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(71) Applicant(s)
The Regents of the University of California

(72) Inventor(s)
Schaffer, David V.;Byrne, Leah C.;Day, Timothy P.;Flannery, John G.

(74) Agent / Attorney
FB Rice Pty Ltd, L 33 477 Collins Street, Melbourne, VIC, 3000, AU

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DENIZ DALKARA ET AL: "In vivo-directed evolution of a new adeno-associated virus for therapeutic outer retinal gene delivery from the vitreous", SCIENCE TRANSLATIONAL MEDICINE, 12 June 2013 (2013-06-12), United States, pages 189ra76.
HANEN KHABOU ET AL: "Insight into the mechanisms of enhanced retinal transduction by the engineered AAV2 capsid variant -7m8 : Mechanisms of Enhanced Transduction by AAV2-7m8", BIOTECHNOLOGY AND BIOENGINEERING, v.113(12):2712-2724 (2016)

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(71) Applicant: **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, 12th Floor, Oakland, California 94607 (US).

(72) Inventors: **SCHAFFER, David V.**; 19 Rima Court, Danville, California 94526 (US). **BYRNE, Leah C.**; 32 Dorland St. #3, San Francisco, California 94110 (US). **DAY, Timothy P.**; 2032 Delaware St., Apt. 1, Berkeley, California 94709 (US). **FLANNERY, John G.**; 1054 Cragmont Avenue, Berkeley, California 94708 (US).

(74) Agent: **BORDEN, Paula A.**; Bozicevic, Field & Francis LLP, 201 Redwood Shores Parkway, Suite 200, Redwood City, California 94065 (US).

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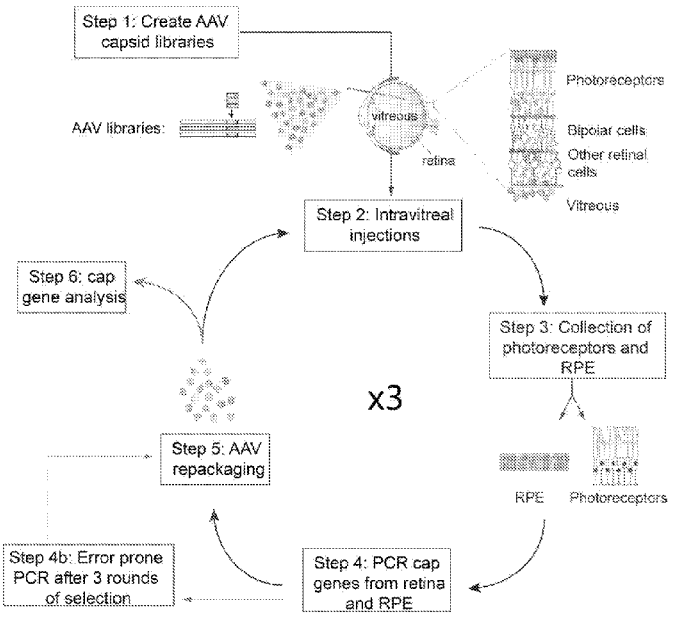
FIG. 1



(57) Abstract: The present disclosure provides recombinant adeno-associated virus (AAV) virions with altered capsid protein, where the recombinant AAV (rAAV) virions exhibit greater ability to cross barriers between intravitreal fluid and retinal cells, and thus greater infectivity of a retinal cell compared to wild-type AAV, and where the rAAV virions comprise a heterologous nucleic acid. The present disclosure provides methods of delivering a gene product to a retinal cell in an individual.

[Continued on next page]

WO 2019/006182 A1

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ADENO-ASSOCIATED VIRUS VIRIONS WITH VARIANT CAPSIDS AND METHODS OF USE THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/527,871, filed June 30, 2017, and 62/535,042, filed July 20, 2017, which applications are incorporated herein by reference in their entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under Grant No. 1R01EY022975-01A1 awarded by the National Institutes of Health. The government has certain rights in the invention.

INTRODUCTION

[0003] Vision is mediated by cells located in the retina, a thin, layered structure lining the back of the eye. Photoreceptors, which lie at the back of the retina, respond to the absorption of photons, initiating a stream of signal processing that passes through second and third order neurons in the retina, including bipolar, horizontal and amacrine cells. Retinal pigment epithelium (RPE) cells, which lie underneath photoreceptors, promote the regeneration of the photon-detecting molecule, 11-cis retinal, via the visual cycle pathway and hence are essential for promoting this photoreceptor function. Retinal ganglion cells (RGCs) in the inner retina receive visual signals from third order neurons, and communicate the visual signals in the form of action potentials to the brain.

[0004] Mutations in genes expressed in retinal cells, including transcripts in photoreceptors, RPE, bipolar cells and other cells, result in a breakdown of visual signal processing and retinal degeneration. Many of the mutations underlying retinal degenerative disease result in the death of photoreceptor and RPE cells.

[0005] Adeno-associated virus (AAV) belongs to the *Parvoviridae* family and Dependovirus genus, whose members require co-infection with a helper virus such as adenovirus to promote replication, and AAV establishes a latent infection in the absence of a helper. Virions are composed of a 25 nm icosahedral capsid encompassing a 4.7 kb single-stranded DNA genome with two open reading frames: *rep* and *cap*. The non-structural *rep* gene encodes four regulatory proteins essential for viral replication, whereas *cap* encodes three structural proteins (VP1–3) that assemble into a 60-mer capsid shell. This viral capsid mediates the ability of AAV vectors to

overcome many of the biological barriers of viral transduction–including cell surface receptor binding, endocytosis, intracellular trafficking, and unpackaging in the nucleus.

SUMMARY

[0006] The present disclosure provides recombinant adeno-associated virus (AAV) virions with altered capsid protein, where the recombinant AAV (rAAV) virions exhibit greater ability to cross barriers between intravitreal fluid and retinal cells, and thus greater infectivity of a retinal cell compared to wild-type AAV, and where the rAAV virions comprise a heterologous nucleic acid. The present disclosure provides methods of delivering a gene product to a retinal cell in an individual.

[0006a] The present disclosure provides a recombinant adeno-associated virus (rAAV) virion comprising:

a) a variant AAV capsid protein, wherein the variant AAV capsid protein comprises an insertion of a heterologous peptide comprising the amino acid sequence LALIQDSMRA (SEQ ID NO: 35) in the GH loop of VP1 of AAV2 or of another AAV serotype; and

b) a heterologous nucleic acid comprising a nucleotide sequence encoding a heterologous gene product.

[0006b] The present disclosure provides a pharmaceutical composition comprising:

a) a recombinant adeno-associated virus virion described herein; and

b) a pharmaceutically acceptable excipient.

[0006c] The present disclosure provides a method of delivering a gene product to a retinal cell in an individual for treating an ocular disease in an individual in need thereof, the method comprising administering to the individual the recombinant adeno-associated virus (rAAV) virion described herein or the composition described herein.

[0006d] The present disclosure provides use of the recombinant the adeno-associated virus (rAAV) virion described herein or the composition described herein in the manufacture of a medicament for treating an ocular disease in an individual in need thereof.

[0006e] The present disclosure provides a variant adeno-associated virus (AAV) capsid protein, wherein the variant AAV capsid protein comprises an insertion of a heterologous peptide comprising the amino acid sequence LALIQDSMRA (SEQ ID NO: 35) in the GH loop of VP1 of AAV2 or another AAV serotype.

[0006f] The present disclosure provides an isolated nucleic acid comprising a nucleotide sequence that encodes a variant adeno-associated virus (AAV) capsid protein described herein.

[0006g] The present disclosure provides an isolated, genetically modified host cell comprising the nucleic acid described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] **FIG. 1** provides a schematic depiction of the directed evolution methodology used to develop primate retinal AAV variants.

[0008] **FIG. 2** provides a table of peptide insertions and peptide replacements in variant AAV capsids.

[0009] **FIG. 3A-3C** provide amino acid sequences of exemplary guide-RNA-directed endonucleases.

[0010] **FIG. 4** provides an amino acid sequence of AAV2 capsid protein VP1. Amino acids 587 and 588 (NP) are in bold and underlined.

[0011] **FIG. 5** provides amino acid sequences corresponding to amino acids 570-610 of AAV capsid protein VP1 of various AAV serotypes.

[0012] **FIG. 6A-6C** provide an alignment of amino acid sequences of AAV capsid protein loop IV (GH loop) regions. Insertion sites are shown in bold and underlining.

[0013] **FIG. 7A-7V** provide amino acid sequences of exemplary heterologous gene products.

[0014] **FIG. 8A-8B** provide amino acid sequences of AAV4 capsid (FIG. 8A) and an ancestral AAV capsid (FIG. 8B).

[0015] **FIG. 9** provides Table 1. Table 1 provides a ranking of primate-derived variants and controls recovered from photoreceptors following injection of a green fluorescent protein (GFP)-Barcode library.

[0016] **FIG. 10** provides Table 2. Table 2 provides a ranking of primate-derived variants and controls recovered from RPE cells following injection of a GFP-Barcode library.

[0017] **FIG. 11** depicts GFP expression of GFP-barcoded libraries in primate retina.

[0018] **FIG. 12A-12F** depict directed evolution of AAV in primate retina. The sequences in FIG. 12F from top to bottom are set forth in SEQ ID NOs:117-135.

[0019] **FIG. 13A-13Q** depict validation of evolved AAV variants in primate retina.

DEFINITIONS

[0020] The term "retinal cell" can refer herein to any of the cell types that comprise the retina, such as retinal ganglion cells; amacrine cells; horizontal cells; bipolar cells; photoreceptor cells including rods and cones; Müller glial cells; astrocytes (e.g., a retinal astrocyte); and retinal pigment epithelium.

[0021] "AAV" is an abbreviation for adeno-associated virus, and may be used to refer to the virus itself or derivatives thereof. The term covers all subtypes and both naturally occurring and recombinant forms, except where required otherwise. The abbreviation "rAAV" refers to recombinant adeno-associated virus, also referred to as a recombinant AAV vector (or "rAAV vector"). The term "AAV" includes AAV type 1 (AAV-1), AAV type 2 (AAV-2), AAV type 3 (AAV-3), AAV type 4 (AAV-4), AAV type 5 (AAV-5), AAV type 6 (AAV-6), AAV type 7 (AAV-7), AAV type 8 (AAV-8), AAV type 9 (AAV-9), AAV type 10 (AAV-10), AAV type 11 (AAV-11), avian AAV, bovine AAV, canine AAV, equine AAV, primate AAV, non-primate AAV, and ovine AAV. See, e.g., Mori et al. (2004) *Virology* 330:375. The term "AAV" also includes chimeric AAV. "Primate AAV" refers to AAV isolated from a primate, "non-primate AAV" refers to AAV isolated from a non-primate mammal, "bovine AAV" refers to AAV isolated from a bovine mammal (e.g., a cow), etc.

[0022] An "rAAV vector" as used herein refers to an AAV vector comprising a polynucleotide sequence not of AAV origin (i.e., a polynucleotide heterologous to AAV), typically a sequence of interest for the genetic transformation of a cell. In general, the heterologous polynucleotide is flanked by at least one, and generally by two AAV inverted terminal repeat sequences (ITRs). The term rAAV vector encompasses both rAAV vector particles and rAAV vector plasmids.

[0023] An "AAV virus" or "AAV viral particle" or "rAAV vector particle" refers to a viral particle composed of at least one AAV capsid protein (typically by all of the capsid proteins of a wild-type AAV) and an encapsidated polynucleotide rAAV vector. If the particle comprises a heterologous polynucleotide (i.e. a polynucleotide other than a wild-type AAV genome, such as a transgene to be delivered to a mammalian cell), it is typically referred to as an "rAAV vector particle" or simply an "rAAV vector". Thus, production of rAAV particle necessarily includes production of rAAV vector, as such a vector is contained within an rAAV particle.

[0024] "Packaging" refers to a series of intracellular events that result in the assembly and encapsidation of an AAV particle.

[0025] AAV "rep" and "cap" genes refer to polynucleotide sequences encoding replication and encapsidation proteins of adeno-associated virus. AAV rep and cap are referred to herein as AAV "packaging genes."

[0026] A "helper virus" for AAV refers to a virus that allows AAV (e.g. wild-type AAV) to be replicated and packaged by a mammalian cell. A variety of such helper viruses for AAV are known in the art, including adenoviruses, herpesviruses and poxviruses such as vaccinia. The adenoviruses encompass a number of different subgroups, although Adenovirus type 5 of subgroup C is most commonly used. Numerous adenoviruses of human, non-human mammalian and avian origin are known and available from depositories such as the ATCC. Viruses of the herpes family include, for example, herpes simplex viruses (HSV) and Epstein-Barr viruses (EBV), as well as cytomegaloviruses (CMV) and pseudorabies viruses (PRV); which are also available from depositories such as ATCC.

[0027] "Helper virus function(s)" refers to function(s) encoded in a helper virus genome which allow AAV replication and packaging (in conjunction with other requirements for replication and packaging described herein). As described herein, "helper virus function" may be provided in a number of ways, including by providing helper virus or providing, for example, polynucleotide sequences encoding the requisite function(s) to a producer cell in trans.

[0028] An "infectious" virus or viral particle is one that comprises a polynucleotide component which it is capable of delivering into a cell for which the viral species is tropic. The term does not necessarily imply any replication capacity of the virus. As used herein, an “infectious” virus or viral particle is one that can access a target cell, can infect a target cell, and can express a heterologous nucleic acid in a target cell. Thus, “infectivity” refers to the ability of a viral particle to access a target cell, infect a target cell, and express a heterologous nucleic acid in a target cell. Infectivity can refer to *in vitro* infectivity or *in vivo* infectivity. Assays for counting infectious viral particles are described elsewhere in this disclosure and in the art. Viral infectivity can be expressed as the ratio of infectious viral particles to total viral particles. Total viral particles can be expressed as the number of viral genome (vg) copies. The ability of a viral particle to express a heterologous nucleic acid in a cell can be referred to as “transduction.” The ability of a viral particle to express a heterologous nucleic acid in a cell can be assayed using a number of techniques, including assessment of a marker gene, such as a green fluorescent protein (GFP) assay (e.g., where the virus comprises a nucleotide sequence encoding GFP), where GFP is produced in a cell infected with the viral particle and is detected and/or measured; or the measurement of a produced protein, for example by an enzyme-linked immunosorbent assay (ELISA). Viral infectivity can be expressed as the ratio of infectious viral particles to total viral particles. Methods of determining the ratio of infectious viral particle to total viral particle

are known in the art. See, e.g., Grainger et al. (2005) *Mol. Ther.* 11:S337 (describing a TCID50 infectious titer assay); and Zolotukhin et al. (1999) *Gene Ther.* 6:973.

[0029] A "replication-competent" virus (e.g. a replication-competent AAV) refers to a phenotypically wild-type virus that is infectious, and is also capable of being replicated in an infected cell (i.e. in the presence of a helper virus or helper virus functions). In the case of AAV, replication competence generally requires the presence of functional AAV packaging genes. In general, rAAV vectors as described herein are replication-incompetent in mammalian cells (especially in human cells) by virtue of the lack of one or more AAV packaging genes. Typically, such rAAV vectors lack any AAV packaging gene sequences in order to minimize the possibility that replication competent AAV are generated by recombination between AAV packaging genes and an incoming rAAV vector. In many embodiments, rAAV vector preparations as described herein are those which contain few if any replication competent AAV (rcAAV, also referred to as RCA) (e.g., less than about 1 rcAAV per 10^2 rAAV particles, less than about 1 rcAAV per 10^4 rAAV particles, less than about 1 rcAAV per 10^8 rAAV particles, less than about 1 rcAAV per 10^{12} rAAV particles, or no rcAAV).

[0030] The term "polynucleotide" refers to a polymeric form of nucleotides of any length, including deoxyribonucleotides or ribonucleotides, or analogs thereof. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs, and may be interrupted by non-nucleotide components. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The term polynucleotide, as used herein, refers interchangeably to double- and single-stranded molecules. Unless otherwise specified or required, any embodiment of the invention described herein that is a polynucleotide encompasses both the double-stranded form and each of two complementary single-stranded forms known or predicted to make up the double-stranded form.

[0031] A polynucleotide or polypeptide has a certain percent "sequence identity" to another polynucleotide or polypeptide, meaning that, when aligned, that percentage of bases or amino acids are the same when comparing the two sequences. Sequence similarity can be determined in a number of different manners. To determine sequence identity, sequences can be aligned using the methods and computer programs, including BLAST, available over the world wide web at ncbi.nlm.nih.gov/BLAST/. Another alignment algorithm is FASTA, available in the Genetics Computing Group (GCG) package, from Madison, Wisconsin, USA, a wholly owned subsidiary of Oxford Molecular Group, Inc. Other techniques for alignment are described in Methods in Enzymology, vol. 266: Computer Methods for Macromolecular Sequence Analysis (1996), ed. Doolittle, Academic Press, Inc., a division of Harcourt Brace & Co., San Diego, California, USA. Of particular interest are alignment programs that permit gaps in the sequence. The

Smith-Waterman is one type of algorithm that permits gaps in sequence alignments. See *Meth. Mol. Biol.* 70: 173-187 (1997). Also, the GAP program using the Needleman and Wunsch alignment method can be utilized to align sequences. See *J. Mol. Biol.* 48: 443-453 (1970)

[0032] Of interest is the BestFit program using the local homology algorithm of Smith Waterman (Advances in Applied Mathematics 2: 482-489 (1981) to determine sequence identity. The gap generation penalty will generally range from 1 to 5, usually 2 to 4 and in many embodiments will be 3. The gap extension penalty will generally range from about 0.01 to 0.20 and in many instances will be 0.10. The program has default parameters determined by the sequences inputted to be compared. Preferably, the sequence identity is determined using the default parameters determined by the program. This program is available also from Genetics Computing Group (GCG) package, from Madison, Wisconsin, USA.

[0033] Another program of interest is the FastDB algorithm. FastDB is described in Current Methods in Sequence Comparison and Analysis, Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp. 127-149, 1988, Alan R. Liss, Inc. Percent sequence identity is calculated by FastDB based upon the following parameters:

[0034] Mismatch Penalty: 1.00;

[0035] Gap Penalty: 1.00;

[0036] Gap Size Penalty: 0.33; and

[0037] Joining Penalty:30.0.

[0038] A "gene" refers to a polynucleotide containing at least one open reading frame that is capable of encoding a particular protein after being transcribed and translated.

[0039] The term “guide RNA”, as used herein, refers to an RNA that comprises: i) an “activator” nucleotide sequence that binds to a guide RNA-directed endonuclease (e.g., a class 2 CRISPR/Cas endonuclease such as a type II, type V, or type VI CRISPR/Cas endonuclease) and activates the RNA-directed endonuclease; and ii) a “targeter” nucleotide sequence that comprises a nucleotide sequence that hybridizes with a target nucleic acid. The “activator” nucleotide sequence and the “targeter” nucleotide sequence can be on separate RNA molecules (e.g., a “dual-guide RNA”); or can be on the same RNA molecule (a “single-guide RNA”).

[0040] A "small interfering" or "short interfering RNA" or siRNA is an RNA duplex of nucleotides that is targeted to a gene interest (a “target gene”). An "RNA duplex" refers to the structure formed by the complementary pairing between two regions of an RNA molecule. siRNA is "targeted" to a gene in that the nucleotide sequence of the duplex portion of the siRNA is complementary to a nucleotide sequence of the targeted gene. In some embodiments, the length of the duplex of siRNAs is less than 30 nucleotides. In some embodiments, the duplex can be 29, 28, 27, 26, 25,

24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 nucleotides in length. In some embodiments, the length of the duplex is 19-25 nucleotides in length. The RNA duplex portion of the siRNA can be part of a hairpin structure. In addition to the duplex portion, the hairpin structure may contain a loop portion positioned between the two sequences that form the duplex. The loop can vary in length. In some embodiments the loop is 5, 6, 7, 8, 9, 10, 11, 12 or 13 nucleotides in length. The hairpin structure can also contain 3' or 5' overhang portions. In some embodiments, the overhang is a 3' or a 5' overhang 0, 1, 2, 3, 4 or 5 nucleotides in length.

[0041] As used herein, the term "microRNA" refers to any type of interfering RNAs, including but not limited to, endogenous microRNAs and artificial microRNAs (e.g., synthetic miRNAs). Endogenous microRNAs are small RNAs naturally encoded in the genome which are capable of modulating the productive utilization of mRNA. An artificial microRNA can be any type of RNA sequence, other than endogenous microRNA, which is capable of modulating the activity of an mRNA. A microRNA sequence can be an RNA molecule composed of any one or more of these sequences. MicroRNA (or “miRNA”) sequences have been described in publications such as Lim, et al., 2003, Genes & Development, 17, 991-1008, Lim et al., 2003, Science, 299, 1540, Lee and Ambrose, 2001, Science, 294, 862, Lau et al., 2001, Science 294, 858-861, Lagos-Quintana et al., 2002, Current Biology, 12, 735-739, Lagos-Quintana et al., 2001, Science, 294, 853-857, and Lagos-Quintana et al., 2003, RNA, 9, 175-179. Examples of microRNAs include any RNA that is a fragment of a larger RNA or is a miRNA, siRNA, stRNA, sncRNA, tncRNA, snoRNA, smRNA, shRNA, snRNA, or other small non-coding RNA. See, e.g., US Patent Applications 20050272923, 20050266552, 20050142581, and 20050075492. A "microRNA precursor" (or “pre-miRNA”) refers to a nucleic acid having a stem-loop structure with a microRNA sequence incorporated therein. A “mature microRNA” (or “mature miRNA”) includes a microRNA that has been cleaved from a microRNA precursor (a “pre-miRNA”), or that has been synthesized (e.g., synthesized in a laboratory by cell-free synthesis), and has a length of from about 19 nucleotides to about 27 nucleotides, e.g., a mature microRNA can have a length of 19 nt, 20 nt, 21 nt, 22 nt, 23 nt, 24 nt, 25 nt, 26 nt, or 27 nt. A mature microRNA can bind to a target mRNA and inhibit translation of the target mRNA.

[0042] "Recombinant," as applied to a polynucleotide means that the polynucleotide is the product of various combinations of cloning, restriction or ligation steps, and other procedures that result in a construct that is distinct from a polynucleotide found in nature. A recombinant virus is a viral particle comprising a recombinant polynucleotide. The terms respectively include replicates of the original polynucleotide construct and progeny of the original virus construct.

[0043] A "control element" or "control sequence" is a nucleotide sequence involved in an interaction of molecules that contributes to the functional regulation of a polynucleotide, including replication,

duplication, transcription, splicing, translation, or degradation of the polynucleotide. The regulation may affect the frequency, speed, or specificity of the process, and may be enhancing or inhibitory in nature. Control elements known in the art include, for example, transcriptional regulatory sequences such as promoters and enhancers. A promoter is a DNA region capable under certain conditions of binding RNA polymerase and initiating transcription of a coding region usually located downstream (in the 3' direction) from the promoter.

[0044] "Operatively linked" or "operably linked" refers to a juxtaposition of genetic elements, wherein the elements are in a relationship permitting them to operate in the expected manner. For instance, a promoter is operatively linked to a coding region if the promoter helps initiate transcription of the coding sequence. There may be intervening residues between the promoter and coding region so long as this functional relationship is maintained.

[0045] An "expression vector" is a vector comprising a region which encodes a polypeptide of interest, and is used for effecting the expression of the protein in an intended target cell. An expression vector also comprises control elements operatively linked to the encoding region to facilitate expression of the protein in the target. The combination of control elements and a gene or genes to which they are operably linked for expression is sometimes referred to as an "expression cassette," a large number of which are known and available in the art or can be readily constructed from components that are available in the art.

[0046] "Heterologous" means derived from a genotypically distinct entity from that of the rest of the entity to which it is being compared. For example, a polynucleotide introduced by genetic engineering techniques into a plasmid or vector derived from a different species is a heterologous polynucleotide. A promoter removed from its native coding sequence and operatively linked to a coding sequence with which it is not naturally found linked is a heterologous promoter. Thus, for example, an rAAV that includes a heterologous nucleic acid encoding a heterologous gene product is an rAAV that includes a nucleic acid not normally included in a naturally-occurring, wild-type AAV, and the encoded heterologous gene product is a gene product not normally encoded by a naturally-occurring, wild-type AAV. As another example, a variant AAV capsid protein that comprises a heterologous peptide inserted into the GH loop of the capsid protein is a variant AAV capsid protein that includes an insertion of a peptide not normally included in a naturally-occurring, wild-type AAV.

[0047] The terms "genetic alteration" and “genetic modification” (and grammatical variants thereof), are used interchangeably herein to refer to a process wherein a genetic element (e.g., a polynucleotide) is introduced into a cell other than by mitosis or meiosis. The element may be heterologous to the cell, or it may be an additional copy or improved version of an element already present in the cell. Genetic alteration may be effected, for example, by transfecting a cell

with a recombinant plasmid or other polynucleotide through any process known in the art, such as electroporation, calcium phosphate precipitation, or contacting with a polynucleotide-liposome complex. Genetic alteration may also be effected, for example, by transduction or infection with a DNA or RNA virus or viral vector. Generally, the genetic element is introduced into a chromosome or mini-chromosome in the cell; but any alteration that changes the phenotype and/or genotype of the cell and its progeny is included in this term.

[0048] A cell is said to be "stably" altered, transduced, genetically modified, or transformed with a genetic sequence if the sequence is available to perform its function during extended culture of the cell in vitro. Generally, such a cell is "heritably" altered (genetically modified) in that a genetic alteration is introduced which is also inheritable by progeny of the altered cell.

[0049] The terms "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, phosphorylation, or conjugation with a labeling component. Polypeptides such as anti-angiogenic polypeptides, neuroprotective polypeptides, and the like, when discussed in the context of delivering a gene product to a mammalian subject, and compositions therefor, refer to the respective intact polypeptide, or any fragment or genetically engineered derivative thereof, which retains the desired biochemical function of the intact protein. Similarly, references to nucleic acids encoding anti-angiogenic polypeptides, nucleic acids encoding neuroprotective polypeptides, and other such nucleic acids for use in delivery of a gene product to a mammalian subject (which may be referred to as "transgenes" to be delivered to a recipient cell), include polynucleotides encoding the intact polypeptide or any fragment or genetically engineered derivative possessing the desired biochemical function.

