cctagtccgt 1020

cagcaactgc ctgagaaata taaggaaata ttctttgatc agtcgaaaaa cgggtacgca 1080

ggttatattg acggcggagc gagtcaagag gaattctaca agtttatcaa acccatatta 1140

gagaagatgg atgggacgga agagttgctt gtaaaactca atcgcgaaga tctactgcga 1200

aagcagcgga ctttcgacaa cggtagcatt ccacatcaaa tccacttagg cgaattgcat 1260

gctatactta gaaggcagga ggatttttat ccgttcctca aagacaatcg tgaaaagatt 1320

gagaaaatcc taacctttcg catacctcac tatgtgggac ccctggcccg agggaactct 1380

cggttcgcat ggatgacaag aaagtccgaa gaaacgatta ctccatggaa ttttgaggaa 1440

gttgtcgata aaggtgcgtc agctcaatcg ttcatcgaga ggatgaccaa ctttgacaag 1500

aatttaccga acgaaaaagt attgcctaag cacagtttac tttacgagta tttcacagtg 1560

tacaatgaac tcacgaaagt taagtatgtc actgagggca tgcgtaaacc cgcctttcta 1620

agcggagaac agaagaaagc aatagtagat ctgttattca agaccaaccg caaagtgaca 1680

gttaagcaat tgaaagagga ctactttaag aaaattgaat gcttcgattc tgtcgagatc 1740

tccggggtag aagatcgatt taatgcgtca cttggtacgt atcatgacct cctaaagata 1800

attaaagata aggacttcct ggataacgaa gagaatgaag atatcttaga agatatagtg 1860

ttgactctta ccctctttga agatcgggaa atgattgagg aaagactaaa aacatacgct 1920

cacctgttcg acgataaggt tatgaaacag ttaaagaggc gtcgctatac gggctgggga 1980

cgattgtcgc ggaaacttat caacgggata agagacaagc aaagtggtaa aactattctc 2040

gattttctaa agagcgacgg cttcgccaat aggaacttta tgcagctgat ccatgatgac 2100

tctttaacct tcaaagagga tatacaaaag gcacaggttt ccggacaagg ggactcattg 2160

cacgaacata ttgcgaatct tgctggttcg ccagccatca aaaagggcat actccagaca 2220

gtcaaagtag tggatgagct agttaaggtc atgggacgtc acaaaccgga aaacattgta 2280

atcgagatgg cacgcgaaaa tcaaacgact cagaaggggc aaaaaaacag tcgagagcgg 2340

atgaagagaa tagaagaggg tattaaagaa ctgggcagcc agatcttaaa ggagcatcct 2400

gtggaaaata cccaattgca gaacgagaaa ctttacctct attacctaca aaatggaagg 2460

gacatgtatg ttgatcagga actggacata aaccgtttat ctgattacga cgtcgatcac 2520

attgtacccc aatccttttt gaaggacgat tcaatcgaca ataaagtgct tacacgctcg 2580

gataagaacc gagggaaaag tgacaatgtt ccaagcgagg aagtcgtaaa gaaaatgaag 2640

aactattggc ggcagctcct aaatgcgaaa ctgataacgc aaagaaagtt cgataactta 2700

actaaagctg agaggggtgg cttgtctgaa cttgacaagg ccggatttat taaacgtcag 2760

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ctcgtggaaa cccgccaaat cacaaagcat gttgcacaga tactagattc ccgaatgaat   2820

acgaaatacg acgagaacga taagctgatt cgggaagtca aagtaatcac tttaaagtca   2880

aaattggtgt cggacttcag aaaggatttt caattctata aagttaggga gataaataac   2940

taccaccatg cgcacgacgc ttatcttaat gccgtcgtag ggaccgcact cattaagaaa   3000

tacccgaagc tagaaagtga gtttgtgtat ggtgattaca aagtttatga cgtccgtaag   3060

atgatcgcga aaagcgaaca ggagataggc aaggctacag ccaaatactt cttttattct   3120

aacattatga atttctttaa gacggaaatc actctggcaa acggagagat acgcaaacga   3180

cctttaattg aaaccaatgg ggagacaggt gaaatcgtat gggataaggg ccgggacttc   3240

gcgacggtga gaaaagtttt gtccatgccc caagtcaaca tagtaaagaa aactgaggtg   3300

cagaccggag ggttttcaaa ggaatcgatt cttccaaaaa ggaatagtga taagctcatc   3360

gctcgtaaaa aggactggga cccgaaaaag tacggtggct tcgatagccc tacagttgcc   3420

tattctgtcc tagtagtggc aaaagttgag aagggaaaat ccaagaaact gaagtcagtc   3480

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tatagtctgt ttgagttaga aaatggccga aaacggatgt tggctagcgc cggagagctt   3660

caaaagggga acgaactcgc actaccgtct aaatacgtga atttcctgta tttagcgtcc   3720

cattacgaga agttgaaagg ttcacctgaa gataacgaac agaagcaact ttttgttgag   3780

cagcacaaac attatctcga cgaaatcata gagcaaattt cggaattcag taagagagtc   3840

atcctagctg atgccaatct ggacaaagta ttaagcgcat acaacaagca cagggataaa   3900

cccatacgtg agcaggcgga aaatattatc catttgttta ctcttaccaa cctcggcgct   3960

ccagccgcat tcaagtattt tgacacaacg atagatcgca aacgatacac ttctaccaag   4020

gaggtgctag acgcgacact gattcaccaa tccatcacgg gattatatga aactcggata   4080

gatttgtcac agcttggggg tgacggatcc cccaagaaga agaggaaagt ctcgagcgac   4140

tacaaagacc atgacggtga ttataaagat catgacatcg attacaagga tgacgatgac   4200

aaggctgcag ga                                                       4212
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<210> SEQ ID NO 4
<211> LENGTH: 1368
<212> TYPE: PRT
<213> ORGANISM: Streptococcus pyogenes

<400> SEQUENCE: 4

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Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val
1               5                   10                  15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
            20                  25                  30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
        35                  40                  45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
    50                  55                  60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65                  70                  75                  80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
                85                  90                  95
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Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
            100                 105                 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
        115                 120                 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
    130                 135                 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145                 150                 155                 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
                165                 170                 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
            180                 185                 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
        195                 200                 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
    210                 215                 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225                 230                 235                 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
                245                 250                 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
            260                 265                 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
        275                 280                 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
    290                 295                 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305                 310                 315                 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
                325                 330                 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
            340                 345                 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
        355                 360                 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
    370                 375                 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385                 390                 395                 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
                405                 410                 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
            420                 425                 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
        435                 440                 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
    450                 455                 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465                 470                 475                 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
                485                 490                 495
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Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
            500                 505                 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
        515                 520                 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
    530                 535                 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545                 550                 555                 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
                565                 570                 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
            580                 585                 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
        595                 600                 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
    610                 615                 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625                 630                 635                 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
                645                 650                 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
            660                 665                 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
        675                 680                 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
    690                 695                 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705                 710                 715                 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
                725                 730                 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
            740                 745                 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
        755                 760                 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
    770                 775                 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785                 790                 795                 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
                805                 810                 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
            820                 825                 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
        835                 840                 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
    850                 855                 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865                 870                 875                 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
                885                 890                 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
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           900                 905                 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
       915                 920                 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
   930                 935                 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945                 950                 955                 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
               965                 970                 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
           980                 985                 990

Val Gly Thr Ala Leu Ile Lys Lys  Tyr Pro Lys Leu Glu  Ser Glu Phe
       995                 1000                1005

Val Tyr  Gly Asp Tyr Lys Val  Tyr Asp Val Arg Lys  Met Ile Ala
   1010                1015                1020

Lys Ser  Glu Gln Glu Ile Gly  Lys Ala Thr Ala Lys  Tyr Phe Phe
   1025                1030                1035

Tyr Ser  Asn Ile Met Asn Phe  Phe Lys Thr Glu Ile  Thr Leu Ala
   1040                1045                1050

Asn Gly  Glu Ile Arg Lys Arg  Pro Leu Ile Glu Thr  Asn Gly Glu
   1055                1060                1065

Thr Gly  Glu Ile Val Trp Asp  Lys Gly Arg Asp Phe  Ala Thr Val
   1070                1075                1080

Arg Lys  Val Leu Ser Met Pro  Gln Val Asn Ile Val  Lys Lys Thr
   1085                1090                1095

Glu Val  Gln Thr Gly Gly Phe  Ser Lys Glu Ser Ile  Leu Pro Lys
   1100                1105                1110

Arg Asn  Ser Asp Lys Leu Ile  Ala Arg Lys Lys Asp  Trp Asp Pro
   1115                1120                1125

Lys Lys  Tyr Gly Gly Phe Asp  Ser Pro Thr Val Ala  Tyr Ser Val
   1130                1135                1140

Leu Val  Val Ala Lys Val Glu  Lys Gly Lys Ser Lys  Lys Leu Lys
   1145                1150                1155

Ser Val  Lys Glu Leu Leu Gly  Ile Thr Ile Met Glu  Arg Ser Ser
   1160                1165                1170

Phe Glu  Lys Asn Pro Ile Asp  Phe Leu Glu Ala Lys  Gly Tyr Lys
   1175                1180                1185

Glu Val  Lys Lys Asp Leu Ile  Ile Lys Leu Pro Lys  Tyr Ser Leu
   1190                1195                1200

Phe Glu  Leu Glu Asn Gly Arg  Lys Arg Met Leu Ala  Ser Ala Gly
   1205                1210                1215

Glu Leu  Gln Lys Gly Asn Glu  Leu Ala Leu Pro Ser  Lys Tyr Val
   1220                1225                1230

Asn Phe  Leu Tyr Leu Ala Ser  His Tyr Glu Lys Leu  Lys Gly Ser
   1235                1240                1245

Pro Glu  Asp Asn Glu Gln Lys  Gln Leu Phe Val Glu  Gln His Lys
   1250                1255                1260

His Tyr  Leu Asp Glu Ile Ile  Glu Gln Ile Ser Glu  Phe Ser Lys
   1265                1270                1275

Arg Val  Ile Leu Ala Asp Ala  Asn Leu Asp Lys Val  Leu Ser Ala
   1280                1285                1290
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Tyr Asn  Lys His Arg Asp Lys  Pro Ile Arg Glu Gln  Ala Glu Asn
    1295                 1300                 1305

Ile Ile  His Leu Phe Thr Leu  Thr Asn Leu Gly Ala  Pro Ala Ala
    1310                 1315                 1320

Phe Lys  Tyr Phe Asp Thr Thr  Ile Asp Arg Lys Arg  Tyr Thr Ser
    1325                 1330                 1335

Thr Lys  Glu Val Leu Asp Ala  Thr Leu Ile His Gln  Ser Ile Thr
    1340                 1345                 1350

Gly Leu  Tyr Glu Thr Arg Ile  Asp Leu Ser Gln Leu  Gly Gly Asp
    1355                 1360                 1365


<210> SEQ ID NO 5
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 5

Glu Ala Ala Ala Lys
1               5


<210> SEQ ID NO 6
<211> LENGTH: 198
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Met Asp Ser Leu Leu Met Asn Arg Arg Lys Phe Leu Tyr Gln Phe Lys
1               5                   10                  15

Asn Val Arg Trp Ala Lys Gly Arg Arg Glu Thr Tyr Leu Cys Tyr Val
            20                  25                  30

Val Lys Arg Arg Asp Ser Ala Thr Ser Phe Ser Leu Asp Phe Gly Tyr
        35                  40                  45

Leu Arg Asn Lys Asn Gly Cys His Val Glu Leu Leu Phe Leu Arg Tyr
    50                  55                  60

Ile Ser Asp Trp Asp Leu Asp Pro Gly Arg Cys Tyr Arg Val Thr Trp
65                  70                  75                  80

Phe Thr Ser Trp Ser Pro Cys Tyr Asp Cys Ala Arg His Val Ala Asp
                85                  90                  95

Phe Leu Arg Gly Asn Pro Asn Leu Ser Leu Arg Ile Phe Thr Ala Arg
            100                 105                 110

Leu Tyr Phe Cys Glu Asp Arg Lys Ala Glu Pro Glu Gly Leu Arg Arg
        115                 120                 125

Leu His Arg Ala Gly Val Gln Ile Ala Ile Met Thr Phe Lys Asp Tyr
    130                 135                 140

Phe Tyr Cys Trp Asn Thr Phe Val Glu Asn His Glu Arg Thr Phe Lys
145                 150                 155                 160

Ala Trp Glu Gly Leu His Glu Asn Ser Val Arg Leu Ser Arg Gln Leu
                165                 170                 175

Arg Arg Ile Leu Leu Pro Leu Tyr Glu Val Asp Asp Leu Arg Asp Ala
            180                 185                 190

Phe Arg Thr Leu Gly Leu
        195
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<210> SEQ ID NO 7
<211> LENGTH: 198
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 7

Met Asp Ser Leu Leu Met Lys Gln Lys Lys Phe Leu Tyr His Phe Lys
1 5 10 15

Asn Val Arg Trp Ala Lys Gly Arg His Glu Thr Tyr Leu Cys Tyr Val
20 25 30

Val Lys Arg Arg Asp Ser Ala Thr Ser Cys Ser Leu Asp Phe Gly His
35 40 45

Leu Arg Asn Lys Ser Gly Cys His Val Glu Leu Leu Phe Leu Arg Tyr
50 55 60

Ile Ser Asp Trp Asp Leu Asp Pro Gly Arg Cys Tyr Arg Val Thr Trp
65 70 75 80

Phe Thr Ser Trp Ser Pro Cys Tyr Asp Cys Ala Arg His Val Ala Glu
85 90 95

Phe Leu Arg Trp Asn Pro Asn Leu Ser Leu Arg Ile Phe Thr Ala Arg
100 105 110

Leu Tyr Phe Cys Glu Asp Arg Lys Ala Glu Pro Glu Gly Leu Arg Arg
115 120 125

Leu His Arg Ala Gly Val Gln Ile Gly Ile Met Thr Phe Lys Asp Tyr
130 135 140

Phe Tyr Cys Trp Asn Thr Phe Val Glu Asn Arg Glu Arg Thr Phe Lys
145 150 155 160

Ala Trp Glu Gly Leu His Glu Asn Ser Val Arg Leu Thr Arg Gln Leu
165 170 175

Arg Arg Ile Leu Leu Pro Leu Tyr Glu Val Asp Asp Leu Arg Asp Ala
180 185 190

Phe Arg Met Leu Gly Phe
195

<210> SEQ ID NO 8
<211> LENGTH: 198
<212> TYPE: PRT
<213> ORGANISM: Canis lupus

<400> SEQUENCE: 8

Met Asp Ser Leu Leu Met Lys Gln Arg Lys Phe Leu Tyr His Phe Lys
1 5 10 15

Asn Val Arg Trp Ala Lys Gly Arg His Glu Thr Tyr Leu Cys Tyr Val
20 25 30

Val Lys Arg Arg Asp Ser Ala Thr Ser Phe Ser Leu Asp Phe Gly His
35 40 45

Leu Arg Asn Lys Ser Gly Cys His Val Glu Leu Leu Phe Leu Arg Tyr
50 55 60

Ile Ser Asp Trp Asp Leu Asp Pro Gly Arg Cys Tyr Arg Val Thr Trp
65 70 75 80

Phe Thr Ser Trp Ser Pro Cys Tyr Asp Cys Ala Arg His Val Ala Asp
85 90 95

Phe Leu Arg Gly Tyr Pro Asn Leu Ser Leu Arg Ile Phe Ala Ala Arg
100 105 110

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Leu Tyr Phe Cys Glu Asp Arg Lys Ala Glu Pro Glu Gly Leu Arg Arg
        115                 120                 125

Leu His Arg Ala Gly Val Gln Ile Ala Ile Met Thr Phe Lys Asp Tyr
    130                 135                 140

Phe Tyr Cys Trp Asn Thr Phe Val Glu Asn Arg Glu Lys Thr Phe Lys
145                 150                 155                 160

Ala Trp Glu Gly Leu His Glu Asn Ser Val Arg Leu Ser Arg Gln Leu
                165                 170                 175

Arg Arg Ile Leu Leu Pro Leu Tyr Glu Val Asp Asp Leu Arg Asp Ala
            180                 185                 190

Phe Arg Thr Leu Gly Leu
        195


<210> SEQ ID NO 9
<211> LENGTH: 199
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 9

Met Asp Ser Leu Leu Lys Lys Gln Arg Gln Phe Leu Tyr Gln Phe Lys
1               5                   10                  15

Asn Val Arg Trp Ala Lys Gly Arg His Glu Thr Tyr Leu Cys Tyr Val
            20                  25                  30

Val Lys Arg Arg Asp Ser Pro Thr Ser Phe Ser Leu Asp Phe Gly His
        35                  40                  45

Leu Arg Asn Lys Ala Gly Cys His Val Glu Leu Leu Phe Leu Arg Tyr
    50                  55                  60

Ile Ser Asp Trp Asp Leu Asp Pro Gly Arg Cys Tyr Arg Val Thr Trp
65                  70                  75                  80

Phe Thr Ser Trp Ser Pro Cys Tyr Asp Cys Ala Arg His Val Ala Asp
                85                  90                  95

Phe Leu Arg Gly Tyr Pro Asn Leu Ser Leu Arg Ile Phe Thr Ala Arg
            100                 105                 110

Leu Tyr Phe Cys Asp Lys Glu Arg Lys Ala Glu Pro Glu Gly Leu Arg
        115                 120                 125

Arg Leu His Arg Ala Gly Val Gln Ile Ala Ile Met Thr Phe Lys Asp
    130                 135                 140

Tyr Phe Tyr Cys Trp Asn Thr Phe Val Glu Asn His Glu Arg Thr Phe
145                 150                 155                 160

Lys Ala Trp Glu Gly Leu His Glu Asn Ser Val Arg Leu Ser Arg Gln
                165                 170                 175

Leu Arg Arg Ile Leu Leu Pro Leu Tyr Glu Val Asp Asp Leu Arg Asp
            180                 185                 190

Ala Phe Arg Thr Leu Gly Leu
        195


<210> SEQ ID NO 10
<211> LENGTH: 429
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 10

Met Gly Pro Phe Cys Leu Gly Cys Ser His Arg Lys Cys Tyr Ser Pro
1               5                   10                  15
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Ile Arg Asn Leu Ile Ser Gln Glu Thr Phe Lys Phe His Phe Lys Asn
            20                  25                  30

Leu Gly Tyr Ala Lys Gly Arg Lys Asp Thr Phe Leu Cys Tyr Glu Val
        35                  40                  45

Thr Arg Lys Asp Cys Asp Ser Pro Val Ser Leu His His Gly Val Phe
    50                  55                  60

Lys Asn Lys Asp Asn Ile His Ala Glu Ile Cys Phe Leu Tyr Trp Phe
65                  70                  75                  80

His Asp Lys Val Leu Lys Val Leu Ser Pro Arg Glu Glu Phe Lys Ile
                85                  90                  95

Thr Trp Tyr Met Ser Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Ile
            100                 105                 110

Val Arg Phe Leu Ala Thr His His Asn Leu Ser Leu Asp Ile Phe Ser
        115                 120                 125

Ser Arg Leu Tyr Asn Val Gln Asp Pro Glu Thr Gln Gln Asn Leu Cys
    130                 135                 140

Arg Leu Val Gln Glu Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu
145                 150                 155                 160

Phe Lys Lys Cys Trp Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe
                165                 170                 175

Arg Pro Trp Lys Arg Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys
            180                 185                 190

Leu Gln Glu Ile Leu Arg Pro Cys Tyr Ile Pro Val Pro Ser Ser Ser
        195                 200                 205

Ser Ser Thr Leu Ser Asn Ile Cys Leu Thr Lys Gly Leu Pro Glu Thr
    210                 215                 220

Arg Phe Cys Val Glu Gly Arg Arg Met Asp Pro Leu Ser Glu Glu Glu
225                 230                 235                 240

Phe Tyr Ser Gln Phe Tyr Asn Gln Arg Val Lys His Leu Cys Tyr Tyr
                245                 250                 255

His Arg Met Lys Pro Tyr Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly
            260                 265                 270

Gln Ala Pro Leu Lys Gly Cys Leu Leu Ser Glu Lys Gly Lys Gln His
        275                 280                 285

Ala Glu Ile Leu Phe Leu Asp Lys Ile Arg Ser Met Glu Leu Ser Gln
    290                 295                 300

Val Thr Ile Thr Cys Tyr Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala
305                 310                 315                 320

Trp Gln Leu Ala Ala Phe Lys Arg Asp Arg Pro Asp Leu Ile Leu His
                325                 330                 335

Ile Tyr Thr Ser Arg Leu Tyr Phe His Trp Lys Arg Pro Phe Gln Lys
            340                 345                 350

Gly Leu Cys Ser Leu Trp Gln Ser Gly Ile Leu Val Asp Val Met Asp
        355                 360                 365

Leu Pro Gln Phe Thr Asp Cys Trp Thr Asn Phe Val Asn Pro Lys Arg
    370                 375                 380

Pro Phe Trp Pro Trp Lys Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln
385                 390                 395                 400

Arg Arg Leu Arg Arg Ile Lys Glu Ser Trp Gly Leu Gln Asp Leu Val
                405                 410                 415

Asn Asp Phe Gly Asn Leu Gln Leu Gly Pro Pro Met Ser
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420 425

<210> SEQ ID NO 11
<211> LENGTH: 429
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 11

Met Gly Pro Phe Cys Leu Gly Cys Ser His Arg Lys Cys Tyr Ser Pro
1 5 10 15

Ile Arg Asn Leu Ile Ser Gln Glu Thr Phe Lys Phe His Phe Lys Asn
20 25 30

Leu Arg Tyr Ala Ile Asp Arg Lys Asp Thr Phe Leu Cys Tyr Glu Val
35 40 45

Thr Arg Lys Asp Cys Asp Ser Pro Val Ser Leu His His Gly Val Phe
50 55 60

Lys Asn Lys Asp Asn Ile His Ala Glu Ile Cys Phe Leu Tyr Trp Phe
65 70 75 80

His Asp Lys Val Leu Lys Val Leu Ser Pro Arg Glu Glu Phe Lys Ile
85 90 95

Thr Trp Tyr Met Ser Trp Ser Pro Cys Phe Glu Cys Ala Glu Gln Val
100 105 110

Leu Arg Phe Leu Ala Thr His His Asn Leu Ser Leu Asp Ile Phe Ser
115 120 125

Ser Arg Leu Tyr Asn Ile Arg Asp Pro Glu Asn Gln Gln Asn Leu Cys
130 135 140

Arg Leu Val Gln Glu Gly Ala Gln Val Ala Ala Met Asp Leu Tyr Glu
145 150 155 160

Phe Lys Lys Cys Trp Lys Lys Phe Val Asp Asn Gly Gly Arg Arg Phe
165 170 175

Arg Pro Trp Lys Lys Leu Leu Thr Asn Phe Arg Tyr Gln Asp Ser Lys
180 185 190

Leu Gln Glu Ile Leu Arg Pro Cys Tyr Ile Pro Val Pro Ser Ser Ser
195 200 205

Ser Ser Thr Leu Ser Asn Ile Cys Leu Thr Lys Gly Leu Pro Glu Thr
210 215 220

Arg Phe Cys Val Glu Arg Arg Arg Val His Leu Leu Ser Glu Glu Glu
225 230 235 240

Phe Tyr Ser Gln Phe Tyr Asn Gln Arg Val Lys His Leu Cys Tyr Tyr
245 250 255

His Gly Val Lys Pro Tyr Leu Cys Tyr Gln Leu Glu Gln Phe Asn Gly
260 265 270

Gln Ala Pro Leu Lys Gly Cys Leu Leu Ser Glu Lys Gly Lys Gln His
275 280 285

Ala Glu Ile Leu Phe Leu Asp Lys Ile Arg Ser Met Glu Leu Ser Gln
290 295 300

Val Ile Ile Thr Cys Tyr Leu Thr Trp Ser Pro Cys Pro Asn Cys Ala
305 310 315 320

Trp Gln Leu Ala Ala Phe Lys Arg Asp Arg Pro Asp Leu Ile Leu His
325 330 335

Ile Tyr Thr Ser Arg Leu Tyr Phe His Trp Lys Arg Pro Phe Gln Lys
340 345 350

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Gly Leu Cys Ser Leu Trp Gln Ser Gly Ile Leu Val Asp Val Met Asp
        355                 360                 365

Leu Pro Gln Phe Thr Asp Cys Trp Thr Asn Phe Val Asn Pro Lys Arg
    370                 375                 380

Pro Phe Trp Pro Trp Lys Gly Leu Glu Ile Ile Ser Arg Arg Thr Gln
385                 390                 395                 400

Arg Arg Leu His Arg Ile Lys Glu Ser Trp Gly Leu Gln Asp Leu Val
                405                 410                 415

Asn Asp Phe Gly Asn Leu Gln Leu Gly Pro Pro Met Ser
            420                 425


<210> SEQ ID NO 12
<211> LENGTH: 370
<212> TYPE: PRT
<213> ORGANISM: Macaca fascicularis

<400> SEQUENCE: 12

Met Val Glu Pro Met Asp Pro Arg Thr Phe Val Ser Asn Phe Asn Asn
1               5                   10                  15

Arg Pro Ile Leu Ser Gly Leu Asn Thr Val Trp Leu Cys Cys Glu Val
            20                  25                  30

Lys Thr Lys Asp Pro Ser Gly Pro Pro Leu Asp Ala Lys Ile Phe Gln
        35                  40                  45

Gly Lys Val Tyr Ser Lys Ala Lys Tyr His Pro Glu Met Arg Phe Leu
    50                  55                  60

Arg Trp Phe His Lys Trp Arg Gln Leu His His Asp Gln Glu Tyr Lys
65                  70                  75                  80

Val Thr Trp Tyr Val Ser Trp Ser Pro Cys Thr Arg Cys Ala Asn Ser
                85                  90                  95

Val Ala Thr Phe Leu Ala Lys Asp Pro Lys Val Thr Leu Thr Ile Phe
            100                 105                 110

Val Ala Arg Leu Tyr Tyr Phe Trp Lys Pro Asp Tyr Gln Gln Ala Leu
        115                 120                 125

Arg Ile Leu Cys Gln Lys Arg Gly Gly Pro His Ala Thr Met Lys Ile
    130                 135                 140

Met Asn Tyr Asn Glu Phe Gln Asp Cys Trp Asn Lys Phe Val Asp Gly
145                 150                 155                 160

Arg Gly Lys Pro Phe Lys Pro Arg Asn Asn Leu Pro Lys His Tyr Thr
                165                 170                 175

Leu Leu Gln Ala Thr Leu Gly Glu Leu Leu Arg His Leu Met Asp Pro
            180                 185                 190

Gly Thr Phe Thr Ser Asn Phe Asn Asn Lys Pro Trp Val Ser Gly Gln
        195                 200                 205

His Glu Thr Tyr Leu Cys Tyr Lys Val Glu Arg Leu His Asn Asp Thr
    210                 215                 220

Trp Val Pro Leu Asn Gln His Arg Gly Phe Leu Arg Asn Gln Ala Pro
225                 230                 235                 240

Asn Ile His Gly Phe Pro Lys Gly Arg His Ala Glu Leu Cys Phe Leu
                245                 250                 255

Asp Leu Ile Pro Phe Trp Lys Leu Asp Gly Gln Gln Tyr Arg Val Thr
            260                 265                 270

Cys Phe Thr Ser Trp Ser Pro Cys Phe Ser Cys Ala Gln Glu Met Ala
        275                 280                 285
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Lys Phe Ile Ser Asn Asn Glu His Val Ser Leu Cys Ile Phe Ala Ala
    290                 295                 300

Arg Ile Tyr Asp Asp Gln Gly Arg Tyr Gln Glu Gly Leu Arg Ala Leu
305                 310                 315                 320

His Arg Asp Gly Ala Lys Ile Ala Met Met Asn Tyr Ser Glu Phe Glu
                325                 330                 335

Tyr Cys Trp Asp Thr Phe Val Asp Arg Gln Gly Arg Pro Phe Gln Pro
            340                 345                 350

Trp Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg
        355                 360                 365

Ala Ile
    370


<210> SEQ ID NO 13
<211> LENGTH: 384
<212> TYPE: PRT
<213> ORGANISM: Pan troglodytes

<400> SEQUENCE: 13

Met Lys Pro His Phe Arg Asn Pro Val Glu Arg Met Tyr Gln Asp Thr
1               5                   10                  15

Phe Ser Asp Asn Phe Tyr Asn Arg Pro Ile Leu Ser His Arg Asn Thr
            20                  25                  30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Gly Pro Ser Arg Pro Pro
        35                  40                  45

Leu Asp Ala Lys Ile Phe Arg Gly Gln Val Tyr Ser Lys Leu Lys Tyr
    50                  55                  60

His Pro Glu Met Arg Phe Phe His Trp Phe Ser Lys Trp Arg Lys Leu
65                  70                  75                  80

His Arg Asp Gln Glu Tyr Glu Val Thr Trp Tyr Ile Ser Trp Ser Pro
                85                  90                  95

Cys Thr Lys Cys Thr Arg Asp Val Ala Thr Phe Leu Ala Glu Asp Pro
            100                 105                 110

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Asp
        115                 120                 125

Pro Asp Tyr Gln Glu Ala Leu Arg Ser Leu Cys Gln Lys Arg Asp Gly
    130                 135                 140

Pro Arg Ala Thr Met Lys Ile Met Asn Tyr Asp Glu Phe Gln His Cys
145                 150                 155                 160

Trp Ser Lys Phe Val Tyr Ser Gln Arg Glu Leu Phe Glu Pro Trp Asn
                165                 170                 175

Asn Leu Pro Lys Tyr Tyr Ile Leu Leu His Ile Met Leu Gly Glu Ile
            180                 185                 190

Leu Arg His Ser Met Asp Pro Pro Thr Phe Thr Ser Asn Phe Asn Asn
        195                 200                 205

Glu Leu Trp Val Arg Gly Arg His Glu Thr Tyr Leu Cys Tyr Glu Val
    210                 215                 220

Glu Arg Leu His Asn Asp Thr Trp Val Leu Leu Asn Gln Arg Arg Gly
225                 230                 235                 240

Phe Leu Cys Asn Gln Ala Pro His Lys His Gly Phe Leu Glu Gly Arg
                245                 250                 255

His Ala Glu Leu Cys Phe Leu Asp Val Ile Pro Phe Trp Lys Leu Asp
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            260                 265                 270

Leu His Gln Asp Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys
        275                 280                 285

Phe Ser Cys Ala Gln Glu Met Ala Lys Phe Ile Ser Asn Asn Lys His
    290                 295                 300

Val Ser Leu Cys Ile Phe Ala Ala Arg Ile Tyr Asp Asp Gln Gly Arg
305                 310                 315                 320

Cys Gln Glu Gly Leu Arg Thr Leu Ala Lys Ala Gly Ala Lys Ile Ser
                325                 330                 335

Ile Met Thr Tyr Ser Glu Phe Lys His Cys Trp Asp Thr Phe Val Asp
            340                 345                 350

His Gln Gly Cys Pro Phe Gln Pro Trp Asp Gly Leu Glu Glu His Ser
        355                 360                 365

Gln Ala Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Gly Asn
    370                 375                 380


<210> SEQ ID NO 14
<211> LENGTH: 377
<212> TYPE: PRT
<213> ORGANISM: Chlorocebus aethiops

<400> SEQUENCE: 14

Met Asn Pro Gln Ile Arg Asn Met Val Glu Gln Met Glu Pro Asp Ile
1               5                   10                  15

Phe Val Tyr Tyr Phe Asn Asn Arg Pro Ile Leu Ser Gly Arg Asn Thr
            20                  25                  30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Asp Pro Ser Gly Pro Pro
        35                  40                  45

Leu Asp Ala Asn Ile Phe Gln Gly Lys Leu Tyr Pro Glu Ala Lys Asp
    50                  55                  60

His Pro Glu Met Lys Phe Leu His Trp Phe Arg Lys Trp Arg Gln Leu
65                  70                  75                  80

His Arg Asp Gln Glu Tyr Glu Val Thr Trp Tyr Val Ser Trp Ser Pro
                85                  90                  95

Cys Thr Arg Cys Ala Asn Ser Val Ala Thr Phe Leu Ala Glu Asp Pro
            100                 105                 110

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Lys
        115                 120                 125

Pro Asp Tyr Gln Gln Ala Leu Arg Ile Leu Cys Gln Glu Arg Gly Gly
    130                 135                 140

Pro His Ala Thr Met Lys Ile Met Asn Tyr Asn Glu Phe Gln His Cys
145                 150                 155                 160

Trp Asn Glu Phe Val Asp Gly Gln Gly Lys Pro Phe Lys Pro Arg Lys
                165                 170                 175

Asn Leu Pro Lys His Tyr Thr Leu Leu His Ala Thr Leu Gly Glu Leu
            180                 185                 190

Leu Arg His Val Met Asp Pro Gly Thr Phe Thr Ser Asn Phe Asn Asn
        195                 200                 205

Lys Pro Trp Val Ser Gly Gln Arg Glu Thr Tyr Leu Cys Tyr Lys Val
    210                 215                 220

Glu Arg Ser His Asn Asp Thr Trp Val Leu Leu Asn Gln His Arg Gly
225                 230                 235                 240
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Phe Leu Arg Asn Gln Ala Pro Asp Arg His Gly Phe Pro Lys Gly Arg
                245                 250                 255

His Ala Glu Leu Cys Phe Leu Asp Leu Ile Pro Phe Trp Lys Leu Asp
            260                 265                 270

Asp Gln Gln Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys Phe
        275                 280                 285

Ser Cys Ala Gln Lys Met Ala Lys Phe Ile Ser Asn Asn Lys His Val
    290                 295                 300

Ser Leu Cys Ile Phe Ala Ala Arg Ile Tyr Asp Asp Gln Gly Arg Cys
305                 310                 315                 320

Gln Glu Gly Leu Arg Thr Leu His Arg Asp Gly Ala Lys Ile Ala Val
                325                 330                 335

Met Asn Tyr Ser Glu Phe Glu Tyr Cys Trp Asp Thr Phe Val Asp Arg
            340                 345                 350

Gln Gly Arg Pro Phe Gln Pro Trp Asp Gly Leu Asp Glu His Ser Gln
        355                 360                 365

Ala Leu Ser Gly Arg Leu Arg Ala Ile
    370                 375


<210> SEQ ID NO 15
<211> LENGTH: 384
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Met Lys Pro His Phe Arg Asn Thr Val Glu Arg Met Tyr Arg Asp Thr
1               5                   10                  15

Phe Ser Tyr Asn Phe Tyr Asn Arg Pro Ile Leu Ser Arg Arg Asn Thr
            20                  25                  30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Gly Pro Ser Arg Pro Pro
        35                  40                  45

Leu Asp Ala Lys Ile Phe Arg Gly Gln Val Tyr Ser Glu Leu Lys Tyr
    50                  55                  60

His Pro Glu Met Arg Phe Phe His Trp Phe Ser Lys Trp Arg Lys Leu
65                  70                  75                  80

His Arg Asp Gln Glu Tyr Glu Val Thr Trp Tyr Ile Ser Trp Ser Pro
                85                  90                  95

Cys Thr Lys Cys Thr Arg Asp Met Ala Thr Phe Leu Ala Glu Asp Pro
            100                 105                 110

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Asp
        115                 120                 125

Pro Asp Tyr Gln Glu Ala Leu Arg Ser Leu Cys Gln Lys Arg Asp Gly
    130                 135                 140

Pro Arg Ala Thr Met Lys Ile Met Asn Tyr Asp Glu Phe Gln His Cys
145                 150                 155                 160

Trp Ser Lys Phe Val Tyr Ser Gln Arg Glu Leu Phe Glu Pro Trp Asn
                165                 170                 175

Asn Leu Pro Lys Tyr Tyr Ile Leu Leu His Ile Met Leu Gly Glu Ile
            180                 185                 190

Leu Arg His Ser Met Asp Pro Pro Thr Phe Thr Phe Asn Phe Asn Asn
        195                 200                 205

Glu Pro Trp Val Arg Gly Arg His Glu Thr Tyr Leu Cys Tyr Glu Val
    210                 215                 220
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Glu Arg Met His Asn Asp Thr Trp Val Leu Leu Asn Gln Arg Arg Gly
225                 230                 235                 240

Phe Leu Cys Asn Gln Ala Pro His Lys His Gly Phe Leu Glu Gly Arg
                245                 250                 255

His Ala Glu Leu Cys Phe Leu Asp Val Ile Pro Phe Trp Lys Leu Asp
            260                 265                 270

Leu Asp Gln Asp Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys
        275                 280                 285

Phe Ser Cys Ala Gln Glu Met Ala Lys Phe Ile Ser Lys Asn Lys His
    290                 295                 300

Val Ser Leu Cys Ile Phe Thr Ala Arg Ile Tyr Asp Asp Gln Gly Arg
305                 310                 315                 320

Cys Gln Glu Gly Leu Arg Thr Leu Ala Glu Ala Gly Ala Lys Ile Ser
                325                 330                 335

Ile Met Thr Tyr Ser Glu Phe Lys His Cys Trp Asp Thr Phe Val Asp
            340                 345                 350

His Gln Gly Cys Pro Phe Gln Pro Trp Asp Gly Leu Asp Glu His Ser
        355                 360                 365

Gln Asp Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Glu Asn
    370                 375                 380


<210> SEQ ID NO 16
<211> LENGTH: 373
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Met Lys Pro His Phe Arg Asn Thr Val Glu Arg Met Tyr Arg Asp Thr
1               5                   10                  15

Phe Ser Tyr Asn Phe Tyr Asn Arg Pro Ile Leu Ser Arg Arg Asn Thr
            20                  25                  30

Val Trp Leu Cys Tyr Glu Val Lys Thr Lys Gly Pro Ser Arg Pro Arg
        35                  40                  45

Leu Asp Ala Lys Ile Phe Arg Gly Gln Val Tyr Ser Gln Pro Glu His
    50                  55                  60

His Ala Glu Met Cys Phe Leu Ser Trp Phe Cys Gly Asn Gln Leu Pro
65                  70                  75                  80

Ala Tyr Lys Cys Phe Gln Ile Thr Trp Phe Val Ser Trp Thr Pro Cys
                85                  90                  95

Pro Asp Cys Val Ala Lys Leu Ala Glu Phe Leu Ala Glu His Pro Asn
            100                 105                 110

Val Thr Leu Thr Ile Ser Ala Ala Arg Leu Tyr Tyr Tyr Trp Glu Arg
        115                 120                 125

Asp Tyr Arg Arg Ala Leu Cys Arg Leu Ser Gln Ala Gly Ala Arg Val
    130                 135                 140

Lys Ile Met Asp Asp Glu Glu Phe Ala Tyr Cys Trp Glu Asn Phe Val
145                 150                 155                 160

Tyr Ser Glu Gly Gln Pro Phe Met Pro Trp Tyr Lys Phe Asp Asp Asn
                165                 170                 175

Tyr Ala Phe Leu His Arg Thr Leu Lys Glu Ile Leu Arg Asn Pro Met
            180                 185                 190

Glu Ala Met Tyr Pro His Ile Phe Tyr Phe His Phe Lys Asn Leu Arg
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        195                 200                 205

Lys Ala Tyr Gly Arg Asn Glu Ser Trp Leu Cys Phe Thr Met Glu Val
    210                 215                 220

Val Lys His His Ser Pro Val Ser Trp Lys Arg Gly Val Phe Arg Asn
225                 230                 235                 240

Gln Val Asp Pro Glu Thr His Cys His Ala Glu Arg Cys Phe Leu Ser
                245                 250                 255

Trp Phe Cys Asp Asp Ile Leu Ser Pro Asn Thr Asn Tyr Glu Val Thr
            260                 265                 270

Trp Tyr Thr Ser Trp Ser Pro Cys Pro Glu Cys Ala Gly Glu Val Ala
        275                 280                 285

Glu Phe Leu Ala Arg His Ser Asn Val Asn Leu Thr Ile Phe Thr Ala
    290                 295                 300

Arg Leu Tyr Tyr Phe Trp Asp Thr Asp Tyr Gln Glu Gly Leu Arg Ser
305                 310                 315                 320

Leu Ser Gln Glu Gly Ala Ser Val Glu Ile Met Gly Tyr Lys Asp Phe
                325                 330                 335

Lys Tyr Cys Trp Glu Asn Phe Val Tyr Asn Asp Asp Glu Pro Phe Lys
            340                 345                 350

Pro Trp Lys Gly Leu Lys Tyr Asn Phe Leu Phe Leu Asp Ser Lys Leu
        355                 360                 365

Gln Glu Ile Leu Glu
    370


<210> SEQ ID NO 17
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Met Asn Pro Gln Ile Arg Asn Pro Met Glu Arg Met Tyr Arg Asp Thr
1               5                   10                  15

Phe Tyr Asp Asn Phe Glu Asn Glu Pro Ile Leu Tyr Gly Arg Ser Tyr
            20                  25                  30

Thr Trp Leu Cys Tyr Glu Val Lys Ile Lys Arg Gly Arg Ser Asn Leu
        35                  40                  45

Leu Trp Asp Thr Gly Val Phe Arg Gly Gln Val Tyr Phe Lys Pro Gln
    50                  55                  60

Tyr His Ala Glu Met Cys Phe Leu Ser Trp Phe Cys Gly Asn Gln Leu
65                  70                  75                  80

Pro Ala Tyr Lys Cys Phe Gln Ile Thr Trp Phe Val Ser Trp Thr Pro
                85                  90                  95

Cys Pro Asp Cys Val Ala Lys Leu Ala Glu Phe Leu Ser Glu His Pro
            100                 105                 110

Asn Val Thr Leu Thr Ile Ser Ala Ala Arg Leu Tyr Tyr Tyr Trp Glu
        115                 120                 125

Arg Asp Tyr Arg Arg Ala Leu Cys Arg Leu Ser Gln Ala Gly Ala Arg
    130                 135                 140

Val Thr Ile Met Asp Tyr Glu Glu Phe Ala Tyr Cys Trp Glu Asn Phe
145                 150                 155                 160

Val Tyr Asn Glu Gly Gln Gln Phe Met Pro Trp Tyr Lys Phe Asp Glu
                165                 170                 175
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Asn Tyr Ala Phe Leu His Arg Thr Leu Lys Glu Ile Leu Arg Tyr Leu
            180                 185                 190

Met Asp Pro Asp Thr Phe Thr Phe Asn Phe Asn Asn Asp Pro Leu Val
        195                 200                 205

Leu Arg Arg Arg Gln Thr Tyr Leu Cys Tyr Glu Val Glu Arg Leu Asp
    210                 215                 220

Asn Gly Thr Trp Val Leu Met Asp Gln His Met Gly Phe Leu Cys Asn
225                 230                 235                 240

Glu Ala Lys Asn Leu Leu Cys Gly Phe Tyr Gly Arg His Ala Glu Leu
                245                 250                 255

Arg Phe Leu Asp Leu Val Pro Ser Leu Gln Leu Asp Pro Ala Gln Ile
            260                 265                 270

Tyr Arg Val Thr Trp Phe Ile Ser Trp Ser Pro Cys Phe Ser Trp Gly
        275                 280                 285

Cys Ala Gly Glu Val Arg Ala Phe Leu Gln Glu Asn Thr His Val Arg
    290                 295                 300

Leu Arg Ile Phe Ala Ala Arg Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys
305                 310                 315                 320

Glu Ala Leu Gln Met Leu Arg Asp Ala Gly Ala Gln Val Ser Ile Met
                325                 330                 335

Thr Tyr Asp Glu Phe Glu Tyr Cys Trp Asp Thr Phe Val Tyr Arg Gln
            340                 345                 350

Gly Cys Pro Phe Gln Pro Trp Asp Gly Leu Glu Glu His Ser Gln Ala
        355                 360                 365

Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Gly Asn
    370                 375                 380


<210> SEQ ID NO 18
<211> LENGTH: 190
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Met Asn Pro Gln Ile Arg Asn Pro Met Lys Ala Met Tyr Pro Gly Thr
1               5                   10                  15

Phe Tyr Phe Gln Phe Lys Asn Leu Trp Glu Ala Asn Asp Arg Asn Glu
            20                  25                  30

Thr Trp Leu Cys Phe Thr Val Glu Gly Ile Lys Arg Arg Ser Val Val
        35                  40                  45

Ser Trp Lys Thr Gly Val Phe Arg Asn Gln Val Asp Ser Glu Thr His
    50                  55                  60

Cys His Ala Glu Arg Cys Phe Leu Ser Trp Phe Cys Asp Asp Ile Leu
65                  70                  75                  80

Ser Pro Asn Thr Lys Tyr Gln Val Thr Trp Tyr Thr Ser Trp Ser Pro
                85                  90                  95

Cys Pro Asp Cys Ala Gly Glu Val Ala Glu Phe Leu Ala Arg His Ser
            100                 105                 110

Asn Val Asn Leu Thr Ile Phe Thr Ala Arg Leu Tyr Tyr Phe Gln Tyr
        115                 120                 125

Pro Cys Tyr Gln Glu Gly Leu Arg Ser Leu Ser Gln Glu Gly Val Ala
    130                 135                 140

Val Glu Ile Met Asp Tyr Glu Asp Phe Lys Tyr Cys Trp Glu Asn Phe
145                 150                 155                 160
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Val Tyr Asn Asp Asn Glu Pro Phe Lys Pro Trp Lys Gly Leu Lys Thr
                165                 170                 175

Asn Phe Arg Leu Leu Lys Arg Arg Leu Arg Glu Ser Leu Gln
            180                 185                 190


<210> SEQ ID NO 19
<211> LENGTH: 199
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Met Glu Ala Ser Pro Ala Ser Gly Pro Arg His Leu Met Asp Pro His
1               5                   10                  15

Ile Phe Thr Ser Asn Phe Asn Asn Gly Ile Gly Arg His Lys Thr Tyr
            20                  25                  30

Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
        35                  40                  45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50                  55                  60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65                  70                  75                  80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85                  90                  95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190

Ile Leu Gln Asn Gln Gly Asn
        195


<210> SEQ ID NO 20
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Met Ala Leu Leu Thr Ala Glu Thr Phe Arg Leu Gln Phe Asn Asn Lys
1               5                   10                  15

Arg Arg Leu Arg Arg Pro Tyr Tyr Pro Arg Lys Ala Leu Leu Cys Tyr
            20                  25                  30

Gln Leu Thr Pro Gln Asn Gly Ser Thr Pro Thr Arg Gly Tyr Phe Glu
        35                  40                  45

Asn Lys Lys Lys Cys His Ala Glu Ile Cys Phe Ile Asn Glu Ile Lys
    50                  55                  60

Ser Met Gly Leu Asp Glu Thr Gln Cys Tyr Gln Val Thr Cys Tyr Leu
65                  70                  75                  80
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Thr Trp Ser Pro Cys Ser Ser Cys Ala Trp Glu Leu Val Asp Phe Ile
                85                  90                  95

Lys Ala His Asp His Leu Asn Leu Gly Ile Phe Ala Ser Arg Leu Tyr
            100                 105                 110

Tyr His Trp Cys Lys Pro Gln Gln Lys Gly Leu Arg Leu Leu Cys Gly
        115                 120                 125

Ser Gln Val Pro Val Glu Val Met Gly Phe Pro Lys Phe Ala Asp Cys
    130                 135                 140

Trp Glu Asn Phe Val Asp His Glu Lys Pro Leu Ser Phe Asn Pro Tyr
145                 150                 155                 160