[0050] An "isolated" plasmid, nucleic acid, vector, virus, virion, host cell, or other substance refers to a preparation of the substance devoid of at least some of the other components that may also be present where the substance or a similar substance naturally occurs or is initially prepared from. Thus, for example, an isolated substance may be prepared by using a purification technique to enrich it from a source mixture. Enrichment can be measured on an absolute basis, such as weight per volume of solution, or it can be measured in relation to a second, potentially interfering substance present in the source mixture. Increasing enrichments of the embodiments of this invention are increasingly more isolated. An isolated plasmid, nucleic acid, vector, virus, host cell, or other substance is in some embodiments purified, e.g., from about 80% to about 90% pure, at least about 90% pure, at least about 95% pure, at least about 98% pure, or at least about 99%, or more, pure.

[0051] As used herein, the terms "treatment," "treating," and the like, refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse affect attributable to the disease. "Treatment," as used herein, covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease or at risk of acquiring the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease.

[0052] The terms "individual," "host," "subject," and "patient" are used interchangeably herein, and refer to a mammal, including, but not limited to, human and non-human primates, including simians and humans; mammalian sport animals (e.g., horses, camels, etc.); mammalian farm animals (e.g., sheep, goats, cows, etc.); mammalian pets (dogs, cats, etc.); and rodents (e.g., mice, rats, etc.). In some cases, the individual is a human.

[0053] Before the present invention is further described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0054] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0055] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0056] It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an rAAV virion" includes a plurality of such virions and reference to "the variant capsid protein" includes reference to one or more variant capsid proteins and equivalents thereof known to those skilled in the art, and so forth. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

[0057] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the invention are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed. In addition, all sub-combinations of the various embodiments and elements thereof are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination was individually and explicitly disclosed herein.

[0058] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

DETAILED DESCRIPTION

[0059] The present disclosure provides recombinant adeno-associated virus (AAV) virions with altered capsid protein, where the recombinant AAV (rAAV) virions exhibit greater ability to cross barriers between intravitreal fluid and retinal cells, and thus greater infectivity of a retinal cell compared to wild-type AAV, and where the rAAV virions comprise a heterologous nucleic acid. The present disclosure provides methods of delivering a gene product to a retinal cell in an individual. The present disclosure also provides methods of modifying a target nucleic acid present in a retinal cell.

[0060] The present disclosure provides recombinant adeno-associated virus (AAV) virions with altered capsid protein, where the recombinant AAV (rAAV) virions exhibit greater infectivity of a retinal cell compared to wild-type AAV; and where the rAAV virions comprise a heterologous

nucleic acid. The rAAV virions exhibit increased ability to cross a barrier between intravitreal fluid and retinal cells. The rAAV virions exhibit greater infectivity of a retinal cell, compared to the infectivity of a corresponding wild-type AAV for the retinal cell. The retinal cell can be a photoreceptor (e.g., rods; cones), a retinal ganglion cell (RGC), a Müller cell (a Müller glial cell), an astrocyte (e.g., a retinal astrocyte), a bipolar cell, an amacrine cell, a horizontal cell, or a retinal pigment epithelium (RPE) cell. The present disclosure further provides methods of delivering a gene product to a retinal cell in an individual, and methods of treating an ocular disease. The present disclosure provides an rAAV virion with an altered capsid protein, where the rAAV virion exhibits at least 5-fold increased localization to one or more of the inner nuclear layer, the outer nuclear layer, the photoreceptor layer, the ganglion cell layer, and the retinal pigment epithelium, compared to the extent of localization to the inner nuclear layer, the outer nuclear layer, the photoreceptor layer, the ganglion cell layer, or the retinal pigment epithelium, by an AAV virion comprising the corresponding parental AAV capsid protein; and where the rAAV virions comprise a heterologous nucleic acid.

VARIANT AAV CAPSID POLYPEPTIDES

[0061] The present disclosure provides a variant AAV capsid protein. As noted above, a variant AAV capsid protein of the present disclosure is altered, compared to a wild-type or other reference AAV capsid protein. Alterations include insertions and swaps (e.g., replacements of a contiguous stretch of amino acids with a different contiguous stretch of amino acids).

[0062] In some cases, a variant AAV capsid protein of the present disclosure comprises an insertion of a heterologous peptide of from 5 amino acids to 20 amino acids in length in an insertion site in a surface-accessible (e.g., solvent-accessible) portion of a parental AAV capsid protein, such that the variant capsid protein, when present in an AAV virion, confers increased infectivity of a retinal cell compared to the infectivity of the retinal cell by an AAV virion comprising the corresponding parental AAV capsid protein, particularly when the AAV virion is injected intravitreally. Thus, a variant AAV capsid protein of the present disclosure, when present in an AAV virion, confers increased ability of the AAV virion to cross a barrier between the intravitreal fluid ("vitreous") and a retinal cell, where such barriers include, e.g., the inner limiting membrane (ILM), the extracellular matrix of the retina, the cell membranes of the retinal cells themselves, inner nuclear layer, the outer nuclear layer, the photoreceptor layer, the ganglion cell layer, and the retinal pigment epithelium. In some cases, the retinal cell is a Müller cell. Other retinal cells include amacrine cells, bipolar cells, and horizontal cells. An "insertion of from about 5 amino acids to about 20 amino acids" is also referred to herein as a "peptide insertion" (e.g., a heterologous peptide insertion). A "corresponding parental AAV capsid protein" refers to an AAV capsid protein of the same AAV serotype, without a heterologous

peptide insertion. In some instances, the variant AAV capsid comprises a single heterologous peptide insert of from 5 amino acids to 20 amino acids (e.g., from 5 to 7, from 7 to 10, from 10 to 12, from 12 to 15, or from 15 to 20 amino acids) in length.

[0063] An alteration in an AAV capsid can also be a swap, e.g., a replacement of a contiguous stretch of amino acids with a heterologous peptide. Thus, a replacement is an insertion of a heterologous peptide in place of a contiguous stretch of amino acids. In some cases, a variant AAV capsid protein of the present disclosure comprises replacement of a contiguous stretch of amino acids with a heterologous peptide of from 5 amino acids to 20 amino acids in length in a site in a surface-accessible (e.g., solvent-accessible) portion of a parental AAV capsid protein, such that the variant capsid protein, when present in an AAV virion, confers increased infectivity of a retinal cell compared to the infectivity of the retinal cell by an AAV virion comprising the corresponding parental AAV capsid protein, particularly when the AAV virion is injected intravitreally. Thus, a variant AAV capsid protein of the present disclosure, when present in an AAV virion, confers increased ability of the AAV virion to cross a barrier between the intravitreal fluid ("vitreous") and a retinal cell, where such barriers include, e.g., ILM, the extracellular matrix of the retina, the cell membranes of the retinal cells themselves, inner nuclear layer, the outer nuclear layer, the photoreceptor layer, the ganglion cell layer, and the retinal pigment epithelium. In some cases, the retinal cell is a Müller cell. Other retinal cells include amacrine cells, bipolar cells, and horizontal cells. A "replacement of from about 5 amino acids to about 20 amino acids" is also referred to herein as a "peptide swap" (e.g., a replacement of a contiguous stretch of amino acids with a heterologous peptide). A "corresponding parental AAV capsid protein" refers to an AAV capsid protein of the same AAV serotype, without a heterologous peptide. In some instances, the variant AAV capsid comprises a single heterologous peptide replacement of from 5 amino acids to 20 amino acids (e.g., from 5 to 7, from 7 to 10, from 10 to 12, from 12 to 15, or from 15 to 20 amino acids) in length.

[0064] For purposes of the following discussion, "insertion" refers to both insertion of a heterologous peptide without replacement of a contiguous stretch of amino acids, and to insertion of a heterologous peptide that replaces a contiguous stretch of amino acids.

[0065] The insertion site is in the GH loop, or loop IV, of the AAV capsid protein, e.g., in a solvent-accessible portion of the GH loop, or loop IV, of the AAV capsid protein. For the GH loop/loop IV of AAV capsid, see, e.g., van Vliet et al. (2006) *Mol. Ther.* 14:809; Padron et al. (2005) *J. Virol.* 79:5047; and Shen et al. (2007) *Mol. Ther.* 15:1955. For example, the insertion site can be within amino acids 411-650 of an AAV capsid protein, as depicted in FIG. 6A-6C. For example, the insertion site can be within amino acids 570-611 of AAV2, within amino acids 571-612 of AAV1, within amino acids 560-601 of AAV5, within amino acids 571 to 612 of AAV6, within

amino acids 572 to 613 of AAV7, within amino acids 573 to 614 of AAV8, within amino acids 571 to 612 of AAV9, or within amino acids 573 to 614 of AAV10, as depicted in FIG. 5. In some cases, the insertion site is between amino acids 588 and 589 of an AAV2 capsid protein, or a corresponding insertion site in an AAV of a different serotype. In some cases, the insertion site is between amino acids 587 and 588 of an AAV2 capsid protein, or a corresponding insertion site in an AAV of a different serotype. In some cases, the insertion site is between amino acids 575 and 576 of an AAV2 capsid protein, or a corresponding insertion site in an AAV of a different serotype. In some cases, the insertion site is between amino acids 584 and 585 of an AAV2 capsid protein, or a corresponding insertion site in an AAV of a different serotype. In some cases, the insertion site is between amino acids 590 and 591 of an AAV2 capsid protein, or a corresponding insertion site in an AAV of a different serotype. In some cases, the insertion site is between amino acids 584 and 585 of an AAV4 capsid protein, or a corresponding insertion site in an AAV of a different serotype. In some cases, the insertion site is between amino acids 575 and 576 of an AAV5 capsid protein, or a corresponding insertion site in an AAV of a different serotype. In some cases, the site for replacement is between amino acids 584 and 598 of an AAV2 capsid protein, or a corresponding site in an AAV of a different serotype.

[0066] In some cases, a heterologous peptide of from about 5 amino acids to about 20 amino acids (e.g., from 5 to 7, from 7 to 10, from 10 to 12, from 12 to 15, or from 15 to 20 amino acids) in length is inserted in an insertion site in the GH loop or loop IV of the capsid protein relative to a corresponding parental AAV capsid protein. For example, the insertion site can be between amino acids 587 and 588 of AAV2, or between amino acids 588 and 589 of AAV2, or the corresponding positions of the capsid subunit of another AAV serotype. It should be noted that the insertion site 587/588 is based on an AAV2 capsid protein. A heterologous peptide of 5 amino acids to about 20 amino acids (e.g., from 5 to 7, from 7 to 10, from 10 to 12, from 12 to 15, or from 15 to 20 amino acids) in length can be inserted in a corresponding site in an AAV serotype other than AAV2 (e.g., AAV8, AAV9, etc.). Those skilled in the art would know, based on a comparison of the amino acid sequences of capsid proteins of various AAV serotypes, where an insertion site "corresponding to amino acids 587-588 of AAV2" would be in a capsid protein of any given AAV serotype. Sequences corresponding to amino acids 570-611 of capsid protein VP1 of AAV2 (see FIG. 4) in various AAV serotypes are shown in FIG. 5. See, e.g., GenBank Accession No. NP_049542 for AAV1; GenBank Accession No. NP_044927 for AAV4; GenBank Accession No. AAD13756 for AAV5; GenBank Accession No. AAB95459 for AAV6; GenBank Accession No. YP_077178 for AAV7; GenBank Accession No. YP_077180 for AAV8; GenBank Accession No. AAS99264 for AAV9; GenBank Accession

No. AAT46337 for AAV10; and GenBank Accession No. AAO88208 for AAVrh10. See, e.g., Santiago-Ortiz et al. (2015) *Gene Ther.* 22:934 for ancestral AAV capsid.

[0067] For example, the insertion site can be between amino acids 587 and 588 of AAV2, between amino acids 590 and 591 of AAV1, between amino acids 575 and 576 of AAV5, between amino acids 590 and 591 of AAV6, between amino acids 589 and 590 of AAV7, between amino acids 590 and 591 of AAV8, between amino acids 588 and 589 of AAV9, between amino acids 588 and 589 of AAV10, or between amino acids 585 and 586 of AAV4. The insertion sites are underlined in FIG. 5; the amino acid numbering is based on the numbering depicted in FIG. 5.

[0068] In some cases, a subject capsid protein includes a GH loop comprising an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence set forth in FIG. 6A-6C; and having an insertion of a heterologous peptide of from 5 to 20 amino acids (e.g., from 5 to 7, from 7 to 10, from 10 to 12, from 12 to 15, or from 15 to 20 amino acids) in length.

[0069] In some cases, a variant AAV capsid protein of the present disclosure comprises a replacement, or substitution, of a segment, or sequence of consecutive amino acids, in a surface-accessible (e.g., solvent-accessible) portion of a parental AAV capsid, such that the variant capsid protein, when present in an AAV virion, confers increased infectivity of a retinal cell compared to the infectivity of the retinal cell by an AAV virion comprising the corresponding parental AAV capsid protein, particularly when the AAV virion is injected intravitreally. Thus, a subject variant AAV capsid protein comprising the sequence substitution, when present in an AAV virion, confers increased ability of the AAV virion to cross a barrier between the vitreous and a retinal cell, where such barriers include, e.g., the inner limiting membrane, the extracellular matrix of the retina, and the cell membranes of the retinal cells themselves. A "replacement of from about 5 consecutive amino acids to about 25 consecutive amino acids" is also referred to herein as a "loop swap" (i.e. a heterologous peptide substitution). A "corresponding parental AAV capsid protein" in such instances refers to an AAV capsid protein of the same AAV serotype, without the subject loop swap. In some instances, the variant AAV capsid comprises a heterologous peptide substitution of from 5 contiguous amino acids to 25 contiguous amino acids, e.g. from 5 to 9, from 9 to 11, from 10 to 15, from 15 to 20, or from 20 to 25 amino acids in length.

[0070] In some cases, a heterologous peptide of from about 5 amino acids to about 25 amino acids (e.g., from 5 to 9, from 9 to 11, from 10 to 15, from 15 to 20, or from 20 to 25 amino acids) in length is substituted in for an equivalent number of consecutive amino acids in a corresponding parental AAV capsid protein. In some embodiments, the substitution begins at around amino acid 588 of AAV2, or the corresponding position of the capsid subunit of another AAV serotype, and ends at

around amino acid 598 of AAV2 or the corresponding position of the capsid subunit of another AAV serotype. It should be noted that the residues 588-598 are based on an AAV2 VP1 capsid protein. A heterologous peptide of 5 amino acids to about 25 amino acids in length can be substituted into a corresponding site in an AAV serotype other than AAV2 (e.g., AAV8, AAV9, etc.). Those skilled in the art would know, based on a comparison of the amino acid sequences of capsid proteins of various AAV serotypes, where a substitution site "corresponding to amino acids 588-598 of AAV2" would be in a capsid protein of any given AAV serotype. The amino acid residue corresponding to amino acids 588-598 of capsid protein VP1 of AAV2 (see FIG. 4) in various AAV serotypes are shown in FIG. 5. See, e.g., GenBank Accession No. NP_049542 for AAV1; GenBank Accession No. NP_044927 for AAV4; GenBank Accession No. AAD13756 for AAV5; GenBank Accession No. AAB95459 for AAV6; GenBank Accession No. YP_077178 for AAV7; GenBank Accession No. YP_077180 for AAV8; GenBank Accession No. AAS99264 for AAV9, GenBank Accession No. AAT46337 for AAV10, and GenBank Accession No. AAO88208 for AAVrh10.

[0071] In some cases, a heterologous peptide of from about 5 amino acids to about 25 amino acids (e.g., from 5 to 9, from 9 to 11, from 10 to 15, from 15 to 20, or from 20 to 25 amino acids) in length is substituted in for an equivalent number of consecutive amino acids in a corresponding parental AAV capsid protein. In some embodiments, the substitution begins at around amino acid 585 of AAV2, or the corresponding position of the capsid subunit of another AAV serotype, and ends at around amino acid 598 of AAV2 or the corresponding position of the capsid subunit of another AAV serotype. It should be noted that the residues 585-598 are based on an AAV2 VP1 capsid protein. A heterologous peptide of 5 amino acids to about 25 amino acids in length can be substituted into a corresponding site in an AAV serotype other than AAV2 (e.g., AAV8, AAV9, etc.). Those skilled in the art would know, based on a comparison of the amino acid sequences of capsid proteins of various AAV serotypes, where a substitution site "corresponding to amino acids 585-598 of AAV2" would be in a capsid protein of any given AAV serotype. The amino acid residue corresponding to amino acids 585-598 of capsid protein VP1 of AAV2 (see FIG. 4) in various AAV serotypes are shown in FIG. 5. See, e.g., GenBank Accession No. NP_049542 for AAV1; GenBank Accession No. NP_044927 for AAV4; GenBank Accession No. AAD13756 for AAV5; GenBank Accession No. AAB95459 for AAV6; GenBank Accession No. YP_077178 for AAV7; GenBank Accession No. YP_077180 for AAV8; GenBank Accession No. AAS99264 for AAV9, GenBank Accession No. AAT46337 for AAV10, and GenBank Accession No. AAO88208 for AAVrh10.

Insertion/replacement peptides

[0072] As noted above, a heterologous peptide of from about 5 amino acids to about 20 amino acids in length is inserted into the GH loop of an AAV capsid, or replaces an equivalent number of consecutive amino acids in the GH loop of an AAV capsid. For simplicity, the term "insertion peptide" is used below to describe both a peptide that is inserted into a parental AAV capsid and a peptide that replaces a segment of contiguous amino acids in the GH loop of an AAV capsid. In some cases, the insertion peptide has a length of from 5 amino acids to 20 amino acids. In some cases, the insertion peptide has a length of from 7 amino acids to 15 amino acids. In some cases, the insertion peptide has a length of from 9 amino acids to 15 amino acids. In some cases, the insertion peptide has a length of from 9 amino acids to 12 amino acids. The insertion peptide has a length of 5 amino acids, 6 amino acids, 7 amino acids, 8 amino acids, 9 amino acids, 10 amino acids, 11 amino acids, 12 amino acids, 13 amino acids, 14 amino acids, 15 amino acids, 16 amino acids, 17 amino acids, 18 amino acids, 19 amino acids, or 20 amino acids. In some cases, the insertion peptide has a length of 7 amino acids. In some cases, the insertion peptide has a length of 8 amino acids. In some cases, the insertion peptide has a length of 9 amino acids. In some cases, the insertion peptide has a length of 10 amino acids. In some cases, the insertion peptide has a length of 11 amino acids. In some cases, the insertion peptide has a length of 12 amino acids. In some cases, the insertion peptide has a length of 13 amino acids. In some cases, the insertion peptide has a length of 14 amino acids. In some cases, the insertion peptide has a length of 15 amino acids.

[0073] The peptide insert is, in some cases, a peptide of **Formula I**:

[0074] LA(L/N)(I/Q)(Q/E)(D/H)(S/V)(M/K)(R/N)A. (SEQ ID NO: 136)

[0075] In some cases, a peptide of Formula I comprises the following amino acid sequence: (21) LALIQDSMRA (SEQ ID NO: 35). In some cases, a peptide of Formula I comprises the following amino acid sequence: (22) LANQEHVKNA (SEQ ID NO:2).

[0076] The peptide insert is, in some cases, a peptide of **Formula II**:

[0077] $TX_1X_2X_3X_4X_5X_6X_7X_8GLX_9$ (SEQ ID NO: 137), where:

[0078] X_1 is G, V, or S;

[0079] X_2 is V, E, P, G, D, M, A, or S;

[0080] X_3 is M, V, Y, H, G, S, or D;

[0081] X_4 is R, D, S, G, V, Y, T, H, or M;

[0082] X_5 is S, L, G, T, Q, P, or A;

[0083] X_6 is T, A, S, M, D, Q, or H;

[0084] X_7 is N, G, S, L, M, P, G, or A;

[0085] X_8 is S, G, D, N, A, I, P, or T; and

[0086] X_9 is **S** or N.

[0087] Peptide inserts of Formula II include, but are not limited to: (1) TGVMRSTNSGLN (SEQ ID NO: 6); (2) TGEVDLAGGGLS (SEQ ID NO: 7); (3) TSPYSGSSDGLS (SEQ ID NO: 8); (4) TGGHDSSLDGLS (SEQ ID NO: 9); (5) TGDGGTTMNGLS (SEQ ID NO: 98); (6) TGGHGSAPDGLS (SEQ ID NO: 99); (7) TGMHVTMMAGLN (SEQ ID NO: 100); (8) TGASYLDNSGLS (SEQ ID NO: 101); (9) TVVSTQAGIGLS (SEQ ID NO: 135); (10) TGVMHSQASGLS (SEQ ID NO: 21); (11) TGDGSPAAPGLS (SEQ ID NO: 22); and (12) TGSDMAHGTGLS (SEQ ID NO: 23). In some cases, the peptide insert is (1) TGVMRSTNSGLN (SEQ ID NO: 6). In some cases, the peptide insert is (2) TGEVDLAGGGLS (SEQ ID NO: 7). In some cases, the peptide insert is (3) TSPYSGSSDGLS (SEQ ID NO: 8). In some cases, the peptide insert is (4) TGGHDSSLDGLS (SEQ ID NO: 9). In some cases, the peptide insert is (5) TGDGGTTMNGLS (SEQ ID NO: 98). In some cases, the peptide insert is (6) TGGHGSAPDGLS (SEQ ID NO: 99). In some cases, the peptide insert is (7) TGMHVTMMAGLN (SEQ ID NO: 100). In some cases, the peptide insert is (8) TGASYLDNSGLS (SEQ ID NO: 101). In some cases, the peptide insert is (9) TVVSTQAGIGLS (SEQ ID NO: 20). In some cases, the peptide insert is (10) TGVMHSQASGLS (SEQ ID NO: 21). In some cases, the peptide insert is (11) TGDGSPAAPGLS (SEQ ID NO: 22). In some cases, the peptide insert is (12) TGSDMAHGTGLS (SEQ ID NO: 23).

[0088] The peptide insert is, in some cases, a peptide of **Formula III**:

[0089] $TGX_1X_2X_3X_4X_5X_6X_7GLS$ (SEQ ID NO: 138), where:

[0090] X_1 is V, E, P, G, D, M, A, or S;

[0091] X_2 is M, V, Y, H, G, S, or D;

[0092] X_3 is R, D, S, G, V, Y, T, H, or M;

[0093] X_4 is S, L, G, T, Q, P, or A;

[0094] X_5 is T, A, S, M, D, Q, or H;

[0095] X_6 is N, G, S, L, M, P, G, or A; and

[0096] X_7 is S, G, D, N, A, I, P, or T.

[0097] Peptide inserts of Formula III include, but are not limited to: (2) TGEVDLAGGGLS (SEQ ID NO: 7); (4) TGGHDSSLDGLS (SEQ ID NO: 9); (5) TGDGGTTMNGLS (SEQ ID NO: 98); (6) TGGHGSAPDGLS (SEQ ID NO: 99); (8) TGASYLDNSGLS (SEQ ID NO: 101); (10) TGVMHSQASGLS (SEQ ID NO: 21); (11) TGDGSPAAPGLS (SEQ ID NO: 22); and (12) TGSDMAHGTGLS (SEQ ID NO: 23).

[0098] The peptide insert is, in some cases, a peptide of **Formula IV**:

[0099] $X_1GX_2X_3X_4X_5X_6X_7X_8GLSPX_9TX_{10}X_{11}$ (SEQ ID NO: 139), where

[00100] X_1 is **T** or N;

[00101] X_2 is L, S,A, or G;

[00102] X_3 is **D** or V;

[00103] X_4 is A, G, or P;

[00104] X_5 is **T** or D;

[00105] X_6 is **R** or Y;

[00106] X_7 is D, T, or G;

[00107] X_8 is H, R, or T;

[00108] X_9 is **V** or A;

[00109] X_{10} is **G** or W; and

[00110] X_{11} is **T** or A.

[00111] Peptide inserts of Formula IV include, but are not limited to: (13) TGLDATRDHGLSPVTGT (SEQ ID NO: 24); (14) TGSDGTRDHGLSPVTWT (SEQ ID NO: 25); (15) NGAVADYTRGLSPATGT (SEQ ID NO: 26); and (16) TGGDPTRGTGLSPVTGA (SEQ ID NO: 27). In some cases, the peptide insert is (13) TGLDATRDHGLSPVTGT (SEQ ID NO: 24). In some cases, the peptide insert is (14) TGSDGTRDHGLSPVTWT (SEQ ID NO: 25). In some cases, the peptide insert is (15) NGAVADYTRGLSPATGT (SEQ ID NO: 26). In some cases, the peptide insert is (16) TGGDPTRGTGLSPVTGA (SEQ ID NO: 27).

[00112] The peptide insert is, in some cases, a peptide of **Formula V**:

[00113] $TGX_1DX_2TRX_3X_4GLSPVTGT$ (SEQ ID NO: 140), where

[00114] X_1 is L, S, A, or G;

[00115] X_2 is A, G, or P;

[00116] X_3 is D, T, or G; and

[00117] X_4 is H, R, or T.

[00118] Peptide inserts of Formula V include, but are not limited to: (13) TGLDATRDHGLSPVTGT (SEQ ID NO: 24); (14) TGSDGTRDHGLSPVTWT (SEQ ID NO: 25); and (16) TGGDPTRGTGLSPVTGA (SEQ ID NO: 27).

[00119] The peptide insert is, in some cases, a peptide of **Formula VI**:

[00120] $LQX_1X_2X_3RX_4X_5X_6X_7X_8X_9VNX_{10}Q$ (SEQ ID NO: 141), where

[00121] X_1 is K or R;

[00122] X_2 is N, G, or A;

[00123] X_3 is A, V, N, or D;

[00124] X_4 is P, I, or Q;

[00125] X_5 is A, P, or V;

[00126] X_6 is S, T, or G;

[00127] X_7 is T or V;

[00128] X_8 is E, L, A, or V;

[00129] X_9 is S, E, D, or V; and

[00130] X_{10} is F, G, T, or C.