Lys Met Leu Glu Glu Leu Asp Lys Asn Ser Arg Ala Ile Lys Arg Arg
                165                 170                 175

Leu Glu Arg Ile Lys Ile Pro Gly Val Arg Ala Gln Gly Arg Tyr Met
            180                 185                 190

Asp Ile Leu Cys Asp Ala Glu Val
        195                 200


<210> SEQ ID NO 21
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Met Asn Pro Gln Ile Arg Asn Pro Met Glu Arg Met Tyr Arg Asp Thr
1               5                   10                  15

Phe Tyr Asp Asn Phe Glu Asn Glu Pro Ile Leu Tyr Gly Arg Ser Tyr
            20                  25                  30

Thr Trp Leu Cys Tyr Glu Val Lys Ile Lys Arg Gly Arg Ser Asn Leu
        35                  40                  45

Leu Trp Asp Thr Gly Val Phe Arg Gly Pro Val Leu Pro Lys Arg Gln
    50                  55                  60

Ser Asn His Arg Gln Glu Val Tyr Phe Arg Phe Glu Asn His Ala Glu
65                  70                  75                  80

Met Cys Phe Leu Ser Trp Phe Cys Gly Asn Arg Leu Pro Ala Asn Arg
                85                  90                  95

Arg Phe Gln Ile Thr Trp Phe Val Ser Trp Asn Pro Cys Leu Pro Cys
            100                 105                 110

Val Val Lys Val Thr Lys Phe Leu Ala Glu His Pro Asn Val Thr Leu
        115                 120                 125

Thr Ile Ser Ala Ala Arg Leu Tyr Tyr Tyr Arg Asp Arg Asp Trp Arg
    130                 135                 140

Trp Val Leu Leu Arg Leu His Lys Ala Gly Ala Arg Val Lys Ile Met
145                 150                 155                 160

Asp Tyr Glu Asp Phe Ala Tyr Cys Trp Glu Asn Phe Val Cys Asn Glu
                165                 170                 175

Gly Gln Pro Phe Met Pro Trp Tyr Lys Phe Asp Asp Asn Tyr Ala Ser
            180                 185                 190

Leu His Arg Thr Leu Lys Glu Ile Leu Arg Asn Pro Met Glu Ala Met
        195                 200                 205

Tyr Pro His Ile Phe Tyr Phe His Phe Lys Asn Leu Leu Lys Ala Cys
    210                 215                 220

Gly Arg Asn Glu Ser Trp Leu Cys Phe Thr Met Glu Val Thr Lys His
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225                 230                 235                 240

His Ser Ala Val Phe Arg Lys Arg Gly Val Phe Arg Asn Gln Val Asp
                245                 250                 255

Pro Glu Thr His Cys His Ala Glu Arg Cys Phe Leu Ser Trp Phe Cys
            260                 265                 270

Asp Asp Ile Leu Ser Pro Asn Thr Asn Tyr Glu Val Thr Trp Tyr Thr
        275                 280                 285

Ser Trp Ser Pro Cys Pro Glu Cys Ala Gly Glu Val Ala Glu Phe Leu
    290                 295                 300

Ala Arg His Ser Asn Val Asn Leu Thr Ile Phe Thr Ala Arg Leu Cys
305                 310                 315                 320

Tyr Phe Trp Asp Thr Asp Tyr Gln Glu Gly Leu Cys Ser Leu Ser Gln
                325                 330                 335

Glu Gly Ala Ser Val Lys Ile Met Gly Tyr Lys Asp Phe Val Ser Cys
            340                 345                 350

Trp Lys Asn Phe Val Tyr Ser Asp Asp Glu Pro Phe Lys Pro Trp Lys
        355                 360                 365

Gly Leu Gln Thr Asn Phe Arg Leu Leu Lys Arg Arg Leu Arg Glu Ile
    370                 375                 380

Leu Gln
385
```

<210> SEQ ID NO 22
<211> LENGTH: 236
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

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Met Thr Ser Glu Lys Gly Pro Ser Thr Gly Asp Pro Thr Leu Arg Arg
1               5                   10                  15

Arg Ile Glu Pro Trp Glu Phe Asp Val Phe Tyr Asp Pro Arg Glu Leu
            20                  25                  30

Arg Lys Glu Ala Cys Leu Leu Tyr Glu Ile Lys Trp Gly Met Ser Arg
        35                  40                  45

Lys Ile Trp Arg Ser Ser Gly Lys Asn Thr Thr Asn His Val Glu Val
    50                  55                  60

Asn Phe Ile Lys Lys Phe Thr Ser Glu Arg Asp Phe His Pro Ser Met
65                  70                  75                  80

Ser Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Trp Glu Cys
                85                  90                  95

Ser Gln Ala Ile Arg Glu Phe Leu Ser Arg His Pro Gly Val Thr Leu
            100                 105                 110

Val Ile Tyr Val Ala Arg Leu Phe Trp His Met Asp Gln Gln Asn Arg
        115                 120                 125

Gln Gly Leu Arg Asp Leu Val Asn Ser Gly Val Thr Ile Gln Ile Met
    130                 135                 140

Arg Ala Ser Glu Tyr Tyr His Cys Trp Arg Asn Phe Val Asn Tyr Pro
145                 150                 155                 160

Pro Gly Asp Glu Ala His Trp Pro Gln Tyr Pro Pro Leu Trp Met Met
                165                 170                 175

Leu Tyr Ala Leu Glu Leu His Cys Ile Ile Leu Ser Leu Pro Pro Cys
            180                 185                 190
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Leu Lys Ile Ser Arg Arg Trp Gln Asn His Leu Thr Phe Phe Arg Leu
        195                 200                 205

His Leu Gln Asn Cys His Tyr Gln Thr Ile Pro Pro His Ile Leu Leu
    210                 215                 220

Ala Thr Gly Leu Ile His Pro Ser Val Ala Trp Arg
225                 230                 235


<210> SEQ ID NO 23
<211> LENGTH: 229
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 23

Met Ser Ser Glu Thr Gly Pro Val Ala Val Asp Pro Thr Leu Arg Arg
1               5                   10                  15

Arg Ile Glu Pro His Glu Phe Glu Val Phe Phe Asp Pro Arg Glu Leu
            20                  25                  30

Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Asn Trp Gly Gly Arg His
        35                  40                  45

Ser Val Trp Arg His Thr Ser Gln Asn Thr Ser Asn His Val Glu Val
    50                  55                  60

Asn Phe Leu Glu Lys Phe Thr Thr Glu Arg Tyr Phe Arg Pro Asn Thr
65                  70                  75                  80

Arg Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Gly Glu Cys
                85                  90                  95

Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg His Pro Tyr Val Thr Leu
            100                 105                 110

Phe Ile Tyr Ile Ala Arg Leu Tyr His His Thr Asp Gln Arg Asn Arg
        115                 120                 125

Gln Gly Leu Arg Asp Leu Ile Ser Ser Gly Val Thr Ile Gln Ile Met
    130                 135                 140

Thr Glu Gln Glu Tyr Cys Tyr Cys Trp Arg Asn Phe Val Asn Tyr Pro
145                 150                 155                 160

Pro Ser Asn Glu Ala Tyr Trp Pro Arg Tyr Pro His Leu Trp Val Lys
                165                 170                 175

Leu Tyr Val Leu Glu Leu Tyr Cys Ile Ile Leu Gly Leu Pro Pro Cys
            180                 185                 190

Leu Lys Ile Leu Arg Arg Lys Gln Pro Gln Leu Thr Phe Phe Thr Ile
        195                 200                 205

Thr Leu Gln Thr Cys His Tyr Gln Arg Ile Pro Pro His Leu Leu Trp
    210                 215                 220

Ala Thr Gly Leu Lys
225


<210> SEQ ID NO 24
<211> LENGTH: 229
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 24

Met Ser Ser Glu Thr Gly Pro Val Ala Val Asp Pro Thr Leu Arg Arg
1               5                   10                  15

Arg Ile Glu Pro His Glu Phe Glu Val Phe Phe Asp Pro Arg Glu Leu
            20                  25                  30
```

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```
Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Asn Trp Gly Gly Arg His
        35                  40                  45

Ser Ile Trp Arg His Thr Ser Gln Asn Thr Asn Lys His Val Glu Val
    50                  55                  60

Asn Phe Ile Glu Lys Phe Thr Thr Glu Arg Tyr Phe Cys Pro Asn Thr
65                  70                  75                  80

Arg Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Gly Glu Cys
                85                  90                  95

Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg Tyr Pro His Val Thr Leu
            100                 105                 110

Phe Ile Tyr Ile Ala Arg Leu Tyr His His Ala Asp Pro Arg Asn Arg
        115                 120                 125

Gln Gly Leu Arg Asp Leu Ile Ser Ser Gly Val Thr Ile Gln Ile Met
    130                 135                 140

Thr Glu Gln Glu Ser Gly Tyr Cys Trp Arg Asn Phe Val Asn Tyr Ser
145                 150                 155                 160

Pro Ser Asn Glu Ala His Trp Pro Arg Tyr Pro His Leu Trp Val Arg
                165                 170                 175

Leu Tyr Val Leu Glu Leu Tyr Cys Ile Ile Leu Gly Leu Pro Pro Cys
            180                 185                 190

Leu Asn Ile Leu Arg Arg Lys Gln Pro Gln Leu Thr Phe Phe Thr Ile
        195                 200                 205

Ala Leu Gln Ser Cys His Tyr Gln Arg Leu Pro Pro His Ile Leu Trp
    210                 215                 220

Ala Thr Gly Leu Lys
225


<210> SEQ ID NO 25
<211> LENGTH: 191
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

Met Glu Ala Lys Ala Ala Pro Lys Pro Ala Ala Ser Gly Ala Cys Ser
1               5                   10                  15

Val Ser Ala Glu Glu Thr Glu Lys Trp Met Glu Glu Ala Met His Met
            20                  25                  30

Ala Lys Glu Ala Leu Glu Asn Thr Glu Val Pro Val Gly Cys Leu Met
        35                  40                  45

Val Tyr Asn Asn Glu Val Val Gly Lys Gly Arg Asn Glu Val Asn Gln
    50                  55                  60

Thr Lys Asn Ala Thr Arg His Ala Glu Met Val Ala Ile Asp Gln Val
65                  70                  75                  80

Leu Asp Trp Cys Arg Gln Ser Gly Lys Ser Pro Ser Glu Val Phe Glu
                85                  90                  95

His Thr Val Leu Tyr Val Thr Val Glu Pro Cys Ile Met Cys Ala Ala
            100                 105                 110

Ala Leu Arg Leu Met Lys Ile Pro Leu Val Val Tyr Gly Cys Gln Asn
        115                 120                 125

Glu Arg Phe Gly Gly Cys Gly Ser Val Leu Asn Ile Ala Ser Ala Asp
    130                 135                 140

Leu Pro Asn Thr Gly Arg Pro Phe Gln Cys Ile Pro Gly Tyr Arg Ala
145                 150                 155                 160
```

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```
Glu Glu Ala Val Glu Met Leu Lys Thr Phe Tyr Lys Gln Glu Asn Pro
                165                 170                 175

Asn Ala Pro Lys Ser Lys Val Arg Lys Lys Glu Cys Gln Lys Ser
            180                 185                 190


<210> SEQ ID NO 26
<211> LENGTH: 191
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 26

Met Glu Glu Lys Val Glu Ser Thr Thr Thr Pro Asp Gly Pro Cys Val
1               5                   10                  15

Val Ser Val Gln Glu Thr Glu Lys Trp Met Glu Glu Ala Met Arg Met
            20                  25                  30

Ala Lys Glu Ala Leu Glu Asn Ile Glu Val Pro Val Gly Cys Leu Met
        35                  40                  45

Val Tyr Asn Asn Glu Val Val Gly Lys Gly Arg Asn Glu Val Asn Gln
    50                  55                  60

Thr Lys Asn Ala Thr Arg His Ala Glu Met Val Ala Ile Asp Gln Val
65                  70                  75                  80

Leu Asp Trp Cys His Gln His Gly Gln Ser Pro Ser Thr Val Phe Glu
                85                  90                  95

His Thr Val Leu Tyr Val Thr Val Glu Pro Cys Ile Met Cys Ala Ala
            100                 105                 110

Ala Leu Arg Leu Met Lys Ile Pro Leu Val Val Tyr Gly Cys Gln Asn
        115                 120                 125

Glu Arg Phe Gly Gly Cys Gly Ser Val Leu Asn Ile Ala Ser Ala Asp
    130                 135                 140

Leu Pro Asn Thr Gly Arg Pro Phe Gln Cys Ile Pro Gly Tyr Arg Ala
145                 150                 155                 160

Glu Glu Ala Val Glu Leu Leu Lys Thr Phe Tyr Lys Gln Glu Asn Pro
                165                 170                 175

Asn Ala Pro Lys Ser Lys Val Arg Lys Lys Asp Cys Gln Lys Ser
            180                 185                 190


<210> SEQ ID NO 27
<211> LENGTH: 499
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 27

Met Trp Thr Ala Asp Glu Ile Ala Gln Leu Cys Tyr Ala His Tyr Asn
1               5                   10                  15

Val Arg Leu Pro Lys Gln Gly Lys Pro Glu Pro Asn Arg Glu Trp Thr
            20                  25                  30

Leu Leu Ala Ala Val Val Lys Ile Gln Ala Ser Ala Asn Gln Ala Cys
        35                  40                  45

Asp Ile Pro Glu Lys Glu Val Gln Val Thr Lys Glu Val Val Ser Met
    50                  55                  60

Gly Thr Gly Thr Lys Cys Ile Gly Gln Ser Lys Met Arg Glu Ser Gly
65                  70                  75                  80

Asp Ile Leu Asn Asp Ser His Ala Glu Ile Ile Ala Arg Arg Ser Phe
                85                  90                  95
```

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```
Gln Arg Tyr Leu Leu His Gln Leu His Leu Ala Ala Val Leu Lys Glu
            100                 105                 110

Asp Ser Ile Phe Val Pro Gly Thr Gln Arg Gly Leu Trp Arg Leu Arg
        115                 120                 125

Pro Asp Leu Ser Phe Val Phe Phe Ser Ser His Thr Pro Cys Gly Asp
    130                 135                 140

Ala Ser Ile Ile Pro Met Leu Glu Phe Glu Glu Gln Pro Cys Cys Pro
145                 150                 155                 160

Val Ile Arg Ser Trp Ala Asn Asn Ser Pro Val Gln Glu Thr Glu Asn
                165                 170                 175

Leu Glu Asp Ser Lys Asp Lys Arg Asn Cys Glu Asp Pro Ala Ser Pro
            180                 185                 190

Val Ala Lys Lys Met Arg Leu Gly Thr Pro Ala Arg Ser Leu Ser Asn
        195                 200                 205

Cys Val Ala His His Gly Thr Gln Glu Ser Gly Pro Val Lys Pro Asp
    210                 215                 220

Val Ser Ser Ser Asp Leu Thr Lys Glu Glu Pro Asp Ala Ala Asn Gly
225                 230                 235                 240

Ile Ala Ser Gly Ser Phe Arg Val Val Asp Val Tyr Arg Thr Gly Ala
                245                 250                 255

Lys Cys Val Pro Gly Glu Thr Gly Asp Leu Arg Glu Pro Gly Ala Ala
            260                 265                 270

Tyr His Gln Val Gly Leu Leu Arg Val Lys Pro Gly Arg Gly Asp Arg
        275                 280                 285

Thr Cys Ser Met Ser Cys Ser Asp Lys Met Ala Arg Trp Asn Val Leu
    290                 295                 300

Gly Cys Gln Gly Ala Leu Leu Met His Phe Leu Glu Lys Pro Ile Tyr
305                 310                 315                 320

Leu Ser Ala Val Val Ile Gly Lys Cys Pro Tyr Ser Gln Glu Ala Met
                325                 330                 335

Arg Arg Ala Leu Thr Gly Arg Cys Glu Glu Thr Leu Val Leu Pro Arg
            340                 345                 350

Gly Phe Gly Val Gln Glu Leu Glu Ile Gln Gln Ser Gly Leu Leu Phe
        355                 360                 365

Glu Gln Ser Arg Cys Ala Val His Arg Lys Arg Gly Asp Ser Pro Gly
    370                 375                 380

Arg Leu Val Pro Cys Gly Ala Ala Ile Ser Trp Ser Ala Val Pro Gln
385                 390                 395                 400

Gln Pro Leu Asp Val Thr Ala Asn Gly Phe Pro Gln Gly Thr Thr Lys
                405                 410                 415

Lys Glu Ile Gly Ser Pro Arg Ala Arg Ser Arg Ile Ser Lys Val Glu
            420                 425                 430

Leu Phe Arg Ser Phe Gln Lys Leu Leu Ser Ser Ile Ala Asp Asp Glu
        435                 440                 445

Gln Pro Asp Ser Ile Arg Val Thr Lys Lys Leu Asp Thr Tyr Gln Glu
    450                 455                 460

Tyr Lys Asp Ala Ala Ser Ala Tyr Gln Glu Ala Trp Gly Ala Leu Arg
465                 470                 475                 480

Arg Ile Gln Pro Phe Ala Ser Trp Ile Arg Asn Pro Pro Asp Tyr His
                485                 490                 495
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Gln Phe Lys

<210> SEQ ID NO 28
<211> LENGTH: 502
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Met Trp Thr Ala Asp Glu Ile Ala Gln Leu Cys Tyr Glu His Tyr Gly
1 5 10 15

Ile Arg Leu Pro Lys Lys Gly Lys Pro Glu Pro Asn His Glu Trp Thr
20 25 30

Leu Leu Ala Ala Val Val Lys Ile Gln Ser Pro Ala Asp Lys Ala Cys
35 40 45

Asp Thr Pro Asp Lys Pro Val Gln Val Thr Lys Glu Val Val Ser Met
50 55 60

Gly Thr Gly Thr Lys Cys Ile Gly Gln Ser Lys Met Arg Lys Asn Gly
65 70 75 80

Asp Ile Leu Asn Asp Ser His Ala Glu Val Ile Ala Arg Arg Ser Phe
85 90 95

Gln Arg Tyr Leu Leu His Gln Leu Gln Leu Ala Ala Thr Leu Lys Glu
100 105 110

Asp Ser Ile Phe Val Pro Gly Thr Gln Lys Gly Val Trp Lys Leu Arg
115 120 125

Arg Asp Leu Ile Phe Val Phe Phe Ser Ser His Thr Pro Cys Gly Asp
130 135 140

Ala Ser Ile Ile Pro Met Leu Glu Phe Glu Asp Gln Pro Cys Cys Pro
145 150 155 160

Val Phe Arg Asn Trp Ala His Asn Ser Ser Val Glu Ala Ser Ser Asn
165 170 175

Leu Glu Ala Pro Gly Asn Glu Arg Lys Cys Glu Asp Pro Asp Ser Pro
180 185 190

Val Thr Lys Lys Met Arg Leu Glu Pro Gly Thr Ala Ala Arg Glu Val
195 200 205

Thr Asn Gly Ala Ala His His Gln Ser Phe Gly Lys Gln Lys Ser Gly
210 215 220

Pro Ile Ser Pro Gly Ile His Ser Cys Asp Leu Thr Val Glu Gly Leu
225 230 235 240

Ala Thr Val Thr Arg Ile Ala Pro Gly Ser Ala Lys Val Ile Asp Val
245 250 255

Tyr Arg Thr Gly Ala Lys Cys Val Pro Gly Glu Ala Gly Asp Ser Gly
260 265 270

Lys Pro Gly Ala Ala Phe His Gln Val Gly Leu Leu Arg Val Lys Pro
275 280 285

Gly Arg Gly Asp Arg Thr Arg Ser Met Ser Cys Ser Asp Lys Met Ala
290 295 300

Arg Trp Asn Val Leu Gly Cys Gln Gly Ala Leu Leu Met His Leu Leu
305 310 315 320

Glu Glu Pro Ile Tyr Leu Ser Ala Val Val Ile Gly Lys Cys Pro Tyr
325 330 335

Ser Gln Glu Ala Met Gln Arg Ala Leu Ile Gly Arg Cys Gln Asn Val
340 345 350

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```
Ser Ala Leu Pro Lys Gly Phe Gly Val Gln Glu Leu Lys Ile Leu Gln
        355                 360                 365

Ser Asp Leu Leu Phe Glu Gln Ser Arg Ser Ala Val Gln Ala Lys Arg
    370                 375                 380

Ala Asp Ser Pro Gly Arg Leu Val Pro Cys Gly Ala Ala Ile Ser Trp
385                 390                 395                 400

Ser Ala Val Pro Glu Gln Pro Leu Asp Val Thr Ala Asn Gly Phe Pro
                405                 410                 415

Gln Gly Thr Thr Lys Lys Thr Ile Gly Ser Leu Gln Ala Arg Ser Gln
            420                 425                 430

Ile Ser Lys Val Glu Leu Phe Arg Ser Phe Gln Lys Leu Leu Ser Arg
        435                 440                 445

Ile Ala Arg Asp Lys Trp Pro His Ser Leu Arg Val Gln Lys Leu Asp
    450                 455                 460

Thr Tyr Gln Glu Tyr Lys Glu Ala Ala Ser Ser Tyr Gln Glu Ala Trp
465                 470                 475                 480

Ser Thr Leu Arg Lys Gln Val Phe Gly Ser Trp Ile Arg Asn Pro Pro
                485                 490                 495

Asp Tyr His Gln Phe Lys
            500


<210> SEQ ID NO 29
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 29

Ser Pro Lys Lys Lys Arg Lys Val Glu Ala Ser
1               5                   10


<210> SEQ ID NO 30
<211> LENGTH: 1580
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 30

Met Asp Ser Leu Leu Met Asn Arg Arg Lys Phe Leu Tyr Gln Phe Lys
1               5                   10                  15

Asn Val Arg Trp Ala Lys Gly Arg Arg Glu Thr Tyr Leu Cys Asp Lys
            20                  25                  30

Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly Trp Ala
        35                  40                  45

Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu
    50                  55                  60

Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu
65                  70                  75                  80

Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr
                85                  90                  95

Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln
            100                 105                 110

Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe Phe His
        115                 120                 125
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```
Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg
    130                 135                 140

His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys
145                 150                 155                 160

Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp
                165                 170                 175

Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys
            180                 185                 190

Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser
        195                 200                 205

Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu
    210                 215                 220

Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile
225                 230                 235                 240

Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala
                245                 250                 255

Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala
            260                 265                 270

Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala
        275                 280                 285

Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu
    290                 295                 300

Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu
305                 310                 315                 320

Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg
                325                 330                 335

Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys
            340                 345                 350

Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val
        355                 360                 365

Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser
    370                 375                 380

Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu
385                 390                 395                 400

Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu
                405                 410                 415

Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg
            420                 425                 430

Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu Gly Glu Leu
        435                 440                 445

His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp
    450                 455                 460

Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr
465                 470                 475                 480

Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg
                485                 490                 495

Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp
            500                 505                 510

Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp
        515                 520                 525
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```
Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr
    530                 535                 540

Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr
545                 550                 555                 560

Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala
                565                 570                 575

Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln
            580                 585                 590

Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu
        595                 600                 605

Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His
    610                 615                 620

Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu
625                 630                 635                 640

Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu
                645                 650                 655

Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe
            660                 665                 670

Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp
        675                 680                 685

Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser
    690                 695                 700

Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg
705                 710                 715                 720

Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp
                725                 730                 735

Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His Glu His
            740                 745                 750

Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln
        755                 760                 765

Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly Arg His Lys
    770                 775                 780

Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln
785                 790                 795                 800

Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly
                805                 810                 815

Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn
            820                 825                 830

Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly
        835                 840                 845

Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp
    850                 855                 860

Tyr Asp Val Asp Ala Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser
865                 870                 875                 880

Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser
                885                 890                 895

Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp
            900                 905                 910

Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
        915                 920                 925

Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly
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    930                 935                 940

Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys His Val
945                 950                 955                 960

Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp
                965                 970                 975

Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val
            980                 985                 990

Ser Asp Phe Arg Lys Asp Phe Gln  Phe Tyr Lys Val Arg  Glu Ile Asn
        995                 1000                1005

Asn Tyr  His His Ala His Asp  Ala Tyr Leu Asn Ala  Val Val Gly
    1010                1015                1020

Thr Ala  Leu Ile Lys Lys Tyr  Pro Lys Leu Glu Ser  Glu Phe Val
    1025                1030                1035

Tyr Gly  Asp Tyr Lys Val Tyr  Asp Val Arg Lys Met  Ile Ala Lys
    1040                1045                1050

Ser Glu  Gln Glu Ile Gly Lys  Ala Thr Ala Lys Tyr  Phe Phe Tyr
    1055                1060                1065

Ser Asn  Ile Met Asn Phe Phe  Lys Thr Glu Ile Thr  Leu Ala Asn
    1070                1075                1080

Gly Glu  Ile Arg Lys Arg Pro  Leu Ile Glu Thr Asn  Gly Glu Thr
    1085                1090                1095

Gly Glu  Ile Val Trp Asp Lys  Gly Arg Asp Phe Ala  Thr Val Arg
    1100                1105                1110

Lys Val  Leu Ser Met Pro Gln  Val Asn Ile Val Lys  Lys Thr Glu
    1115                1120                1125

Val Gln  Thr Gly Gly Phe Ser  Lys Glu Ser Ile Leu  Pro Lys Arg
    1130                1135                1140

Asn Ser  Asp Lys Leu Ile Ala  Arg Lys Lys Asp Trp  Asp Pro Lys
    1145                1150                1155

Lys Tyr  Gly Gly Phe Asp Ser  Pro Thr Val Ala Tyr  Ser Val Leu
    1160                1165                1170

Val Val  Ala Lys Val Glu Lys  Gly Lys Ser Lys Lys  Leu Lys Ser
    1175                1180                1185

Val Lys  Glu Leu Leu Gly Ile  Thr Ile Met Glu Arg  Ser Ser Phe
    1190                1195                1200

Glu Lys  Asn Pro Ile Asp Phe  Leu Glu Ala Lys Gly  Tyr Lys Glu
    1205                1210                1215

Val Lys  Lys Asp Leu Ile Ile  Lys Leu Pro Lys Tyr  Ser Leu Phe
    1220                1225                1230

Glu Leu  Glu Asn Gly Arg Lys  Arg Met Leu Ala Ser  Ala Gly Glu
    1235                1240                1245

Leu Gln  Lys Gly Asn Glu Leu  Ala Leu Pro Ser Lys  Tyr Val Asn
    1250                1255                1260

Phe Leu  Tyr Leu Ala Ser His  Tyr Glu Lys Leu Lys  Gly Ser Pro
    1265                1270                1275

Glu Asp  Asn Glu Gln Lys Gln  Leu Phe Val Glu Gln  His Lys His
    1280                1285                1290

Tyr Leu  Asp Glu Ile Ile Glu  Gln Ile Ser Glu Phe  Ser Lys Arg
    1295                1300                1305

Val Ile  Leu Ala Asp Ala Asn  Leu Asp Lys Val Leu  Ser Ala Tyr
    1310                1315                1320
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Asn Lys  His Arg Asp Lys Pro  Ile Arg Glu Gln Ala  Glu Asn Ile
    1325                 1330                 1335

Ile His  Leu Phe Thr Leu Thr  Asn Leu Gly Ala Pro  Ala Ala Phe
    1340                 1345                 1350

Lys Tyr  Phe Asp Thr Thr Ile  Asp Arg Lys Arg Tyr  Thr Ser Thr
    1355                 1360                 1365

Lys Glu  Val Leu Asp Ala Thr  Leu Ile His Gln Ser  Ile Thr Gly
    1370                 1375                 1380

Leu Tyr  Glu Thr Arg Ile Asp  Leu Ser Gln Leu Gly  Gly Asp Gly
    1385                 1390                 1395

Gly Gly  Gly Ser Gly Gly Gly  Gly Ser Gly Gly Gly  Gly Ser Tyr
    1400                 1405                 1410

Val Val  Lys Arg Arg Asp Ser  Ala Thr Ser Phe Ser  Leu Asp Phe
    1415                 1420                 1425

Gly Tyr  Leu Arg Asn Lys Asn  Gly Cys His Val Glu  Leu Leu Phe
    1430                 1435                 1440

Leu Arg  Tyr Ile Ser Asp Trp  Asp Leu Asp Pro Gly  Arg Cys Tyr
    1445                 1450                 1455

Arg Val  Thr Trp Phe Thr Ser  Trp Ser Pro Cys Tyr  Asp Cys Ala
    1460                 1465                 1470

Arg His  Val Ala Asp Phe Leu  Arg Gly Asn Pro Asn  Leu Ser Leu
    1475                 1480                 1485

Arg Ile  Phe Thr Ala Arg Leu  Tyr Phe Cys Glu Asp  Arg Lys Ala
    1490                 1495                 1500

Glu Pro  Glu Gly Leu Arg Arg  Leu His Arg Ala Gly  Val Gln Ile
    1505                 1510                 1515

Ala Ile  Met Thr Phe Lys Asp  Tyr Phe Tyr Cys Trp  Asn Thr Phe
    1520                 1525                 1530

Val Glu  Asn His Glu Arg Thr  Phe Lys Ala Trp Glu  Gly Leu His
    1535                 1540                 1545

Glu Asn  Ser Val Arg Leu Ser  Arg Gln Leu Arg Arg  Ile Leu Leu
    1550                 1555                 1560

Pro Leu  Tyr Glu Val Asp Asp  Leu Arg Asp Ala Phe  Arg Thr Leu
    1565                 1570                 1575

Gly Leu
    1580
```

<210> SEQ ID NO 31
<211> LENGTH: 1564
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 31

```
Met Asp Ser Leu Leu Met Asn Arg Arg Lys Phe Leu Tyr Gln Phe Lys
1               5                  10                  15

Asn Val Arg Trp Ala Lys Gly Arg Arg Glu Thr Tyr Leu Cys Tyr Val
            20                  25                  30

Val Lys Arg Arg Asp Ser Ala Thr Ser Phe Ser Leu Asp Phe Gly Tyr
        35                  40                  45

Leu Arg Asn Lys Asn Gly Cys His Val Glu Leu Leu Phe Leu Arg Tyr
    50                  55                  60
```

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```
Ile Ser Asp Trp Asp Leu Asp Pro Gly Arg Cys Tyr Arg Val Thr Trp
65                  70                  75                  80

Phe Thr Ser Trp Ser Pro Cys Tyr Asp Cys Ala Arg His Val Ala Asp
                85                  90                  95

Phe Leu Arg Gly Asn Pro Asn Leu Ser Leu Arg Ile Phe Thr Ala Arg
            100                 105                 110

Leu Tyr Phe Cys Glu Asp Arg Lys Ala Glu Pro Glu Gly Leu Arg Arg
        115                 120                 125

Leu His Arg Ala Gly Val Gln Ile Ala Ile Met Thr Phe Lys Asp Tyr
    130                 135                 140

Phe Tyr Cys Trp Asn Thr Phe Val Glu Asn His Glu Arg Thr Phe Lys
145                 150                 155                 160

Ala Trp Glu Gly Leu His Glu Asn Ser Val Arg Leu Ser Arg Gln Leu
                165                 170                 175

Arg Arg Ile Leu Leu Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
            180                 185                 190

Gly Gly Gly Gly Ser Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly
        195                 200                 205

Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro
    210                 215                 220

Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys
225                 230                 235                 240

Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu
                245                 250                 255

Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys
            260                 265                 270

Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys
        275                 280                 285

Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu
    290                 295                 300

Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp
305                 310                 315                 320

Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys
                325                 330                 335

Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu
            340                 345                 350

Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly
        355                 360                 365

Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu
    370                 375                 380

Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser
385                 390                 395                 400

Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg
                405                 410                 415

Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly
            420                 425                 430

Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe
        435                 440                 445

Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys
    450                 455                 460
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Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp
465                 470                 475                 480

Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile
                485                 490                 495

Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro
            500                 505                 510

Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu
        515                 520                 525

Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys
    530                 535                 540

Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp
545                 550                 555                 560

Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu
                565                 570                 575

Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu
            580                 585                 590

Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His
        595                 600                 605

Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp
    610                 615                 620

Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu
625                 630                 635                 640

Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser
                645                 650                 655

Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp
            660                 665                 670

Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile
        675                 680                 685

Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu
    690                 695                 700

Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu
705                 710                 715                 720

Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu
                725                 730                 735

Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn
            740                 745                 750

Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile
        755                 760                 765

Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn
    770                 775                 780

Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys
785                 790                 795                 800

Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val
                805                 810                 815

Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu
            820                 825                 830

Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys
        835                 840                 845

Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn
    850                 855                 860

Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys
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865                 870                 875                 880

Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp
                885                 890                 895

Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln
            900                 905                 910

Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala
        915                 920                 925

Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val
    930                 935                 940

Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala
945                 950                 955                 960

Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg
                965                 970                 975

Met Lys Arg Ile Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu
            980                 985                 990

Lys Glu His Pro Val Glu Asn Thr  Gln Leu Gln Asn Glu  Lys Leu Tyr
        995                 1000                1005

Leu Tyr  Tyr Leu Gln Asn Gly  Arg Asp Met Tyr Val  Asp Gln Glu
    1010                1015                1020

Leu Asp  Ile Asn Arg Leu Ser  Asp Tyr Asp Val Asp  Ala Ile Val
    1025                1030                1035

Pro Gln  Ser Phe Leu Lys Asp  Asp Ser Ile Asp Asn  Lys Val Leu
    1040                1045                1050

Thr Arg  Ser Asp Lys Asn Arg  Gly Lys Ser Asp Asn  Val Pro Ser
    1055                1060                1065

Glu Glu  Val Val Lys Lys Met  Lys Asn Tyr Trp Arg  Gln Leu Leu
    1070                1075                1080

Asn Ala  Lys Leu Ile Thr Gln  Arg Lys Phe Asp Asn  Leu Thr Lys
    1085                1090                1095

Ala Glu  Arg Gly Gly Leu Ser  Glu Leu Asp Lys Ala  Gly Phe Ile
    1100                1105                1110

Lys Arg  Gln Leu Val Glu Thr  Arg Gln Ile Thr Lys  His Val Ala
    1115                1120                1125

Gln Ile  Leu Asp Ser Arg Met  Asn Thr Lys Tyr Asp  Glu Asn Asp
    1130                1135                1140

Lys Leu  Ile Arg Glu Val Lys  Val Ile Thr Leu Lys  Ser Lys Leu
    1145                1150                1155

Val Ser  Asp Phe Arg Lys Asp  Phe Gln Phe Tyr Lys  Val Arg Glu
    1160                1165                1170

Ile Asn  Asn Tyr His His Ala  His Asp Ala Tyr Leu  Asn Ala Val
    1175                1180                1185

Val Gly  Thr Ala Leu Ile Lys  Lys Tyr Pro Lys Leu  Glu Ser Glu
    1190                1195                1200

Phe Val  Tyr Gly Asp Tyr Lys  Val Tyr Asp Val Arg  Lys Met Ile
    1205                1210                1215

Ala Lys  Ser Glu Gln Glu Ile  Gly Lys Ala Thr Ala  Lys Tyr Phe
    1220                1225                1230

Phe Tyr  Ser Asn Ile Met Asn  Phe Phe Lys Thr Glu  Ile Thr Leu
    1235                1240                1245

Ala Asn  Gly Glu Ile Arg Lys  Arg Pro Leu Ile Glu  Thr Asn Gly
    1250                1255                1260
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Glu Thr  Gly Glu Ile Val Trp  Asp Lys Gly Arg Asp  Phe Ala Thr
    1265                1270                1275

Val Arg  Lys Val Leu Ser Met  Pro Gln Val Asn Ile  Val Lys Lys
    1280                1285                1290

Thr Glu  Val Gln Thr Gly Gly  Phe Ser Lys Glu Ser  Ile Leu Pro
    1295                1300                1305

Lys Arg  Asn Ser Asp Lys Leu  Ile Ala Arg Lys Lys  Asp Trp Asp
    1310                1315                1320

Pro Lys  Lys Tyr Gly Gly Phe  Asp Ser Pro Thr Val  Ala Tyr Ser
    1325                1330                1335

Val Leu  Val Val Ala Lys Val  Glu Lys Gly Lys Ser  Lys Lys Leu
    1340                1345                1350

Lys Ser  Val Lys Glu Leu Leu  Gly Ile Thr Ile Met  Glu Arg Ser
    1355                1360                1365

Ser Phe  Glu Lys Asn Pro Ile  Asp Phe Leu Glu Ala  Lys Gly Tyr
    1370                1375                1380

Lys Glu  Val Lys Lys Asp Leu  Ile Ile Lys Leu Pro  Lys Tyr Ser
    1385                1390                1395

Leu Phe  Glu Leu Glu Asn Gly  Arg Lys Arg Met Leu  Ala Ser Ala
    1400                1405                1410

Gly Glu  Leu Gln Lys Gly Asn  Glu Leu Ala Leu Pro  Ser Lys Tyr
    1415                1420                1425

Val Asn  Phe Leu Tyr Leu Ala  Ser His Tyr Glu Lys  Leu Lys Gly
    1430                1435                1440

Ser Pro  Glu Asp Asn Glu Gln  Lys Gln Leu Phe Val  Glu Gln His
    1445                1450                1455

Lys His  Tyr Leu Asp Glu Ile  Ile Glu Gln Ile Ser  Glu Phe Ser
    1460                1465                1470

Lys Arg  Val Ile Leu Ala Asp  Ala Asn Leu Asp Lys  Val Leu Ser
    1475                1480                1485

Ala Tyr  Asn Lys His Arg Asp  Lys Pro Ile Arg Glu  Gln Ala Glu
    1490                1495                1500

Asn Ile  Ile His Leu Phe Thr  Leu Thr Asn Leu Gly  Ala Pro Ala
    1505                1510                1515

Ala Phe  Lys Tyr Phe Asp Thr  Thr Ile Asp Arg Lys  Arg Tyr Thr
    1520                1525                1530

Ser Thr  Lys Glu Val Leu Asp  Ala Thr Leu Ile His  Gln Ser Ile
    1535                1540                1545

Thr Gly  Leu Tyr Glu Thr Arg  Ile Asp Leu Ser Gln  Leu Gly Gly
    1550                1555                1560

Asp
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<210> SEQ ID NO 32
<211> LENGTH: 1580
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 32

```
Met Asp Ser Leu Leu Met Asn Arg Arg Lys Phe Leu Tyr Gln Phe Lys
1               5                  10                  15
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Asn Val Arg Trp Ala Lys Gly Arg Arg Glu Thr Tyr Leu Cys Asp Lys
            20                  25                  30

Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly Trp Ala
        35                  40                  45

Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu
    50                  55                  60

Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu
65                  70                  75                  80

Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr
                85                  90                  95

Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln
            100                 105                 110

Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe Phe His
        115                 120                 125

Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg
    130                 135                 140

His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys
145                 150                 155                 160

Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp
                165                 170                 175

Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys
            180                 185                 190

Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser
        195                 200                 205

Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu
    210                 215                 220

Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile
225                 230                 235                 240

Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala
                245                 250                 255

Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala
            260                 265                 270

Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala
        275                 280                 285

Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu
    290                 295                 300

Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu
305                 310                 315                 320

Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg
                325                 330                 335

Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys
            340                 345                 350

Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val
        355                 360                 365

Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser
    370                 375                 380

Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu
385                 390                 395                 400

Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu
                405                 410                 415

Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg
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            420                 425                 430

Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu Gly Glu Leu
        435                 440                 445

His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp
    450                 455                 460

Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr
465                 470                 475                 480

Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg
                485                 490                 495

Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp
            500                 505                 510

Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp
        515                 520                 525

Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr
    530                 535                 540

Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr
545                 550                 555                 560

Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala
                565                 570                 575

Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln
            580                 585                 590

Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu
        595                 600                 605

Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His
    610                 615                 620

Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu
625                 630                 635                 640

Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu
                645                 650                 655

Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe
            660                 665                 670

Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp
        675                 680                 685

Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser
    690                 695                 700

Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg
705                 710                 715                 720

Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp
                725                 730                 735

Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His Glu His
            740                 745                 750

Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln
        755                 760                 765

Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly Arg His Lys
    770                 775                 780

Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln
785                 790                 795                 800

Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly
                805                 810                 815

Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn
            820                 825                 830
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Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly
        835                 840                 845

Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp
    850                 855                 860

Tyr Asp Val Asp Ala Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser
865                 870                 875                 880

Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser
                885                 890                 895

Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp
            900                 905                 910

Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
        915                 920                 925

Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly
    930                 935                 940

Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys His Val
945                 950                 955                 960

Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp
                965                 970                 975

Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val
            980                 985                 990

Ser Asp Phe Arg Lys Asp Phe Gln  Phe Tyr Lys Val Arg  Glu Ile Asn
        995                 1000                1005

Asn Tyr  His His Ala His Asp  Ala Tyr Leu Asn Ala  Val Val Gly
    1010                1015                1020

Thr Ala  Leu Ile Lys Lys Tyr  Pro Lys Leu Glu Ser  Glu Phe Val
    1025                1030                1035

Tyr Gly  Asp Tyr Lys Val Tyr  Asp Val Arg Lys Met  Ile Ala Lys
    1040                1045                1050

Ser Glu  Gln Glu Ile Gly Lys  Ala Thr Ala Lys Tyr  Phe Phe Tyr
    1055                1060                1065

Ser Asn  Ile Met Asn Phe Phe  Lys Thr Glu Ile Thr  Leu Ala Asn
    1070                1075                1080

Gly Glu  Ile Arg Lys Arg Pro  Leu Ile Glu Thr Asn  Gly Glu Thr
    1085                1090                1095

Gly Glu  Ile Val Trp Asp Lys  Gly Arg Asp Phe Ala  Thr Val Arg
    1100                1105                1110

Lys Val  Leu Ser Met Pro Gln  Val Asn Ile Val Lys  Lys Thr Glu
    1115                1120                1125

Val Gln  Thr Gly Gly Phe Ser  Lys Glu Ser Ile Leu  Pro Lys Arg
    1130                1135                1140

Asn Ser  Asp Lys Leu Ile Ala  Arg Lys Lys Asp Trp  Asp Pro Lys
    1145                1150                1155

Lys Tyr  Gly Gly Phe Asp Ser  Pro Thr Val Ala Tyr  Ser Val Leu
    1160                1165                1170

Val Val  Ala Lys Val Glu Lys  Gly Lys Ser Lys Lys  Leu Lys Ser
    1175                1180                1185

Val Lys  Glu Leu Leu Gly Ile  Thr Ile Met Glu Arg  Ser Ser Phe
    1190                1195                1200

Glu Lys  Asn Pro Ile Asp Phe  Leu Glu Ala Lys Gly  Tyr Lys Glu
    1205                1210                1215
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Val Lys  Lys Asp Leu Ile Ile  Lys Leu Pro Lys Tyr  Ser Leu Phe
    1220                 1225                 1230

Glu Leu  Glu Asn Gly Arg Lys  Arg Met Leu Ala Ser  Ala Gly Glu
    1235                 1240                 1245

Leu Gln  Lys Gly Asn Glu Leu  Ala Leu Pro Ser Lys  Tyr Val Asn
    1250                 1255                 1260

Phe Leu  Tyr Leu Ala Ser His  Tyr Glu Lys Leu Lys  Gly Ser Pro
    1265                 1270                 1275

Glu Asp  Asn Glu Gln Lys Gln  Leu Phe Val Glu Gln  His Lys His
    1280                 1285                 1290

Tyr Leu  Asp Glu Ile Ile Glu  Gln Ile Ser Glu Phe  Ser Lys Arg
    1295                 1300                 1305

Val Ile  Leu Ala Asp Ala Asn  Leu Asp Lys Val Leu  Ser Ala Tyr
    1310                 1315                 1320

Asn Lys  His Arg Asp Lys Pro  Ile Arg Glu Gln Ala  Glu Asn Ile
    1325                 1330                 1335

Ile His  Leu Phe Thr Leu Thr  Asn Leu Gly Ala Pro  Ala Ala Phe
    1340                 1345                 1350

Lys Tyr  Phe Asp Thr Thr Ile  Asp Arg Lys Arg Tyr  Thr Ser Thr
    1355                 1360                 1365

Lys Glu  Val Leu Asp Ala Thr  Leu Ile His Gln Ser  Ile Thr Gly
    1370                 1375                 1380

Leu Tyr  Glu Thr Arg Ile Asp  Leu Ser Gln Leu Gly  Gly Asp Gly
    1385                 1390                 1395

Gly Gly  Gly Ser Gly Gly Gly  Gly Ser Gly Gly Gly  Gly Ser Tyr
    1400                 1405                 1410

Val Val  Lys Arg Arg Asp Ser  Ala Thr Ser Cys Ser  Leu Asp Phe
    1415                 1420                 1425

Gly His  Leu Arg Asn Lys Ser  Gly Cys His Val Glu  Leu Leu Phe
    1430                 1435                 1440

Leu Arg  Tyr Ile Ser Asp Trp  Asp Leu Asp Pro Gly  Arg Cys Tyr
    1445                 1450                 1455

Arg Val  Thr Trp Phe Thr Ser  Trp Ser Pro Cys Tyr  Asp Cys Ala
    1460                 1465                 1470

Arg His  Val Ala Glu Phe Leu  Arg Trp Asn Pro Asn  Leu Ser Leu
    1475                 1480                 1485

Arg Ile  Phe Thr Ala Arg Leu  Tyr Phe Cys Glu Asp  Arg Lys Ala
    1490                 1495                 1500

Glu Pro  Glu Gly Leu Arg Arg  Leu His Arg Ala Gly  Val Gln Ile
    1505                 1510                 1515

Gly Ile  Met Thr Phe Lys Asp  Tyr Phe Tyr Cys Trp  Asn Thr Phe
    1520                 1525                 1530

Val Glu  Asn Arg Glu Arg Thr  Phe Lys Ala Trp Glu  Gly Leu His
    1535                 1540                 1545

Glu Asn  Ser Val Arg Leu Thr  Arg Gln Leu Arg Arg  Ile Leu Leu
    1550                 1555                 1560

Pro Leu  Tyr Glu Val Asp Asp  Leu Arg Asp Ala Phe  Arg Met Leu
    1565                 1570                 1575

Gly Phe
    1580
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<210> SEQ ID NO 33
<211> LENGTH: 1724
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 33