[00131] Peptides of Formula VI include, but are not limited to: (17) LQKNARPASTESVNFQ (SEQ ID NO: 28); (18) LQRGVRIPSVLEVNGQ (SEQ ID NO: 29); (19) LQRGNRPVTTADVNTQ (SEQ ID NO: 30); and (20) LQKADRQPGVVVVNCQ (SEQ ID NO: 31). In some cases, the peptide insert is (17) LQKNARPASTESVNFQ (SEQ ID NO: 28). In some cases, the peptide insert is (18) LQRGVRIPSVLEVNGQ (SEQ ID NO: 29). In some cases, the peptide insert is (19) LQRGNRPVTTADVNTQ (SEQ ID NO: 30). In some cases, the peptide insert is (20) LQKADRQPGVVVVNCQ (SEQ ID NO: 31).

[00132] Any of the above-described peptide inserts can replace an equal number of contiguous amino acids in the GH loop of an AAV capsid polypeptide. For example, in some cases, a peptide of **Formula VI**:

[00133] $LQX_1X_2X_3RX_4X_5X_6X_7X_8X_9VNX_{10}Q$ (SEQ ID NO: 141), where

[00134] X_1 is K or R;

[00135] X_2 is N, G, or A;

[00136] X_3 is A, V, N, or D;

[00137] X_4 is P, I, or Q;

[00138] X_5 is A, P, or V;

[00139] X_6 is S, T, or G;

[00140] X_7 is T or V;

[00141] X_8 is E, L, A, or V;

[00142] X_9 is S, E, D, or V; and

[00143] X_{10} is F, G, T, or C,

[00144] replaces a contiguous stretch of from 5 amino acids to 20 amino acids in the GH loop of an AAV capsid polypeptide. In other words, in some cases, an "insert peptide" replaces an endogenous peptide (e.g., a contiguous stretch of from 5 amino acids to 20 amino acids) present in in the GH loop of an AAV capsid polypeptide, resulting in a variant AAV capsid comprising a heterologous peptide in the GH loop. In some cases, the "insert peptide" replaces an endogenous

contiguous stretch of amino acids of the same length as the insert peptide. Thus, for example, where the "insert peptide" has a length of 16 amino acids, in some cases, an endogenous contiguous stretch of 16 amino acids is replaced by the insert peptide.

[00145] Peptides of Formula VI include, but are not limited to: (17) LQKNARPASTESVNFQ (SEQ ID NO: 28); (18) LQRGVRIPSVLEVNGQ (SEQ ID NO: 29); (19) LQRGNRPVTTADVNTQ (SEQ ID NO:30); and (20) LQKADRQPGVVVVNCQ (SEQ ID NO: 31). In some cases, the peptide that replaces an endogenous amino acid sequence in the GH loop of an AAV capsid is (17) LQKNARPASTESVNFQ (SEQ ID NO: 28). In some cases, the peptide insert is (18) LQRGVRIPSVLEVNGQ (SEQ ID NO: 29). In some cases, the peptide that replaces an endogenous amino acid sequence in the GH loop of an AAV capsid is (19) LQRGNRPVTTADVNTQ (SEQ ID NO: 30). In some cases, the peptide that replaces an endogenous amino acid sequence in the GH loop of an AAV capsid is (20) LQKADRQPGVVVVNCQ (SEQ ID NO: 31).

[00146] In some cases, a peptide insert of any one of Formulas I-VI further includes one or two linker amino acids at the N-terminus of the peptide and/or one or more amino acids at the C-terminus of the peptide. For example, in some cases, a peptide insert comprises: Thr-Gly-[peptide of any one of Formulas I-VI]-Gly-Leu-Ser (SEQ ID NO: 142). As another example, in some cases, a peptide insert comprises: Leu-Ala-[peptide of any one of Formulas I-VI]-Ala (SEQ ID NO: 143). As another example, in some cases, a peptide insert comprises: Leu-Gln-[peptide of any one of Formulas I-VI]-Gln. In some cases, a peptide insert does not include any linker amino acids.

[00147] In some embodiments, a subject rAAV virion capsid does not include any other amino acid substitutions, insertions, or deletions, other than an insertion of from about 5 amino acids to about 20 amino acids (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids; e.g., 9 amino acids, 10 amino acids, 11 amino acids, or 12 amino acids) in the GH loop or loop IV relative to a corresponding parental AAV capsid protein. In other embodiments, a subject rAAV virion capsid includes from 1 to about 25 amino acid insertions, deletions, or substitutions, compared to the parental AAV capsid protein, in addition to an insertion of from about 5 amino acids to about 20 amino acids (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids; e.g., 9 amino acids, 10 amino acids, 11 amino acids, or 12 amino acids) in the GH loop or loop IV relative to a corresponding parental AAV capsid protein. For example, in some embodiments, a subject rAAV virion capsid includes from 1 to about 5, from about 5 to about 10, from about 10 to about 15, from about 15 to about 20, or from about 20 to about 25 amino acid insertions, deletions, or substitutions, compared to the parental AAV capsid protein, in addition to an insertion of from about 5 amino acids to about 20 amino acids (e.g., 5, 6, 7, 8, 9,

10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids; e.g., 9 amino acids, 10 amino acids, 11 amino acids, or 12 amino acids) in the GH loop or loop IV relative to a corresponding parental AAV capsid protein. In certain embodiments, the deletion of one or more amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids) compared to the parental AAV capsid protein occurs at the site of peptide insertion.

[00148] In some cases, a variant AAV capsid polypeptide of the present disclosure does not include one, two, three, or four, of the following amino acid substitutions: Y273F, Y444F, Y500F, and Y730F.

[00149] In some cases, a variant AAV capsid polypeptide of the present disclosure comprises, in addition to an insertion peptide as described above, one, two, three, or four, of the following amino acid substitutions: Y273F, Y444F, Y500F, and Y730F.

[00150] In some cases, a variant AAV capsid polypeptide of the present disclosure is a chimeric capsid, e.g., the capsid comprises a portion of an AAV capsid of a first AAV serotype and a portion of an AAV capsid of a second serotype; and comprises an insertion of from about 5 amino acids to about 20 amino acids (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids; e.g., 9 amino acids, 10 amino acids, 11 amino acids, or 12 amino acids) in the GH loop or loop IV relative to a corresponding parental AAV capsid protein.

RECOMBINANT AAV VIRIONS

[00151] The present disclosure provides a recombinant AAV (rAAV) virion comprising: i) a variant AAV capsid polypeptide of the present disclosure; and ii) a heterologous nucleic acid comprising a nucleotide sequence encoding a heterologous polypeptide (i.e., a non-AAV polypeptide).

[00152] In some cases, an rAAV virion of the present disclosure comprises a capsid protein comprising an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 98%, or at least about 99%, amino acid sequence identity to the amino acid sequence provided in FIG. 4; and an insertion of from about 5 amino acids to about 20 amino acids (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids; e.g., 9 amino acids, 10 amino acids, 11 amino acids, or 12 amino acids) in the GH loop or loop IV relative to a corresponding parental AAV capsid protein. In some embodiments, a subject rAAV virion comprises a capsid protein comprising an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 98%, or at least about 99%, amino acid sequence identity to the amino acid sequence provided in FIG. 4; and an insertion of from about 5 amino acids to about 20 amino acids (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids; e.g., 9 amino acids, 10 amino acids, 11 amino acids, or 12 amino acids) between

amino acids 587 and 588 relative to the amino acid sequence depicted in FIG. 4, or at a corresponding site relative to a corresponding parental AAV capsid protein.

[00153] In some cases, an rAAV virion of the present disclosure comprises a capsid protein comprising an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 98%, or at least about 99%, amino acid sequence identity to the amino acid sequence provided in FIG. 4; and an insertion of from about 5 amino acids to about 20 amino acids (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids; e.g., 9 amino acids, 10 amino acids, 11 amino acids, or 12 amino acids) in the GH loop or loop IV relative to a corresponding parental AAV capsid protein. In some cases, a subject rAAV virion comprises a capsid protein comprising an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 98%, or at least about 99%, amino acid sequence identity to the amino acid sequence provided in FIG. 4; and an insertion of from about 5 amino acids to about 20 amino acids (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids; e.g., 9 amino acids, 10 amino acids, 11 amino acids, or 12 amino acids) between amino acids 585 and 598 relative to the amino acid sequence depicted in FIG. 4, or at a corresponding site relative to a corresponding parental AAV capsid protein.

[00154] In some embodiments, a subject rAAV virion comprises a capsid protein that includes a GH loop comprising an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence set forth in FIG. 5, and comprising an insertion of from about 5 amino acids to about 20 amino acids (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids; e.g., 9 amino acids, 10 amino acids, 11 amino acids, or 12 amino acids) between the bolded and underlined amino acids.

[00155] In some embodiments, a subject rAAV virion comprises a capsid protein comprising an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 98%, or at least about 99%, amino acid sequence identity to any one of the amino acid sequences provided in FIG. 6A-6C; and an insertion of from about 5 amino acids to about 20 amino acids (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids; e.g., 9 amino acids, 10 amino acids, 11 amino acids, or 12 amino acids) between amino acids 587 and 588 of AAV2, or at a corresponding site relative to another AAV genotype. In some cases, the corresponding insertion site is a site as indicated by bold text and underlining in FIG. 6B.

[00156] An rAAV virion of the present disclosure exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a retinal cell, compared to the infectivity of the retinal cell by an AAV virion comprising the corresponding parental AAV capsid protein.

[00157] Whether a given rAAV virion exhibits increased infectivity of a retinal cell can be determined by detecting expression in a retinal cell of a heterologous gene product encoded by the rAAV virion, following intravitreal administration of the rAAV virion. For example, an rAAV virion of the present disclosure that comprises: a) a variant capsid of the present disclosure comprising a peptide insert or a peptide replacement, as described above; and b) a heterologous nucleotide sequence encoding a heterologous gene product, when administered intravitreally, results in a level of the heterologous gene product in a retinal cell, that is at least 2-fold, at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, greater than the level of the gene product in the retinal cell that results when a control rAAV virion that comprises: a) a control AAV capsid that does not comprises the peptide insert or the peptide replacement; and b) heterologous nucleotide sequence encoding the heterologous gene product is administered intravitreally.

[00158] Whether a given rAAV virion exhibits increased infectivity of a retinal cell can be determined by assessing a therapeutic effect of a therapeutic gene product encoded by the rAAV virion in a retinal cell. Therapeutic effects can include, e.g., a) a decrease in the rate of loss of visual function, e.g. visual field, visual acuity; b) an improvement in visual function, e.g. an improvement in visual field or visual acuity; c) a decrease in sensitivity to light, i.e. photophobia; a decrease in nystagmus; etc. For example, an rAAV virion of the present disclosure that comprises: a) a variant capsid of the present disclosure comprising a peptide insert or a peptide replacement, as described above; and b) a heterologous nucleotide sequence encoding a heterologous therapeutic gene product, when administered intravitreally, results in a therapeutic effect of the therapeutic gene product in a retinal cell, that is at least 2-fold, at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, greater than the therapeutic effect in the retinal cell that results when a control rAAV virion that comprises: a) a control AAV capsid that does not comprises the peptide insert or the peptide replacement; and b) heterologous nucleotide sequence encoding the heterologous therapeutic gene product is administered intravitreally. Tests for visual function are known in the art; and any such test can be used to determine whether an rAAV virion of the present disclosure exhibits increased infectivity of a retinal cell.

[00159] An rAAV virion of the present disclosure exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased ability to cross a barrier between the intravitreal fluid and a retinal cell, compared to the ability of a control rAAV virion comprising the corresponding parental AAV capsid protein (i.e., the AAV capsid protein without the insert peptide or replacement peptide).

[00160] In some cases, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a retinal cell, when administered via intravitreal injection, compared to the infectivity of the retinal cell by an AAV virion comprising the corresponding parental AAV capsid protein, when administered via intravitreal injection.

[00161] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a photoreceptor (rod or cone) cell, compared to the infectivity of the photoreceptor cell by an AAV virion comprising the corresponding parental AAV capsid protein.

[00162] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a photoreceptor (rod or cone) cell, when administered via intravitreal injection, compared to the infectivity of the photoreceptor cell by an AAV virion comprising the corresponding parental AAV capsid protein, when administered via intravitreal injection.

[00163] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of an RGC, compared to the infectivity of the RGC by an AAV virion comprising the corresponding parental AAV capsid protein.

[00164] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of an RGC, when administered via intravitreal injection, compared to the infectivity of the RGC by an AAV virion comprising the corresponding parental AAV capsid protein, when administered via intravitreal injection.

[00165] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of an RPE cell, compared to the infectivity of the RPE cell by an AAV virion comprising the corresponding parental AAV capsid protein.

[00166] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of an RPE cell, when administered via intravitreal injection, compared to the infectivity of the RPE cell by an AAV virion comprising the corresponding parental AAV capsid protein, when administered via intravitreal injection.

[00167] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased

infectivity of a Müller cell, compared to the infectivity of the Müller cell by an AAV virion comprising the corresponding parental AAV capsid protein.

[00168] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a Müller cell, when administered via intravitreal injection, compared to the infectivity of the Müller cell by an AAV virion comprising the corresponding parental AAV capsid protein, when administered via intravitreal injection.

[00169] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a bipolar cell, compared to the infectivity of the bipolar cell by an AAV virion comprising the corresponding parental AAV capsid protein.

[00170] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a bipolar cell, when administered via intravitreal injection, compared to the infectivity of the bipolar cell by an AAV virion comprising the corresponding parental AAV capsid protein, when administered via intravitreal injection.

[00171] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of an amacrine cell, compared to the infectivity of the amacrine cell by an AAV virion comprising the corresponding parental AAV capsid protein.

[00172] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of an amacrine cell, when administered via intravitreal injection, compared to the infectivity of the amacrine cell by an AAV virion comprising the corresponding parental AAV capsid protein, when administered via intravitreal injection.

[00173] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a horizontal cell, compared to the infectivity of the horizontal cell by an AAV virion comprising the corresponding parental AAV capsid protein.

[00174] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a horizontal cell, when administered via intravitreal injection, compared to the infectivity of the horizontal cell by an AAV virion comprising the corresponding parental AAV capsid protein, when administered via intravitreal injection.

[00175] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a retinal astrocyte, compared to the infectivity of the retinal astrocyte by an AAV virion comprising the corresponding parental AAV capsid protein.

[00176] In some embodiments, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a retinal astrocyte, when administered via intravitreal injection, compared to the infectivity of the retinal astrocyte by an AAV virion comprising the corresponding parental AAV capsid protein, when administered via intravitreal injection.

[00177] In some cases, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased ability to cross extracellular matrix (ECM) of the retina, compared to the ability of an AAV virion comprising the corresponding parental AAV capsid protein to cross the ECM of the retina.

[00178] In some cases, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased ability, when administered via intravitreal injection, to cross extracellular matrix (ECM) of the retina, compared to the ability of an AAV virion comprising the corresponding parental AAV capsid protein to cross the ECM of the retina when administered via intravitreal injection.

[00179] In some cases, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased ability to cross the internal limiting membrane (ILM), compared to the ability of an AAV virion comprising the corresponding parental AAV capsid protein to cross the ILM.

[00180] In some cases, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased ability, when administered via intravitreal injection, to cross the ILM, compared to the ability of an AAV virion comprising the corresponding parental AAV capsid protein to cross the ILM when administered via intravitreal injection.

[00181] A subject rAAV virion can cross the ILM, and can also traverse cell layers, including Müller cells, amacrine cells, etc., to reach the photoreceptor cells and or RPE cells. For example, a subject rAAV virion, when administered via intravitreal injection, can cross the ILM, and can also traverse cell layers, including Müller cells, amacrine cells, etc., to reach the photoreceptor cells and or RPE cells.

[00182] In some cases, a subject rAAV virion exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased

localization to one or more of the inner nuclear layer, the outer nuclear layer, the photoreceptor layer, the ganglion cell layer, and the retinal pigment epithelium, compared to the extent of localization to the inner nuclear layer, the outer nuclear layer, the photoreceptor layer, the ganglion cell layer, or the retinal pigment epithelium, by an AAV virion comprising the corresponding parental AAV capsid protein.

[00183] In some cases, a subject rAAV virion, when injected intravitreally, exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased localization past the ILM, compared to the extent of localization past the ILM by an intravitreally injected control AAV virion comprising the corresponding parental AAV capsid protein. For example, in some cases, a subject rAAV virion, when injected intravitreally, exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased localization to the retinal pigment epithelium (RPE), compared to the extent of localization to the RPE layer by an intravitreally injected control AAV virion comprising the corresponding parental AAV capsid protein. As another example, in some cases, a subject rAAV virion, when injected intravitreally, exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased localization to the photoreceptor (PR) layer, compared to the extent of localization to the PR layer by an intravitreally injected control AAV virion comprising the corresponding parental AAV capsid protein. As another example, in some cases, a subject rAAV virion, when injected intravitreally, exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased localization to the inner nuclear layer, compared to the extent of localization to the inner nuclear layer by an intravitreally injected control AAV virion comprising the corresponding parental AAV capsid protein. As another example, in some cases, a subject rAAV virion, when injected intravitreally, exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased localization to the outer nuclear layer, compared to the extent of localization to the outer nuclear layer by an intravitreally injected control AAV virion comprising the corresponding parental AAV capsid protein. As another example, in some cases, a subject rAAV virion, when injected intravitreally, exhibits at least 5-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased localization to the ganglion cell layer, compared to the extent of localization to the ganglion cell layer by an intravitreally injected control AAV virion comprising the corresponding parental AAV capsid protein.

[00184] In some embodiments, a subject rAAV virion selectively infects a retinal cell, e.g., a subject rAAV virion infects a retinal cell with 10-fold, 15-fold, 20-fold, 25-fold, 50-fold, or

more than 50-fold, specificity than a non-retinal cell, e.g., a cell outside the eye. For example, in some embodiments, a subject rAAV virion selectively infects a retinal cell, e.g., a subject rAAV virion infects a photoreceptor cell with 10-fold, 15-fold, 20-fold, 25-fold, 50-fold, or more than 50-fold, specificity than a non-retinal cell, e.g., a cell outside the eye.

[00185] In some embodiments, a subject rAAV virion selectively infects a photoreceptor cell, e.g., a subject rAAV virion infects a photoreceptor cell with 10-fold, 15-fold, 20-fold, 25-fold, 50-fold, or more than 50-fold, specificity than a non-photoreceptor cell present in the eye, e.g., a retinal ganglion cell, a Müller cell, etc.

[00186] In some embodiments, a subject rAAV virion exhibits at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, or more than 50-fold, increased infectivity of a photoreceptor cell, when administered via intravitreal injection, compared to the infectivity of the photoreceptor cell by an AAV virion comprising the corresponding parental AAV capsid protein, when administered via intravitreal injection.

Gene products

[00187] An rAAV virion of the present disclosure comprises a heterologous nucleic acid comprising a nucleotide sequence encoding one or more gene products (one or more heterologous gene products). In some cases, the gene product is a polypeptide. In some cases, the gene product is an RNA. In some cases, an rAAV virion of the present disclosure comprises a heterologous nucleotide sequence encoding both a heterologous nucleic acid gene product and a heterologous polypeptide gene product. Where the gene product is an RNA, in some cases, the RNA gene product encodes a polypeptide. Where the gene product is an RNA, in some cases, the RNA gene product does not encode a polypeptide. In some cases, an rAAV virion of the present disclosure comprises a single heterologous nucleic acid comprising a nucleotide sequence encoding a single heterologous gene product. In some cases, an rAAV virion of the present disclosure comprises a single heterologous nucleic acid comprising a nucleotide sequence encoding two heterologous gene products. Where the single heterologous nucleic acid encodes two heterologous gene products, in some cases, nucleotide sequences encoding the two heterologous gene products are operably linked to the same promoter. Where the single heterologous nucleic acid encodes two heterologous gene products, in some cases, nucleotide sequences encoding the two heterologous gene products are operably linked to two different promoters. In some cases, an rAAV virion of the present disclosure comprises a single heterologous nucleic acid comprising a nucleotide sequence encoding three heterologous gene products. Where the single heterologous nucleic acid encodes three heterologous gene products, in some cases, nucleotide sequences encoding the three heterologous gene products are operably linked to the same promoter. Where the single heterologous nucleic acid encodes three

heterologous gene products, in some cases, nucleotide sequences encoding the three heterologous gene products are operably linked to two or three different promoters. In some cases, an rAAV virion of the present disclosure comprises two heterologous nucleic acids, each comprising a nucleotide sequence encoding a heterologous gene product.

[00188] In some cases, the gene product is a polypeptide-encoding RNA. In some cases, the gene product is an interfering RNA. In some cases, the gene product is an aptamer. In some cases, the gene product is a polypeptide. In some cases, the gene product is a therapeutic polypeptide, e.g., a polypeptide that provides clinical benefit. In some embodiments, the gene product is a site-specific nuclease that provide for site-specific knock-down of gene function. In some embodiments, the gene product is an RNA-guided endonuclease that provides for modification of a target nucleic acid. In some cases, the gene products are: i) an RNA-guided endonuclease that provides for modification of a target nucleic acid; and ii) a guide RNA that comprises a first segment that binds to a target sequence in a target nucleic acid and a second segment that binds to the RNA-guided endonuclease. In some cases, the gene products are: i) an RNA-guided endonuclease that provides for modification of a target nucleic acid; ii) a first guide RNA that comprises a first segment that binds to a first target sequence in a target nucleic acid and a second segment that binds to the RNA-guided endonuclease; and iii) a first guide RNA that comprises a first segment that binds to a second target sequence in the target nucleic acid and a second segment that binds to the RNA-guided endonuclease.

Interfering RNA

[00189] Where the gene product is an interfering RNA (RNAi), suitable RNAi include RNAi that decrease the level of an apoptotic or angiogenic factor in a cell. For example, an RNAi can be an shRNA or siRNA that reduces the level of a gene product that induces or promotes apoptosis in a cell. Genes whose gene products induce or promote apoptosis are referred to herein as "pro-apoptotic genes" and the products of those genes (mRNA; protein) are referred to as "pro-apoptotic gene products." Pro-apoptotic gene products include, e.g., *Bax*, *Bid*, *Bak*, and *Bad* gene products. See, e.g., U.S. Patent No. 7,846,730.

[00190] Interfering RNAs could also be against an angiogenic product, for example vascular endothelial growth factor (VEGF) (e.g., Cand5; see, e.g., U.S. Patent Publication No. 2011/0143400; U.S. Patent Publication No. 2008/0188437; and Reich et al. (2003) *Mol. Vis.* 9:210); VEGF receptor-1 (VEGFR1) (e.g., Sirna-027; see, e.g., Kaiser et al. (2010) *Am. J. Ophthalmol.* 150:33; and Shen et al. (2006) *Gene Ther.* 13:225); or VEGF receptor-2 (VEGFR2) (Kou et al. (2005) *Biochem.* 44:15064). See also, U.S. Patent Nos. 6,649,596, 6,399,586, 5,661,135, 5,639,872, and 5,639,736; and U.S. Patent Nos. 7,947,659 and 7,919,473.

Aptamers

[00191] Where the gene product is an aptamer, exemplary aptamers of interest include an aptamer against VEGF. See, e.g., Ng et al. (2006) *Nat. Rev. Drug Discovery* 5:123; and Lee et al. (2005) *Proc. Natl. Acad. Sci. USA* 102:18902. For example, a VEGF aptamer can comprise the nucleotide sequence 5'-cgcaaucagugaaugcuuauacauccg-3' (SEQ ID NO:3). Also suitable for use is a platelet-derived growth factor (PDGF)-specific aptamer, e.g., E10030; see, e.g., Ni and Hui (2009) *Ophthalmologica* 223:401; and Akiyama et al. (2006) *J. Cell Physiol.* 207:407).

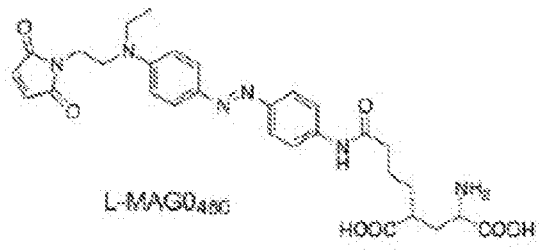
Polypeptides

[00192] Where the gene product is a polypeptide, in some cases, the polypeptide is a polypeptide that enhances function of a retinal cell, e.g., the function of a rod or cone photoreceptor cell, a retinal ganglion cell, a Müller cell, a bipolar cell, an amacrine cell, a horizontal cell, or a retinal pigment epithelial cell. Exemplary polypeptides include neuroprotective polypeptides (e.g., glial cell derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), neurotrophin-4 (NT4), nerve growth factor (NGF), and neurturin (NTN)); anti-angiogenic polypeptides (e.g., a soluble VEGF receptor; a VEGF-binding antibody; a VEGF-binding antibody fragment (e.g., a single chain anti-VEGF antibody); endostatin; tumstatin; angiostatin; a soluble Flt polypeptide (Lai et al. (2005) *Mol. Ther.* 12:659); an Fc fusion protein comprising a soluble Flt polypeptide (see, e.g., Pechan et al. (2009) *Gene Ther.* 16:10); pigment epithelium-derived factor (PEDF); a soluble Tie-2 receptor; etc.); tissue inhibitor of metalloproteinases-3 (TIMP-3); a light-responsive opsin, e.g., a rhodopsin; anti-apoptotic polypeptides (e.g., Bcl-2, Bcl-Xl; XIAP); and the like. Suitable polypeptides include, but are not limited to, glial derived neurotrophic factor (GDNF); fibroblast growth factor; fibroblast growth factor 2; neurturin (NTN); ciliary neurotrophic factor (CNTF); nerve growth factor (NGF); neurotrophin-4 (NT4); brain derived neurotrophic factor (BDNF; e.g., a polypeptide comprising an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from about 200 amino acids to 247 amino acids of the amino acid sequence depicted in Figure 7B (SEQ ID NO:11)); epidermal growth factor; rhodopsin; X-linked inhibitor of apoptosis; and Sonic hedgehog.

[00193] Suitable light-responsive opsins include, e.g., a light-responsive opsin as described in U.S. Patent Publication No. 2007/0261127 (e.g., channelrhodopsin-2; ChR2; Chop2); U.S. Patent Publication No. 2001/0086421; U.S. Patent Publication No. 2010/0015095; U.S. Patent Publication No. 2016/0002302; U.S. Patent Publication No. 2013/0347137; U.S. Patent Publication No. 2013/0019325; and Diester et al. (2011) *Nat. Neurosci.* 14:387. See, Thyagarajan et al. (2010) J Neurosci. 30(26):8745–8758; Lagali et al. (2008) Nat Neurosci.

11(6):667–675; Doroudchi et al. (2011) Mol Ther. 19(7):1220–1229; Henriksen et al. (2014) *J. Ophthalmic Vis. Res.* 9:374; Tomita et al. (2014) *Mol. Ther.* 22:1434.

[00194] Suitable polypeptides include light-gated ion channel polypeptides. See, e.g., Gaub et al. (2014) *Proc. Natl. Acad. Sci. USA* 111:E5574. For example, a suitable polypeptide is a light-gated ionotropic glutamate receptor (LiGluR). Expression of LiGluR in retinal ganglion cells and ON-bipolar cells, in the presence of a photoisomerizable compound, renders the cells responsive to light. LiGluR comprises a L439C substitution; see, Caporale et al. (2011) *Mol Ther.* 19:1212–1219; Volgraf et al. (2006) Nat Chem Biol. 2:47–52; and Gorostiza et al. (2007) Proc Natl Acad Sci USA. 104:10865–10870. Photoisomerizable compounds include, e.g., maleimide-azobenzene-glutamate 0 with peak efficiency at 460 nm ($MAG0_{460}$). $MAG0_{460}$ has the following structure:



[00195] Suitable polypeptides also include retinoschisin (e.g., a polypeptide comprising an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from about 200 amino acids to 224 amino acids of the amino acid sequence depicted in FIG. 7A (SEQ ID NO:10). Suitable polypeptides include, e.g., retinitis pigmentosa GTPase regulator (RPGR)-interacting protein-1 (see, e.g., GenBank Accession Nos. Q96KN7, Q9EPQ2, and Q9GLM3) (e.g., a polypeptide comprising an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from about 1150 amino acids to about 1200 amino acids, or from about 1200 amino acids to 1286 amino acids, of the amino acid sequence depicted in FIG. 7F (SEQ ID NO:15); peripherin-2 (Prph2) (see, e.g., GenBank Accession No. NP_000313 (e.g., a polypeptide comprising an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from about 300 amino acids to 346 amino acids of the amino acid sequence depicted in FIG. 7D (SEQ ID NO:13); and Travis et al. (1991) *Genomics* 10:733); peripherin (e.g., a polypeptide comprising an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from about 400 amino acids to about 470 amino acids of the amino acid sequence

depicted in FIG. 7E (SEQ ID NO:14); a retinal pigment epithelium-specific protein (RPE65), (e.g., a polypeptide comprising an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from about 200 amino acids to 247 amino acids of the amino acid sequence depicted in FIG. 7C (SEQ ID NO:12)) (see, e.g., GenBank AAC39660; and Morimura et al. (1998) *Proc. Natl. Acad. Sci. USA* 95:3088); rod-derived cone viability factor (RdCVF) (e.g., a polypeptide comprising an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in any one of FIG. 7H, 7I, and 7J; Rab escort protein 1 (REP1) (e.g., a polypeptide comprising an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 7G); retinitis pigmentosa GTPase regulator (RPGR) (e.g., a polypeptide comprising an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in one of FIG. 7S-7V); and the like. For example, in some cases, a suitable RPGR polypeptide comprises an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 7S. As another example, in some cases, a suitable RPGR polypeptide comprises an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 7T. example, in some cases, a suitable RPGR polypeptide comprises an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 7U. example, in some cases, a suitable RPGR polypeptide comprises an amino acid sequence having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 7V.

[00196] Suitable polypeptides also include: CHM (choroideremia (Rab escort protein 1 (REP1))), a polypeptide that, when defective or missing, causes choroideremia (see, e.g., Donnelly et al. (1994) *Hum. Mol. Genet.* 3:1017; and van Bokhoven et al. (1994) *Hum. Mol. Genet.* 3:1041); and Crumbs homolog 1 (CRB1), a polypeptide that, when defective or missing, causes Leber congenital amaurosis and retinitis pigmentosa (see, e.g., den Hollander et al. (1999) *Nat. Genet.* 23:217; and GenBank Accession No. CAM23328). For example, a suitable REP1 polypeptide can comprise an amino acid having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence set depicted in FIG. 7G.

[00197] Suitable polypeptides include Rod cGMP-specific 3',5'-cyclic phosphodiesterase subunit alpha (PDE6α), Rod cGMP-specific 3',5'-cyclic phosphodiesterase subunit beta isoform 1 (PDE6β isoform 1), Rod cGMP-specific 3',5'-cyclic phosphodiesterase subunit beta isoform 2 (PDE6β isoform 2), Rod cGMP-specific 3',5'-cyclic phosphodiesterase subunit beta isoform 3 (PDE6β isoform 3). For example, a suitable PDE6α polypeptide can comprise an amino acid having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence set depicted in FIG. 7K. As another example, a suitable PDE6β6 isoform 1 polypeptide can comprise an amino acid having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence set depicted in FIG. 7L. As another example, a suitable PDE6β6 isoform 2 polypeptide can comprise an amino acid having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence set depicted in FIG. 7M. As another example, a suitable PDE6β6 isoform 3 polypeptide can comprise an amino acid having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence set depicted in FIG. 7N.

[00198] Suitable polypeptides also include polypeptides that, when defective or missing, lead to achromotopsia, where such polypeptides include, e.g., cone photoreceptor cGMP-gated channel subunit alpha (CNGA3) (see, e.g., GenBank Accession No. NP_001289; and Booij et al. (2011) *Ophthalmology* 118:160-167); cone photoreceptor cGMP-gated cation channel beta-subunit (CNGB3) (see, e.g., Kohl et al.(2005) *Eur J Hum Genet.* 13(3):302); guanine nucleotide binding protein (G protein), alpha transducing activity polypeptide 2 (GNAT2) (ACHM4); and ACHM5; and polypeptides that, when defective or lacking, lead to various forms of color blindness (e.g., L-opsin, M-opsin, and S-opsin). See Mancuso et al. (2009) *Nature* 461(7265):784–787.

[00199] For example, a suitable CNGA3 (also known as ACHM2) isoform 1 polypeptide can comprise an amino acid having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence set depicted in FIG. 7O. As another example, a suitable CNGA3 (also known as ACHM2) isoform 2 polypeptide can comprise an amino acid having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence set depicted in FIG. 7P.

[00200] As another example, a suitable CNGB3 (also known as ACHM3) polypeptide can comprise an amino acid having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence set depicted in FIG. 7Q. As another example, GNAT2 (also known as ACHM4) can comprise an amino acid

having at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence set depicted in FIG. 7R.

Site-specific endonucleases

[00201] In some cases, a gene product of interest is a site-specific endonuclease that provide for site-specific knock-down of gene function, e.g., where the endonuclease knocks out an allele associated with a retinal disease. For example, where a dominant allele encodes a defective copy of a gene that, when wild-type, is a retinal structural protein and/or provides for normal retinal function, a site-specific endonuclease can be targeted to the defective allele and knock out the defective allele. In some cases, a site-specific endonuclease is an RNA-guided endonuclease.

[00202] In addition to knocking out a defective allele, a site-specific nuclease can also be used to stimulate homologous recombination with a donor DNA that encodes a functional copy of the protein encoded by the defective allele. Thus, e.g., a subject rAAV virion can be used to deliver both a site-specific endonuclease that knocks out a defective allele, and can be used to deliver a functional copy of the defective allele, resulting in repair of the defective allele, thereby providing for production of a functional retinal protein (e.g., functional retinoschisin, functional RPE65, functional peripherin, etc.). See, e.g., Li et al. (2011) *Nature* 475:217. In some embodiments, a subject rAAV virion comprises a heterologous nucleotide sequence that encodes a site-specific endonuclease; and a heterologous nucleotide sequence that encodes a functional copy of a defective allele, where the functional copy encodes a functional retinal protein. Functional retinal proteins include, e.g., retinoschisin, RPE65, retinitis pigmentosa GTPase regulator (RGPR)-interacting protein-1, peripherin, peripherin-2, RdCVF, and the like.

[00203] Site-specific endonucleases that are suitable for use include, e.g., zinc finger nucleases (ZFNs); meganucleases; and transcription activator-like effector nucleases (TALENs), where such site-specific endonucleases are non-naturally occurring and are modified to target a specific gene. Such site-specific nucleases can be engineered to cut specific locations within a genome, and non-homologous end joining can then repair the break while inserting or deleting several nucleotides. Such site-specific endonucleases (also referred to as "INDELs") then throw the protein out of frame and effectively knock out the gene. See, e.g., U.S. Patent Publication No. 2011/0301073. Suitable site-specific endonucleases include engineered meganucleases and re-engineered homing endonucleases. Suitable endonucleases include an I-TevI nuclease. Suitable meganucleases include I-SceI (see, e.g., Bellaiche et al. (1999) *Genetics* 152:1037); and I-CreI (see, e.g., Heath et al. (1997) *Nature Structural Biology* 4:468).

<u>RNA-guided endonucleases</u>

[00204] In some cases, the gene product is an RNA-guided endonuclease. In some cases, the gene product is an RNA comprising a nucleotide sequence encoding an RNA-guided

endonuclease. In some cases, the gene product is a guide RNA, e.g., a single-guide RNA. In some cases, the gene products are: 1) a guide RNA; and 2) an RNA-guided endonuclease. The guide RNA can comprise: a) a protein-binding region that binds to the RNA-guided endonuclease; and b) a region that binds to a target nucleic acid. An RNA-guided endonuclease is also referred to herein as a "genome editing nuclease."

[00205] Examples of suitable genome editing nucleases are CRISPR/Cas endonucleases (e.g., class 2 CRISPR/Cas endonucleases such as a type II, type V, or type VI CRISPR/Cas endonucleases). A suitable genome editing nuclease is a CRISPR/Cas endonuclease (e.g., a class 2 CRISPR/Cas endonuclease such as a type II, type V, or type VI CRISPR/Cas endonuclease). In some cases, a genome targeting composition includes a class 2 CRISPR/Cas endonuclease. In some cases, a genome targeting composition includes a class 2 type II CRISPR/Cas endonuclease (e.g., a Cas9 protein). In some cases, a genome targeting composition includes a class 2 type V CRISPR/Cas endonuclease (e.g., a Cpf1 protein, a C2c1 protein, or a C2c3 protein). In some cases, a genome targeting composition includes a class 2 type VI CRISPR/Cas endonuclease (e.g., a C2c2 protein; also referred to as a "Cas13a" protein). Also suitable for use is a CasX protein. Also suitable for use is a CasY protein.

[00206] In some cases, a genome editing nuclease is a fusion protein that is fused to a heterologous polypeptide (also referred to as a "fusion partner"). In some cases, a genome editing nuclease is fused to an amino acid sequence (a fusion partner) that provides for subcellular localization, i.e., the fusion partner is a subcellular localization sequence (e.g., one or more nuclear localization signals (NLSs) for targeting to the nucleus, two or more NLSs, three or more NLSs, etc.).

[00207] In some cases, the genome-editing endonuclease is a Type II CRISPR/Cas endonuclease. In some cases, the genome-editing endonuclease is a Cas9 polypeptide. The Cas9 protein is guided to a target site (e.g., stabilized at a target site) within a target nucleic acid sequence (e.g., a chromosomal sequence or an extrachromosomal sequence, e.g., an episomal sequence, a minicircle sequence, a mitochondrial sequence, a chloroplast sequence, etc.) by virtue of its association with the protein-binding segment of the Cas9 guide RNA. In some cases, a Cas9 polypeptide comprises an amino acid sequence having at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or more than 99%, amino acid sequence identity to the *Streptococcus pyogenes* Cas9 depicted in FIG. 3A. In some cases, the Cas9 polypeptide used in a composition or method of the present disclosure is a *Staphylococcus aureus* Cas9 (saCas9) polypeptide. In some cases, the saCas9 polypeptide comprises an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the saCas9 amino acid sequence depicted in FIG. 3B.

[00208] In some cases, a suitable Cas9 polypeptide is a high-fidelity (HF) Cas9 polypeptide. Kleinstiver et al. (2016) *Nature* 529:490. For example, amino acids N497, R661, Q695, and Q926 of the amino acid sequence depicted in FIG. 3A are substituted, e.g., with alanine. For example, an HF Cas9 polypeptide can comprise an amino acid sequence having at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence depicted in FIG. 3A, where amino acids N497, R661, Q695, and Q926 are substituted, e.g., with alanine.

[00209] In some cases, a suitable Cas9 polypeptide exhibits altered PAM specificity. See, e.g., Kleinstiver et al. (2015) *Nature* 523:481.

[00210] In some cases, the genome-editing endonuclease is a type V CRISPR/Cas endonuclease. In some cases a type V CRISPR/Cas endonuclease is a Cpf1 protein. In some cases, a Cpf1 protein comprises an amino acid sequence having at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 90%, or 100%, amino acid sequence identity to the Cpf1 amino acid sequence depicted in FIG. 3C.

[00211] In some cases, the genome-editing endonuclease is a CasX or a CasY polypeptide. CasX and CasY polypeptides are described in Burstein et al. (2017) *Nature* 542:237.

Enzymatically inactive RNA-guided endonucleases

[00212] Also suitable for use is an RNA-guided endonuclease with reduced enzymatic activity. Such an RNA-guided endonuclease is referred to as a "dead" RNA-guided endonuclease; for example, a Cas9 polypeptide that comprises certain amino acid substitutions such that it exhibits substantially no endonuclease activity, but such that it still binds to a target nucleic acid when complexed with a guide RNA, is referred to as a "dead" Cas9 or "dCas9." In some cases, a "dead" Cas9 protein has a reduced ability to cleave both the complementary and the non-complementary strands of a double stranded target nucleic acid. For example, a "nuclease defective" Cas9 lacks a functioning RuvC domain (i.e., does not cleave the non-complementary strand of a double stranded target DNA) and lacks a functioning HNH domain (i.e., does not cleave the complementary strand of a double stranded target DNA). As a non-limiting example, in some cases, the nuclease defective Cas9 protein harbors mutations at amino acid positions corresponding to residues D10 and H840 (e.g., D10A and H840A) of SEQ ID NO: 15 (or the corresponding residues of a homolog of Cas9) such that the polypeptide has a reduced ability to cleave (e.g., does not cleave) both the complementary and the non-complementary strands of a target nucleic acid. Such a Cas9 protein has a reduced ability to cleave a target nucleic acid (e.g., a single stranded or double stranded target nucleic acid) but retains the ability to bind a target

nucleic acid. A Cas9 protein that cannot cleave target nucleic acid (e.g., due to one or more mutations, e.g., in the catalytic domains of the RuvC and HNH domains) is referred to as a "nuclease defective Cas9", "dead Cas9" or simply "dCas9." Other residues can be mutated to achieve the above effects (i.e. inactivate one or the other nuclease portions). As non-limiting examples, residues D10, G12, G17, E762, H840, N854, N863, H982, H983, A984, D986, and/or A987 of *Streptococcus pyogenes* Cas9 (or the corresponding amino acids of a Cas9 homolog) can be altered (i.e., substituted). In some cases, two or more of D10, E762, H840, N854, N863, and D986 of *Streptococcus pyogenes* Cas9 (or the corresponding amino acids of a Cas9 homolog) are substituted. In some cases, D10 and N863 of *Streptococcus pyogenes* Cas9 (or the corresponding amino acids of a Cas9 homolog) are substituted with Ala. Also, mutations other than alanine substitutions are suitable.

[00213] In some cases, the genome-editing endonuclease is an RNA-guided endonuclease (and it corresponding guide RNA) known as Cas9-synergistic activation mediator (Cas9-SAM). The RNA-guided endonuclease (e.g., Cas9) of the Cas9-SAM system is a "dead" Cas9 fused to a transcriptional activation domain (wherein suitable transcriptional activation domains include, e.g., VP64, p65, MyoD1, HSF1, RTA, and SET7/9) or a transcriptional repressor domain (where suitable transcriptional repressor domains include, e.g., a KRAB domain, a NuE domain, an NcoR domain, a SID domain, and a SID4X domain). The guide RNA of the Cas9-SAM system comprises a loop that binds an adapter protein fused to a transcriptional activator domain (e.g., VP64, p65, MyoD1, HSF1, RTA, or SET7/9) or a transcriptional repressor domain (e.g., a KRAB domain, a NuE domain, an NcoR domain, a SID domain, or a SID4X domain). For example, in some cases, the guide RNA is a single-guide RNA comprising an MS2 RNA aptamer inserted into one or two loops of the sgRNA; the dCas9 is a fusion polypeptide comprising dCas9 fused to VP64; and the adaptor/functional protein is a fusion polypeptide comprising: i) MS2; ii) p65; and iii) HSF1. See, e.g., U.S. Patent Publication No. 2016/0355797.

[00214] Also suitable for use is a chimeric polypeptide comprising: a) a dead RNA-guided endonuclease; and b) a heterologous fusion polypeptide. Examples of suitable heterologous fusion polypeptides include a polypeptide having, e.g., methylase activity, demethylase activity, transcription activation activity, transcription repression activity, transcription release factor activity, histone modification activity, RNA cleavage activity, DNA cleavage activity, DNA integration activity, or nucleic acid binding activity.

Guide RNA

[00215] A nucleic acid that binds to a class 2 CRISPR/Cas endonuclease (e.g., a Cas9 protein; a type V or type VI CRISPR/Cas protein; a Cpf1 protein; etc.) and targets the complex to a specific location within a target nucleic acid is referred to herein as a "guide RNA" or

"CRISPR/Cas guide nucleic acid" or "CRISPR/Cas guide RNA." A guide RNA provides target specificity to the complex (the RNP complex) by including a targeting segment, which includes a guide sequence (also referred to herein as a targeting sequence), which is a nucleotide sequence that is complementary to a sequence of a target nucleic acid.

[00216] In some cases, a guide RNA includes two separate nucleic acid molecules: an "activator" and a "targeter" and is referred to herein as a "dual guide RNA", a "double-molecule guide RNA", a "two-molecule guide RNA", or a "dgRNA." In some cases, the guide RNA is one molecule (e.g., for some class 2 CRISPR/Cas proteins, the corresponding guide RNA is a single molecule; and in some cases, an activator and targeter are covalently linked to one another, e.g., via intervening nucleotides), and the guide RNA is referred to as a "single guide RNA", a "single-molecule guide RNA," a "one-molecule guide RNA", or simply "sgRNA."

[00217] Where the gene product is an RNA-guided endonuclease, or is both an RNA-guided endonuclease and a guide RNA, the gene product can modify a target nucleic acid. In some cases, e.g., where a target nucleic acid comprises a deleterious mutation in a defective allele (e.g., a deleterious mutation in a retinal cell target nucleic acid), the RNA-guided endonuclease/guide RNA complex, together with a donor nucleic acid comprising a nucleotide sequence that corrects the deleterious mutation (e.g., a donor nucleic acid comprising a nucleotide sequence that encodes a functional copy of the protein encoded by the defective allele), can be used to correct the deleterious mutation, e.g., via homology-directed repair (HDR).

[00218] In some cases, the gene products are an RNA-guided endonuclease and 2 separate sgRNAs, where the 2 separate sgRNAs provide for deletion of a target nucleic acid via non-homologous end joining (NHEJ).

[00219] In some cases, the gene products are: i) an RNA-guided endonuclease; and ii) one guide RNA. In some cases, the guide RNA is a single-molecule (or "single guide") guide RNA (an "sgRNA"). In some cases, the guide RNA is a dual-molecule (or "dual-guide") guide RNA ("dgRNA").

[00220] In some cases, the gene products are: i) an RNA-guided endonuclease; and ii) 2 separate sgRNAs, where the 2 separate sgRNAs provide for deletion of a target nucleic acid via non-homologous end joining (NHEJ). In some cases, the guide RNAs are sgRNAs. In some cases, the guide RNAs are dgRNAs.

[00221] In some cases, the gene products are: i) a Cpf1 polypeptide; and ii) a guide RNA precursor; in these cases, the precursor can be cleaved by the Cpf1 polypeptide to generate 2 or more guide RNAs.

[00222] The present disclosure provides a method of modifying a target nucleic acid in a retinal cell in an individual, where the target nucleic acid comprises a deleterious mutation, the method comprising administering to the individual (e.g., by intraocular; intravitreal; etc. administration) an rAAV virion of the present disclosure, where the rAAV virion comprises a heterologous nucleic acid comprising: i) a nucleotide sequence encoding an RNA-guided endonuclease (e.g., a Cas9 endonuclease); ii) a nucleotide sequence encoding a sgRNA that comprises a nucleotide sequence that is complementary to the target nucleic acid; and iii) a nucleotide sequence encoding a donor DNA template that comprises a nucleotide sequence that corrects the deleterious mutation. Administration of the rAAV virion results in correction of the deleterious mutation in the target nucleic acid by HDR.

[00223] The present disclosure provides a method of modifying a target nucleic acid in a retinal cell in an individual, where the target nucleic acid comprises a deleterious mutation, the method comprising administering to the individual (e.g., by intraocular; intravitreal; etc. administration) an rAAV virion of the present disclosure, where the rAAV virion comprises a heterologous nucleic acid comprising: i) a nucleotide sequence encoding an RNA-guided endonuclease (e.g., a Cas9 endonuclease); ii) a nucleotide sequence encoding a first sgRNA that comprises a nucleotide sequence that is complementary to a first sequence in the target nucleic acid; and iii) a nucleotide sequence encoding a second sgRNA that comprises a nucleotide sequence that is complementary to a second sequence in the target nucleic acid. Administration of the rAAV virion results in excision of the deleterious mutation in the target nucleic acid by NHEJ.

Regulatory sequences

[00224] In some cases, a nucleotide sequence encoding a gene product of interest is operably linked to a transcriptional control element. For example, in some cases, a nucleotide sequence encoding a gene product of interest is operably linked to a constitutive promoter. In other cases, a nucleotide sequence encoding a gene product of interest is operably linked to an inducible promoter. In some instances, a nucleotide sequence encoding a gene product of interest is operably linked to a tissue-specific or cell type-specific regulatory element. For example, in some instances, a nucleotide sequence encoding a gene product of interest is operably linked to a retinal cell-specific promoter. For example, in some instances, a nucleotide sequence encoding a gene product of interest is operably linked to a photoreceptor-specific regulatory element (e.g., a photoreceptor-specific promoter), e.g., a regulatory element that confers selective expression of the operably linked gene in a photoreceptor cell. Suitable photoreceptor-specific regulatory elements include, e.g., a rhodopsin promoter; a rhodopsin kinase promoter (Young et al. (2003) *Ophthalmol. Vis. Sci.* 44:4076); a beta phosphodiesterase gene promoter (Nicoud et al. (2007) *J. Gene Med.* 9:1015); a retinitis pigmentosa gene promoter (Nicoud et al. (2007) *supra*); an

interphotoreceptor retinoid-binding protein (IRBP) gene enhancer (Nicoud et al. (2007) *supra*); an IRBP gene promoter (Yokoyama et al. (1992) *Exp Eye Res.* 55:225).

PHARMACEUTICAL COMPOSITIONS

[00225] The present disclosure provides a pharmaceutical composition comprising: a) a subject rAAV virion, as described above; and b) a pharmaceutically acceptable carrier, diluent, excipient, or buffer. In some embodiments, the pharmaceutically acceptable carrier, diluent, excipient, or buffer is suitable for use in a human.

[00226] Such excipients, carriers, diluents, and buffers include any pharmaceutical agent that can be administered without undue toxicity. Pharmaceutically acceptable excipients include, but are not limited to, liquids such as water, saline, glycerol and ethanol. Pharmaceutically acceptable salts can be included therein, for example, mineral acid salts such as hydrochlorides, hydrobromides, phosphates, sulfates, and the like; and the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like. Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present in such vehicles. A wide variety of pharmaceutically acceptable excipients are known in the art and need not be discussed in detail herein. Pharmaceutically acceptable excipients have been amply described in a variety of publications, including, for example, A. Gennaro (2000) "Remington: The Science and Practice of Pharmacy," 20th edition, Lippincott, Williams, & Wilkins; Pharmaceutical Dosage Forms and Drug Delivery Systems (1999) H.C. Ansel et al., eds., 7th ed., Lippincott, Williams, & Wilkins; and Handbook of Pharmaceutical Excipients (2000) A.H. Kibbe et al., eds., 3rd ed. Amer. Pharmaceutical Assoc.

METHODS OF DELIVERING A GENE PRODUCT TO A RETINAL CELL AND TREATMENT METHODS

[00227] The present disclosure provides a method of delivering a gene product to a retinal cell in an individual, the method comprising administering to the individual a subject rAAV virion as described above. The gene product can be a polypeptide or an interfering RNA (e.g., an shRNA, an siRNA, and the like), an aptamer, or a site-specific endonuclease (e.g., an RNA-guided endonuclease), as described above. Delivering a gene product to a retinal cell can provide for treatment of a retinal disease. The retinal cell can be a photoreceptor, a retinal ganglion cell, a Müller cell, a bipolar cell, an amacrine cell, a horizontal cell, or a retinal pigmented epithelial cell. In some cases, the retinal cell is a photoreceptor cell, e.g., a rod or cone cell.

[00228] The present disclosure provides a method modifying a target nucleic acid in a retinal cell, the method comprising contacting the retinal cell with: 1) an rAAV virion of the present disclosure, wherein the rAAV virion comprises a heterologous nucleic acid comprising a nucleotide sequence encoding an RNA-guided endonuclease that binds a guide RNA; and 2) the

guide RNA. The present disclosure provides a method modifying a target nucleic acid in a retinal cell, the method comprising contacting the retinal cell with an rAAV virion of the present disclosure, wherein the rAAV virion comprises a heterologous nucleic acid comprising a nucleotide sequence encoding: i) an RNA-guided endonuclease that binds a guide RNA; and ii) the guide RNA. In some cases, the method comprises contacting the retinal cell with a donor DNA template. In some cases, the RNA-guided endonuclease is a Cas9 polypeptide. In some cases, the guide RNA is a single-guide RNA.

[00229] The present disclosure provides a method of treating an ocular disease (e.g., a retinal disease), the method comprising administering to an individual in need thereof an effective amount of a subject rAAV virion as described above. A subject rAAV virion can be administered via intraocular injection, e.g. by intravitreal injection, by subretinal injection, by suprachoroidal injection, or by any other convenient mode or route of administration. Other convenient modes or routes of administration include, e.g., intravenous, intranasal, etc.