Ser Pro Lys Lys Lys Arg Lys Val Glu Ala Ser Met Glu Leu Lys Tyr
1 5 10 15

His Pro Glu Met Arg Phe Phe His Trp Phe Ser Lys Trp Arg Lys Leu
20 25 30

His Arg Asp Gln Glu Tyr Glu Val Thr Trp Tyr Ile Ser Trp Ser Pro
35 40 45

Cys Thr Lys Cys Thr Arg Asp Met Ala Thr Phe Leu Ala Glu Asp Pro
50 55 60

Lys Val Thr Leu Thr Ile Phe Val Ala Arg Leu Tyr Tyr Phe Trp Asp
65 70 75 80

Pro Asp Tyr Gln Glu Ala Leu Arg Ser Leu Cys Gln Lys Arg Asp Gly
85 90 95

Pro Arg Ala Thr Met Lys Ile Met Asn Tyr Asp Glu Phe Gln His Cys
100 105 110

Trp Ser Lys Phe Val Tyr Ser Gln Arg Glu Leu Phe Glu Pro Trp Asn
115 120 125

Asn Leu Pro Lys Tyr Tyr Ile Leu Leu His Ile Met Leu Gly Glu Ile
130 135 140

Leu Arg His Ser Met Asp Pro Pro Thr Phe Thr Phe Asn Phe Asn Asn
145 150 155 160

Glu Pro Trp Val Arg Gly Arg His Glu Thr Tyr Leu Cys Tyr Glu Val
165 170 175

Glu Arg Met His Asn Asp Thr Trp Val Leu Leu Asn Gln Arg Arg Gly
180 185 190

Phe Leu Cys Asn Gln Ala Pro His Lys His Gly Phe Leu Glu Gly Arg
195 200 205

His Ala Glu Leu Cys Phe Leu Asp Val Ile Pro Phe Trp Lys Leu Asp
210 215 220

Leu Asp Gln Asp Tyr Arg Val Thr Cys Phe Thr Ser Trp Ser Pro Cys
225 230 235 240

Phe Ser Cys Ala Gln Glu Met Ala Lys Phe Ile Ser Lys Asn Lys His
245 250 255

Val Ser Leu Cys Ile Phe Thr Ala Arg Ile Tyr Asp Asp Gln Gly Arg
260 265 270

Cys Gln Glu Gly Leu Arg Thr Leu Ala Glu Ala Gly Ala Lys Ile Ser
275 280 285

Ile Met Thr Tyr Ser Glu Phe Lys His Cys Trp Asp Thr Phe Val Asp
290 295 300

His Gln Gly Cys Pro Phe Gln Pro Trp Asp Gly Leu Asp Glu His Ser
305 310 315 320

Gln Asp Leu Ser Gly Arg Leu Arg Ala Ile Leu Gln Asn Gln Glu Asn
325 330 335

Ser Pro Lys Lys Lys Arg Lys Val Glu Ala Ser Ser Pro Lys Lys Lys
340 345 350

Arg Lys Val Glu Ala Ser Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly

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        355                 360                 365

Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro
    370                 375                 380

Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys
385                 390                 395                 400

Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu
                405                 410                 415

Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys
            420                 425                 430

Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys
        435                 440                 445

Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu
    450                 455                 460

Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp
465                 470                 475                 480

Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys
                485                 490                 495

Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu
            500                 505                 510

Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly
        515                 520                 525

Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu
    530                 535                 540

Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser
545                 550                 555                 560

Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg
                565                 570                 575

Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly
            580                 585                 590

Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe
        595                 600                 605

Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys
    610                 615                 620

Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp
625                 630                 635                 640

Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile
                645                 650                 655

Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro
            660                 665                 670

Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu
        675                 680                 685

Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys
    690                 695                 700

Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp
705                 710                 715                 720

Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu
                725                 730                 735

Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu
            740                 745                 750

Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His
        755                 760                 765
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```
Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp
    770                 775                 780

Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu
785                 790                 795                 800

Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser
                805                 810                 815

Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp
            820                 825                 830

Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile
        835                 840                 845

Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu
    850                 855                 860

Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu
865                 870                 875                 880

Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu
                885                 890                 895

Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn
            900                 905                 910

Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile
        915                 920                 925

Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn
    930                 935                 940

Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys
945                 950                 955                 960

Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val
                965                 970                 975

Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu
            980                 985                 990

Lys Thr Tyr Ala His Leu Phe Asp  Asp Lys Val Met Lys  Gln Leu Lys
        995                 1000                1005

Arg Arg  Arg Tyr Thr Gly Trp  Gly Arg Leu Ser Arg  Lys Leu Ile
    1010                1015                1020

Asn Gly  Ile Arg Asp Lys Gln  Ser Gly Lys Thr Ile  Leu Asp Phe
    1025                1030                1035

Leu Lys  Ser Asp Gly Phe Ala  Asn Arg Asn Phe Met  Gln Leu Ile
    1040                1045                1050

His Asp  Asp Ser Leu Thr Phe  Lys Glu Asp Ile Gln  Lys Ala Gln
    1055                1060                1065

Val Ser  Gly Gln Gly Asp Ser  Leu His Glu His Ile  Ala Asn Leu
    1070                1075                1080

Ala Gly  Ser Pro Ala Ile Lys  Lys Gly Ile Leu Gln  Thr Val Lys
    1085                1090                1095

Val Val  Asp Glu Leu Val Lys  Val Met Gly Arg His  Lys Pro Glu
    1100                1105                1110

Asn Ile  Val Ile Glu Met Ala  Arg Glu Asn Gln Thr  Thr Gln Lys
    1115                1120                1125

Gly Gln  Lys Asn Ser Arg Glu  Arg Met Lys Arg Ile  Glu Glu Gly
    1130                1135                1140

Ile Lys  Glu Leu Gly Ser Gln  Ile Leu Lys Glu His  Pro Val Glu
    1145                1150                1155
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Asn Thr  Gln Leu Gln Asn Glu  Lys Leu Tyr Leu Tyr  Tyr Leu Gln
    1160                1165                1170

Asn Gly  Arg Asp Met Tyr Val  Asp Gln Glu Leu Asp  Ile Asn Arg
    1175                1180                1185

Leu Ser  Asp Tyr Asp Val Asp  Ala Ile Val Pro Gln  Ser Phe Leu
    1190                1195                1200

Lys Asp  Asp Ser Ile Asp Asn  Lys Val Leu Thr Arg  Ser Asp Lys
    1205                1210                1215

Asn Arg  Gly Lys Ser Asp Asn  Val Pro Ser Glu Glu  Val Val Lys
    1220                1225                1230

Lys Met  Lys Asn Tyr Trp Arg  Gln Leu Leu Asn Ala  Lys Leu Ile
    1235                1240                1245

Thr Gln  Arg Lys Phe Asp Asn  Leu Thr Lys Ala Glu  Arg Gly Gly
    1250                1255                1260

Leu Ser  Glu Leu Asp Lys Ala  Gly Phe Ile Lys Arg  Gln Leu Val
    1265                1270                1275

Glu Thr  Arg Gln Ile Thr Lys  His Val Ala Gln Ile  Leu Asp Ser
    1280                1285                1290

Arg Met  Asn Thr Lys Tyr Asp  Glu Asn Asp Lys Leu  Ile Arg Glu
    1295                1300                1305

Val Lys  Val Ile Thr Leu Lys  Ser Lys Leu Val Ser  Asp Phe Arg
    1310                1315                1320

Lys Asp  Phe Gln Phe Tyr Lys  Val Arg Glu Ile Asn  Asn Tyr His
    1325                1330                1335

His Ala  His Asp Ala Tyr Leu  Asn Ala Val Val Gly  Thr Ala Leu
    1340                1345                1350

Ile Lys  Lys Tyr Pro Lys Leu  Glu Ser Glu Phe Val  Tyr Gly Asp
    1355                1360                1365

Tyr Lys  Val Tyr Asp Val Arg  Lys Met Ile Ala Lys  Ser Glu Gln
    1370                1375                1380

Glu Ile  Gly Lys Ala Thr Ala  Lys Tyr Phe Phe Tyr  Ser Asn Ile
    1385                1390                1395

Met Asn  Phe Phe Lys Thr Glu  Ile Thr Leu Ala Asn  Gly Glu Ile
    1400                1405                1410

Arg Lys  Arg Pro Leu Ile Glu  Thr Asn Gly Glu Thr  Gly Glu Ile
    1415                1420                1425

Val Trp  Asp Lys Gly Arg Asp  Phe Ala Thr Val Arg  Lys Val Leu
    1430                1435                1440

Ser Met  Pro Gln Val Asn Ile  Val Lys Lys Thr Glu  Val Gln Thr
    1445                1450                1455

Gly Gly  Phe Ser Lys Glu Ser  Ile Leu Pro Lys Arg  Asn Ser Asp
    1460                1465                1470

Lys Leu  Ile Ala Arg Lys Lys  Asp Trp Asp Pro Lys  Lys Tyr Gly
    1475                1480                1485

Gly Phe  Asp Ser Pro Thr Val  Ala Tyr Ser Val Leu  Val Val Ala
    1490                1495                1500

Lys Val  Glu Lys Gly Lys Ser  Lys Lys Leu Lys Ser  Val Lys Glu
    1505                1510                1515

Leu Leu  Gly Ile Thr Ile Met  Glu Arg Ser Ser Phe  Glu Lys Asn
    1520                1525                1530

Pro Ile  Asp Phe Leu Glu Ala  Lys Gly Tyr Lys Glu  Val Lys Lys
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    1535                1540                1545

Asp Leu  Ile Ile Lys Leu Pro  Lys Tyr Ser Leu Phe  Glu Leu Glu
    1550                1555                1560

Asn Gly  Arg Lys Arg Met Leu  Ala Ser Ala Gly Glu  Leu Gln Lys
    1565                1570                1575

Gly Asn  Glu Leu Ala Leu Pro  Ser Lys Tyr Val Asn  Phe Leu Tyr
    1580                1585                1590

Leu Ala  Ser His Tyr Glu Lys  Leu Lys Gly Ser Pro  Glu Asp Asn
    1595                1600                1605

Glu Gln  Lys Gln Leu Phe Val  Glu Gln His Lys His  Tyr Leu Asp
    1610                1615                1620

Glu Ile  Ile Glu Gln Ile Ser  Glu Phe Ser Lys Arg  Val Ile Leu
    1625                1630                1635

Ala Asp  Ala Asn Leu Asp Lys  Val Leu Ser Ala Tyr  Asn Lys His
    1640                1645                1650

Arg Asp  Lys Pro Ile Arg Glu  Gln Ala Glu Asn Ile  Ile His Leu
    1655                1660                1665

Phe Thr  Leu Thr Asn Leu Gly  Ala Pro Ala Ala Phe  Lys Tyr Phe
    1670                1675                1680

Asp Thr  Thr Ile Asp Arg Lys  Arg Tyr Thr Ser Thr  Lys Glu Val
    1685                1690                1695

Leu Asp  Ala Thr Leu Ile His  Gln Ser Ile Thr Gly  Leu Tyr Glu
    1700                1705                1710

Thr Arg  Ile Asp Leu Ser Gln  Leu Gly Gly Asp
    1715                1720


<210> SEQ ID NO 34
<211> LENGTH: 1368
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 34

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val
1               5                   10                  15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
            20                  25                  30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
        35                  40                  45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
    50                  55                  60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65                  70                  75                  80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
                85                  90                  95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
            100                 105                 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
        115                 120                 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
    130                 135                 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
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145                 150                 155                 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
                165                 170                 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
            180                 185                 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
        195                 200                 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
    210                 215                 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225                 230                 235                 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
                245                 250                 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
            260                 265                 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
        275                 280                 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
    290                 295                 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305                 310                 315                 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
                325                 330                 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
            340                 345                 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
        355                 360                 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
    370                 375                 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385                 390                 395                 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
                405                 410                 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
            420                 425                 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
        435                 440                 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
    450                 455                 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465                 470                 475                 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
                485                 490                 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
            500                 505                 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
        515                 520                 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
    530                 535                 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545                 550                 555                 560
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Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
               565                 570                 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
            580                 585                 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
        595                 600                 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
    610                 615                 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625                 630                 635                 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
                645                 650                 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
            660                 665                 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
        675                 680                 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
    690                 695                 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705                 710                 715                 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
                725                 730                 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
            740                 745                 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
        755                 760                 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
    770                 775                 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785                 790                 795                 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
                805                 810                 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
            820                 825                 830

Leu Ser Asp Tyr Asp Val Asp Ala Ile Val Pro Gln Ser Phe Leu Lys
        835                 840                 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
    850                 855                 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865                 870                 875                 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
                885                 890                 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
            900                 905                 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
        915                 920                 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
    930                 935                 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945                 950                 955                 960
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Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
                965                 970                 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
            980                 985                 990

Val Gly Thr Ala Leu Ile Lys Lys  Tyr Pro Lys Leu Glu  Ser Glu Phe
        995                 1000                1005

Val Tyr  Gly Asp Tyr Lys Val  Tyr Asp Val Arg Lys  Met Ile Ala
    1010                1015                1020

Lys Ser  Glu Gln Glu Ile Gly  Lys Ala Thr Ala Lys  Tyr Phe Phe
    1025                1030                1035

Tyr Ser  Asn Ile Met Asn Phe  Phe Lys Thr Glu Ile  Thr Leu Ala
    1040                1045                1050

Asn Gly  Glu Ile Arg Lys Arg  Pro Leu Ile Glu Thr  Asn Gly Glu
    1055                1060                1065

Thr Gly  Glu Ile Val Trp Asp  Lys Gly Arg Asp Phe  Ala Thr Val
    1070                1075                1080

Arg Lys  Val Leu Ser Met Pro  Gln Val Asn Ile Val  Lys Lys Thr
    1085                1090                1095

Glu Val  Gln Thr Gly Gly Phe  Ser Lys Glu Ser Ile  Leu Pro Lys
    1100                1105                1110

Arg Asn  Ser Asp Lys Leu Ile  Ala Arg Lys Lys Asp  Trp Asp Pro
    1115                1120                1125

Lys Lys  Tyr Gly Gly Phe Asp  Ser Pro Thr Val Ala  Tyr Ser Val
    1130                1135                1140

Leu Val  Val Ala Lys Val Glu  Lys Gly Lys Ser Lys  Lys Leu Lys
    1145                1150                1155

Ser Val  Lys Glu Leu Leu Gly  Ile Thr Ile Met Glu  Arg Ser Ser
    1160                1165                1170

Phe Glu  Lys Asn Pro Ile Asp  Phe Leu Glu Ala Lys  Gly Tyr Lys
    1175                1180                1185

Glu Val  Lys Lys Asp Leu Ile  Ile Lys Leu Pro Lys  Tyr Ser Leu
    1190                1195                1200

Phe Glu  Leu Glu Asn Gly Arg  Lys Arg Met Leu Ala  Ser Ala Gly
    1205                1210                1215

Glu Leu  Gln Lys Gly Asn Glu  Leu Ala Leu Pro Ser  Lys Tyr Val
    1220                1225                1230

Asn Phe  Leu Tyr Leu Ala Ser  His Tyr Glu Lys Leu  Lys Gly Ser
    1235                1240                1245

Pro Glu  Asp Asn Glu Gln Lys  Gln Leu Phe Val Glu  Gln His Lys
    1250                1255                1260

His Tyr  Leu Asp Glu Ile Ile  Glu Gln Ile Ser Glu  Phe Ser Lys
    1265                1270                1275

Arg Val  Ile Leu Ala Asp Ala  Asn Leu Asp Lys Val  Leu Ser Ala
    1280                1285                1290

Tyr Asn  Lys His Arg Asp Lys  Pro Ile Arg Glu Gln  Ala Glu Asn
    1295                1300                1305

Ile Ile  His Leu Phe Thr Leu  Thr Asn Leu Gly Ala  Pro Ala Ala
    1310                1315                1320

Phe Lys  Tyr Phe Asp Thr Thr  Ile Asp Arg Lys Arg  Tyr Thr Ser
    1325                1330                1335

Thr Lys  Glu Val Leu Asp Ala  Thr Leu Ile His Gln  Ser Ile Thr
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    1340                1345                1350

Gly Leu  Tyr Glu Thr Arg Ile  Asp Leu Ser Gln Leu  Gly Gly Asp
    1355                1360                1365


<210> SEQ ID NO 35
<211> LENGTH: 1851
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 35

Met Asp Ser Leu Leu Met Asn Arg Arg Lys Phe Leu Tyr Gln Phe Lys
1               5                   10                  15

Asn Val Arg Trp Ala Lys Gly Arg Arg Glu Thr Tyr Leu Cys Ser Met
            20                  25                  30

Gly Thr Gly Thr Lys Cys Ile Gly Gln Ser Lys Met Arg Lys Asn Gly
        35                  40                  45

Asp Ile Leu Asn Asp Ser His Ala Glu Val Ile Ala Arg Arg Ser Phe
    50                  55                  60

Gln Arg Tyr Leu Leu His Gln Leu Gln Leu Ala Ala Thr Leu Lys Glu
65                  70                  75                  80

Asp Ser Ile Phe Val Pro Gly Thr Gln Lys Gly Val Trp Lys Leu Arg
                85                  90                  95

Arg Asp Leu Ile Phe Val Phe Phe Ser Ser His Thr Pro Cys Gly Asp
            100                 105                 110

Ala Ser Ile Ile Pro Met Leu Glu Phe Glu Asp Gln Pro Cys Cys Pro
        115                 120                 125

Val Phe Arg Asn Trp Ala His Asn Ser Ser Val Glu Ala Ser Ser Asn
    130                 135                 140

Leu Glu Ala Pro Gly Asn Glu Arg Lys Cys Glu Asp Pro Asp Ser Pro
145                 150                 155                 160

Val Thr Lys Lys Met Arg Leu Glu Pro Gly Thr Ala Ala Arg Glu Val
                165                 170                 175

Thr Asn Gly Ala Ala His His Gln Ser Phe Gly Lys Gln Lys Ser Gly
            180                 185                 190

Pro Ile Ser Pro Gly Ile His Ser Cys Asp Leu Thr Val Glu Gly Leu
        195                 200                 205

Ala Thr Val Thr Arg Ile Ala Pro Gly Ser Ala Lys Val Ile Asp Val
    210                 215                 220

Tyr Arg Thr Gly Ala Lys Cys Val Pro Gly Glu Ala Gly Asp Ser Gly
225                 230                 235                 240

Lys Pro Gly Ala Ala Phe His Gln Val Gly Leu Leu Arg Val Lys Pro
                245                 250                 255

Gly Arg Gly Asp Arg Thr Arg Ser Met Ser Cys Ser Asp Lys Met Ala
            260                 265                 270

Arg Trp Asn Val Leu Gly Cys Gln Gly Ala Leu Leu Met His Leu Leu
        275                 280                 285

Glu Glu Pro Ile Tyr Leu Ser Ala Val Val Ile Gly Lys Cys Pro Tyr
    290                 295                 300

Ser Gln Glu Ala Met Gln Arg Ala Leu Ile Gly Arg Cys Gln Asn Val
305                 310                 315                 320

Ser Ala Leu Pro Lys Gly Phe Gly Val Gln Glu Leu Lys Ile Leu Gln
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               325                 330                 335

Ser Asp Leu Leu Phe Glu Gln Ser Arg Ser Ala Val Gln Ala Lys Arg
            340                 345                 350

Ala Asp Ser Pro Gly Arg Leu Val Pro Cys Gly Ala Ala Ile Ser Trp
        355                 360                 365

Ser Ala Val Pro Glu Gln Pro Leu Asp Val Thr Ala Asn Gly Phe Pro
    370                 375                 380

Gln Gly Thr Thr Lys Lys Thr Ile Gly Ser Leu Gln Ala Arg Ser Gln
385                 390                 395                 400

Ile Ser Lys Val Glu Leu Phe Arg Ser Phe Gln Lys Leu Leu Ser Arg
                405                 410                 415

Ile Ala Arg Asp Lys Trp Pro His Ser Leu Arg Val Gln Lys Leu Asp
            420                 425                 430

Thr Tyr Gln Glu Tyr Lys Glu Ala Ala Ser Ser Tyr Gln Glu Ala Trp
        435                 440                 445

Ser Thr Leu Arg Lys Gln Val Phe Gly Ser Trp Ile Arg Asn Pro Pro
    450                 455                 460

Asp Tyr His Gln Phe Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
465                 470                 475                 480

Gly Gly Gly Ser Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr
                485                 490                 495

Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser
            500                 505                 510

Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys
        515                 520                 525

Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala
    530                 535                 540

Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn
545                 550                 555                 560

Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val
                565                 570                 575

Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu
            580                 585                 590

Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu
        595                 600                 605

Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys
    610                 615                 620

Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala
625                 630                 635                 640

Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp
                645                 650                 655

Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val
            660                 665                 670

Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly
        675                 680                 685

Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg
    690                 695                 700

Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu
705                 710                 715                 720

Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys
                725                 730                 735
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Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp
            740                 745                 750

Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln
        755                 760                 765

Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu
    770                 775                 780

Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu
785                 790                 795                 800

Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr
                805                 810                 815

Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu
            820                 825                 830

Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly
        835                 840                 845

Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu
    850                 855                 860

Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp
865                 870                 875                 880

Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln
                885                 890                 895

Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe
            900                 905                 910

Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr
        915                 920                 925

Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg
    930                 935                 940

Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn
945                 950                 955                 960

Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu
                965                 970                 975

Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro
            980                 985                 990

Lys His Ser Leu Leu Tyr Glu Tyr  Phe Thr Val Tyr Asn  Glu Leu Thr
        995                 1000                1005

Lys Val  Lys Tyr Val Thr Glu  Gly Met Arg Lys Pro  Ala Phe Leu
    1010                1015                1020

Ser Gly  Glu Gln Lys Lys Ala  Ile Val Asp Leu Leu  Phe Lys Thr
    1025                1030                1035

Asn Arg  Lys Val Thr Val Lys  Gln Leu Lys Glu Asp  Tyr Phe Lys
    1040                1045                1050

Lys Ile  Glu Cys Phe Asp Ser  Val Glu Ile Ser Gly  Val Glu Asp
    1055                1060                1065

Arg Phe  Asn Ala Ser Leu Gly  Thr Tyr His Asp Leu  Leu Lys Ile
    1070                1075                1080

Ile Lys  Asp Lys Asp Phe Leu  Asp Asn Glu Glu Asn  Glu Asp Ile
    1085                1090                1095

Leu Glu  Asp Ile Val Leu Thr  Leu Thr Leu Phe Glu  Asp Arg Glu
    1100                1105                1110

Met Ile  Glu Glu Arg Leu Lys  Thr Tyr Ala His Leu  Phe Asp Asp
    1115                1120                1125
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Lys Val  Met Lys Gln Leu Lys  Arg Arg Arg Tyr Thr  Gly Trp Gly
    1130                1135                1140

Arg Leu  Ser Arg Lys Leu Ile  Asn Gly Ile Arg Asp  Lys Gln Ser
    1145                1150                1155

Gly Lys  Thr Ile Leu Asp Phe  Leu Lys Ser Asp Gly  Phe Ala Asn
    1160                1165                1170

Arg Asn  Phe Met Gln Leu Ile  His Asp Asp Ser Leu  Thr Phe Lys
    1175                1180                1185

Glu Asp  Ile Gln Lys Ala Gln  Val Ser Gly Gln Gly  Asp Ser Leu
    1190                1195                1200

His Glu  His Ile Ala Asn Leu  Ala Gly Ser Pro Ala  Ile Lys Lys
    1205                1210                1215

Gly Ile  Leu Gln Thr Val Lys  Val Val Asp Glu Leu  Val Lys Val
    1220                1225                1230

Met Gly  Arg His Lys Pro Glu  Asn Ile Val Ile Glu  Met Ala Arg
    1235                1240                1245

Glu Asn  Gln Thr Thr Gln Lys  Gly Gln Lys Asn Ser  Arg Glu Arg
    1250                1255                1260

Met Lys  Arg Ile Glu Glu Gly  Ile Lys Glu Leu Gly  Ser Gln Ile
    1265                1270                1275

Leu Lys  Glu His Pro Val Glu  Asn Thr Gln Leu Gln  Asn Glu Lys
    1280                1285                1290

Leu Tyr  Leu Tyr Tyr Leu Gln  Asn Gly Arg Asp Met  Tyr Val Asp
    1295                1300                1305

Gln Glu  Leu Asp Ile Asn Arg  Leu Ser Asp Tyr Asp  Val Asp Ala
    1310                1315                1320

Ile Val  Pro Gln Ser Phe Leu  Lys Asp Asp Ser Ile  Asp Asn Lys
    1325                1330                1335

Val Leu  Thr Arg Ser Asp Lys  Asn Arg Gly Lys Ser  Asp Asn Val
    1340                1345                1350

Pro Ser  Glu Glu Val Val Lys  Lys Met Lys Asn Tyr  Trp Arg Gln
    1355                1360                1365

Leu Leu  Asn Ala Lys Leu Ile  Thr Gln Arg Lys Phe  Asp Asn Leu
    1370                1375                1380

Thr Lys  Ala Glu Arg Gly Gly  Leu Ser Glu Leu Asp  Lys Ala Gly
    1385                1390                1395

Phe Ile  Lys Arg Gln Leu Val  Glu Thr Arg Gln Ile  Thr Lys His
    1400                1405                1410

Val Ala  Gln Ile Leu Asp Ser  Arg Met Asn Thr Lys  Tyr Asp Glu
    1415                1420                1425