[00230] A "therapeutically effective amount" will fall in a relatively broad range that can be determined through experimentation and/or clinical trials. For example, for *in vivo* injection, i.e., injection directly into the eye, a therapeutically effective dose will be on the order of from about 10^6 to about 10^{15} of the rAAV virions, e.g., from about 10^8 to 10^{12} rAAV virions. For example, for *in vivo* injection, i.e., injection directly into the eye, a therapeutically effective dose will be on the order of from about 10^6 viral genomes (vg) to about 10^{15} vg of the rAAV virions, e.g., from about 10^8 vg to 10^{12} vg. For *in vitro* transduction, an effective amount of rAAV virions to be delivered to cells will be on the order of from about 10^8 to about 10^{13} of the rAAV virions. For example, for *in vitro* transduction, an effective amount of rAAV virions to be delivered to cells will be on the order of from about 10^8 to about 10^{13} vg of the rAAV virions. As another example, for *in vitro* transduction, an effective amount of rAAV virions to be delivered to cells will be on the order of from about 10 vg/cell to about 10^4 vg/cell. Other effective dosages can be readily established by one of ordinary skill in the art through routine trials establishing dose response curves.

[00231] In some embodiments, more than one administration (e.g., two, three, four or more administrations) may be employed to achieve the desired level of gene expression. In some cases, the more than one administration is administered at various intervals, e.g., daily, weekly, twice monthly, monthly, every 3 months, every 6 months, yearly, etc. In some cases, multiple administrations are administered over a period of time of from 1 month to 2 months, from 2 months to 4 months, from 4 months to 8 months, from 8 months to 12 months, from 1 year to 2 years, from 2 years to 5 years, or more than 5 years.

[00232] Ocular diseases that can be treated using a subject method include, but are not limited to, acute macular neuroretinopathy; Behcet's disease; choroidal neovascularization; diabetic uveitis; histoplasmosis; macular degeneration, such as acute macular degeneration, non-exudative age related macular degeneration and exudative age related macular degeneration; edema, such as macular edema, cystoid macular edema and diabetic macular edema; multifocal choroiditis; ocular trauma which affects a posterior ocular site or location; ocular tumors; retinal disorders, such as central retinal vein occlusion, diabetic retinopathy (including proliferative diabetic retinopathy), proliferative vitreoretinopathy (PVR), retinal arterial occlusive disease, retinal detachment, uveitic retinal disease; sympathetic opthalmia; Vogt Koyanagi-Harada (VKH) syndrome; uveal diffusion; a posterior ocular condition caused by or influenced by an ocular laser treatment; posterior ocular conditions caused by or influenced by a photodynamic therapy; photocoagulation, radiation retinopathy; epiretinal membrane disorders; branch retinal vein occlusion; anterior ischemic optic neuropathy; non-retinopathy diabetic retinal dysfunction; retinoschisis; retinitis pigmentosa; glaucoma; Usher syndrome, cone-rod dystrophy; Stargardt disease (fundus flavimaculatus); inherited macular degeneration; chorioretinal degeneration; Leber congenital amaurosis; congenital stationary night blindness; choroideremia; Bardet-Biedl syndrome; macular telangiectasia; Leber's hereditary optic neuropathy; retinopathy of prematurity; disorders of color vision, including achromatopsia, protanopia, deuteranopia, and tritanopia; and Bietti's crystalline dystrophy.

[00233] The present disclosure provides methods of treating retinal disease. The methods generally involve administering an rAAV virion of the present disclosure, or a composition comprising an rAAV virion of the present disclosure, to an eye of an individual in need thereof. Non-limiting methods for assessing treatment of retinal diseases include measuring functional changes, e.g. changes in visual acuity (e.g. BCVA), visual field (e.g. visual field perimetry), electrophysiological responsiveness to light and dark (e.g. ERG, VEP), color vision, and/or contrast sensitivity; measuring changes in anatomy or health using anatomical and/or photographic measures, e.g. OCT, fundus photography, and/or autofluorescence; and measuring ocular motility (e.g. nystagmus, fixation preference, and stability).

[00234] For example, one of ordinary skill in the art could readily determine an effective amount of rAAV virions by testing for an effect on one or more parameters, e.g. visual acuity, visual field, electrophysiological responsiveness to light and dark, color vision, contrast sensitivity, anatomy, retinal health and vasculature, ocular motility, fixation preference, and stability. In some cases, administering an effective amount of an rAAV virion of the present disclosure results in a decrease in the rate of loss of retinal function, anatomical integrity, or retinal health, e.g. a 2-fold, 3-fold, 4-fold, or 5-fold or more decrease in the rate of loss and hence progression

of disease, e.g. a 10-fold decrease or more in the rate of loss and hence progression of disease. In some cases, administering an effective amount of an rAAV virion of the present disclosure results in a gain in retinal function, an improvement in retinal anatomy or health, and/or a stabilization in ocular motility, e.g. a 2-fold, 3-fold, 4-fold or 5-fold improvement or more in retinal function, retinal anatomy or health, and/or stability of the orbital, e.g. a 10-fold improvement or more in retinal function, retinal anatomy or health, and/or stability of the orbital.

NUCLEIC ACIDS AND HOST CELLS

[00235] The present disclosure provides an isolated nucleic acid comprising a nucleotide sequence that encodes a subject variant adeno-associated virus (AAV) capsid protein as described above, where the variant AAV capsid protein comprises an insertion of from about 5 amino acids to about 20 amino acids in the GH loop or loop IV relative to a corresponding parental AAV capsid protein, or where the variant AAV capsid protein comprises a replacement of from about 5 amino acids to about 20 amino acids in the GH loop or loop IV relative to a corresponding parental AAV capsid protein with a heterologous peptide of from about 5 amino acids to about 20 amino acids; and where the variant capsid protein, when present in an AAV virion, provides for increased infectivity of a retinal cell compared to the infectivity of the retinal cell by an AAV virion comprising the corresponding parental AAV capsid protein. A subject isolated nucleic acid can be an AAV vector, e.g., a recombinant AAV vector.

Insertion peptides

[00236] A variant AAV capsid protein encoded by a subject nucleic acid has an insertion peptide of from about 5 amino acids to about 20 amino acids in length is inserted into the GH loop of an AAV capsid. The insertion peptide has a length of 5 amino acids, 6 amino acids, 7 amino acids, 8 amino acids, 9 amino acids, 10 amino acids, 11 amino acids, 12 amino acids, 13 amino acids, 14 amino acids, 15 amino acids, 16 amino acids, 17 amino acids, 18 amino acids, 19 amino acids, or 20 amino acids. Suitable insertion peptides are as described above. Suitable insertion peptides include a peptide of any one of Formulas I-VI, as described above. The insertion of the insertion peptide into a parental AAV capsid will in some cases replace an endogenous stretch of from about 5 amino acids to about 20 amino acids in the GH loop or loop IV. Thus, in some cases, a variant AAV capsid protein encoded by a subject nucleic acid comprises a replacement of from about 5 amino acids to about 20 amino acids in the GH loop or loop IV relative to a corresponding parental AAV capsid protein with a heterologous peptide of from about 5 amino acids to about 20 amino acids, where suitable heterologous peptides include a peptide of any one of Formulas I-VI, as described above.

[00237] A subject recombinant AAV vector can be used to generate a subject recombinant AAV virion, as described above. Thus, the present disclosure provides a recombinant AAV vector that,

when introduced into a suitable cell, can provide for production of a subject recombinant AAV virion.

[00238] The present invention further provides host cells, e.g., isolated (genetically modified) host cells, comprising a subject nucleic acid. A subject host cell can be an isolated cell, e.g., a cell in *in vitro* culture. A subject host cell is useful for producing a subject rAAV virion, as described below. Where a subject host cell is used to produce a subject rAAV virion, it is referred to as a "packaging cell." In some embodiments, a subject host cell is stably genetically modified with a subject nucleic acid. In other embodiments, a subject host cell is transiently genetically modified with a subject nucleic acid.

[00239] A subject nucleic acid is introduced stably or transiently into a host cell, using established techniques, including, but not limited to, electroporation, calcium phosphate precipitation, liposome-mediated transfection, and the like. For stable transformation, a subject nucleic acid will generally further include a selectable marker, e.g., any of several well-known selectable markers such as neomycin resistance, and the like.

[00240] A subject host cell is generated by introducing a subject nucleic acid into any of a variety of cells, e.g., mammalian cells, including, e.g., murine cells, and primate cells (e.g., human cells). Suitable mammalian cells include, but are not limited to, primary cells and cell lines, where suitable cell lines include, but are not limited to, 293 cells, 293T cells, COS cells, HeLa cells, Vero cells, 3T3 mouse fibroblasts, C3H10T1/2 fibroblasts, CHO cells, and the like. Non-limiting examples of suitable host cells include, e.g., HeLa cells (e.g., American Type Culture Collection (ATCC) No. CCL-2), CHO cells (e.g., ATCC Nos. CRL9618, CCL61, CRL9096), 293 cells (e.g., ATCC No. CRL-1573), Vero cells, NIH 3T3 cells (e.g., ATCC No. CRL-1658), Huh-7 cells, BHK cells (e.g., ATCC No. CCL10), PC12 cells (ATCC No. CRL1721), COS cells, COS-7 cells (ATCC No. CRL1651), RAT1 cells, mouse L cells (ATCC No. CCLI.3), human embryonic kidney (HEK) cells (ATCC No. CRL1573), HLHepG2 cells, and the like. A subject host cell can also be made using a baculovirus to infect insect cells such as Sf9 cells, which produce AAV (see, e.g., U.S. Patent No. 7,271,002; US patent application 12/297,958)

[00241] In some embodiments, a subject genetically modified host cell includes, in addition to a nucleic acid comprising a nucleotide sequence encoding a variant AAV capsid protein, as described above, a nucleic acid that comprises a nucleotide sequence encoding one or more AAV rep proteins. In other embodiments, a subject host cell further comprises an rAAV vector. An rAAV virion can be generated using a subject host cell. Methods of generating an rAAV virion are described in, e.g., U.S. Patent Publication No. 2005/0053922 and U.S. Patent Publication No. 2009/0202490.

Examples of Non-Limiting Aspects of the Disclosure

[00242] Aspects, including embodiments, of the present subject matter described above may be beneficial alone or in combination, with one or more other aspects or embodiments. Without limiting the foregoing description, certain non-limiting aspects of the disclosure numbered 1-63 are provided below. As will be apparent to those of skill in the art upon reading this disclosure, each of the individually numbered aspects may be used or combined with any of the preceding or following individually numbered aspects. This is intended to provide support for all such combinations of aspects and is not limited to combinations of aspects explicitly provided below:

[00243] Aspect 1. A recombinant adeno-associated virus (rAAV) virion comprising: a) a variant AAV capsid protein , wherein the variant AAV capsid protein comprises an insertion of a heterologous peptide of any one of Formulas I-VI, and wherein the variant capsid protein confers increased infectivity of a retinal cell compared to the infectivity of the retinal cell by a control AAV virion comprising the corresponding parental AAV capsid protein; and b) a heterologous nucleic acid comprising a nucleotide sequence encoding a heterologous gene product.

[00244] Aspect 2. The rAAV virion of aspect 1, wherein the rAAV virion exhibits at least 5-fold increased infectivity of a retinal cell compared to the infectivity of the retinal cell by a control AAV virion comprising the corresponding parental AAV capsid protein.

[00245] Aspect 3. The rAAV virion of aspect 1, wherein the rAAV virion exhibits at least 10-fold increased infectivity of a retinal cell compared to the infectivity of the retinal cell by an AAV virion comprising the corresponding parental AAV capsid protein.

[00246] Aspect 4. The rAAV virion of aspect 1, wherein the insertion of the heterologous peptide replaces a contiguous stretch of from 5 amino acids to 20 amino acids of the parental AAV capsid protein.

[00247] Aspect 5. The rAAV virion of aspect 1, wherein the insertion site is between amino acids corresponding to amino acids 570 and 611 of VP1 of AAV2, or the corresponding position in the capsid protein of another AAV serotype.

[00248] Aspect 6. The rAAV virion of aspect 4, wherein the insertion site is located between amino acids corresponding to amino acids 587 and 588 of VP1 of AAV2, or the corresponding position in the capsid protein of another AAV serotype; or wherein the insertion site is located between amino acids corresponding to amino acids 585 and 598 of VP1 of AAV2, or the corresponding position in the capsid protein of another AAV serotype.

[00249] Aspect 7. The rAAV virion of any one of aspects 1-6, wherein gene product is an interfering RNA or an aptamer.

[00250] Aspect 8. The rAAV virion of any one of aspects 1-6, wherein the gene product is a polypeptide.

[00251] Aspect 9. The rAAV virion of aspect 8, wherein the polypeptide is a neuroprotective polypeptide, an anti-angiogenic polypeptide, or a polypeptide that enhances function of a retinal cell.

[00252] Aspect 10. The rAAV virion of aspect 8, wherein the polypeptide is an RNA-guided endonuclease selected from a type II CRISPR/Cas polypeptide, a type V CRISPR/Cas polypeptide, and a type VI CRISPR/Cas polypeptide.

[00253] Aspect 11. The rAAV virion of aspect 10, wherein the RNA-guided endonuclease is an enzymatically inactive type II CRISPR/Cas polypeptide.

[00254] Aspect 12. The rAAV virion of aspect 10, wherein the gene product is an RNA-guided endonuclease and a guide RNA.

[00255] Aspect 13. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide is a peptide of Formula I: LA(L/N)(I/Q)(Q/E)(D/H)(S/V)(M/K)(R/N)A (SEQ ID NO: 136).

[00256] Aspect 14. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide comprises (21) LALIQDSMRA (SEQ ID NO: 35) or (22) LANQEHVKNA (SEQ ID NO: 2).

[00257] Aspect 15. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide is a peptide of Formula II: $TX_1X_2X_3X_4X_5X_6X_7X_8GLX_9$ (SEQ ID NO: 137), where:

[00258] X_1 is G, V, or S;

[00259] X_2 is V, E, P, G, D, M, A, or S;

[00260] X_3 is M, V, Y, H, G, S, or D;

[00261] X_4 is R, D, S, G, V, Y, T, H, or M;

[00262] X_5 is S, L, G, T, Q, P, or A;

[00263] X_6 is T, A, S, M, D, Q, or H;

[00264] X_7 is N, G, S, L, M, P, G, or A;

[00265] X_8 is S, G, D, N, A, I, P, or T; and

[00266] X_9 is **S** or N.

[00267] Aspect 16. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide comprises: (1) TGVMRSTNSGLN (SEQ ID NO: 6); (2) TGEVDLAGGGLS (SEQ ID No: 7); (3) TSPYSGSSDGLS (SEQ ID NO: 8); (4) TGGHDSSLDGLS (SEQ ID NO: 9); (5) TGDGGTTMNGLS (SEQ ID NO: 98); (6) TGGHGSAPDGLS (SEQ ID NO: 99); (7) TGMHVTMMAGLN (SEQ ID NO: 100); (8) TGASYLDNSGLS (SEQ ID NO: 101); (9)

TVVSTQAGIGLS (SEQ ID NO: 135); (10) TGVMHSQASGLS (SEQ ID NO: 21); (11) TGDGSPAAPGLS (SEQ ID NO: 22); or (12) TGSDMAHGTGLS (SEQ ID NO: 23)

[00268] Aspect 17. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide is a peptide of Formula III: $TGX_1X_2X_3X_4X_5X_6X_7GLS$ (SEQ ID NO: 138), where:

[00269] X_1 is V, E, P, G, D, M, A, or S;

[00270] X_2 is M, V, Y, H, G, S, or D;

[00271] X_3 is R, D, S, G, V, Y, T, H, or M;

[00272] X_4 is S, L, G, T, Q, P, or A;

[00273] X_5 is T, A, S, M, D, Q, or H;

[00274] X_6 is N, G, S, L, M, P, G, or A; and

[00275] X_7 is S, G, D, N, A, I, P, or T.

[00276] Aspect 18. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide comprises: (2) TGEVDLAGGGLS (SEQ ID NO: 7); (4) TGGHDSSLDGLS (SEQ ID NO: 9); (5) TGDGGTTMNGLS (SEQ ID NO: 98); (6) TGGHGSAPDGLS (SEQ ID NO: 99); (8) TGASYLDNSGLS (SEQ ID NO: 101); (10) TGVMHSQASGLS (SEQ ID NO: 21); (11) TGDGSPAAPGLS (SEQ ID NO: 22); or (12) TGSDMAHGTGLS (SEQ ID NO: 23).

[00277] Aspect 19. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide is a peptide of Formula IV: $X_1GX_2X_3X_4X_5X_6X_7X_8GLSPX_9TX_{10}X_{11}$ (SEQ ID NO: 139), where

[00278] X_1 is **T** or N;

[00279] X_2 is L, S,A, or G;

[00280] X_3 is **D** or V;

[00281] X_4 is A, G, or P;

[00282] X_5 is **T** or D;

[00283] X_6 is **R** or Y;

[00284] X_7 is D, T, or G;

[00285] X_8 is H, R, or T;

[00286] X_9 is **V** or A;

[00287] X_{10} is **G** or W; and

[00288] X_{11} is **T** or A.

[00289] Aspect 20. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide comprises: (13) TGLDATRDHGLSPVTGT (SEQ ID NO: 24); (14) TGSDGTRDHGLSPVTWT (SEQ ID NO: 25); (15) NGAVADYTRGLSPATGT (SEQ ID NO: 26); or (16) TGGDPTRGTGLSPVTGA (SEQ ID NO: 27).

[00290] Aspect 21. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide is a peptide of Formula V: $TGX_1DX_2TRX_3X_4GLSPVTGT$ (SEQ ID NO: 140), where

[00291] X_1 is L, S,A, or G;

[00292] X_2 is A, G, or P;

[00293] X_3 is D, T, or G; and

[00294] X_4 is H, R, or T

[00295] Aspect 22. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide is a peptide of Formula VI: $LQX_1X_2X_3RX_4X_5X_6X_7X_8X_9VNX_{10}Q$ (SEQ ID NO: 141), where

[00296] X_1 is K or R;

[00297] X_2 is N, G, or A;

[00298] X_3 is A, V, N, or D;

[00299] X_4 is P, I, or Q;

[00300] X_5 is A, P, or V;

[00301] X_6 is S, T, or G;

[00302] X_7 is T or V;

[00303] X_8 is E, L, A, or V;

[00304] X_9 is S, E, D, or V; and

[00305] X_{10} is F, G, T, or C.

[00306] Aspect 23. The rAAV virion of any one of aspects 1-12, wherein the heterologous peptide comprises: (17) LQKNARPASTESVNFQ (SEQ ID NO: 28); (18) LQRGVRIPSVLEVNGQ (SEQ ID NO: 29); (19) LQRGNRPVTTADVNTQ (SEQ ID NO: 30); or (20) LQKADRQPGVVVVNCQ (SEQ ID NO: 31).

[00307] Aspect 24. A pharmaceutical composition comprising:

[00308] a) a recombinant adeno-associated virus virion of any one of aspects 1-23; and

[00309] b) a pharmaceutically acceptable excipient.

[00310] Aspect 25. A method of delivering a gene product to a retinal cell in an individual, the method comprising administering to the individual a recombinant adeno-associated virus (rAAV) virion according any one of aspects 1-23 or the composition of aspect 24.

[00311] Aspect 26. The method of aspect 25, wherein the gene product is a polypeptide.

[00312] Aspect 27. The method of aspect 25, wherein the gene product is a short interfering RNA or an aptamer.

[00313] Aspect 28. The method of aspect 26, wherein the polypeptide is a neuroprotective factor, an anti-angiogenic polypeptide, an anti-apoptotic factor, or a polypeptide that enhances function of a retinal cell.

[00314] Aspect 29. The method of aspect 26, wherein the polypeptide is glial derived neurotrophic factor, fibroblast growth factor 2, neurturin, ciliary neurotrophic factor, nerve growth factor, brain derived neurotrophic factor, epidermal growth factor, rhodopsin, X-linked inhibitor of apoptosis, retinoschisin, RPE65, retinitis pigmentosa GTPase-interacting protein-1, peripherin, peripherin-2, a rhodopsin, RdCVF, retinitis pigmentosa GTPase regulator (RPGR), or Sonic hedgehog.

[00315] Aspect 30. The method of aspect 26, wherein the polypeptide is an RNA-guided endonuclease.

[00316] Aspect 31. A method of treating an ocular disease, the method comprising administering to an individual in need thereof an effective amount of a recombinant adeno-associated virus (rAAV) virion according to any one of aspects 1-23 or the composition of aspect 24.

[00317] Aspect 32. The method of aspect 31, wherein said administering is by intraocular injection.

[00318] Aspect 33. The method of aspect 31, wherein said administering is by intravitreal injection or by suprachoroidal injection.

[00319] Aspect 34. The method of any one of aspects 31-33, wherein the ocular disease is glaucoma, retinitis pigmentosa, macular degeneration, retinoschisis, Leber's Congenital Amaurosis, diabetic retinopathy, achromotopsia, or color blindness.

[00320] Aspect 35. An isolated nucleic acid comprising a nucleotide sequence that encodes a variant adeno-associated virus (AAV) capsid protein, wherein the variant AAV capsid protein comprises an insertion of from about 5 amino acids to about 20 amino acids in the capsid protein GH loop relative to a corresponding parental AAV capsid protein, and wherein the variant capsid protein, when present in an AAV virion, provides for increased infectivity of the AAV virion of a retinal cell, and wherein the amino acid insertion is in the GH loop of a native AAV capsid, wherein the insertion is a peptide of any one of Formulas I-VI.

[00321] Aspect 36. The isolated nucleic acid of aspect 35, wherein the insertion site is between amino acids 587 and 588 of AAV2, between amino acids 585 and 598 of AAV2, between amino acids 590 and 591 of AAV1, between amino acids 575 and 576 of AAV5, between amino acids 590 and 591 of AAV6, between amino acids 589 and 590 of AAV7, between amino acids 590 and 591 of AAV8, between amino acids 588 and 589 of AAV9, or between amino acids 588 and 589 of AAV10.

[00322] Aspect 37. An isolated, genetically modified host cell comprising the nucleic acid of aspect 35 or aspect 36.

[00323] Aspect 38. A variant adeno-associated virus (AAV) capsid protein, wherein the variant AAV capsid protein comprises an insertion of from about 5 amino acids to about 20 amino acids wherein the amino acid insertion is in the GH loop of a native AAV capsid, wherein the insertion is a peptide of any one of Formulas I-VI.

[00324] Aspect 39. A recombinant adeno-associated virus (rAAV) virion comprising:

[00325] a) a variant AAV capsid protein, wherein the variant AAV capsid protein comprises an insertion of a heterologous peptide of Formula VI, and wherein the variant capsid protein confers increased infectivity of a retinal cell compared to the infectivity of the retinal cell by a control AAV virion comprising the corresponding parental AAV capsid protein; and

[00326] b) a heterologous nucleic acid comprising a nucleotide sequence encoding a heterologous gene product.

[00327] Aspect 40. The rAAV virion of aspect 39, wherein the rAAV virion exhibits at least 5-fold increased infectivity of a retinal cell compared to the infectivity of the retinal cell by a control AAV virion comprising the corresponding parental AAV capsid protein.

[00328] Aspect 41. The rAAV virion of aspect 39, wherein the rAAV virion exhibits at least 10-fold increased infectivity of a retinal cell compared to the infectivity of the retinal cell by an AAV virion comprising the corresponding parental AAV capsid protein.

[00329] Aspect 42. The rAAV virion of any one of aspects 39-41, wherein the insertion of the heterologous peptide replaces a contiguous stretch of from 5 amino acids to 20 amino acids of the parental AAV capsid protein.

[00330] Aspect 43. The rAAV virion of any one of aspects 39-42, wherein the insertion site is between amino acids corresponding to amino acids 570 and 611 of VP1 of AAV2, or the corresponding position in the capsid protein of another AAV serotype.

[00331] Aspect 44. The rAAV virion of aspect 43, wherein the insertion site is located between amino acids corresponding to amino acids 587 and 588 of VP1 of AAV2, or the corresponding position in the capsid protein of another AAV serotype; or wherein the insertion site is located between amino acids corresponding to amino acids 585 and 598 of VP1 of AAV2, or the corresponding position in the capsid protein of another AAV serotype.

[00332] Aspect 45. The rAAV virion of any one of aspects 39-44, wherein gene product is an interfering RNA.

[00333] Aspect 46. The rAAV virion of any one of aspects 39-44, wherein gene product is an aptamer.

[00334] Aspect 47. The rAAV virion of any one of aspects 39-44, wherein the gene product is a polypeptide.

[00335] Aspect 48. The rAAV virion of aspect 47, wherein the polypeptide is a neuroprotective polypeptide, an anti-angiogenic polypeptide, or a polypeptide that enhances function of a retinal cell.

[00336] Aspect 49. The rAAV virion of aspect 47, wherein the polypeptide is an RNA-guided endonuclease selected from a type II CRISPR/Cas polypeptide, a type V CRISPR/Cas polypeptide, and a type VI CRISPR/Cas polypeptide.

[00337] Aspect 50. The rAAV virion of aspect 49, wherein the RNA-guided endonuclease is an enzymatically inactive type II CRISPR/Cas polypeptide.

[00338] Aspect 51. The rAAV virion of one of aspects 39-44, wherein the gene product is an RNA-guided endonuclease and a guide RNA.

[00339] Aspect 52. The rAAV virion of any one of aspects 39-51, wherein the heterologous peptide comprises: (17) LQKNARPASTESVNFQ (SEQ ID NO: 28); (18) LQRGVRIPSVLEVNGQ (SEQ ID NO: 29); (19) LQRGNRPVTTADVNTQ (SEQ ID NO: 30); or (20) LQKADRQPGVVVVNCQ (SEQ ID NO: 31).

[00340] Aspect 53. A pharmaceutical composition comprising:

[00341] a) a recombinant adeno-associated virus virion of any one of aspects 39-52; and

[00342] b) a pharmaceutically acceptable excipient.

[00343] Aspect 54. A method of delivering a gene product to a retinal cell in an individual, the method comprising administering to the individual a recombinant adeno-associated virus (rAAV) virion according any one of aspects 39-52 or the composition of aspect 53.