Asn Asp  Lys Leu Ile Arg Glu  Val Lys Val Ile Thr  Leu Lys Ser
    1430                1435                1440

Lys Leu  Val Ser Asp Phe Arg  Lys Asp Phe Gln Phe  Tyr Lys Val
    1445                1450                1455

Arg Glu  Ile Asn Asn Tyr His  His Ala His Asp Ala  Tyr Leu Asn
    1460                1465                1470

Ala Val  Val Gly Thr Ala Leu  Ile Lys Lys Tyr Pro  Lys Leu Glu
    1475                1480                1485

Ser Glu  Phe Val Tyr Gly Asp  Tyr Lys Val Tyr Asp  Val Arg Lys
    1490                1495                1500

Met Ile  Ala Lys Ser Glu Gln  Glu Ile Gly Lys Ala  Thr Ala Lys
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    1505                1510                1515

Tyr Phe  Phe Tyr Ser Asn Ile  Met Asn Phe Phe Lys  Thr Glu Ile
    1520                1525                1530

Thr Leu  Ala Asn Gly Glu Ile  Arg Lys Arg Pro Leu  Ile Glu Thr
    1535                1540                1545

Asn Gly  Glu Thr Gly Glu Ile  Val Trp Asp Lys Gly  Arg Asp Phe
    1550                1555                1560

Ala Thr  Val Arg Lys Val Leu  Ser Met Pro Gln Val  Asn Ile Val
    1565                1570                1575

Lys Lys  Thr Glu Val Gln Thr  Gly Gly Phe Ser Lys  Glu Ser Ile
    1580                1585                1590

Leu Pro  Lys Arg Asn Ser Asp  Lys Leu Ile Ala Arg  Lys Lys Asp
    1595                1600                1605

Trp Asp  Pro Lys Lys Tyr Gly  Gly Phe Asp Ser Pro  Thr Val Ala
    1610                1615                1620

Tyr Ser  Val Leu Val Val Ala  Lys Val Glu Lys Gly  Lys Ser Lys
    1625                1630                1635

Lys Leu  Lys Ser Val Lys Glu  Leu Leu Gly Ile Thr  Ile Met Glu
    1640                1645                1650

Arg Ser  Ser Phe Glu Lys Asn  Pro Ile Asp Phe Leu  Glu Ala Lys
    1655                1660                1665

Gly Tyr  Lys Glu Val Lys Lys  Asp Leu Ile Ile Lys  Leu Pro Lys
    1670                1675                1680

Tyr Ser  Leu Phe Glu Leu Glu  Asn Gly Arg Lys Arg  Met Leu Ala
    1685                1690                1695

Ser Ala  Gly Glu Leu Gln Lys  Gly Asn Glu Leu Ala  Leu Pro Ser
    1700                1705                1710

Lys Tyr  Val Asn Phe Leu Tyr  Leu Ala Ser His Tyr  Glu Lys Leu
    1715                1720                1725

Lys Gly  Ser Pro Glu Asp Asn  Glu Gln Lys Gln Leu  Phe Val Glu
    1730                1735                1740

Gln His  Lys His Tyr Leu Asp  Glu Ile Ile Glu Gln  Ile Ser Glu
    1745                1750                1755

Phe Ser  Lys Arg Val Ile Leu  Ala Asp Ala Asn Leu  Asp Lys Val
    1760                1765                1770

Leu Ser  Ala Tyr Asn Lys His  Arg Asp Lys Pro Ile  Arg Glu Gln
    1775                1780                1785

Ala Glu  Asn Ile Ile His Leu  Phe Thr Leu Thr Asn  Leu Gly Ala
    1790                1795                1800

Pro Ala  Ala Phe Lys Tyr Phe  Asp Thr Thr Ile Asp  Arg Lys Arg
    1805                1810                1815

Tyr Thr  Ser Thr Lys Glu Val  Leu Asp Ala Thr Leu  Ile His Gln
    1820                1825                1830

Ser Ile  Thr Gly Leu Tyr Glu  Thr Arg Ile Asp Leu  Ser Gln Leu
    1835                1840                1845

Gly Gly  Asp
    1850
```

<210> SEQ ID NO 36
<211> LENGTH: 1846
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 36

Met Asp Ser Leu Leu Met Asn Arg Arg Lys Phe Leu Tyr Gln Phe Lys
1 5 10 15

Asn Val Arg Trp Ala Lys Gly Arg Arg Glu Thr Tyr Leu Cys Asp Lys
20 25 30

Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly Trp Ala
35 40 45

Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu
50 55 60

Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu
65 70 75 80

Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr
85 90 95

Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln
100 105 110

Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe Phe His
115 120 125

Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg
130 135 140

His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys
145 150 155 160

Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp
165 170 175

Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys
180 185 190

Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser
195 200 205

Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu
210 215 220

Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile
225 230 235 240

Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala
245 250 255

Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala
260 265 270

Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala
275 280 285

Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu
290 295 300

Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu
305 310 315 320

Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg
325 330 335

Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys
340 345 350

Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val
355 360 365

Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser
370 375 380

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Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu
385                 390                 395                 400

Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu
                405                 410                 415

Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg
            420                 425                 430

Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu Gly Glu Leu
        435                 440                 445

His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp
    450                 455                 460

Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr
465                 470                 475                 480

Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg
                485                 490                 495

Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp
            500                 505                 510

Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp
        515                 520                 525

Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr
    530                 535                 540

Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr
545                 550                 555                 560

Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala
                565                 570                 575

Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln
            580                 585                 590

Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu
        595                 600                 605

Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His
    610                 615                 620

Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu
625                 630                 635                 640

Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu
                645                 650                 655

Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe
            660                 665                 670

Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp
        675                 680                 685

Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser
    690                 695                 700

Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg
705                 710                 715                 720

Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp
                725                 730                 735

Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His Glu His
            740                 745                 750

Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln
        755                 760                 765

Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly Arg His Lys
    770                 775                 780
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Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln Thr Thr Gln
785                 790                 795                 800

Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile Glu Glu Gly
                805                 810                 815

Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro Val Glu Asn
            820                 825                 830

Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly
        835                 840                 845

Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp
    850                 855                 860

Tyr Asp Val Asp Ala Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser
865                 870                 875                 880

Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser
                885                 890                 895

Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp
            900                 905                 910

Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
        915                 920                 925

Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala Gly
    930                 935                 940

Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys His Val
945                 950                 955                 960

Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp Glu Asn Asp
                965                 970                 975

Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser Lys Leu Val
            980                 985                 990

Ser Asp Phe Arg Lys Asp Phe Gln  Phe Tyr Lys Val Arg  Glu Ile Asn
        995                 1000                1005

Asn Tyr  His His Ala His Asp  Ala Tyr Leu Asn Ala  Val Val Gly
    1010                1015                1020

Thr Ala  Leu Ile Lys Lys Tyr  Pro Lys Leu Glu Ser  Glu Phe Val
    1025                1030                1035

Tyr Gly  Asp Tyr Lys Val Tyr  Asp Val Arg Lys Met  Ile Ala Lys
    1040                1045                1050

Ser Glu  Gln Glu Ile Gly Lys  Ala Thr Ala Lys Tyr  Phe Phe Tyr
    1055                1060                1065

Ser Asn  Ile Met Asn Phe Phe  Lys Thr Glu Ile Thr  Leu Ala Asn
    1070                1075                1080

Gly Glu  Ile Arg Lys Arg Pro  Leu Ile Glu Thr Asn  Gly Glu Thr
    1085                1090                1095

Gly Glu  Ile Val Trp Asp Lys  Gly Arg Asp Phe Ala  Thr Val Arg
    1100                1105                1110

Lys Val  Leu Ser Met Pro Gln  Val Asn Ile Val Lys  Lys Thr Glu
    1115                1120                1125

Val Gln  Thr Gly Gly Phe Ser  Lys Glu Ser Ile Leu  Pro Lys Arg
    1130                1135                1140

Asn Ser  Asp Lys Leu Ile Ala  Arg Lys Lys Asp Trp  Asp Pro Lys
    1145                1150                1155

Lys Tyr  Gly Gly Phe Asp Ser  Pro Thr Val Ala Tyr  Ser Val Leu
    1160                1165                1170

Val Val  Ala Lys Val Glu Lys  Gly Lys Ser Lys Lys  Leu Lys Ser
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    1175                1180                1185

Val Lys  Glu Leu Leu Gly Ile  Thr Ile Met Glu Arg  Ser Ser Phe
    1190                1195                1200

Glu Lys  Asn Pro Ile Asp Phe  Leu Glu Ala Lys Gly  Tyr Lys Glu
    1205                1210                1215

Val Lys  Lys Asp Leu Ile Ile  Lys Leu Pro Lys Tyr  Ser Leu Phe
    1220                1225                1230

Glu Leu  Glu Asn Gly Arg Lys  Arg Met Leu Ala Ser  Ala Gly Glu
    1235                1240                1245

Leu Gln  Lys Gly Asn Glu Leu  Ala Leu Pro Ser Lys  Tyr Val Asn
    1250                1255                1260

Phe Leu  Tyr Leu Ala Ser His  Tyr Glu Lys Leu Lys  Gly Ser Pro
    1265                1270                1275

Glu Asp  Asn Glu Gln Lys Gln  Leu Phe Val Glu Gln  His Lys His
    1280                1285                1290

Tyr Leu  Asp Glu Ile Ile Glu  Gln Ile Ser Glu Phe  Ser Lys Arg
    1295                1300                1305

Val Ile  Leu Ala Asp Ala Asn  Leu Asp Lys Val Leu  Ser Ala Tyr
    1310                1315                1320

Asn Lys  His Arg Asp Lys Pro  Ile Arg Glu Gln Ala  Glu Asn Ile
    1325                1330                1335

Ile His  Leu Phe Thr Leu Thr  Asn Leu Gly Ala Pro  Ala Ala Phe
    1340                1345                1350

Lys Tyr  Phe Asp Thr Thr Ile  Asp Arg Lys Arg Tyr  Thr Ser Thr
    1355                1360                1365

Lys Glu  Val Leu Asp Ala Thr  Leu Ile His Gln Ser  Ile Thr Gly
    1370                1375                1380

Leu Tyr  Glu Thr Arg Ile Asp  Leu Ser Gln Leu Gly  Gly Asp Gly
    1385                1390                1395

Gly Gly  Gly Ser Gly Gly Gly  Gly Ser Ser Met Gly  Thr Gly Thr
    1400                1405                1410

Lys Cys  Ile Gly Gln Ser Lys  Met Arg Lys Asn Gly  Asp Ile Leu
    1415                1420                1425

Asn Asp  Ser His Ala Glu Val  Ile Ala Arg Arg Ser  Phe Gln Arg
    1430                1435                1440

Tyr Leu  Leu His Gln Leu Gln  Leu Ala Ala Thr Leu  Lys Glu Asp
    1445                1450                1455

Ser Ile  Phe Val Pro Gly Thr  Gln Lys Gly Val Trp  Lys Leu Arg
    1460                1465                1470

Arg Asp  Leu Ile Phe Val Phe  Phe Ser Ser His Thr  Pro Cys Gly
    1475                1480                1485

Asp Ala  Ser Ile Ile Pro Met  Leu Glu Phe Glu Asp  Gln Pro Cys
    1490                1495                1500

Cys Pro  Val Phe Arg Asn Trp  Ala His Asn Ser Ser  Val Glu Ala
    1505                1510                1515

Ser Ser  Asn Leu Glu Ala Pro  Gly Asn Glu Arg Lys  Cys Glu Asp
    1520                1525                1530

Pro Asp  Ser Pro Val Thr Lys  Lys Met Arg Leu Glu  Pro Gly Thr
    1535                1540                1545

Ala Ala  Arg Glu Val Thr Asn  Gly Ala Ala His His  Gln Ser Phe
    1550                1555                1560
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Gly Lys  Gln Lys Ser Gly Pro  Ile Ser Pro Gly Ile  His Ser Cys
    1565                 1570                 1575

Asp Leu  Thr Val Glu Gly Leu  Ala Thr Val Thr Arg  Ile Ala Pro
    1580                 1585                 1590

Gly Ser  Ala Lys Val Ile Asp  Val Tyr Arg Thr Gly  Ala Lys Cys
    1595                 1600                 1605

Val Pro  Gly Glu Ala Gly Asp  Ser Gly Lys Pro Gly  Ala Ala Phe
    1610                 1615                 1620

His Gln  Val Gly Leu Leu Arg  Val Lys Pro Gly Arg  Gly Asp Arg
    1625                 1630                 1635

Thr Arg  Ser Met Ser Cys Ser  Asp Lys Met Ala Arg  Trp Asn Val
    1640                 1645                 1650

Leu Gly  Cys Gln Gly Ala Leu  Leu Met His Leu Leu  Glu Glu Pro
    1655                 1660                 1665

Ile Tyr  Leu Ser Ala Val Val  Ile Gly Lys Cys Pro  Tyr Ser Gln
    1670                 1675                 1680

Glu Ala  Met Gln Arg Ala Leu  Ile Gly Arg Cys Gln  Asn Val Ser
    1685                 1690                 1695

Ala Leu  Pro Lys Gly Phe Gly  Val Gln Glu Leu Lys  Ile Leu Gln
    1700                 1705                 1710

Ser Asp  Leu Leu Phe Glu Gln  Ser Arg Ser Ala Val  Gln Ala Lys
    1715                 1720                 1725

Arg Ala  Asp Ser Pro Gly Arg  Leu Val Pro Cys Gly  Ala Ala Ile
    1730                 1735                 1740

Ser Trp  Ser Ala Val Pro Glu  Gln Pro Leu Asp Val  Thr Ala Asn
    1745                 1750                 1755

Gly Phe  Pro Gln Gly Thr Thr  Lys Lys Thr Ile Gly  Ser Leu Gln
    1760                 1765                 1770

Ala Arg  Ser Gln Ile Ser Lys  Val Glu Leu Phe Arg  Ser Phe Gln
    1775                 1780                 1785

Lys Leu  Leu Ser Arg Ile Ala  Arg Asp Lys Trp Pro  His Ser Leu
    1790                 1795                 1800

Arg Val  Gln Lys Leu Asp Thr  Tyr Gln Glu Tyr Lys  Glu Ala Ala
    1805                 1810                 1815

Ser Ser  Tyr Gln Glu Ala Trp  Ser Thr Leu Arg Lys  Gln Val Phe
    1820                 1825                 1830

Gly Ser  Trp Ile Arg Asn Pro  Pro Asp Tyr His Gln  Phe
    1835                 1840                 1845


<210> SEQ ID NO 37
<211> LENGTH: 1368
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 37

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val
1               5                  10                  15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
            20                  25                  30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
        35                  40                  45
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Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
    50                  55                  60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65                  70                  75                  80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
                85                  90                  95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
            100                 105                 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
        115                 120                 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
    130                 135                 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145                 150                 155                 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
                165                 170                 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
            180                 185                 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
        195                 200                 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
    210                 215                 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225                 230                 235                 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
                245                 250                 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
            260                 265                 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
        275                 280                 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
    290                 295                 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305                 310                 315                 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
                325                 330                 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
            340                 345                 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
        355                 360                 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
    370                 375                 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385                 390                 395                 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
                405                 410                 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
            420                 425                 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
        435                 440                 445
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Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
    450                 455                 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465                 470                 475                 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
                485                 490                 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
            500                 505                 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
        515                 520                 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
    530                 535                 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545                 550                 555                 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
                565                 570                 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
            580                 585                 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
        595                 600                 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
    610                 615                 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625                 630                 635                 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
                645                 650                 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
            660                 665                 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
        675                 680                 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
    690                 695                 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705                 710                 715                 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
                725                 730                 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
            740                 745                 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
        755                 760                 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
    770                 775                 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785                 790                 795                 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
                805                 810                 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
            820                 825                 830

Leu Ser Asp Tyr Asp Val Asp Ala Ile Val Pro Gln Ser Phe Leu Lys
        835                 840                 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
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    850                 855                 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865                 870                 875                 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
                885                 890                 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
            900                 905                 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
        915                 920                 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
    930                 935                 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945                 950                 955                 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
                965                 970                 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
            980                 985                 990

Val Gly Thr Ala Leu Ile Lys Lys  Tyr Pro Lys Leu Glu  Ser Glu Phe
        995                 1000                1005

Val Tyr  Gly Asp Tyr Lys Val  Tyr Asp Val Arg Lys  Met Ile Ala
    1010                1015                1020

Lys Ser  Glu Gln Glu Ile Gly  Lys Ala Thr Ala Lys  Tyr Phe Phe
    1025                1030                1035

Tyr Ser  Asn Ile Met Asn Phe  Phe Lys Thr Glu Ile  Thr Leu Ala
    1040                1045                1050

Asn Gly  Glu Ile Arg Lys Arg  Pro Leu Ile Glu Thr  Asn Gly Glu
    1055                1060                1065

Thr Gly  Glu Ile Val Trp Asp  Lys Gly Arg Asp Phe  Ala Thr Val
    1070                1075                1080

Arg Lys  Val Leu Ser Met Pro  Gln Val Asn Ile Val  Lys Lys Thr
    1085                1090                1095

Glu Val  Gln Thr Gly Gly Phe  Ser Lys Glu Ser Ile  Leu Pro Lys
    1100                1105                1110

Arg Asn  Ser Asp Lys Leu Ile  Ala Arg Lys Lys Asp  Trp Asp Pro
    1115                1120                1125

Lys Lys  Tyr Gly Gly Phe Asp  Ser Pro Thr Val Ala  Tyr Ser Val
    1130                1135                1140

Leu Val  Val Ala Lys Val Glu  Lys Gly Lys Ser Lys  Lys Leu Lys
    1145                1150                1155

Ser Val  Lys Glu Leu Leu Gly  Ile Thr Ile Met Glu  Arg Ser Ser
    1160                1165                1170

Phe Glu  Lys Asn Pro Ile Asp  Phe Leu Glu Ala Lys  Gly Tyr Lys
    1175                1180                1185

Glu Val  Lys Lys Asp Leu Ile  Ile Lys Leu Pro Lys  Tyr Ser Leu
    1190                1195                1200

Phe Glu  Leu Glu Asn Gly Arg  Lys Arg Met Leu Ala  Ser Ala Gly
    1205                1210                1215

Glu Leu  Gln Lys Gly Asn Glu  Leu Ala Leu Pro Ser  Lys Tyr Val
    1220                1225                1230

Asn Phe  Leu Tyr Leu Ala Ser  His Tyr Glu Lys Leu  Lys Gly Ser
    1235                1240                1245
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Pro Glu  Asp Asn Glu Gln Lys  Gln Leu Phe Val Glu  Gln His Lys
    1250                 1255                 1260

His Tyr  Leu Asp Glu Ile Ile  Glu Gln Ile Ser Glu  Phe Ser Lys
    1265                 1270                 1275

Arg Val  Ile Leu Ala Asp Ala  Asn Leu Asp Lys Val  Leu Ser Ala
    1280                 1285                 1290

Tyr Asn  Lys His Arg Asp Lys  Pro Ile Arg Glu Gln  Ala Glu Asn
    1295                 1300                 1305

Ile Ile  His Leu Phe Thr Leu  Thr Asn Leu Gly Ala  Pro Ala Ala
    1310                 1315                 1320

Phe Lys  Tyr Phe Asp Thr Thr  Ile Asp Arg Lys Arg  Tyr Thr Ser
    1325                 1330                 1335

Thr Lys  Glu Val Leu Asp Ala  Thr Leu Ile His Gln  Ser Ile Thr
    1340                 1345                 1350

Gly Leu  Tyr Glu Thr Arg Ile  Asp Leu Ser Gln Leu  Gly Gly Asp
    1355                 1360                 1365


<210> SEQ ID NO 38
<211> LENGTH: 82
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 38

guuuuagagc uagaaauagc aaguuaaaau aaaggcuagu ccguuaucaa cuugaaaaag     60

uggcaccgag ucggugcuuu uu                                              82


<210> SEQ ID NO 39
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 39

gatgacattg catacattcg aaagacccta gccttagata aaactgagca agaggctttg     60

gagtatttca tgaaacaaat gaatgatgca cgtcatggtg gctggacaac aaaaatggat    120

tggatcttcc acacaattaa acagcatgca ttgaactgaa agataactga gaaaatgaaa    180


<210> SEQ ID NO 40
<211> LENGTH: 59
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 40

Asp Asp Ile Ala Tyr Ile Arg Lys Thr Leu Ala Leu Asp Lys Thr Glu
1               5                  10                  15

Gln Glu Ala Leu Glu Tyr Phe Met Lys Gln Met Asn Asp Ala Arg His
            20                  25                  30

Gly Gly Trp Thr Thr Lys Met Asp Trp Ile Phe His Thr Ile Lys Gln
        35                  40                  45

His Ala Leu Asn Lys Ile Thr Glu Lys Met Lys
    50                  55
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<210> SEQ ID NO 41
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 41

aucggaauct auuuugacuc 20

<210> SEQ ID NO 42
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 42

ucggaaucua uuuugacucg 20

<210> SEQ ID NO 43
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 43

cuuagauaaa acugagcaag 20

<210> SEQ ID NO 44
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 44

aucuauuuug acucguucuc 20

<210> SEQ ID NO 45
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 45

uaaaacugag caagaggcuu 20

<210> SEQ ID NO 46
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 46

ugguggcugg acaacaaaaa 20

<210> SEQ ID NO 47
<211> LENGTH: 20

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 47

gcuggacaac aaaaauggau 20

<210> SEQ ID NO 48
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 48

guguuaauuu gucguacgua 20

<210> SEQ ID NO 49
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 49

aatcacattt ttccacttct tgaaaagtac tgtggcttcc atgaagataa cattccccag 60

ctggaagacg tttctcaatt cctgcagact tgcactggtc tccgcctccg acctgtggct 120

ggcctgcttt cctctcggga tttcttgggt ggcctggcct tccgagtctt ccactgcaca 180

<210> SEQ ID NO 50
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 50

Asn His Ile Phe Pro Leu Leu Glu Lys Tyr Cys Gly Phe His Glu Asp
1 5 10 15

Asn Ile Pro Gln Leu Glu Asp Val Ser Gln Phe Leu Gln Thr Cys Thr
20 25 30

Gly Ser Arg Leu Arg Pro Val Ala Gly Leu Leu Ser Ser Arg Asp Phe
35 40 45

Leu Gly Gly Leu Ala Phe Arg Val Phe His Cys Thr
50 55 60

<210> SEQ ID NO 51
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 51

atgcctgcct ggggagccct gttcctgctc tgggccacag cagaggccac caaggactgc 60

cccagcccac gtacctgccg cgccctggaa accatggggc tgtgggtgga ctgcaggggc 120

cacggactca cggccctgcc tgccctgccg gcccgcaccc gccaccttct gctggccaac 180

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<210> SEQ ID NO 52
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 52

Met Pro Ala Trp Gly Ala Leu Phe Leu Leu Trp Ala Thr Ala Glu Ala
1 5 10 15

Thr Lys Asp Cys Pro Ser Pro Arg Thr Cys Arg Ala Leu Glu Thr Met
20 25 30

Gly Leu Trp Val Asp Cys Arg Gly His Gly Leu Thr Ala Leu Pro Ala
35 40 45

Leu Pro Ala Arg Thr Arg His Leu Leu Leu Ala Asn
50 55 60

<210> SEQ ID NO 53
<211> LENGTH: 120
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 53

ggttatggtc ctgtctgccc tcctggtggc atacaagaag tcactatcaa ccagagccct 60

cttcagcccc tcaatgtgga gattgaccct gagatccaaa aggtgaagtc tcgagaaagg 120

<210> SEQ ID NO 54
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 54

Gly Tyr Gly Pro Val Cys Pro Pro Gly Gly Ile Gln Glu Val Thr Ile
1 5 10 15

Asn Gln Ser Pro Leu Gln Pro Leu Asn Val Glu Ile Asp Pro Glu Ile
20 25 30

Gln Lys Val Lys Ser Arg Glu Arg
35 40

<210> SEQ ID NO 55
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 55

gtctccctgg ctgaggatcc ccagggagat gctgcccaga agacagatac atcccaccat 60

gatcaggatc acccaacctt caacaagatc acccccaacc cggctgagtt cgccttcagc 120

ctataccgcc agctggcaca ccagtccaac agcaccaata tcttcttctc cccagtgagc 180

<210> SEQ ID NO 56
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 56

Val Ser Leu Ala Glu Asp Pro Gln Gly Asp Ala Ala Gln Lys Thr Asp
1 5 10 15

Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn Lys Ile Thr Pro
20 25 30

Asn Pro Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln Leu Ala His Gln
35 40 45

Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser
50 55 60

<210> SEQ ID NO 57
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 57

ggccactgcc tcattatcaa caatgtgaac ttctgccgtg agtccgggct ccgcacccgc 60

actggctcca acatcgactg tgagaagttg cggcgtcgct tctcctcgcc gcatttcatg 120

gtggaggtga agggcgacct gactgccaag aaaatggtgc tggctttgct ggagctggcg 180

<210> SEQ ID NO 58
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 58

Gly His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly
1 5 10 15

Leu Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg
20 25 30

Arg Phe Ser Ser Pro His Phe Met Val Glu Val Lys Gly Asp Leu Thr
35 40 45

Ala Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala
50 55 60

<210> SEQ ID NO 59
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 59

actagagcta gatactttct agttgggagc aataatgcag aaacgaaata tcgtgtcttg 60

aagactgata gaacagaacc aaaagatttg gtcataattg atgacaggca tgtctatact 120

caacaagaag taagggaact tcttggccgc ttggatcttg gaaatagaac aaagatggga 180

<210> SEQ ID NO 60
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 60

Thr Arg Ala Arg Tyr Phe Leu Val Gly Ser Asn Asn Ala Glu Thr Lys
1 5 10 15

Tyr Arg Val Leu Lys Thr Asp Arg Thr Glu Pro Lys Asp Leu Val Ile
20 25 30

Ile Asp Asp Arg His Val Tyr Thr Gln Gln Glu Val Arg Glu Leu Leu
35 40 45

Gly Arg Leu Asp Leu Gly Asn Arg Thr Lys Met Gly
50 55 60

<210> SEQ ID NO 61
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 61

acagatgccc cggtgagccc caccactctg tatgtggagg acatctcgga accgccgttg 60

cacgatttct accgcagcag gctactggac ctggtcttcc tgctggatgg ctcctccagg 120

ctgtccgagg ctgagtttga agtgctgaag gcctttgtgg tggacatgat ggagcggctg 180

<210> SEQ ID NO 62
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 62

Thr Asp Ala Pro Val Ser Pro Thr Thr Leu Tyr Val Glu Asp Ile Ser
1 5 10 15

Glu Pro Pro Leu His Asp Phe Tyr Arg Ser Arg Leu Leu Asp Leu Val
20 25 30

Phe Leu Leu Asp Gly Ser Ser Arg Leu Ser Glu Ala Glu Phe Glu Val
35 40 45

Leu Lys Ala Phe Val Val Asp Met Met Glu Arg Leu
50 55 60

<210> SEQ ID NO 63
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 63

atctgtgctg ctgtcctcag caaattcatg tctgtgttct gcggggtata tgagcagcca 60

tactactact ctgatatcct gacggtgggc tgtgctgtgg gagtcggccg ttgttttggg 120

acaccacttg gaggagtgct atttagcatc gaggtcacct ccacctactt tgctgttcgg 180

<210> SEQ ID NO 64
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 64

Ile Cys Ala Ala Val Leu Ser Lys Phe Met Ser Val Phe Cys Gly Val
1 5 10 15

Tyr Glu Gln Pro Tyr Tyr Tyr Ser Asp Ile Leu Thr Val Gly Cys Ala
20 25 30

Val Gly Val Gly Arg Cys Phe Gly Thr Pro Leu Gly Gly Val Leu Phe
35 40 45

Ser Ile Glu Val Thr Ser Thr Tyr Phe Ala Val Arg
50 55 60

<210> SEQ ID NO 65
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 65

tactttgaaa agtcaaagga gcagctgaca cccctgatca agaaggctgg aacggaactg 60

gttaacttct tgagctattt cgtggaactt ggaacacagc ctgccaccca gcgaagtgtc 120

cagcaccatt gtcttccaac cccagctggc ctctagaaca cccactggcc agtcctagag 180

<210> SEQ ID NO 66
<211> LENGTH: 59
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 66

Tyr Phe Glu Lys Ser Lys Glu Gln Leu Thr Pro Leu Ile Lys Lys Ala
1 5 10 15

Gly Thr Glu Leu Val Asn Phe Leu Ser Tyr Phe Val Glu Leu Gly Thr
20 25 30

Gln Pro Ala Thr Gln Arg Ser Val Gln His His Cys Leu Pro Thr Pro
35 40 45

Ala Gly Leu Asn Thr His Trp Pro Val Leu Glu
50 55

<210> SEQ ID NO 67
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 67

ccgcacaagc gcctcacgct cagcggcatc tgcgccttca ttagtgaccg cttcccctac 60

taccgccgca agttccccgc ccggcagaac agcatccgcc acaacctctc gctgaacgac 120

tgcttcgtca agatcccccg cgagccgggc cgcccaggca agggcaacta ctggagcctg 180

<210> SEQ ID NO 68
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 68

Pro His Lys Arg Leu Thr Leu Ser Gly Ile Cys Ala Phe Ile Ser Asp
1 5 10 15

Arg Phe Pro Tyr Tyr Arg Arg Lys Phe Pro Ala Arg Gln Asn Ser Ile
20 25 30

Arg His Asn Leu Ser Leu Asn Asp Cys Phe Val Lys Ile Pro Arg Glu
35 40 45

Pro Gly Arg Pro Gly Lys Gly Asn Tyr Trp Ser Leu
50 55 60

<210> SEQ ID NO 69
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 69

gctgaggacc tgtggctgag cccgctgacc atggaagatc ttgtctgcta cagcttccag 60

gtggccagag ggatggagtt cctggcttcc cgaaagtgca tccgcagaga cctggctgct 120

cggaacattc tgctgtcgga aagcgacgtg gtgaagatct gtgactttgg ccttgcccgg 180

<210> SEQ ID NO 70
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 70

Ala Glu Asp Leu Trp Leu Ser Pro Leu Thr Met Glu Asp Leu Val Cys
1 5 10 15

Tyr Ser Phe Gln Val Ala Arg Gly Met Glu Phe Leu Ala Ser Arg Lys
20 25 30

Cys Ile Arg Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser Glu Ser
35 40 45

Asp Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg
50 55 60

<210> SEQ ID NO 71
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 71

gataccgaga ctgtgggcca gagagccctg cactcaattc tgaatgctgc catcatgatc 60

agtgtcgttg ttgtcatgac tatcctcctg gtggttctgt ataaatacag gtgctataag 120

gtcatccatg cctggcttat tatatcatct ctattgttgc tgttcttttt ttcattcatt 180

<210> SEQ ID NO 72
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 72

Asp Thr Glu Thr Val Gly Gln Arg Ala Leu His Ser Ile Leu Asn Ala
1 5 10 15

Ala Ile Met Ile Ser Val Val Val Val Met Thr Ile Leu Leu Val Val
20 25 30

Leu Tyr Lys Tyr Arg Cys Tyr Lys Val Ile His Ala Trp Leu Ile Ile
35 40 45

Ser Ser Leu Leu Leu Leu Phe Phe Phe Ser Phe Ile
50 55 60

<210> SEQ ID NO 73
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 73

aagccgagta agccaaaaac caacatgaag cacatggctg gtgctgcagc agctggggca 60

gtggtggggg gccttggcgg ctacgtgctg ggaagtgcca tgagcaggcc catcatacat 120

ttcggcagtg actatgagga ccgttactat cgtgaaaaca tgcaccgtta ccccaaccaa 180

<210> SEQ ID NO 74
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 74

Lys Pro Ser Lys Pro Lys Thr Asn Met Lys His Met Ala Gly Ala Ala
1 5 10 15

Ala Ala Gly Ala Val Val Gly Gly Leu Gly Gly Tyr Val Leu Gly Ser
20 25 30

Ala Met Ser Arg Pro Ile Ile His Phe Gly Ser Asp Tyr Glu Asp Arg
35 40 45

Tyr Tyr Arg Glu Asn Met His Arg Tyr Pro Asn Gln
50 55 60

<210> SEQ ID NO 75
<211> LENGTH: 120
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 75

cttcccagcc gagacgtgac agtccttctg gaaaactatg gcaaattcga aaaggggtgt 60

ttgatttttg ttgtacgttt cctctttggc ctggtaaacc aggagaggac ctcctacttg 120

<210> SEQ ID NO 76
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

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<400> SEQUENCE: 76

Leu Pro Ser Arg Asp Val Thr Val Leu Leu Glu Asn Tyr Gly Lys Phe
1 5 10 15

Glu Lys Gly Cys Leu Ile Phe Val Val Arg Phe Leu Phe Gly Leu Val
            20 25 30

Asn Gln Glu Arg Thr Ser Tyr Leu
        35 40

<210> SEQ ID NO 77
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 77

gtgaagcact tctccccaga ggaactcaaa gttaaggtgt tgggagatgt gattgaggtg 60

catggaaaac atgaagagcg ccaggatgaa catggtttca tctccaggga gttccacggg 120

aaataccgga tcccagctga tgtagaccct ctcaccatta cttcatccct gtcatctgat 180

<210> SEQ ID NO 78
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 78

Val Lys His Phe Ser Pro Glu Glu Leu Lys Val Lys Val Leu Gly Asp
1 5 10 15

Val Ile Glu Val His Gly Lys His Glu Glu Arg Gln Asp Glu His Gly
            20 25 30

Phe Ile Ser Arg Glu Phe His Gly Lys Tyr Arg Ile Pro Ala Asp Val
        35 40 45

Asp Pro Leu Thr Ile Thr Ser Ser Leu Ser Ser Asp
    50 55 60

<210> SEQ ID NO 79
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 79

gagctgcact gtgacaagct gcacgtggat cctgagaact tcaggctcct gggcaacgtg 60

ctggtctgtg tgccggccca tcactttggc aaagaattca ccccaccagt gcaggctgcc 120

tatcagaaag tggtggctgg tgtggctaat gccctggccc acaagtatca ctaagctcgc 180

<210> SEQ ID NO 80
<211> LENGTH: 59
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 80

Glu Leu His Cys Asp Lys Leu His Val Asp Pro Glu Asn Phe Arg Leu

-continued

1 5 10 15

Leu Gly Asn Val Leu Val Cys Val Pro Ala His His Phe Gly Lys Glu
20 25 30

Phe Thr Pro Pro Val Gln Ala Ala Tyr Gln Lys Val Val Ala Gly Val
35 40 45

Ala Asn Ala Leu Ala His Lys Tyr His Ala Arg
50 55

<210> SEQ ID NO 81
<211> LENGTH: 102
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 81

aucggaauct auuuugacuc guuuuagagc uagaaauagc aaguuaaaau aaaggcuagu 60

ccguuaucaa cuugaaaaag uggcaccgag ucggugcuuu uu 102

<210> SEQ ID NO 82
<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 82

ucggaaucua uuuugacucg guuuuagagc uagaaauagc aaguuaaaau aaaggcuagu 60

ccguuaucaa cuugaaaaag uggcaccgag ucggugcuuu uu 102

<210> SEQ ID NO 83
<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 83

cuuagauaaa acugagcaag guuuuagagc uagaaauagc aaguuaaaau aaaggcuagu 60

ccguuaucaa cuugaaaaag uggcaccgag ucggugcuuu uu 102

<210> SEQ ID NO 84
<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 84

aucuauuuug acucguucuc guuuuagagc uagaaauagc aaguuaaaau aaaggcuagu 60

ccguuaucaa cuugaaaaag uggcaccgag ucggugcuuu uu 102

<210> SEQ ID NO 85
<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 85

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uaaaacugag caagaggcuu guuuuagagc uagaaauagc aaguuaaaau aaaggcuagu 60

ccguuaucaa cuugaaaaag uggcaccgag ucggugcuuu uu 102

<210> SEQ ID NO 86
<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 86

ugguggcugg acaacaaaaa guuuuagagc uagaaauagc aaguuaaaau aaaggcuagu 60

ccguuaucaa cuugaaaaag uggcaccgag ucggugcuuu uu 102

<210> SEQ ID NO 87
<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 87

gcuggacaac aaaaauggau guuuuagagc uagaaauagc aaguuaaaau aaaggcuagu 60

ccguuaucaa cuugaaaaag uggcaccgag ucggugcuuu uu 102

<210> SEQ ID NO 88
<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 88

guguuaauuu gucguacgua guuuuagagc uagaaauagc aaguuaaaau aaaggcuagu 60

ccguuaucaa cuugaaaaag uggcaccgag ucggugcuuu uu 102

<210> SEQ ID NO 89
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 89

gcctccgcca acgtggactt cgctttcagc ctgtacaagc agttagtcct gaaggcccct 60

gataagaatg tcatcttctc cccaccgagc atctccaccg ccttggcctt cctgtctctg 120

ggggcccata ataccaccct gacagagatt ctcaaaggcc tcaagttcta cctcacggag 180

<210> SEQ ID NO 90
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 90

Ala Ser Ala Asn Val Asp Phe Ala Phe Ser Leu Tyr Lys Gln Leu Val
1 5 10 15

-continued

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Leu Lys Ala Pro Asp Lys Asn Val Ile Phe Ser Pro Pro Ser Ile Ser
            20                  25                  30

Thr Ala Leu Ala Phe Leu Ser Leu Gly Ala His Asn Thr Thr Leu Thr
        35                  40                  45

Glu Ile Leu Lys Gly Leu Lys Phe Tyr Leu Thr Glu
    50                  55                  60


<210> SEQ ID NO 91
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 91

Gly Gly Gly Gly Ser
1               5


<210> SEQ ID NO 92
<211> LENGTH: 1636
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 92

Ser Pro Lys Lys Lys Arg Lys Val Glu Ala Ser Met Thr Ser Glu Lys
1               5                   10                  15

Gly Pro Ser Thr Gly Asp Pro Thr Leu Arg Arg Arg Ile Glu Pro Trp
            20                  25                  30

Glu Phe Asp Val Phe Tyr Asp Pro Arg Glu Leu Arg Lys Glu Ala Cys
        35                  40                  45

Leu Leu Tyr Glu Ile Lys Trp Gly Met Ser Arg Lys Ile Trp Arg Ser
    50                  55                  60

Ser Gly Lys Asn Thr Thr Asn His Val Glu Val Asn Phe Ile Lys Lys
65                  70                  75                  80

Phe Thr Ser Glu Arg Asp Phe His Pro Ser Met Ser Cys Ser Ile Thr
                85                  90                  95

Trp Phe Leu Ser Trp Ser Pro Cys Trp Glu Cys Ser Gln Ala Ile Arg
            100                 105                 110

Glu Phe Leu Ser Arg His Pro Gly Val Thr Leu Val Ile Tyr Val Ala
        115                 120                 125

Arg Leu Phe Trp His Met Asp Gln Gln Asn Arg Gln Gly Leu Arg Asp
    130                 135                 140

Leu Val Asn Ser Gly Val Thr Ile Gln Ile Met Arg Ala Ser Glu Tyr
145                 150                 155                 160

Tyr His Cys Trp Arg Asn Phe Val Asn Tyr Pro Pro Gly Asp Glu Ala
                165                 170                 175

His Trp Pro Gln Tyr Pro Pro Leu Trp Met Met Leu Tyr Ala Leu Glu
            180                 185                 190

Leu His Cys Ile Ile Leu Ser Leu Pro Pro Cys Leu Lys Ile Ser Arg
        195                 200                 205

Arg Trp Gln Asn His Leu Thr Phe Phe Arg Leu His Leu Gln Asn Cys
    210                 215                 220

His Tyr Gln Thr Ile Pro Pro His Ile Leu Leu Ala Thr Gly Leu Ile
225                 230                 235                 240
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His Pro Ser Val Ala Trp Arg Ser Pro Lys Lys Lys Arg Lys Val Glu
               245                 250                 255

Ala Ser Ser Pro Lys Lys Lys Arg Lys Val Glu Ala Ser Asp Lys Lys
            260                 265                 270

Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly Trp Ala Val
        275                 280                 285

Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly
    290                 295                 300

Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu
305                 310                 315                 320

Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala
               325                 330                 335

Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu
            340                 345                 350

Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg
        355                 360                 365

Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His
    370                 375                 380

Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr
385                 390                 395                 400

Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys
               405                 410                 415

Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe
            420                 425                 430

Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp
        435                 440                 445

Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe
    450                 455                 460

Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu
465                 470                 475                 480

Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln
               485                 490                 495

Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu
            500                 505                 510

Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu
        515                 520                 525

Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp
    530                 535                 540

Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala
545                 550                 555                 560

Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val
               565                 570                 575

Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg
            580                 585                 590

Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg
        595                 600                 605

Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys
    610                 615                 620

Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe
625                 630                 635                 640
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Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu
                645                 650                 655

Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr
            660                 665                 670

Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His
        675                 680                 685

Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn
    690                 695                 700

Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val
705                 710                 715                 720

Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys
                725                 730                 735

Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys
            740                 745                 750

Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys
        755                 760                 765

Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu
    770                 775                 780

Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu
785                 790                 795                 800

Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile
                805                 810                 815

Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu
            820                 825                 830

Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile
        835                 840                 845

Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp
    850                 855                 860

Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn
865                 870                 875                 880

Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp
                885                 890                 895

Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp
            900                 905                 910

Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly
        915                 920                 925

Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly
    930                 935                 940

Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn
945                 950                 955                 960

Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile
                965                 970                 975

Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile
            980                 985                 990

Ala Asn Leu Ala Gly Ser Pro Ala  Ile Lys Lys Gly Ile  Leu Gln Thr
        995                 1000                1005

Val Lys  Val Val Asp Glu Leu  Val Lys Val Met Gly  Arg His Lys
    1010                1015                1020

Pro Glu  Asn Ile Val Ile Glu  Met Ala Arg Glu Asn  Gln Thr Thr
    1025                1030                1035

Gln Lys  Gly Gln Lys Asn Ser  Arg Glu Arg Met Lys  Arg Ile Glu
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    1040                1045                1050

Glu Gly  Ile Lys Glu Leu Gly  Ser Gln Ile Leu Lys  Glu His Pro
    1055                1060                1065

Val Glu  Asn Thr Gln Leu Gln  Asn Glu Lys Leu Tyr  Leu Tyr Tyr
    1070                1075                1080

Leu Gln  Asn Gly Arg Asp Met  Tyr Val Asp Gln Glu  Leu Asp Ile
    1085                1090                1095

Asn Arg  Leu Ser Asp Tyr Asp  Val Asp Ala Ile Val  Pro Gln Ser
    1100                1105                1110

Phe Leu  Lys Asp Asp Ser Ile  Asp Asn Lys Val Leu  Thr Arg Ser
    1115                1120                1125

Asp Lys  Asn Arg Gly Lys Ser  Asp Asn Val Pro Ser  Glu Glu Val
    1130                1135                1140

Val Lys  Lys Met Lys Asn Tyr  Trp Arg Gln Leu Leu  Asn Ala Lys
    1145                1150                1155

Leu Ile  Thr Gln Arg Lys Phe  Asp Asn Leu Thr Lys  Ala Glu Arg
    1160                1165                1170

Gly Gly  Leu Ser Glu Leu Asp  Lys Ala Gly Phe Ile  Lys Arg Gln
    1175                1180                1185

Leu Val  Glu Thr Arg Gln Ile  Thr Lys His Val Ala  Gln Ile Leu
    1190                1195                1200

Asp Ser  Arg Met Asn Thr Lys  Tyr Asp Glu Asn Asp  Lys Leu Ile
    1205                1210                1215

Arg Glu  Val Lys Val Ile Thr  Leu Lys Ser Lys Leu  Val Ser Asp
    1220                1225                1230

Phe Arg  Lys Asp Phe Gln Phe  Tyr Lys Val Arg Glu  Ile Asn Asn
    1235                1240                1245

Tyr His  His Ala His Asp Ala  Tyr Leu Asn Ala Val  Val Gly Thr
    1250                1255                1260

Ala Leu  Ile Lys Lys Tyr Pro  Lys Leu Glu Ser Glu  Phe Val Tyr
    1265                1270                1275

Gly Asp  Tyr Lys Val Tyr Asp  Val Arg Lys Met Ile  Ala Lys Ser
    1280                1285                1290

Glu Gln  Glu Ile Gly Lys Ala  Thr Ala Lys Tyr Phe  Phe Tyr Ser
    1295                1300                1305

Asn Ile  Met Asn Phe Phe Lys  Thr Glu Ile Thr Leu  Ala Asn Gly
    1310                1315                1320

Glu Ile  Arg Lys Arg Pro Leu  Ile Glu Thr Asn Gly  Glu Thr Gly
    1325                1330                1335

Glu Ile  Val Trp Asp Lys Gly  Arg Asp Phe Ala Thr  Val Arg Lys
    1340                1345                1350

Val Leu  Ser Met Pro Gln Val  Asn Ile Val Lys Lys  Thr Glu Val
    1355                1360                1365

Gln Thr  Gly Gly Phe Ser Lys  Glu Ser Ile Leu Pro  Lys Arg Asn
    1370                1375                1380

Ser Asp  Lys Leu Ile Ala Arg  Lys Lys Asp Trp Asp  Pro Lys Lys
    1385                1390                1395

Tyr Gly  Gly Phe Asp Ser Pro  Thr Val Ala Tyr Ser  Val Leu Val
    1400                1405                1410

Val Ala  Lys Val Glu Lys Gly  Lys Ser Lys Lys Leu  Lys Ser Val
    1415                1420                1425
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Lys Glu  Leu Leu Gly Ile Thr  Ile Met Glu Arg Ser  Ser Phe Glu
    1430                 1435                 1440

Lys Asn  Pro Ile Asp Phe Leu  Glu Ala Lys Gly Tyr  Lys Glu Val
    1445                 1450                 1455

Lys Lys  Asp Leu Ile Ile Lys  Leu Pro Lys Tyr Ser  Leu Phe Glu
    1460                 1465                 1470

Leu Glu  Asn Gly Arg Lys Arg  Met Leu Ala Ser Ala  Gly Glu Leu
    1475                 1480                 1485

Gln Lys  Gly Asn Glu Leu Ala  Leu Pro Ser Lys Tyr  Val Asn Phe
    1490                 1495                 1500

Leu Tyr  Leu Ala Ser His Tyr  Glu Lys Leu Lys Gly  Ser Pro Glu
    1505                 1510                 1515

Asp Asn  Glu Gln Lys Gln Leu  Phe Val Glu Gln His  Lys His Tyr
    1520                 1525                 1530

Leu Asp  Glu Ile Ile Glu Gln  Ile Ser Glu Phe Ser  Lys Arg Val
    1535                 1540                 1545

Ile Leu  Ala Asp Ala Asn Leu  Asp Lys Val Leu Ser  Ala Tyr Asn
    1550                 1555                 1560

Lys His  Arg Asp Lys Pro Ile  Arg Glu Gln Ala Glu  Asn Ile Ile
    1565                 1570                 1575

His Leu  Phe Thr Leu Thr Asn  Leu Gly Ala Pro Ala  Ala Phe Lys
    1580                 1585                 1590

Tyr Phe  Asp Thr Thr Ile Asp  Arg Lys Arg Tyr Thr  Ser Thr Lys
    1595                 1600                 1605

Glu Val  Leu Asp Ala Thr Leu  Ile His Gln Ser Ile  Thr Gly Leu
    1610                 1615                 1620

Tyr Glu  Thr Arg Ile Asp Leu  Ser Gln Leu Gly Gly  Asp
    1625                 1630                 1635


<210> SEQ ID NO 93
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 93

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
1               5                   10                  15


<210> SEQ ID NO 94
<211> LENGTH: 1600
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 94

Met Ser Ser Glu Thr Gly Pro Val Ala Val Asp Pro Thr Leu Arg Arg
1               5                   10                  15

Arg Ile Glu Pro His Glu Phe Glu Val Phe Phe Asp Pro Arg Glu Leu
            20                  25                  30

Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Asn Trp Gly Gly Arg His
        35                  40                  45

Ser Ile Trp Arg His Thr Ser Gln Asn Thr Asn Lys His Val Glu Val
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    50                  55                  60

Asn Phe Ile Glu Lys Phe Thr Thr Glu Arg Tyr Phe Cys Pro Asn Thr
65                  70                  75                  80

Arg Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Gly Glu Cys
                85                  90                  95

Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg Tyr Pro His Val Thr Leu
            100                 105                 110

Phe Ile Tyr Ile Ala Arg Leu Tyr His His Ala Asp Pro Arg Asn Arg
        115                 120                 125

Gln Gly Leu Arg Asp Leu Ile Ser Ser Gly Val Thr Ile Gln Ile Met
    130                 135                 140

Thr Glu Gln Glu Ser Gly Tyr Cys Trp Arg Asn Phe Val Asn Tyr Ser
145                 150                 155                 160

Pro Ser Asn Glu Ala His Trp Pro Arg Tyr Pro His Leu Trp Val Arg
                165                 170                 175

Leu Tyr Val Leu Glu Leu Tyr Cys Ile Ile Leu Gly Leu Pro Pro Cys
            180                 185                 190

Leu Asn Ile Leu Arg Arg Lys Gln Pro Gln Leu Thr Phe Phe Thr Ile
        195                 200                 205

Ala Leu Gln Ser Cys His Tyr Gln Arg Leu Pro Pro His Ile Leu Trp
    210                 215                 220

Ala Thr Gly Leu Lys Gly Gly Ser Met Asp Lys Lys Tyr Ser Ile Gly
225                 230                 235                 240

Leu Ala Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu
                245                 250                 255

Tyr Lys Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg
            260                 265                 270

His Ser Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly
        275                 280                 285

Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr
    290                 295                 300

Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn
305                 310                 315                 320

Glu Met Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser
                325                 330                 335

Phe Leu Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly
            340                 345                 350

Asn Ile Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr
        355                 360                 365

His Leu Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg
    370                 375                 380

Leu Ile Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe
385                 390                 395                 400

Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu
                405                 410                 415

Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro
            420                 425                 430

Ile Asn Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu
        435                 440                 445

Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu
    450                 455                 460
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Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu
465                 470                 475                 480

Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu
                485                 490                 495

Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala
            500                 505                 510

Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu
        515                 520                 525

Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile
    530                 535                 540

Thr Lys Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His
545                 550                 555                 560

His Gln Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro
                565                 570                 575

Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala
            580                 585                 590

Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile
        595                 600                 605

Lys Pro Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys
    610                 615                 620

Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly
625                 630                 635                 640

Ser Ile Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg
                645                 650                 655

Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile
            660                 665                 670

Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala
        675                 680                 685

Arg Gly Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr
    690                 695                 700

Ile Thr Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala
705                 710                 715                 720

Gln Ser Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn
                725                 730                 735

Glu Lys Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val
            740                 745                 750

Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys
        755                 760                 765

Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu
    770                 775                 780

Phe Lys Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr
785                 790                 795                 800

Phe Lys Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu
                805                 810                 815

Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile
            820                 825                 830

Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu
        835                 840                 845

Glu Asp Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile
    850                 855                 860
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Glu Glu Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met
865                 870                 875                 880

Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg
                885                 890                 895

Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu
            900                 905                 910

Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu
        915                 920                 925

Ile His Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln
    930                 935                 940

Val Ser Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala
945                 950                 955                 960

Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val
                965                 970                 975

Asp Glu Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val
            980                 985                 990

Ile Glu Met Ala Arg Glu Asn Gln  Thr Thr Gln Lys Gly  Gln Lys Asn
        995                 1000                1005

Ser Arg  Glu Arg Met Lys Arg  Ile Glu Glu Gly Ile  Lys Glu Leu
    1010                1015                1020

Gly Ser  Gln Ile Leu Lys Glu  His Pro Val Glu Asn  Thr Gln Leu
    1025                1030                1035

Gln Asn  Glu Lys Leu Tyr Leu  Tyr Tyr Leu Gln Asn  Gly Arg Asp
    1040                1045                1050

Met Tyr  Val Asp Gln Glu Leu  Asp Ile Asn Arg Leu  Ser Asp Tyr
    1055                1060                1065

Asp Val  Asp Ala Ile Val Pro  Gln Ser Phe Leu Lys  Asp Asp Ser
    1070                1075                1080

Ile Asp  Asn Lys Val Leu Thr  Arg Ser Asp Lys Asn  Arg Gly Lys
    1085                1090                1095

Ser Asp  Asn Val Pro Ser Glu  Glu Val Val Lys Lys  Met Lys Asn
    1100                1105                1110

Tyr Trp  Arg Gln Leu Leu Asn  Ala Lys Leu Ile Thr  Gln Arg Lys
    1115                1120                1125

Phe Asp  Asn Leu Thr Lys Ala  Glu Arg Gly Gly Leu  Ser Glu Leu
    1130                1135                1140

Asp Lys  Ala Gly Phe Ile Lys  Arg Gln Leu Val Glu  Thr Arg Gln
    1145                1150                1155

Ile Thr  Lys His Val Ala Gln  Ile Leu Asp Ser Arg  Met Asn Thr
    1160                1165                1170

Lys Tyr  Asp Glu Asn Asp Lys  Leu Ile Arg Glu Val  Lys Val Ile
    1175                1180                1185

Thr Leu  Lys Ser Lys Leu Val  Ser Asp Phe Arg Lys  Asp Phe Gln
    1190                1195                1200

Phe Tyr  Lys Val Arg Glu Ile  Asn Asn Tyr His His  Ala His Asp
    1205                1210                1215

Ala Tyr  Leu Asn Ala Val Val  Gly Thr Ala Leu Ile  Lys Lys Tyr
    1220                1225                1230

Pro Lys  Leu Glu Ser Glu Phe  Val Tyr Gly Asp Tyr  Lys Val Tyr
    1235                1240                1245

Asp Val  Arg Lys Met Ile Ala  Lys Ser Glu Gln Glu  Ile Gly Lys
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    1250                1255                1260

Ala Thr  Ala Lys Tyr Phe Phe  Tyr Ser Asn Ile Met  Asn Phe Phe
    1265                1270                1275

Lys Thr  Glu Ile Thr Leu Ala  Asn Gly Glu Ile Arg  Lys Arg Pro
    1280                1285                1290

Leu Ile  Glu Thr Asn Gly Glu  Thr Gly Glu Ile Val  Trp Asp Lys
    1295                1300                1305

Gly Arg  Asp Phe Ala Thr Val  Arg Lys Val Leu Ser  Met Pro Gln
    1310                1315                1320

Val Asn  Ile Val Lys Lys Thr  Glu Val Gln Thr Gly  Gly Phe Ser
    1325                1330                1335

Lys Glu  Ser Ile Leu Pro Lys  Arg Asn Ser Asp Lys  Leu Ile Ala
    1340                1345                1350

Arg Lys  Lys Asp Trp Asp Pro  Lys Lys Tyr Gly Gly  Phe Asp Ser
    1355                1360                1365

Pro Thr  Val Ala Tyr Ser Val  Leu Val Val Ala Lys  Val Glu Lys
    1370                1375                1380

Gly Lys  Ser Lys Lys Leu Lys  Ser Val Lys Glu Leu  Leu Gly Ile
    1385                1390                1395

Thr Ile  Met Glu Arg Ser Ser  Phe Glu Lys Asn Pro  Ile Asp Phe
    1400                1405                1410

Leu Glu  Ala Lys Gly Tyr Lys  Glu Val Lys Lys Asp  Leu Ile Ile
    1415                1420                1425

Lys Leu  Pro Lys Tyr Ser Leu  Phe Glu Leu Glu Asn  Gly Arg Lys
    1430                1435                1440

Arg Met  Leu Ala Ser Ala Gly  Glu Leu Gln Lys Gly  Asn Glu Leu
    1445                1450                1455

Ala Leu  Pro Ser Lys Tyr Val  Asn Phe Leu Tyr Leu  Ala Ser His
    1460                1465                1470

Tyr Glu  Lys Leu Lys Gly Ser  Pro Glu Asp Asn Glu  Gln Lys Gln
    1475                1480                1485

Leu Phe  Val Glu Gln His Lys  His Tyr Leu Asp Glu  Ile Ile Glu
    1490                1495                1500

Gln Ile  Ser Glu Phe Ser Lys  Arg Val Ile Leu Ala  Asp Ala Asn
    1505                1510                1515

Leu Asp  Lys Val Leu Ser Ala  Tyr Asn Lys His Arg  Asp Lys Pro
    1520                1525                1530

Ile Arg  Glu Gln Ala Glu Asn  Ile Ile His Leu Phe  Thr Leu Thr
    1535                1540                1545

Asn Leu  Gly Ala Pro Ala Ala  Phe Lys Tyr Phe Asp  Thr Thr Ile
    1550                1555                1560

Asp Arg  Lys Arg Tyr Thr Ser  Thr Lys Glu Val Leu  Asp Ala Thr
    1565                1570                1575

Leu Ile  His Gln Ser Ile Thr  Gly Leu Tyr Glu Thr  Arg Ile Asp
    1580                1585                1590

Leu Ser  Gln Leu Gly Gly Asp
    1595                1600
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<210> SEQ ID NO 95
<211> LENGTH: 1606
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 95

Met Ser Ser Glu Thr Gly Pro Val Ala Val Asp Pro Thr Leu Arg Arg
1 5 10 15

Arg Ile Glu Pro His Glu Phe Glu Val Phe Phe Asp Pro Arg Glu Leu
20 25 30

Arg Lys Glu Thr Cys Leu Leu Tyr Glu Ile Asn Trp Gly Gly Arg His
35 40 45

Ser Ile Trp Arg His Thr Ser Gln Asn Thr Asn Lys His Val Glu Val
50 55 60

Asn Phe Ile Glu Lys Phe Thr Thr Glu Arg Tyr Phe Cys Pro Asn Thr
65 70 75 80

Arg Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Gly Glu Cys
85 90 95

Ser Arg Ala Ile Thr Glu Phe Leu Ser Arg Tyr Pro His Val Thr Leu
100 105 110

Phe Ile Tyr Ile Ala Arg Leu Tyr His His Ala Asp Pro Arg Asn Arg
115 120 125

Gln Gly Leu Arg Asp Leu Ile Ser Ser Gly Val Thr Ile Gln Ile Met
130 135 140

Thr Glu Gln Glu Ser Gly Tyr Cys Trp Arg Asn Phe Val Asn Tyr Ser
145 150 155 160

Pro Ser Asn Glu Ala His Trp Pro Arg Tyr Pro His Leu Trp Val Arg
165 170 175

Leu Tyr Val Leu Glu Leu Tyr Cys Ile Ile Leu Gly Leu Pro Pro Cys
180 185 190

Leu Asn Ile Leu Arg Arg Lys Gln Pro Gln Leu Thr Phe Phe Thr Ile
195 200 205

Ala Leu Gln Ser Cys His Tyr Gln Arg Leu Pro Pro His Ile Leu Trp
210 215 220

Ala Thr Gly Leu Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Met Asp
225 230 235 240

Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val Gly Trp
245 250 255

Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe Lys Val
260 265 270

Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile Gly Ala
275 280 285

Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu Lys Arg
290 295 300

Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys Tyr Leu
305 310 315 320

Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser Phe Phe
325 330 335

His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys His Glu
340 345 350

Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr His Glu
355 360 365

Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp Ser Thr
370 375 380

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Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His Met Ile
385                 390                 395                 400

Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro Asp Asn
                405                 410                 415

Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr Asn Gln
            420                 425                 430

Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala Lys Ala
        435                 440                 445

Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn Leu Ile
    450                 455                 460

Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn Leu Ile
465                 470                 475                 480

Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe Asp Leu
                485                 490                 495

Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp Asp Asp
            500                 505                 510

Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp Leu Phe
        515                 520                 525

Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp Ile Leu
    530                 535                 540

Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser Met Ile
545                 550                 555                 560

Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys Ala Leu
                565                 570                 575

Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe Asp Gln
            580                 585                 590

Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser Gln Glu
        595                 600                 605

Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp Gly Thr
    610                 615                 620

Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg Lys Gln
625                 630                 635                 640

Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu Gly Glu
                645                 650                 655

Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe Leu Lys
            660                 665                 670

Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile Pro Tyr
        675                 680                 685

Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp Met Thr
    690                 695                 700

Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu Val Val
705                 710                 715                 720

Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr Asn Phe
                725                 730                 735

Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser Leu Leu
            740                 745                 750

Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys Tyr Val
        755                 760                 765

Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln Lys Lys
    770                 775                 780
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Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr Val Lys
785                 790                 795                 800

Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp Ser Val
                805                 810                 815

Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly Thr Tyr
            820                 825                 830

His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp Asn Glu
        835                 840                 845

Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr Leu Phe
    850                 855                 860

Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala His Leu
865                 870                 875                 880

Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr Thr Gly
                885                 890                 895

Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp Lys Gln
            900                 905                 910

Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe Ala Asn
        915                 920                 925

Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe Lys Glu
    930                 935                 940

Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu His Glu
945                 950                 955                 960

His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly Ile Leu
                965                 970                 975

Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly Arg His
            980                 985                 990

Lys Pro Glu Asn Ile Val Ile Glu  Met Ala Arg Glu Asn  Gln Thr Thr
        995                 1000                1005

Gln Lys  Gly Gln Lys Asn Ser  Arg Glu Arg Met Lys  Arg Ile Glu
    1010                1015                1020

Glu Gly  Ile Lys Glu Leu Gly  Ser Gln Ile Leu Lys  Glu His Pro
    1025                1030                1035

Val Glu  Asn Thr Gln Leu Gln  Asn Glu Lys Leu Tyr  Leu Tyr Tyr
    1040                1045                1050

Leu Gln  Asn Gly Arg Asp Met  Tyr Val Asp Gln Glu  Leu Asp Ile
    1055                1060                1065

Asn Arg  Leu Ser Asp Tyr Asp  Val Asp Ala Ile Val  Pro Gln Ser
    1070                1075                1080

Phe Leu  Lys Asp Asp Ser Ile  Asp Asn Lys Val Leu  Thr Arg Ser
    1085                1090                1095

Asp Lys  Asn Arg Gly Lys Ser  Asp Asn Val Pro Ser  Glu Glu Val
    1100                1105                1110

Val Lys  Lys Met Lys Asn Tyr  Trp Arg Gln Leu Leu  Asn Ala Lys
    1115                1120                1125

Leu Ile  Thr Gln Arg Lys Phe  Asp Asn Leu Thr Lys  Ala Glu Arg
    1130                1135                1140

Gly Gly  Leu Ser Glu Leu Asp  Lys Ala Gly Phe Ile  Lys Arg Gln
    1145                1150                1155

Leu Val  Glu Thr Arg Gln Ile  Thr Lys His Val Ala  Gln Ile Leu
    1160                1165                1170

Asp Ser  Arg Met Asn Thr Lys  Tyr Asp Glu Asn Asp  Lys Leu Ile
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    1175                1180                1185

Arg Glu  Val Lys Val Ile Thr  Leu Lys Ser Lys Leu  Val Ser Asp
    1190                1195                1200

Phe Arg  Lys Asp Phe Gln Phe  Tyr Lys Val Arg Glu  Ile Asn Asn
    1205                1210                1215

Tyr His  His Ala His Asp Ala  Tyr Leu Asn Ala Val  Val Gly Thr
    1220                1225                1230

Ala Leu  Ile Lys Lys Tyr Pro  Lys Leu Glu Ser Glu  Phe Val Tyr
    1235                1240                1245

Gly Asp  Tyr Lys Val Tyr Asp  Val Arg Lys Met Ile  Ala Lys Ser
    1250                1255                1260

Glu Gln  Glu Ile Gly Lys Ala  Thr Ala Lys Tyr Phe  Phe Tyr Ser
    1265                1270                1275

Asn Ile  Met Asn Phe Phe Lys  Thr Glu Ile Thr Leu  Ala Asn Gly
    1280                1285                1290

Glu Ile  Arg Lys Arg Pro Leu  Ile Glu Thr Asn Gly  Glu Thr Gly
    1295                1300                1305

Glu Ile  Val Trp Asp Lys Gly  Arg Asp Phe Ala Thr  Val Arg Lys
    1310                1315                1320

Val Leu  Ser Met Pro Gln Val  Asn Ile Val Lys Lys  Thr Glu Val
    1325                1330                1335

Gln Thr  Gly Gly Phe Ser Lys  Glu Ser Ile Leu Pro  Lys Arg Asn
    1340                1345                1350

Ser Asp  Lys Leu Ile Ala Arg  Lys Lys Asp Trp Asp  Pro Lys Lys
    1355                1360                1365

Tyr Gly  Gly Phe Asp Ser Pro  Thr Val Ala Tyr Ser  Val Leu Val
    1370                1375                1380

Val Ala  Lys Val Glu Lys Gly  Lys Ser Lys Lys Leu  Lys Ser Val
    1385                1390                1395

Lys Glu  Leu Leu Gly Ile Thr  Ile Met Glu Arg Ser  Ser Phe Glu
    1400                1405                1410

Lys Asn  Pro Ile Asp Phe Leu  Glu Ala Lys Gly Tyr  Lys Glu Val
    1415                1420                1425

Lys Lys  Asp Leu Ile Ile Lys  Leu Pro Lys Tyr Ser  Leu Phe Glu
    1430                1435                1440

Leu Glu  Asn Gly Arg Lys Arg  Met Leu Ala Ser Ala  Gly Glu Leu
    1445                1450                1455

Gln Lys  Gly Asn Glu Leu Ala  Leu Pro Ser Lys Tyr  Val Asn Phe
    1460                1465                1470

Leu Tyr  Leu Ala Ser His Tyr  Glu Lys Leu Lys Gly  Ser Pro Glu
    1475                1480                1485

Asp Asn  Glu Gln Lys Gln Leu  Phe Val Glu Gln His  Lys His Tyr
    1490                1495                1500

Leu Asp  Glu Ile Ile Glu Gln  Ile Ser Glu Phe Ser  Lys Arg Val
    1505                1510                1515

Ile Leu  Ala Asp Ala Asn Leu  Asp Lys Val Leu Ser  Ala Tyr Asn
    1520                1525                1530

Lys His  Arg Asp Lys Pro Ile  Arg Glu Gln Ala Glu  Asn Ile Ile
    1535                1540                1545

His Leu  Phe Thr Leu Thr Asn  Leu Gly Ala Pro Ala  Ala Phe Lys
    1550                1555                1560
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Tyr Phe  Asp Thr Thr Ile Asp  Arg Lys Arg Tyr Thr  Ser Thr Lys
    1565                1570                1575

Glu Val  Leu Asp Ala Thr Leu  Ile His Gln Ser Ile  Thr Gly Leu
    1580                1585                1590

Tyr Glu  Thr Arg Ile Asp Leu  Ser Gln Leu Gly Gly  Asp
    1595                1600                1605


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<223> OTHER INFORMATION: n is a, c, g, or t
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<400> SEQUENCE: 97

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<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 98

nnnnnnagga ggnnnnnnnn acgnnnnngg aagat 35

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attattatta ttc                                                          13


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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: these amino acids may be absent
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<222> LOCATION: (8)..(29)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
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<223> OTHER INFORMATION: these amnio acids may be absent
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 106

His Xaa Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1               5                   10                  15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Pro Cys Xaa
            20                  25                  30

Xaa Xaa Xaa Cys
        35
```