[00344] Aspect 55. The method of aspect 54, wherein the gene product is a polypeptide.

[00345] Aspect 56. The method of aspect 54, wherein the gene product is a short interfering RNA or an aptamer.

[00346] Aspect 57. The method of aspect 55, wherein the polypeptide is a neuroprotective factor, an anti-angiogenic polypeptide, an anti-apoptotic factor, or a polypeptide that enhances function of a retinal cell.

[00347] Aspect 58. The method of aspect 57, wherein the polypeptide is glial derived neurotrophic factor, fibroblast growth factor 2, neurturin, ciliary neurotrophic factor, nerve growth factor, brain derived neurotrophic factor, epidermal growth factor, rhodopsin, X-linked inhibitor of apoptosis, retinoschisin, RPE65, retinitis pigmentosa GTPase-interacting protein-1, peripherin, peripherin-2, a rhodopsin, RdCVF, retinitis pigmentosa GTPase regulator (RPGR), or Sonic hedgehog.

[00348] Aspect 59. The method of aspect 55, wherein the polypeptide is an RNA-guided endonuclease.

[00349] Aspect 60. A method of treating an ocular disease, the method comprising administering to an individual in need thereof an effective amount of a recombinant adeno-associated virus (rAAV) virion according to any one of aspects 39-52 or the composition of aspect 53.

[00350] Aspect 61. The method of aspect 60, wherein said administering is by intraocular injection.

[00351] Aspect 62. The method of aspect 60, wherein said administering is by intravitreal injection or by suprachoroidal injection.

[00352] Aspect 63. The method of any one of aspects 60-62, wherein the ocular disease is glaucoma, retinitis pigmentosa, macular degeneration, retinoschisis, Leber's Congenital Amaurosis, diabetic retinopathy, achromotopsia, or color blindness.

EXAMPLES

[00353] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric. Standard abbreviations may be used, e.g., bp, base pair(s); kb, kilobase(s); pl, picoliter(s); s or sec, second(s); min, minute(s); h or hr, hour(s); aa, amino acid(s); kb, kilobase(s); bp, base pair(s); nt, nucleotide(s); i.m., intramuscular(ly); i.p., intraperitoneal(ly); s.c., subcutaneous(ly); and the like.

Example 1: AAV virions comprising variant AAV capsids

[00354] A number of variants of AAV capsids were derived through a directed evolution approach; AAV virions comprising the variant AAV capsids infect the primate retina, e.g., when administered via intravitreal injection. Primates are an important preclinical model for human retinal disease, with a fovea for high acuity vision, similar to humans.

AAV packaging

[00355] AAV virions comprising variant AAV capsids were identified by screening. Five libraries were used for this screen: 1) a 7mer peptide display library based on AAV2, containing

a 7mer peptide insertion at amino acid ~588, and surrounded by a 5' LA linker and a 3'A linker; 2) a 7mer peptide display library based on AAV4, with a 7mer peptide insertion at amino acid ~584, with a 5'TG linker and a 3'GLS linker; 3) a 7mer peptide display library based on AAV5 with a 7mer peptide insertion at amino acid ~575 with 5'TG linker and a 3'GLS linker; 4) a library based on an ancestral AAV sequence (Santiago-Ortiz et al., 2015) and containing a 7mer peptide display library at position amino acid ~591 with a 5'TG linker and a 3'GLS linker; and 5) an AAV2-based library with semi-random mutations at surface exposed position amino acid ~588 (Koerber, Jang, & Schaffer, 2008). Virus was packaged such that each viral genome was encapsidated within the capsid protein shell that that genome encoded, as previously described Koerber et al. (2008) *supra*; Fowler et al. *Nat Protoc* **9**, 2267–2284 (2014). Therefore functional improvements identified through selection can be linked to the genome sequence contained within the viral capsid. Briefly, AAV vectors were produced by triple transient transfection of HEK293T cells, purified via iodixanol density centrifugation, and buffer exchanged into PBS by Amicon filtration. DNase-resistant viral genomic titers were measured by quantitative real time PCR using a BioRad iCycler. From this library, an iterative *in vivo* screening selection process was used to identify variants with the ability to infect the primate retina from the vitreous (FIG. 1). Primate eyes were injected in each round with ~250 µL of 1 x 10^13 (1E13) – 1 x 10^14 (1E14) vg/mL titer virus. Three weeks after injection, eyes were enucleated, and retinal punches were taken from central and peripheral regions of the retina (FIG.1). DNA from various retinal layers was assayed, and the capsid inserts were identified. After each round of injection, capsid sequences were recovered by PCR from harvested cells using primers HindIII_F1 and NotI_R1, AscI_R1, or SpeI_R1, with reverse primers being specific to unique AAV backbones, in order to maintain separation of groups of libraries. PCR amplicons were then digested, and recloned into the backbone. RPE cells were separated from retinal tissue, and tissue was frozen. Retinal tissue was embedded and sectioned on a cryostat to isolate photoreceptors in the outer nuclear layer. DNA was then collected from the isolated photoreceptors or RPE, and cap genes were PCR amplified. Recovered cap genes were used for subsequent AAV packaging.

[00356] FIG. 1. Illustration of the directed evolution methodology used to develop primate retinal AAV variants. Peptide display libraries were created, packaged into AAV vectors, and injected into the primate eye via intravitreal injections. Iterative round of selection were used to positively select AAV variants from the pool of vectors. Three rounds of selection were followed by a round of error prone PCR, followed by additional selection rounds.

Deep sequencing of AAV libraries from rounds of selection

[00357] Following 5 rounds of selection, Illumina deep sequencing was used to identify variants that increased over the rounds in relative representation in the library of AAV variants. An

increase of representation in the viral library indicates positive selection and ability to infect the primate retina from the vitreous. A ~75-85 base pair region containing the 7mer insertion or Loop Swap mutation site was PCR amplified from harvested DNA. Primers included Illumina adapter sequences containing unique barcodes to allow for multiplexing of amplicons from multiple rounds of selection. PCR amplicons were purified and sequenced with a 100-cycle single-read run on an Illumina HiSeq 2500. Custom Python code was written to translate DNA sequences into amino acid sequences, and to identify and count reads containing unique 7mer insert sequences. Read counts were normalized by the total number of reads in the run. Python and Pandas were used to analyze dynamics of directed evolution and create plots.

Deep sequencing analysis

[00358] Out of a library of ~1 x 10^7 (~1E7) variants per library, top variants were selected. Best performing variants were chosen as ones with the greatest fold increase in the final round of selection relative to the initial plasmid library (# reads in final round, normalized to total number of reads in the round / # of reads in library, normalized to total number of reads in the round). A pseudo-count of 1 was added before normalization to each individual variant to allow analysis of variants not appearing in sequencing of the plasmid library. Fowler et al. (2014) *supra*. Amino acid sequences of the peptide insertions are shown in FIG. 2.

[00359] The variants generated through this approach enable non-invasive panretinal gene therapy strategies in the primate retina using intravitreal injections. These AAV vectors can be used for gene augmentation therapies for retinal degenerative diseases including retinitis pigmentosa, Leber Congenital Amaurosis, Rod-cone dystrophy, cone dystrophy, achromatopsia, X-linked retinoschisis, CRB1, optogenetic therapies, expression of trophic and survival factors such as GDNF, BDNF, FGF, RdCVF, RdCVFL, XIAP, and expression of blockers of neovascularization such as sFLT. The vectors can also be used to deliver gene editing tools such as CRISPR/Cas9 for gene correction or the creation of additional models of retinal disease.

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Example 2: Methods for construction and sequencing of GFP-barcode libraries

GFP barcode library construction

[00360] Unique 25 bp DNA barcodes were cloned behind an AAV ITR construct containing a self-complementary CAG promoter driving eGFP (CAG-GFP-Barcode-pA). Individual variants were packaged separately with constructs containing different barcodes. Variants were then titer matched and mixed in equal ratios before injection into mice, dogs, and primates.

Deep sequencing of GFP-barcode libraries

[00361] Barcodes were PCR amplified directly from DNA or cDNA (created from mRNA using Superscript III reverse transcriptase), which was harvested from dog or primate retinal tissue. Samples were collected from areas across the retina, and from ONL or RPE. Primers amplified a ~50 bp region surrounding the GFP barcode and contained Illumina adapter sequences and secondary barcodes to allow for multiplexing of multiple samples. PCR amplicons were purified and sequenced with a 100-cycle single-read run on a MiSeq. Read counts were normalized by total number of reads in the run. Analysis of barcode abundance was performed using custom code written in Python, followed by creation of plots in Pandas. Best performing variants were selected based on the fold increase in the percent of total library, relative to the injected library (% of total in recovered sample / % of total in injected library). Analysis was performed on n=1 primate.

[00362] FIG. 9 provides Table 1; FIG. 10 provides Table 2.

[00363] Table 1 provides a ranking of primate-derived variants and controls recovered from photoreceptors following injection of a GFP-Barcode library. Table 2 provides a ranking of primate-derived variants and controls recovered from RPE cells following injection of a GFP-Barcode library. The library contained individual variants packaged with GFP fused to a unique

DNA barcode. Polymerase chain reaction (PCR) was used to amplify barcodes from DNA recovered from specific cell types in the retina. "Region" in Tables 1 and 2 indicates the region from which the DNA was recovered. The fold increase of reads of each of the variants was calculated by dividing number of reads for each unique barcode in the recovered cells (corresponding to each unique variant), by the number of reads for each variant in the injected library. This table indicates the average of the fold increase across multiple locations in the retina. Variants were ranked by fold increase of the barcode.

[00364] FIG. 11. GFP expression of GFP-barcoded libraries in primate retina. GFP expression resulting from intravitreal injection of pooled, GFP-barcoded library (which contains all the tested viruses) was located primarily in the outer retina, with a tropism that was directed more toward the outer retina than expression of AAV24YF.

Example 3

Primate studies

[00365] Cynomolgous monkeys between 4-10 years old were used for all studies, and intravitreal injections were made. The monkey used for fluorophore expression received daily subcutaneous injections of cyclosporine at a dose of 6 mg/kg for immune suppression, and adjusted based on blood trough levels to within a 150-200 ng/ml target range. Confocal scanning laser ophthalmoscopic images (Spectralis HRA, Heidelberg Engineering) were obtained from the two retinas at 3 weeks after injection, with autofluorescence settings, which leads to effective tdTomato and GFP visualization. For histology, the monkey was euthanized, both retinas were lightly fixed in 4% paraformaldehyde, and tissue was examined by confocal microscopy. At the conclusion of the experiment, euthanasia was achieved by administering an IV overdose of sodium pentobarbital (75 mg kg−1), as recommended by the Panel on Euthanasia of the American Veterinary Medical Association. Pieces of primate retina were then prepared in 30% sucrose, embedded in OCT media, flash frozen, and sectioned at 20 μm for confocal microscopy imaging of native fluorophore expression. Antibodies for labeling were: anti-GFP (A11122, Thermo, 1:250) anti-vimentin (Dako, 1:1000), peanut agglutinin (PNA) (Molecular Probes, 1:200), and anti-cone arrestin (7G6, 1:50). The procedures were conducted according to the ARVO Statement for the Use of Animals and the guidelines of the Office of Laboratory Animal Care at the University of Rochester.

RESULTS

Directed evolution of AAV in primate retina

[00366] In addition to canine, the nonhuman primate is a critical preclinical model for human therapeutic development, as it is most closely related to, and has a retinal anatomy similar to that of humans. In particular, primates are the only large animal model that possesses a fovea, the

specialized high acuity area of the retina that is most important for daily activities such as reading, is critical to quality of life, and is lost in numerous retinal degenerations. The species specificity observed in the canine study motivated us to pursue an additional course of directed evolution in primate retina. Nine libraries were packaged and included in the primate screen: EP2, EP5, EP6, EP8, EP9, EP-Ancestral, AAV2-7mer, Ancestral-7mer (Santiago-Ortiz et al. *Gene Ther* **22**, 934–946 (2015)) and LoopSwap (Koerber et al. *Mol Ther* **17**, 2088–2095 (2009)). Libraries were injected, harvested, and repackaged for 5 sequential rounds of selection, with one round of error prone PCR performed after round 3. AAV cap genes were PCR amplified from ONL, and in parallel from overlying RPE. EP libraries were abandoned at round 3, as no variants from these libraries were recovered from retinal tissue. At round 4, additional libraries (AAV4-7mer and AAV5-7mer) were added to the selection, using a separate backbone that was isolated from other libraries by separate PCR annealing sites and restriction sites.

[00367] Deep sequencing revealed that, similar to observations from the canine screen, libraries contained ~1E+6 - ~1E+7 individual variants, which converged to ~1E+4 - ~1E+5 variants over 6 rounds of selection, a diversity not possible to observe through Sanger sequencing (Fig. 12A). As observed in the canine screen, in each of the libraries analyzed, a small portion of library members were over-represented in the initial plasmid library (Fig. 12B). Analysis of results from high throughput sequencing over the rounds of selection revealed, for each of the libraries, a subset of variants that increased significantly in their representation during rounds of selection (Fig. 12C).

Secondary barcoded-GFP library screening in primate retina

[00368] Sixteen variants, from these 5 libraries (Fig. 12C), were selected to be included in a secondary round of selection with GFP-barcoded libraries, along with AAV2, AAV2-4YF+TV, AAV4 and AAV5 as controls. This new library was injected in both eyes of a primate, and 3 weeks after injection, biopsies were collected from locations across the retina (Fig. 12D). GFP expression resulting from injection of the GFP-barcode libraries was primarily found in photoreceptors, as well as some inner retinal cells, a tropism that is shifted from AAV2 or 7m8, which yielded stronger inner retinal expression (Fig. 12E).

[00369] **Fig. 12A-12F. Directed evolution of AAV in primate retina. (A)** Deep sequencing of variant libraries revealed convergence of variants over rounds of selection. **(B)** In each of the libraries evaluated, a small proportion of variants are overrepresented in the plasmid library. **(C)** Scatterplots illustrate the behavior of individual variants at the final round of selection for each of the libraries injected in primate retinas. Variants overrepresented in the original library are colored blue. Variants that had the greatest fold increase in representation in the final round of selection are shown in magenta. Variants that were overrepresented in the original library and

increased significantly in representation over rounds of selection are colored orange. **(D)** A map of the primate retina shows the distribution of samples that were collected for rounds of selection and the GFP-barcode library. Color coding of variants is the same as in Fig. 2. **(E)** GFP expression resulting from the barcoded library revealed that expression was shifted to an outer retinal tropism in selected variants**. (F)** GFP-barcode library injection results, for primate outer retina. The lists of variants are ordered from best (top) to worst (bottom) performing vectors, along with a value indicating the extent to which the variant competed with other vectors, expressed as: % of total in AAV library / % of total in recovered library.

Validation of the top-performing primate variants

[00370] Quantification of vector performance in outer retina revealed that AAV2-based variants outperformed viruses based on other serotypes. One vector, Loop Swap variant AAV2 588~LQRGVRIPSVLEVNGQ (SEQ ID NO:116), outperformed other variants, though it yielded lower viral titers (~5E+11 vg/mL).

[00371] AAV2-LALIQDSMRA (SEQ ID NO:117; designated NHP#9), the second ranking variant from the GFP-barcode screen, which packaged at high titers (~5E+13 vg/mL), was therefore selected for a first round of validation studies focusing on ganglion cells of the inner retina and cones of the outer retina. Cone photoreceptors are involved in adult macular degeneration (AMD), the most common cause of blindness in developed countries that are predicted to affect 288 million people worldwide by the year 2040, and are therefore a primary target for retinal gene therapy. NHP#9 was packaged with an SNCG promoter driving tdTomato in RGCs and the pR1.7 promoter driving expression of GFP in cones. Vectors encoding both these constructs were mixed in equal ratios (~1.5E+12 vg/construct/eye, and injected intravitreally in a cynomolgous monkey. A previously described variant, 7m8 (Dalkara et al. (2013) *supra*), packaged with equal titers of the same constructs was injected into the vitreous of the contralateral eye. Expression of tdTomato reporter in RGC's was lower in NHP#9-injected eyes compared to 7m8, which infected ganglion cells across the expanse of the retina efficiently; however, expression in foveal cones was greatly increased relative to 7m8, indicating a shift in tropism away from the inner retina towards photoreceptors in the outer retina. qRT-PCR, performed using the ddCT method, revealed an 11.71 (10.37 - 13.22) fold increase of GFP expression in foveal cones relative to 7m8. Counting of labeled cells, performed with Imaris software on images collected from flatmounted retinas, also confirmed a substantial decrease in numbers of transduced ganglion cells and an increase in the number of cones targeted with NHP#9.

[00372] Next, the top-ranking variant from the GFP barcode screen, Loopswap variant ~588-LQRGVRIPSVLEVNGQ (SEQ ID NO:118; designated NHP#26) was also tested for validation,

although low numbers of viral particles were produced. ~5E+10 particles of NHP#26-scCAG-eGFP were injected intravitreally into one eye of a cynomolgous monkey. Although the number of particles injected was low, efficient expression of GFP was observed in the fovea and across the retina (Fig. 13G). In contrast to the foveal-spot-and-ring pattern of expression that was observed with 7m8, NHP#9 (Fig 13A), and other naturally occurring serotypes, fundus imaging of NHP#26 resulted in a disc of GFP expression centered on the foveola (Fig. 13G). Confocal imaging of the flatmounted retina confirmed this disc pattern of expression around the fovea (Fig. 13H), with very few GFP positive ganglion cell axons. Punctate regions of GFP expression were often strongest around retinal blood vessels (Fig. 13I), and were located across the expanse of the retina. Imaging of cryostat sections taken from the retina confirmed that there was little GFP expression in ganglion cells, as indicated by the lack of GFP+ ganglion cell axons, while high levels of GFP expression were found in Müller cells, additional cells in the inner nuclear layer, foveal cones and rods across the retina (Fig. 13J-13Q).

[00373] Fig. 13A-13Q. Validation of evolved AAV variants in primate retina. (A-F) Co-injection of ~1.5E+12 particles of SCNG-tdTomato and ~1.5E+12 pR1.7-eGFP packaged in 7m8 and variant NHP#9 in primate retina. Intravitreal injection of 7m8 (A,C,E) resulted in robust tdTomato expression in ganglion cells and expression of GFP in foveal cones. In contrast, injection of equal number of particles of NHP#9 resulted in reduced ganglion cell expression, and increased GFP expression in cones relative to 7m8 (B,D,F). (G) Fundus imaging in a primate eye following injection of 5E+10 particles of NHP#26-scCAG-GFP resulted in a disc of GFP expression centered on the fovea, and a punctate pattern of GFP expression across the retina. (H) Confocal imaging of native GFP expression in the flatmounted fovea. (I) Confocal imaging of native GFP expression in the area outside of the vascular arcade. (J) Confocal imaging of native GFP expression in a cryostat section through the fovea. (K) Native GFP expression in inferior retina, outside the vascular arcade, shows little GFP expression in ganglion cells, but high levels of expression in Müller cells and in photoreceptors in outer retina. Autofluorescence was also observed in RPE. (L) Anti-GFP labeling in a cryostat section revealed GFP expression in photoreceptors, evident by their outer segments, Müller cells, evident by their retina-spanning processes, as well as cells in the inner nuclear layer with horizontal processes that are likely interneurons. (M) Anti-GFP labeling in a foveal section reveals additional transfected cones, Müller glia and interneurons. (N) Co-labeling with anti-cone arrestin and anti-GFP reveals GFP expression in rod photoreceptors, as well as cells in the inner nuclear layer, in a section taken next to the optic nerve head. (O) Co-labeling with anti-cone arrestin and anti-GFP antibodies in an area of low expression reveals GFP expression in inner nuclear layer cells. (P,Q) Montages of

confocal images from cryostat sections collected outside the vascular arcade show efficient expression of GFP in the inner nuclear layer and outer retina.

[00374] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

[00375] Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

[00376] Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each of the appended claims.

CLAIMS

What is claimed is:

1. A recombinant adeno-associated virus (rAAV) virion comprising:

a) a variant AAV capsid protein, wherein the variant AAV capsid protein comprises an insertion of a heterologous peptide comprising the amino acid sequence LALIQDSMRA (SEQ ID NO: 35) in the GH loop of VP1 of AAV2 or of another AAV serotype; and

b) a heterologous nucleic acid comprising a nucleotide sequence encoding a heterologous gene product.

2. The rAAV of claim 1, wherein the variant capsid protein confers increased infectivity of a retinal cell compared to the infectivity of the retinal cell by a control AAV comprising the corresponding parental AAV capsid protein.

3. The rAAV virion of claim 2, wherein the rAAV virion exhibits at least 5-fold or at least 10-fold increased infectivity of a retinal cell compared to the infectivity of the retinal cell by a control AAV virion comprising the corresponding parental AAV capsid protein.

4. The rAAV virion of any one of claims 1-3, wherein the insertion of the heterologous peptide replaces a contiguous stretch of from 5 amino acids to 20 amino acids of the parental AAV capsid protein.

5. The rAAV virion of any one of claims 1-4, wherein the insertion site is between amino acids corresponding to amino acids 570 and 611 of VP1 of AAV2.

6. The rAAV virion of any one of claims 1-4, wherein the insertion site is located between amino acids corresponding to amino acids 587 and 588 of VP1 of AAV2, or the corresponding position in the capsid protein of another AAV serotype; or wherein the insertion site is located between amino acids corresponding to amino acids 585 and 598 of VP1 of AAV2, or the corresponding position in the capsid protein of another AAV serotype.

7. The rAAV virion of any one of claims 1-6, wherein gene product is an interfering RNA or an aptamer or a polypeptide.

8. The rAAV virion of claim 7, wherein the gene product is:

(i) a polypeptide, wherein the polypeptide is a neuroprotective polypeptide, an anti-angiogenic polypeptide, a polypeptide that enhances function of a retinal cell, or an RNA-guided endonuclease selected from a type II CRISPR/Cas polypeptide, an enzymatically inactive type II CRISPR/Cas polypeptide, a type V CRISPR/Cas polypeptide, and a type VI CRISPR/Cas polypeptide; or

(ii) wherein the gene product is an RNA-guided endonuclease and a guide RNA.

9. A pharmaceutical composition comprising:

a) a recombinant adeno-associated virus virion of any one of claims 1-8; and

b) a pharmaceutically acceptable excipient.

10. A method of delivering a gene product to a retinal cell in an individual for treating an ocular disease in an individual in need thereof, the method comprising administering to the individual the recombinant adeno-associated virus (rAAV) virion according any one of claims 1-8 or the composition of claim 9.

11. Use of the recombinant adeno-associated virus (rAAV) virion according to any one of claims 1-8 or the composition of claim 9 in the manufacture of a medicament for treating an ocular disease in an individual in need thereof.

12. The method of claim 10 or the use of claim 11, wherein the gene product is a polypeptide and wherein the polypeptide is selected from the group consisting of glial derived neurotrophic factor, fibroblast growth factor 2, neurturin, ciliary neurotrophic factor, nerve growth factor, brain derived neurotrophic factor, epidermal growth factor, rhodopsin, X-linked inhibitor of apoptosis, retinoschisin, RPE65, retinitis pigmentosa GTPase-interacting protein-1,

peripherin, peripherin-2, a rhodopsin, RdCVF, retinitis pigmentosa GTPase regulator (RPGR) or Sonic hedgehog.

13. The method of claim 10 or 12, wherein said administering is by intraocular injection, intravitreal injection or by suprachoroidal injection.

14. The method of any one of claims 10 or 12-13 or the use of claim 11 or 12, wherein the ocular disease is selected from the group consisting of glaucoma, retinitis pigmentosa, macular degeneration, retinoschisis, Leber's Congenital Amaurosis, diabetic retinopathy, achromotopsia or color blindness.

15. A variant adeno-associated virus (AAV) capsid protein, wherein the variant AAV capsid protein comprises an insertion of a heterologous peptide comprising the amino acid sequence LALIQDSMRA (SEQ ID NO: 35) in the GH loop of VP1 of AAV2 or another AAV serotype.

16. The variant AAV capsid protein of claim 15, wherein the insertion site is between amino acids 587 and 588 of AAV2, between amino acids 585 and 598 of AAV2, between amino acids 590 and 591 of AAV1, between amino acids 575 and 576 of AAV5, between amino acids 590 and 591 of AAV6, between amino acids 589 and 590 of AAV7, between amino acids 590 and 591 of AAV8, between amino acids 588 and 589 of AAV9 or between amino acids 588 and 589 of AAV10.

17. An isolated nucleic acid comprising a nucleotide sequence that encodes a variant adeno-associated virus (AAV) capsid protein of any one of claims 15 to 16.

18. An isolated, genetically modified host cell comprising the nucleic acid of claim 17.

FIG. 1

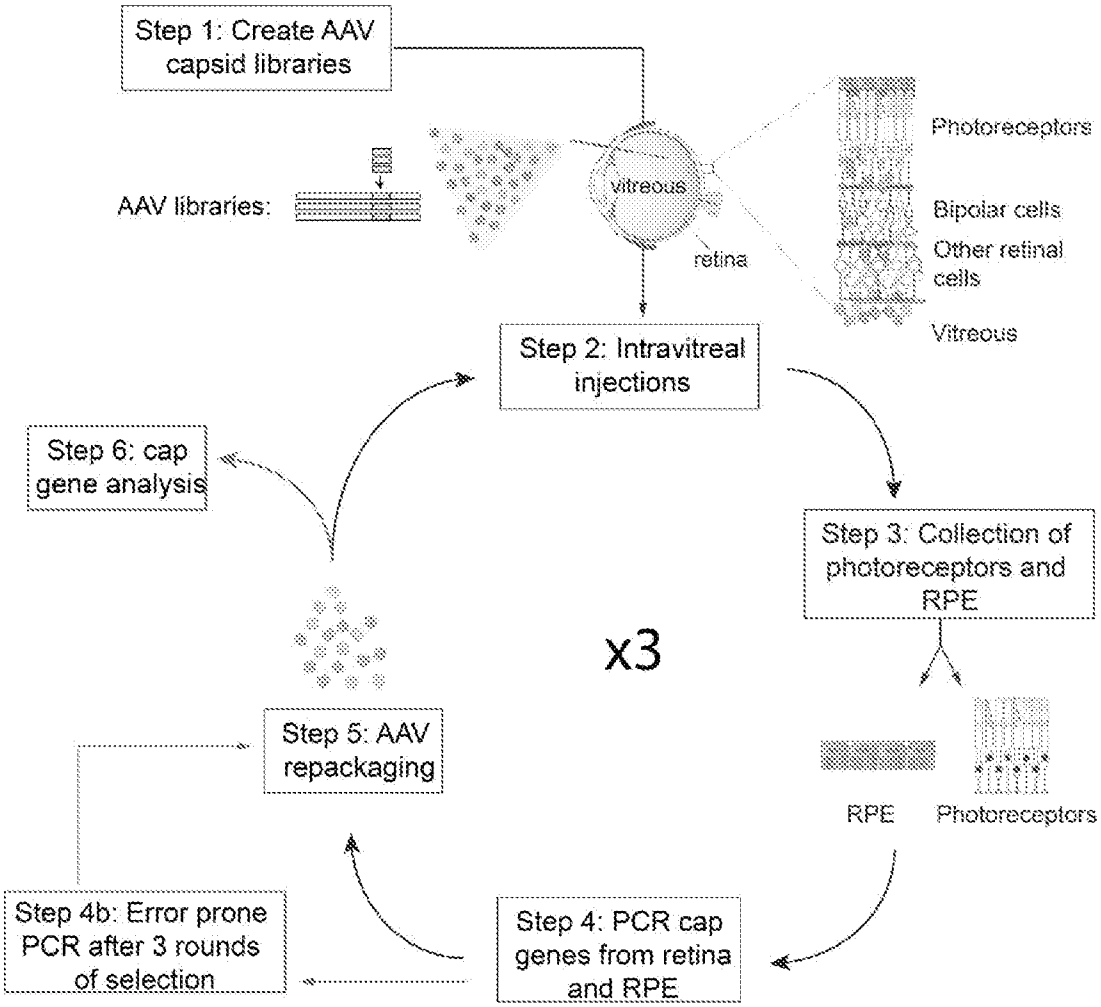

Step 1: Create AAV capsid libraries
AAV libraries:
vitreous
retina
Photoreceptors
Bipolar cells
Other retinal cells
Vitreous
Step 2: Intravitreal injections
Step 3: Collection of photoreceptors and RPE
RPE
Photoreceptors
x3
Step 4: PCR cap genes from retina and RPE
Step 4b: Error prone PCR after 3 rounds of selection
Step 5: AAV repackaging
Step 6: cap gene analysis

FIG. 2

Source library	peptide insertion	Peptide No.	SEQ ID NO:
AAV2-7mer	LALIQDSMRA	21	35
AAV2-7mer	LTHQDTTKNA		4
AAV2-7mer	LANQEHVKNA	22	2
AAV2-7mer	QAHQDTTKNA		5
AAV4-7mer	TGVMRSTNSGLN	1	6
AAV4-7mer	TGEVDLAGGGLS	2	7
AAV4-7mer	TSPYSGSSDGLS	3	8
AAV4-7mer	TGGHDSSLDGLS	4	9
AAV4-7mer	TGDGGTTMNGLS	5	98
AAV4-7mer	TGGHGSAPDGLS	6	99
AAV5-7mer	TGMHVTMMAGLN	7	100
AAV5-7mer	TGASYLDNSGLS	8	101
AAV5-7mer	TVVSTQAGIGLS	9	20
AAV5-7mer	TGVMHSQASGLS	10	21
AAV5-7mer	TGDGSPAAPGLS	11	22
AAV5-7mer	TGSDMAHGTGLS	12	23
Anc-7mer	TGLDATRDHGLSPVTGT	13	24
Anc-7mer	TGSDGTRDHGLSPVTWT	14	25
Anc-7mer	NGAVADYTRGLSPATGT	15	26
Anc-7mer	TGGDPTRGTGLSPVTGA	16	27
LoopSwap588	LQKNARPASTESVNFQ	17	28
LoopSwap588	LQRGVRIPSVLEVNGQ	18	29
LoopSwap588	LQRGNRPVTTADVNTQ	19	30
LoopSwap588	LQKADRQPGVVVVNCQ	20	31

FIG. 3A

Streptococcus pyogenes Cas9

```
   1 mdkkysigld igtnsvgwav itdeykvpsk kfkvlgntdr hsikknliga llfdsgetae
  61 atrlkrtarr rytrrknric ylqeifsnem akvddsffhr leesflveed kkherhpifg
 121 nivdevayhe kyptiyhlrk klvdstdkad lrliylalah mikfrghfli egdlnpdnsd
 181 vdklfiqlvq tynqlfeenp inasgvdaka ilsarlsksr rlenliaqlp gekknglfgn
 241 lialslgltp nfksnfdlae daklqlskdt ydddldnlla qigdqyadlf laaknlsdai
 301 llsdilrvnt eitkaplsas mikrydehhq dltllkalvr qqlpekykei ffdqskngya
 361 gyidggasqe efykfikpil ekmdgteell vklnredllr kqrtfdngsi phqihlgelh
 421 ailrrqedfy pflkdnreki ekiltfripy yvgplargns rfawmtrkse etitpwnfee
 481 vvdkgasaqs fiermtnfdk nlpnekvlpk hsllyeyftv yneltkvkyv tegmrkpafl
 541 sgeqkkaivd llfktnrkvt vkqlkedyfk kiecfdsvei sgvedrfnas lgtyhdllki
 601 ikdkdfldne enediledіv ltltlfedre mieerlktya hlfddkvmkq lkrrrytgwg
 661 rlsrklingi rdkqsgktil dflksdgfan rnfmqlihdd sltfkediqk aqvsgqgdsl
 721 hehianlags paikkgilqt vkvvdelvkv mgrhkpeniv iemarenqtt qkgqknsrer
 781 mkrieegike lgsqilkehp ventqlqnek lylyylqngr dmyvdqeldi nrlsdydvdh
 841 ivpqsflkdd sidnkvltrs dknrgksdnv pseevvkkmk nywrqllnak litqrkfdnl
 901 tkaergglse ldkagfikrq lvetrqitkh vaqildsrmn tkydendkli revkvitlks
 961 klvsdfrkdf qfykvreinn yhhahdayln avvgtalikk ypklesefvy gdykvydvrk
1021 miakseqeig katakyffys nimnffktei tlangeirkr plietngetg eivwdkgrdf
1081 atvrkvlsmp qvnivkktev qtggfskesi lpkrnsdkli arkkdwdpkk yggfdsptva
1141 ysvlvvakve kgkskklksv kellgitime rssfeknpid fleakgykev kkdliiklpk
1201 yslfelengr krmlasagel qkgnelalps kyvnflylas hyeklkgspe dneqkqlfve
1261 qhkhyldeii eqisefskrv iladanldkv lsaynkhrdk pireqaenii hlftltnlga
1321 paafkyfdtt idrkrytstk evldatlihq sitglyetri dlsqlggd (SEQ ID NO: 32)
```

FIG. 3B
Staphylococcus aureus Cas9

```
   1 mkrnyilgld igitsvgygi idyetrdvid agvrlfkean vennegrrsk rgarrlkrrr
  61 rhriqrvkkl lfdynlltdh selsginpye arvkglsqkl seeefsaall hlakrrgvhn
 121 vneveedtgn elstkeqisr nskaleekyv aelqlerlkk dgevrgsinr fktsdyvkea
 181 kqllkvqkay hqldqsfidt yidlletrrt yyegpgegsp fgwkdikewy emlmghctyf
 241 peelrsvkya ynadlynaln dlnnlvitrd enekleyyek fqiienvfkq kkkptlkqia
 301 keilvneedi kgyrvtstgk peftnlkvyh dikditarke iienaelldq iakiltiygs
 361 sediqeeltn lnseltqeei eqisnlkgyt gthnlslkai nlildelwht ndnqiaifnr
 421 lklvpkkvdl sqqkeipttl vddfilspvv krsfiqsikv inaiikkygl pndiiielar
 481 eknskdaqkm inemqkrnrq tnerieeiir ttgkenakyl iekiklhdmq egkclyslea
 541 ipledllnnp fnyevdhiip rsvsfdnsfn nkvlvkqeen skkgnrtpfq ylsssdskis
 601 yetfkkhiln lakgkgrisk tkkeylleer dinrfsvqkd finrnlvdtr yatrglmnll
 661 rsyfrvnnld vkvksinggf tsflrrkwkf kkernkgykh haedalilan adfifkewkk
 721 ldkakkvmen qmfeekqaes mpeietegey keifitphqi khikdfkdyk yshrvdkkpn
 781 relindtlys trkddkgntl ivnnlnglyd kdndklkkli nkspekllmy hhdpqtyqkl
 841 klimeqygde knplykyyee tgnyltkysk kdngpvikki kyygnklnah lditddypns
 901 rnkvvklslk pyrfdvyldn gvykfvtvkn ldvikkenyy evnskcyeea kklkkisnqa
 961 efiasfynnd likingelyr vigvnndlln rievnmnidit yreylenmnd krppriikti
1021 asktqsikky stdilgnlye vkskkhpqii kkg (SEQ ID NO: 33)
```

FIG. 3C
Francisella tularensis Cpf1

```
   1 msiyqefvnk yslsktlrfe lipqgktlen ikarglildd ekrakdykka kqiidkyhqf
  61 fieeilssvc isedllqnys dvyfklkksd ddnlqkdfks akdtikkqis eyikdsekfk
 121 nlfnqnlida kkgqesdlil wlkqskdngi elfkansdit didealeiik sfkgwttyfk
 181 gfhenrknvy ssndiptsii yrivddnlpk flenkakyes lkdkapeain yeqikkdlae
 241 eltfdidykt sevnqrvfsl devfeianfn nylnqsgitk fntiiggkfv ngentkrkgi
 301 neyinlysqq indktlkkyk msvlfkqils dtesksfvid kleddsdvvt tmqsfyeqia
 361 afktveeksi ketlslfdd lkaqkldlsk iyfkndkslt dlsqqvfddy svigtavley
 421 itqqiapknl dnpskkeqel iakktekaky lsletiklal eefnkhrdid kqcrfeeila
 481 nfaaipmifd eiaqnkdnla qisikyqnqg kkdllqasae ddvkaikdll dqtnnllhkl
 541 kifhisqsed kanildkdeh fylvfeecyf elanivplyn kirnyitqkp ysdekfklnf
 601 enstlangwd knkepdntai lfikddkyyl gvmnkknnki fddkaikenk gegykkivyk
 661 llpgankmlp kvffsaksik fynpsedilr irnhsthtkn gspqkgyekf efniedcrkf
 721 idfykqsisk hpewkdfgfr fsdtqrynsi defyrevenq gykltfenis esyidsvvnq
 781 gklylfqiyn kdfsayskgr pnlhtlywka lfdernlqdv vyklngeael fyrkqsipkk
 841 ithpakeaia nknkdnpkke svfeydlikd krftedkfff hcpitinfks sgankfndei
 901 nlllkekand vhilsidrge rhlayytlvd gkgniikqdt fniignderme tnyhdklaai
 961 ekdrdsarkd wkkinnikem kegylsqvvh eiaklvieyn aivvfedlnf gfkrgrfkve
1021 kqvyqklekm lieklnylvf kdnefdktgg vlrayqltap fetfkkmgkq tgiiyyvpag
1081 ftskicpvtg fvnqlypkye svsksqeffs kfdkicynld kgyfefsfdy knfgdkaakg
1141 kwtiasfgsr linfrnsdkn hnwdtrevyp tkelekllkd ysieyghgec ikaaicgesd
1201 kkffakltsv lntilqmrns ktgteldyli spvadvngnf fdsrqapknm pqdadangay
1261 higlkglmll griknnqegk klnlviknee yfefvqnrnn (SEQ ID NO: 34)
```

Figure 4

AAV2 VP1 1 MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLD

AAV2 VP1 61 KGEPVNEADAAALEHDKAYDRQLDSGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ

AAV2 VP1 121 AKKRVLEPLGLVEEPVKTAPGKKRPVEHSPVEPDSSSGTGKAGQQPARKRLNFGQTGDAD

AAV2 VP1 181 SVPDPQPLGQPPAAPSGLGTNTMATGSGAPMADNNEGADGVGNSSGNWHCDSTWMGDRVI

AAV2 VP1 241 TTSTRTWALPTYNNHLYKQISSQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDWQRLI

AAV2 VP1 301 NNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGSAHQG

AAV2 VP1 361 CLPPFPADVFMVPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFTFSYTFEDVPF

AAV2 VP1 421 HSSYAHSQSLDRLMNPLIDQYLYYLSRTNTPSGTTTQSRLQFSQAGASDIRDQSRNWLPG

AAV2 VP1 481 PCYRQQRVSKTSADNNNSEYSWTGATKYHLNGRDSLVNPGPAMASHKDDEEKFFPQSGVL

AAV2 VP1 541 IFGKQGSEKTNVDIEKVMITDEEEIRTTNPVATEQYGSVSTNLQRGNRQAATADVNTQGV

AAV2 VP1 601 LPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPPQILIKNTPVPANPSTT

AAV2 VP1 661 FSAAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYNKSVNVDFTVDTNGVY

AAV2 VP1 721 SEPRPIGTRYLTR (SEQ ID NO:1)

FIG. 5

```
AAV-2      570 PVATEQYGSVSTNLQRGNRQAATADVNTQGVLPGMVWQDRDV 611 (SEQ ID NO: 36)
AAV-1      571 PVATERFGTVAVNFQSSSTDPATGDVHAMGALPGMVWQDRDV 612 (SEQ ID NO: 37)
AAV-5      560 RVAYNVGGQMATNNQSSTTAPATGTYNLQEIVPGSVWMERDV 601 (SEQ ID NO: 38)
AAV-6      571 PVATERFGTVAVNLQSSSTDPATGDVHVMGALPGMVWQDRDV 612 (SEQ ID NO: 39)
AAV-7      572 PVATEEYGIVSSNLQAANTAAQTQVVNNQGALPGMVWQNRDV 613 (SEQ ID NO: 40)
AAV-8      573 PVATEEYGIVADNLQQQNTAPQIGTVNSQGALPGMVWQNRDV 614 (SEQ ID NO: 41)
AAV-9      571 PVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDRDV 612 (SEQ ID NO: 42)
AAV-10     573 PVATEQYGVVADNLQQANTGPIVGNVNSQGALPGMVWQNRDV 614 (SEQ ID NO: 43)
AAV-4      569 ATDTDMWGNLPGGDQSNSNLPTVDRLTALGAVPGMVWQNRDI 610 (SEQ ID NO: 44)
Ancestral  573 PVATEXYGVVAXNLQSSNTAPXTGXVNSQGALPGMVWQNRDV 613 (SEQ ID NO: 45)
```

Figure 6A

```
AAV1            --TFSYTFEEVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQ-NQSGSAQNKDLLFSRGS 467 (SEQ ID NO: 46)
AAV6            --TFSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQ-NQSGSAQNKDLLFSRGS 467 (SEQ ID NO: 47)
AAV3            ---FSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQGTTSGTTNQSRLLFSQAG 467 (SEQ ID NO: 48)
AAV2            ---FSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTN-TPSGTTTQSRLQFSQAG 466 (SEQ ID NO: 49)
AAV8            NFQFTYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQTT-GGTANTQTLGFSQGG 469 (SEQ ID NO: 50)
AAV8.1          NFQFTYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQTT-GGTANTQTLGFSQGG 469 (SEQ ID NO: 51)
AAV8 rh8         FQFSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLVRTQTTGTGGTQTLAFSQAGPS 469 (SEQ ID NO: 52)
AAV10           NFEFSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQST-GGTQGTQQLLFSQAG 469 (SEQ ID NO: 53)
AAV7            -FEFSYSFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLARTQSNPGGTAGNRELQFYQGG 469 (SEQ ID NO: 54)
AAV9            -FQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTI--NGSGQNQQTLKFSVAG 467 (SEQ ID NO: 55)
AAV9.1          -FQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTI--NGSGQNQQTLKFSVAG 467 (SEQ ID NO: 56)
AAV5            NFEFTYNFEEVPFHSSFAPSQNLFKLANPLVDQYLYRFVSTN-------NTGGVQFNKNL 453 (SEQ ID NO: 57)
                   *:* **:******:* **.* :* ***:***** :  *           : *

AAV1            PAGMSVQPKNWLPGPCYRQQRVSKTKTDNNNSNFTWTGASKYNLNGRESIINPGTAMASH 527 (SEQ ID NO: 58)
AAV6            PAGMSVQPKNWLPGPCYRQQRVSKTKTDNNNSNFTWTGASKYNLNGRESIINPGTAMASH 527 (SEQ ID NO: 59)
AAV3            PQSMSLQARNWLPGPCYRQQRLSKTANDNNNSNFPWTAASKYHLNGRDSLVNPGPAMASH 527 (SEQ ID NO: 60)
AAV2            ASDIRDQSRNWLPGPCYRQQRVSKTSADNNNSEYSWTGATKYHLNGRDSLVNPGPAMASH 526 (SEQ ID NO: 61)
AAV8            PNTMANQAKNWLPGPCYRQQRVSTTTGQNNNSNFAWTAGTKYHLNGRNSLANPGIAMATH 529 (SEQ ID NO: 62)
AAV8.1          PNTMANQAKNWLPGPCYRQQRVSTTTGQNNNSNFAWTAGTKYHLNGRNSLANPGIAMATH 529 (SEQ ID NO: 63)
AAV8 rh8        S--MANQARNWVPGPCYRQQRVSTTTNQNNNSNFAWTGAAKFKLNGRDSLMNPGVAMASH 527 (SEQ ID NO: 64)
AAV10           PANMSAQAKNWLPGPCYRQQRVSTTLSQNNNSNFAWTGATKYHLNGRDSLVNPGVAMATH 529 (SEQ ID NO: 65)
AAV7            PSTMAEQAKNWLPGPCFRQQRVSKTLDQNNNSNFAWTGATKYHLNGRNSLVNPGVAMATH 529 (SEQ ID NO: 66)
AAV9            PSNMAVQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASH 527 (SEQ ID NO: 67)
AAV9.1          PSNMAVQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASH 527 (SEQ ID NO: 68)
AAV5            AGRYANTYKNWFPGPMGRTQGWNLGSGVNRASVSAFATTNRMELEGASYQVPPQPNGMTN 513 (SEQ ID NO: 69)
                .       :*::***  * *  .     *. *  .:.  .   *:* .    *     ::
```

Figure 6B

```
AAV1          KDDEDKFFPMSGVMIFGK--ESAGASNTALD-NVMITDEEEIKATNPVATERFGTVAVNF 584 (SEQ ID NO: 70)
AAV6          KDDKDKFFPMSGVMIFGK--ESAGASNTALD-NVMITDEEEIKATNPVATERFGTVAVNL 584 (SEQ ID NO: 71)
AAV3          KDDEEKFFPMHGNLIFGK--EGTTASNAELD-NVMITDEEEIRTTNPVATEQYGTVANNL 584 (SEQ ID NO: 72)
AAV2          KDDEEKFFPQSGVLIFGK--QGSEKTNVDIE-KVMITDEEEIRTTNPVATEQYGSVSTNL 583 (SEQ ID NO: 73)
AAV8          KDDEERFFPSNGILIFGK--QNAARDNADYS-DVMLTSEEEIKTTNPVATEYGIVADNL 586 (SEQ ID NO: 74)
AAV8.1        KDDEERFFPSNGILIFGK--QNAARDNADYS-DVMLTSEEEIKTTNPVATEEYGIVADNL 586 (SEQ ID NO: 75)
AAV8 rh8      KDDDRFFPSSGVLIFGK--QGAGNDGVDYS-QVLITDEEEIKATNPVATEEYGAVAINN 584 (SEQ ID NO: 76)
AAV10         KDDEERFFPSSGVLMFGK--QGAGRDNVDYS-SVMLTSEEEIKTTNPVATEQYGVVADNL 586 (SEQ ID NO: 77)
AAV7          KDDEDRFFPSSGVLIFGK--TGAT-NKTTLE-NVLMTNEEEIRPTNPVATEEYGIVSSNL 585 (SEQ ID NO: 78)
AAV9          KEGEDRFFPLSGSLIFGK--QGTGRDNVDAD-KVMITNEEEIKTTNPVATESYGQVATNH 584 (SEQ ID NO: 79)
AAV9.1        KEGEDRFFPLSGSLIFGK--QGTGRDNVDAD-KVMITNEEEIKTTNPVATESYGQVATNH 584 (SEQ ID NO: 80)
AAV5          NLQGSNTYALENTMIFNSQPANPGTTATYLEGNMLITSESETQPVNRVAYNVGGQMATNN 573 (SEQ ID NO: 81)
              :   .. :.  . ::*..   ..    .  . .:::*.*.* :..* ** :  * :: *

AAV1          QSSSTDPATGDVHAMGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKNPP 644 (SEQ ID NO: 82)
AAV6          QSSSTDPATGDVHVMGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPP 644 (SEQ ID NO: 83)
AAV3          QSSNTAPTTGTVNHQGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPP 644 (SEQ ID NO: 84)
AAV2          QRGNRQAATADVNTQGVLPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPP 643 (SEQ ID NO: 85)
AAV8          QQQNTAPQIGTVNSQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPP 646 (SEQ ID NO: 86)
AAV8.1        QGQRQAAQIGTVNSQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPP 646 (SEQ ID NO: 87)
AAV8 rh8      QAANTQAQTGLVHNQGVIPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPP 644 (SEQ ID NO: 88)
AAV10         QQANTGPIVGNVNSQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPP 646 (SEQ ID NO: 89)
AAV7          QAANTAAQTQVVNNQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPP 645 (SEQ ID NO: 90)
AAV9          QSAQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPP 644 (SEQ ID NO: 91)
AAV9.1        QSGQAQAATGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPP 644 (SEQ ID NO: 92)
AAV5          QSSTTAPATGTYNLQEIVPGSVWMERDVYLQGPIWAKIPETGAHFHPSPAMGGFGLKHPP 633 (SEQ ID NO: 93)
              *     .      :  :** ** :*********************.*..:*****  *****:*:**
```

Figure 6C

```
AAV1          PQILIK- 650 (SEQ ID NO: 94)
AAV6          PQILIK- 650 (SEQ ID NO: 94)
AAV3          PQIMIK- 650 (SEQ ID NO: 95)
AAV2          PQILIKN 650 (SEQ ID NO: 96)
AAV8          PQILIKN 653 (SEQ ID NO: 96)
AAV8.1        PQILIKN 653 (SEQ ID NO: 96)
AAV8 rh8      PQILIKN 651 (SEQ ID NO: 96)
AAV10         PQILIKN 653 (SEQ ID NO: 96)
AAV7          PQILIKN 652 (SEQ ID NO: 96)
AAV9          PQILIK- 650 (SEQ ID NO: 94)
AAV9.1        PQILIK- 650 (SEQ ID NO: 94)
AAV5          PMMLIKN 640 (SEQ ID NO: 97)
              * ::**
```

FIG. 7A
Retinoschisin-1
Homo sapiens

```
  1 msrkiegfll lllfgyeatl glsstedege dpwyqkackc dcqggpnalw sagatsldci
 61 pecpyhkplg fesgevtpdq itcsnpeqyv gwysswtank arlnsqgfgc awlskfqdss
121 qwlqidlkei kvisgiltqg rcdidewmtk ysvqyrtder lnwiyykdqt gnnrvfygns
181 drtstvqnll rppiisrfir liplgwhvri airmellecv skca (SEQ ID NO:10)
```

FIG. 7B
BDNF
Homo sapiens

```
  1 mtilfltmvi syfgcmkaap mkeanirgqg glaypgvrth gtlesvngpk agsrgltsla
 61 dtfehvieel ldedhkvrpn eennkdadly tsrvmlssqv pleppllfll eeyknyldaa
121 nmsmmvlrhs dparrgelsv cdsisewvta adkktavdms ggtvtvlekv pvskgqlkqy
181 fyetkcnpmg ytkegcrgid krhwnsqcrt tqsyvraltm dskkrigwrf iridtscvct
241 ltikrgr (SEQ ID NO:11)
```

FIG. 7C
RPE65
Homo sapiens

```
   1 msiqvehpag gykklfetve elsspltahv tgriplwltg sllrcgpglf evgsepfyhl
  61 fdgqallhkf dfkeghvtyh rrfirtdayv ramtekrivi tefgtcafpd pcknifsrff
 121 syfrgvevtd nalvnvypvg edyyactetn fitkinpetl etikqvdlcn yvsvngatah
 181 phiendgtvy nigncfgknf siaynivkip plqadkedpi skseivvqfp csdrfkpsyv
 241 hsfgltpnyi vfvetpvkin lfkflsswsl wganymdcfe snetmgvwlh iadkkrkkyl
 301 nnkyrtspfn lfhhintyed ngflivdlcc wkgfefvyny lylanlrenw eevkknarka
 361 pqpevrryvl plnidkadtg knlvtlpntt atailcsdet iwlepevlfs gprqafefpq
 421 inyqkycgkp ytyayglgln hfvpdrlckl nvktketwvw qepdsypsep ifvshpdale
 481 eddgvvlsvv vspgaggkpa yllilnakdl sevaraevei nipvtfhglf kks (SEQ ID NO:12)
```

FIG. 7D
Peripherin-2
Homo sapiens

```
   1 mallkvkfdq kkrvklaqgl wlmnwfsvla giiifslglf lkielrkrsd vmnnseshfv
  61 pnsligmgvl scvfnslagk icydaldpak yarwkpwlkp ylaicvlfni illflvalccf
 121 llrgslentl gqglkngmky yrdtdtpgrc fmkktidmlq iefkccgnng frdwfeiqwi
 181 snryldfssk evkdriksnv dgrylvdgvp fsccnpsspr pciqyqitnn sahysydhqt
 241 eelnlwvrgc raallsyyss lmnsmgvvtl liwlfevtit iglrylqtsl dgvsnpeese
 301 sesqgwller svpetwkafl esvkklgkgn qveaegadag qapeag (SEQ ID NO:13)
```