1.-**62**. (canceled)

63. A method of nucleic acid editing, the method comprising contacting a nucleic acid with:

(a) a deaminase, and

(b) a Cas9 variant comprising an inactivating mutation within a RuvC1 subdomain or a HNH subdomain,

wherein the method results in a deamination of a nucleotide base in the nucleic acid.

64. The method of claim **63**, wherein the Cas9 variant comprises the inactivating mutation within the RuvC1 subdomain.

65. The method of claim **64**, wherein the Cas9 variant comprises the inactivating mutation at an amino acid position corresponding to position D10 of a wild type *Streptococcus pyogenes* Cas9.

66. The method of claim **65**, wherein the Cas9 variant comprises an amino acid sequence that is at least about 90% identical to SEQ ID NO: 2.

67. The method of claim **65**, wherein the Cas9 variant comprises an amino acid sequence that is at least about 95% identical to SEQ ID NO: 2.

68. The method of claim **65**, wherein the Cas9 variant comprises an amino acid sequence that is at least about 99% identical to SEQ ID NO: 2.

69. The method of claim **65**, wherein the amino acid position in the Cas9 variant that corresponds to position D10 of the wild type *Streptococcus pyogenes* Cas9 is mutated to an alanine residue.

70. The method of claim **63**, wherein the Cas9 variant comprises the inactivating mutation within the HNH subdomain.

71. The method of claim **70**, wherein the Cas9 variant comprises the inactivating mutation at an amino acid position corresponding to position H840 of a wild type *Streptococcus pyogenes* Cas9.

72. The method of claim **70**, wherein the Cas9 variant comprises an amino acid sequence that is at least about 90% identical to SEQ ID NO: 2.

73. The method of claim **70**, wherein the Cas9 variant comprises an amino acid sequence that is at least about 95% identical to SEQ ID NO: 2.

74. The method of claim **70**, wherein the Cas9 variant comprises an amino acid sequence that is at least about 99% identical to SEQ ID NO: 2.

75. The method of claim **70**, wherein the amino acid position in the Cas9 variant that corresponds to position H840 is mutated to an alanine residue.

76. The method of claim **63**, wherein the deaminase is a cytidine deaminase.

77. The method of claim **76**, wherein the cytidine deaminase is an apolipoprotein B mRNA-editing complex (APOBEC) family deaminase.

78. The method of claim **76**, wherein the cytidine deaminase is an APOBEC1 family deaminase.

79. The method of claim **76**, wherein the cytidine deaminase is an activation-induced cytidine deaminase (AID).

80. The method of claim **63**, wherein the deaminase is an ACF1/ASE deaminase.

81. The method of claim **63**, wherein the deaminase is an adenosine deaminase.

82. The method of claim **81**, wherein the deaminase is an ADAT family deaminase.

83. The method of claim **63**, wherein the contacting comprises contacting with a fusion protein that comprises the deaminase and the Cas9 variant.

84. The method of claim **83**, wherein the fusion protein comprises a linker between the deaminase and the Cas9 variant.

85. The method of claim **84**, wherein the linker comprises a (GGGGS)n (SEQ ID NO: 91), a (G)n, an (EAAAK)n (SEQ ID NO: 5), or an (XP)n motif, or a combination of any of these, wherein n is independently an integer between 1 and 30.

86. The method of claim **83**, wherein the deaminase is linked to an N-terminus of the Cas9 variant or a C-terminus of the Cas9 variant.

87. The method of claim **63**, wherein the nucleic acid comprises a sequence associated with a disorder.

88. The method of claim **87**, wherein the sequence associated with the disorder encodes a protein, and wherein the deamination introduces a stop codon into the sequence associated with the disorder, resulting in a truncation of the encoded protein.

89. The method of claim **63**, wherein the deamination corrects a point mutation in the nucleic acid, wherein the point mutation is associated with a disorder.

90. The method of claim **89**, wherein the nucleic acid comprises a T to C point mutation, and wherein the deamination of the mutant C base results in a nucleic acid sequence that is not associated with the disorder.

91. The method of claim **89**, wherein the nucleic acid comprises an A to G point mutation, and wherein the deamination of the mutant G base results in a nucleic acid sequence that is not associated with the disorder.

92. The method of claim **63**, wherein the contacting occurs in vivo in a subject.

* * * * *