FIG. 7E
Peripherin
Homo sapiens

```
   1 mshhpsglra gfsstsyrrt fgpppslspg afsyssssrf sssrllgsas psssvrlgsf
  61 rspragagal lrlpserldf smaealnqef latrsnekqe lqelndrfan fiekvrfleq
 121 qnaalrgels qargqepara dqlcqqelre lrrelellgr erdrvqverd glaedlaalk
 181 qrleeetrkr edaehnlvlf rkdvddatls rlelerkies lmdeieflkk lheeelrdlq
 241 vsvesqqvqq veveatvkpe ltaalrdira qyesiaaknl qeaeewyksk yadlsdaanr
 301 nhealrqakq emnesrrqiq sltcevdglr qtneallrql releeqfale aggyqagaar
 361 leeelrqlke emarhlreyq ellnvkmald ieiatyrkll egeesrisvp vhsfaslnik
 421 ttvpeveppq dshsrktvli ktietrngev vtesqkeqrs eldkssahsy (SEQ ID NO:14)
```

FIG. 7F
RPGR-interacting protein-1
Homo sapiens

```
   1 mshlvdptsg dlpvrdidai plvlpaskgk nmktqpplsr mnreeledsf frlredhmlv
  61 kelswkqgde ikrlrttllr ltaagrdlrv aeeaaplset arrgqkagwr qrlsmhqrpq
 121 mhrlqghfhc vgpasprraq prvqvghrql htagapvpek pkrgprdrls ytappsfkeh
 181 atnenrgeva skpselvsgs nsiisfssvi smakpiglcm pnsahimasn tmqveeppks
 241 pekmwpkden feqrssleca qkaaelrasi kekvelirlk kllhernasl vmtkaqltev
 301 qeayetllqk nqgilsaahe allkqvnelr aelkeeskka vslksqledv silqmtlkef
 361 qervedleke rkllndnydk llesmldssd sssqphwsne liaeqlqqqv sqlqdqldae
 421 ledkrkvlle lsrekaqned lklevtnilq khkqevellq naatisqppd rqsepathpa
 481 vlqentqiep sepknqeekk lsqvlnelqv shaettlele ktrdmlilqr kinvcyqeel
 541 eammtkadnd nrdhkekler ltrlldlknn rikqlegilr shdlptseql kdvaygtrpl
 601 slcletlpah gdedkvdisl lhqgenlfel hihqafltsa alaqagdtqp ttfctysfyd
 661 fethctplsv qpqplydfts qyvmetdslf lhylqeasar ldihqamase hstlaagwic
 721 fdrvletvek vhglatliga ggeefgvley wmrlrfpikp slqacnkrkk aqvylstdvl
 781 ggrkaqeeef rseswepqne lwieitkccg lrsrwlgtqp spyavyrfft fsdhdtaiip
 841 asnnpyfrdq arfpvlvtsd ldhylrreal sihvfddedl epgsylgrar vpllplakne
 901 sikgdfnltd paekpngsiq vqldwkfpyi ppesflkpea qtkgkdtkds skisseeeka
 961 sfpsqdqmas pevpieaggy rskrkpphgg erkekehqvv sysrrkhgkr igvqgknrme
1021 ylslnilngn tpeqvnytew kfsetnsfig dgfknqheee emtlshsalk qkeplhpvnd
1081 kesseqgsev seaqttdsdd vivppmsqky pkadsekmci eivslafype aevmsdenik
1141 qvyveykfyd lplsetetpv slrkpragee ihfhfskvid ldpqeqqgrr rflfdmlngq
1201 dpdqghlkft vvsdpldeek keceevgyay lqlwqilesg rdileqeldi vspedlatpi
1261 grlkvslqaa avlhaiykem tedlfs (SEQ ID NO:15)
```

FIG. 7G
Rab escort protein-1

```
   1 madtlpsefd vivigtglpe siiaaacsrs grrvlhvdsr syyggnwasf sfsgllswlk
  61 eyqensdivs dspvwqdqil eneeaialsr kdktiqhvev fcyasqdlhe dveeagalqk
 121 nhalvtsans teaadsaflp tedeslstms cemlteqtps sdpenalevn gaevtgeken
 181 hcddktcvps tsaedmsenv piaedtteqp kknritysqi ikegrrfnid lvskllysrg
 241 llidlliksn vsryaefkni trilafregr veqvpcsrad vfnskqltmv ekrmlmkflt
 301 fcmeyekypd eykgyeeitf yeylktqklt pnlqyivmhs iamtsetass tidglkatkn
 361 flhclgrygn tpflfplygq gelpqcfcrm cavfggiycl rhsvqclvvd kesrkckaii
 421 dqfgqriise hflvedsyfp enmcsrvqyr qisravlitd rsvlktdsdq qisiltvpae
 481 epgtfavrvi elcsstmtcm kgtylvhltc tssktaredl esvvqklfvp ytemeieneq
 541 vekprilwal yfnmrdssdi srscyndlps nvyvcsgpdc glgndnavkq aetlfqeicp
 601 nedfcppppn pediildgds lqpeasessa ipeansetfk estnlgnlee sse (SEQ ID NO:16)
```

FIG. 7H
212-amino acid isoform of RdCVF

```
  1 maslfsgril irnnsdqdel dteaevsrrl enrlvllffg agacpqcqaf vpilkdffvr
 61 ltdefyvlra aqlalvyvsq dsteeqqdlf lkdmpkkwlf lpfeddlrrd lgrqfsverl
121 pavvvlkpdg dvltrdgade iqrlgtacfa nwqeaaevld rnfqlpedle dqeprsltec
181 lrrhkyrvek aarggrdpgg gggeeggagg lf (SEQ ID NO:17)
```

FIG. 7I
156-amino acid isoform of RdCVF (isoform 1)

```
  1 mvdilgerhl vtckgatvea eaalqnkvva lyfaaarcap srdftpllcd fytalvaear
 61 rpapfevvfv sadgssqeml dfmrelhgaw lalpfhdpyr helrkrynvt aipklvivkq
121 ngevitnkgr kqirerglac fqdwveaadi fqnfsv (SEQ ID NO:18)
```

FIG. 7J
135-amino acid isoform of RdCVF (isoform 2)

```
  1 mvdilgerhl vtckgatvea eaalqnkvva lyfaaarcap srdftpllcd fytalvaear
 61 rpapfevvfv sadgssqeml dfmrelhgaw lalpfhdpyr qrslallprl ecsgvilahc
121 nlcllgssds lalas (SEQ ID NO:19)
```

FIG. 7K

Rod cGMP-specific 3',5'-cyclic phosphodiesterase subunit alpha (PDE6α)
GenBank NP_00431

```
  1 mgevtaeeve kfldsnigfa kqyynlhyra klisdllgak eaavdfsnyh spssmeesei
 61 ifdllrdfqe nlqtekcifn vmkklcfllq adrmslfmyr trngiaelat rlfnvhkdav
121 ledclvmpdq eivfpldmgi vghvahskki anvpnteede hfcdfvdilt eyktknilas
181 pimngkdvva iimavnkvdg shftkrdeei llkylnfanl imkvyhlsyl hncetrrgqi
241 llwsgskvfe eltdierqfh kalytvrafl ncdrysvgll dmtkqkeffd vwpvlmgevp
301 pysgprtpdg reinfykvid yilhgkedik vipnpppdhw alvsglpayv aqnglicnim
361 napaedffaf qkepldesgw miknvlsmpi vnkkeeivgv atfynrkdgk pfdemdetlm
421 esltqflgws vlnpdtyesm nklenrkdif qdivkyhvkc dneeiqkilk trevygkepw
481 eceeeelaei lqaelpdadk yeinkfhfsd lpltelelvk cgiqmyyelk vvdkfhipqe
541 alvrfmysls kgyrkityhn wrhgfnvgqt mfsllvtgkl kryftdleal amvtaafchd
601 idhrgtnnly qmksqnplak lhgssilerh hlefgktllr deslnifqnl nrrqhehaih
661 mmdiaiiatd lalyfkkrtm fqkivdqskt yeseqewtqy mmleqtrkei vmammmtacd
721 lsaitkpwev qsqvallvaa efweqgdler tvlqqnpipm mdrnkadelp klqvgfidfv
781 ctfvykefsr fheeitpmld gitnnrkewk aladeydakm kvqeekkqkq qsaksaaagn
841 qpggnpspgg attskscciq (SEQ ID NO:102)
```

FIG. 7L

Rod cGMP-specific 3',5'-cyclic phosphodiesterase subunit beta isoform 1 (PDE6β isoform 1)
GenBank NP_000274

```
  1 mslseeqars fldqnpdfar qyfgkklspe nvaaacedgc ppdcdslrdl cqveestall
 61 elvqdmqesi nmervvfkvl rrlctllqad rcslfmyrqr ngvaelatrl fsvqpdsvle
121 dclvppdsei vfpldigvvg hvaqtkkmvn vedvaecphf ssfadeltdy ktknmlatpi
181 mngkdvvavi mavnklngpf ftsededvfl kylnfatlyl kiyhlsylhn cetrrgqvll
241 wsankvfeel tdierqfhka fytvraylnc erysvglldm tkekeffdvw svlmgesqpy
301 sgprtpdgre ivfykvidyi lhgkeeikvi ptpsadhwal asglpsyvae sgficnimna
361 sademfkfqe galddsgwli knvlsmpivn kkeeivgvat fynrkdgkpf deqdevlmes
421 ltqflgwsvm ntdtydkmnk lenrkdiaqd mvlyhvkcdr deiqlilptr arlgkepadc
481 dedelgeilk eelpgpttfd iyefhfsdle cteldlvkcg iqmyyelgvv rkfqipqevl
541 vrflfsiskg yrrityhnwr hgfnvaqtmf tllmtgklks yytdleafam vtaglchdid
601 hrgtnnlyqm ksqnplaklh gssilerhhl efgkfllsee tlniyqnlnr rqhehvihlm
661 diaiiatdla lyfkkramfq kivdesknyq dkkswveyls lettrkeivm ammmtacdls
721 aitkpwevqs kvallvaaef weqgdlertv ldqqpipmmd rnkaaelpkl qvgfidfvct
781 fvykefsrfh eeilpmfdrl qnnrkewkal adeyeakvka leekeeeerv aakkvgteic
841 nggpapksst ccil (SEQ ID NO: 103)
```

FIG. 7M

Rod cGMP-specific 3',5'-cyclic phosphodiesterase subunit beta isoform 2 (PDE6β isoform 2)
GenBank NP_001138763

```
  1 mslseeqars fldqnpdfar qyfgkklspe nvaaacedgc ppdcdslrdl cqveestall
 61 elvqdmqesi nmervvfkvl rrlctllqad rcslfmyrqr ngvaelatrl fsvqpdsvle
121 dclvppdsei vfpldigvvg hvaqtkkmvn vedvaecphf ssfadeltdy ktknmlatpi
181 mngkdvvavi mavnklngpf ftsededvfl kylnfatlyl kiyhlsylhn cetrrgqvll
241 wsankvfeel tdierqfhka fytvraylnc erysvglldm tkekeffdvw svlmgesqpy
301 sgprtpdgre ivfykvidyi lhgkeeikvi ptpsadhwal asglpsyvae sgficnimna
361 sademfkfqe galddsgwli knvlsmpivn kkeeivgvat fynrkdgkpf deqdevlmes
421 ltqflgwsvm ntdtydkmnk lenrkdiaqd mvlyhvkcdr deiqlilptr arlgkepadc
481 dedelgeilk eelpgpttfd iyefhfsdle cteldlvkcg iqmyyelgvv rkfqipqevl
541 vrflfsiskg yrrityhnwr hgfnvaqtmf tllmtgklks yytdleafam vtaglchdid
601 hrgtnnlyqm ksqnplaklh gssilerhhl efgkfllsee tlniyqnlnr rqhehvihlm
661 diaiiatdla lyfkkramfq kivdesknyq dkkswveyls lettrkeivm ammmtacdls
721 aitkpwevqs kvallvaaef weqgdlertv ldqqpipmmd rnkaaelpkl qvgfidfvct
781 fvykefsrfh eeilpmfdrl qnnrkewkal adeyeakvka leekeeeerv aakkgteicn
841 ggpapksstc cil (SEQ ID NO: 104)
```

FIG. 7N

Rod cGMP-specific 3',5'-cyclic phosphodiesterase subunit beta isoform 3 (PDE6β isoform 3)
GenBank NP_001138764

```
  1 mtkekeffdv wsvlmgesqp ysgprtpdgr eivfykvidy ilhgkeeikv iptpsadhwa
 61 lasglpsyva esgficnimn asademfkfq egalddsgwl iknvlsmpiv nkkeeivgva
121 tfynrkdgkp fdeqdevlme sltqflgwsv mntdtydkmn klenrkdiaq dmvlyhvkcd
181 rdeiqlilpt rarlgkepad cdedelgeil keelpgpttf diyefhfsdl ecteldlvkc
241 giqmyyelgv vrkfqipqev lvrflfsisk gyrrityhnw rhgfnvaqtm ftllmtgklk
301 syytdleafa mvtaglchdi dhrgtnnlyq mksqnplakl hgssilerhh lefgkfllse
361 etlniyqnln rrqhehvihl mdiaiiatdl alyfkkramf qkivdeskny qdkkswveyl
421 slettrkeiv mammmtacdl saitkpwevq skvallvaae fweqgdlert vldqqpipmm
481 drnkaaelpk lqvgfidfvc tfvykefsrf heeilpmfdr lqnnrkewka ladeyeakvk
541 aleekeeeer vaakkvgtei cnggpapkss tccil (SEQ ID NO: 105)
```

FIG. 7O

Cyclic nucleotide-gated cation channel alpha-3 isoform 1 (CNGA3 isoform 1)
GenBank NP_001289

```
  1 makintqysh psrthlkvkt sdrdlnraen glsrahssse etssvlqpgi ametrglads
 61 gqgsftgqgi arlsrlifll rrwaarhvhh qdqgpdsfpd rfrgaelkev ssqesnaqan
121 vgsqepadrg rsawplakcn tntsnnteee kktkkkdaiv vdpssnlyyr wltaialpvf
181 ynwyllicra cfdelqseyl mlwlvldysa dvlyvldvlv rartgfleqg lmvsdtnrlw
241 qhyktttqfk ldvlslvptd laylkvgtny pevrfnrllk fsrlfeffdr tetrtnypnm
301 frignlvlyi liiihwnaci yfaiskfigf gtdswvypni sipehgrlsr kyiyslywst
361 ltlttigetp ppvkdeeylf vvvdflvgvl ifativgnvg smisnmnasr aefqakidsi
421 kqymqfrkvt kdletrvirw fdylwankkt vdekevlksl pdklkaeiai nvhldtlkkv
481 rifqdceagl lvelvlklrp tvfspgdyic kkgdigkemy iinegklavv addgvtqfvv
541 lsdgsyfgei silnikgsks gnrrtanirs igysdlfcls kddlmealte ypeakkalee
601 kgrqilmkdn lideelarag adpkdleekv eqlgssldtl qtrfarllae ynatqmkmkq
661 rlsqlesqvk gggdkpladg evpgdatkte dkqq (SEQ ID NO: 106)
```

FIG. 7P

Cyclic nucleotide-gated cation channel alpha-3 isoform 2 (CNGA3 isoform 2)
GenBank NP_001073347

```
  1 makintqysh psrthlkvkt sdrdlnraen glsrahssse etssvlqpgi ametrglads
 61 gqgsftgqgi arlsrlifll rrwaarhvhh qdqgpdsfpd rfrgaelkev ssqesnaqan
121 vgsqepadrg rrkktkkkda ivvdpssnly yrwltaialp vfynwyllic racfdelqse
181 ylmlwlvldy sadvlyvldv lvrartgfle qglmvsdtnr lwqhykttтq fkldvlslvp
241 tdlaylkvgt nypevrfnrl lkfsrlfeff drtetrtnyp nmfrignlvl yiliiihwna
301 ciyfaiskfi gfgtdswvyp nisipehgrl srkyiyslyw stltlttige tpppvkdeey
361 lfvvvdflvg vlifativgn vgsmisnmna sraefqakid sikqymqfrk vtkdletrvi
421 rwfdylwank ktvdekevlk slpdklkaei ainvhldtlk kvrifqdcea gllvelvlkl
481 rptvfspgdy ickkgdigke myiinegkla vvaddgvtqf vvlsdgsyfg eisilnikgs
541 ksgnrrtani rsigysdlfc lskddlmeal teypeakkal eekgrqilmk dnlideelar
601 agadpkdlee kveqlgssld tlqtrfarll aeynatqmkm kqrlsqlesq vkgggdkpla
661 dgevpgdatk tedkqq (SEQ ID NO: 107)
```

FIG. 7Q

Cyclic nucleotide-gated cation channel beta-3 (CNGB3)
GenBank NP_061971

```
  1 mfksltkvnk vkpigennen eqssrrneeg shpsnqsqqt taqeenkgee kslktkstpv
 61 tseephtniq dklskknssg dlttnpdpqn aaeptgtvpe qkemdpgkeg pnspqnkppa
121 apvineyada qlhnlvkrmr qrtalykkkl vegdlsspea spqtakptav ppvkesddkp
181 tehyyrllwf kvkkmpltey lkriklpnsi dsytdrlyll wlllvtlayn wnccfiplrl
241 vfpyqtadni hywliadiic diiylydmlf iqprlqfvrg gdiivdsnel rkhyrtstkf
301 qldvasiipf dicylffgfn pmfranrmlk ytsffefnhh lesimdkayi yrvirttgyl
361 lfilhinacv yywasnyegi gttrwvydge gneylrcyyw avrtlitigg lpepqtlfei
421 vfqllnffsg vfvfssligq mrdvigaata nqnyfracmd dtiaymnnys ipklvqkrvr
481 twyeytwdsq rmldesdllk tlpttvqlal aidvnfsiis kvdlfkgcdt qmiydmllrl
541 ksvlylpgdf vckkgeigke myiikhgevq vlggpdgtkv lvtlkagsvf geisllaagg
601 gnrrtanvva hgfanlltld kktlqeilvh ypdserilmk karvllkqka ktaeatpprk
661 dlallfppke etpklfktll ggtgkaslar llklkreqaa qkkensegge eegkenedkq
721 kenedkqken edkgkenedk dkgrepeekp ldrpectasp iaveeephsv rrtvlprgts
781 rqsliismap saeggeevlt ievkekakq (SEQ ID NO: 108)
```

FIG. 7R

Guanine nucleotide-binding protein G(t) subunit alpha-2 (GNAT2)
GenBank NP_005263

```
  1 mgsgasaedk elakrskele kklqedadke aktvkllllg agesgkstiv kqmkiihqdg
 61 yspeeclefk aiiygnvlqs ilaiiramtt lgidyaepsc addgrqlnnl adsieegtmp
121 pelvevirrl wkdggvqacf eraaeyqlnd sasyylnqle ritdpeylps eqdvlrsrvk
181 ttgiietkfs vkdlnfrmfd vggqrserkk wihcfegvtc iifcaalsay dmvlveddev
241 nrmheslhlf nsicnhkffa atsivlflnk kdlfeekikk vhlsicfpey dgnnsyddag
301 nyiksqfldl nmrkdvkeiy shmtcatdtq nvkfvfdavt diiikenlkd cglf (SEQ ID NO: 109)
```

FIG. 7S

RPGR – 815 amino acids
GenBank NP_000319

```
  1 mrepeelmpd sgavftfgks kfaennpgkf wfkndvpvhl scgdehsavv tgnnklymfg
 61 snnwgqlglg sksaiskptc vkalkpekvk laacgrnhtl vsteggnvya tggnnegqlg
121 lgdteerntf hvisfftseh kikqlsagsn tsaaltedgr lfmwgdnseg qiglknvsnv
181 cvpqqvtigk pvswiscgyy hsafvttdge lyvfgepeng klglpnqllg nhrtpqlvse
241 ipekviqvac ggehtvvlte navytfglgq fgqlglgtfl fetsepkvie nirdqtisyi
301 scgenhtali tdiglmytfg dgrhgklglg lenftnhfip tlcsnflrfi vklvacggch
361 mvvfaaphrg vakeiefdei ndtclsvatf lpyssltsgn vlqrtlsarm rrrererspd
421 sfsmrrtlpp iegtlglsac flpnsvfprc sernlqesvl seqdlmqpee pdylldemtk
481 eaeidnsstv eslgettdil nmthimslns nekslklspv qkqkkqqtig eltqdtalte
541 nddsdeyeem semkegkack qhvsqgifmt qpattieafs deeveipeek egaedskgng
601 ieeqeveane envkvhggrk ekteilsddl tdkaedhefs kteelkledv deeinaenve
661 skkktvgdde svptgyhskt egaertndds saetiekkek anleeraice ynenpkgyml
721 ddadssslei lensettpsk dmkktkkifl fkrvpsinqk ivknnneplp eiksigdqii
781 lksdnkdadq nhmsqnhqni pptnterrsk sctil  (SEQ ID NO: 110)
```

FIG. 7T

RPGR – 646 amino acids
GenBank CAB54002

```
  1 mrepeelmpd sgavftfgks kfaennpgkf wfkndvpvhl scgdehsavv tgnnklymfg
 61 snnwgqlglg sksaiskptc vkalkpekvk laacgrnhtl vsteggnvya tggnnegqlg
121 lgdteerntf hvisfftseh kikqlsagsn tsaaltedgr lfmwgdnseg qiglknvsnv
181 cvpqqvtigk pvswiscgyy hsafvttdge lyvfgepeng klglpnqllg nhrtpqlvse
241 ipekviqvac ggehtvvlte navytfglgq fgqlglgtfl fetsepkvie nirdqtisyi
301 scgenhtali tdiglmytfg dgrhgklglg lenftnhfip tlcsnflrfi vklvacggch
361 mvvfaaphrg vakeiefdei ndtclsvatf lpyssltsgn vlqrtlsarm rrrererspd
421 sfsmrrtlpp iegtlglsac flpnsvfprc sernlqesvl seqdlmqpee pdylldemtk
481 eaeidnsstv eslgettdil nmthimslns nekslklspv qkqkkqqtig eltqdtalte
541 nddsdeyeem semkegkack qhvsqgifmt qpattieafs deeveipeek egaedskgng
601 ieeqeveane envkvhggrk ekteilsddl tdkaeysash sqivsv (SEQ ID NO: 111)
```

FIG. 7U

RPGR – 1152 amino acids

```
   1 mrepeelmpd sgavftfgks kfaennpgkf wfkndvpvhl scgdehsavv tgnnklymfg
  61 snnwgqlglg sksaiskptc vkalkpekvk laacgrnhtl vsteggnvya tggnnegqlg
 121 lgdteerntf hvisfftseh kikqlsagsn tsaaltedgr lfmwgdnseg qiglknvsnv
 181 cvpqqvtigk pvswiscgyy hsafvttdge lyvfgepeng klglpnqllg nhrtpqlvse
 241 ipekviqvac ggehtvvlte navytfglgq fgqlglgtfl fetsepkvie nirdqtisyi
 301 scgenhtali tdiglmytfg dgrhgklglg lenftnhfip tlcsnflrfi vklvacggch
 361 mvvfaaphrg vakeiefdei ndtclsvatf lpyssltsgn vlqrtlsarm rrrererspd
 421 sfsmrrtlpp iegtlglsac flpnsvfprc sernlqesvl seqdlmqpee pdylldemtk
 481 eaeidnsstv eslgettdil nmthimslns nekslklspv qkqkkqqtig eltqdtalte
 541 nddsdeyeem semkegkack qhvsqgifmt qpattieafs deeveipeek egaedskgng
 601 ieeqeveane envkvhggrk ekteilsddl tdkaevsegk aksvgeaedg pegrgdgtce
 661 egssgaehwq deerekgekd kgrgemerpg egekelaeke ewkkrdgeeq eqkereqghq
 721 kernqemeeg geeehgegee eegdreeeee kegegkeege geevegerek eegerkkeer
 781 agkeekgeee gdqgegeeee tegrgeekee ggeveggeve egkgereeee eegegeeeeg
 841 egeeeegege eeegegkgee egeegegeee geegegegee eegegegeee gegegeeeeg
 901 egegeeegeg egeeeegegk geeegeegeg egeeeegege gedgegegee eegewegeee
 961 egegegeeeg egegeegege geeeegegeg eeeegeeege eegegeeege gegeeeeege
1021 vegevegeeg egegeeeege eegeerekeg egeenrrnre eeeeeegkyq etgeeenerq
1081 dgeeykkvsk ikgsvkygkh ktyqkksvtn tqgngkeqrs kmpvqskrll kngpsgskkf
1141 wnnvlphyle lk (SEQ ID NO: 112)
```

FIG. 7V

RPGR – 1020 amino acids

```
   1 mrepeelmpd sgavftfgks kfaennpgkf wfkndvpvhl scgdehsavv tgnnklymfg
  61 snnwgqlglg sksaiskptc vkalkpekvk laacgrnhtl vsteggnvya tggnnegqlg
 121 lgdteerntf hvisfftseh kikqlsagsn tsaaltedgr lfmwgdnseg qiglknvsnv
 181 cvpqqvtigk pvswiscgyy hsafvttdge lyvfgepeng klglpnqllg nhrtpqlvse
 241 ipekviqvac ggehtvvlte navytfglgq fgqlglgtfl fetsepkvie nirdqtisyi
 301 scgenhtali tdiglmytfg dgrhgklglg lenftnhfip tlcsnflrfi vklvacggch
 361 mvvfaaphrg vakeiefdei ndtclsvatf lpyssltsgn vlqrtlsarm rrrererspd
 421 sfsmrrtlpp iegtlglsac flpnsvfprc sernlqesvl seqdlmqpee pdylldemtk
 481 eaeidnsstv eslgettdil nmthimslns nekslklspv qkqkkqqtig eltqdtalte
 541 nddsdeyeem semkegkack qhvsqgifmt qpattieafs deevgndtgq vgpqadtdge
 601 glqkevyrhe nnngvdqlda keiekesdgg hsqkeseaee idseketkla eiagmkdlre
 661 rekstkkmsp ffgnlpdrgm nteseenkdf vkkresckqd vifdseresv ekpdsymega
 721 sesqqgiadg fqqpeaiefs sgekeddeve tdqnirygrk lieqgneket kpiisksmak
 781 ydfkcdrlse ipeekegaed skgngieeqe veaneenvkv hggrkektei lsddltdkae
 841 dhefskteel kledvdeein aenveskkkt vgddesvptg yhsktegaer tnddssaeti
 901 ekkekanlee raiceynenp kgymlddads ssleilense ttpskdmkkt kkiflfkrvp
 961 sinqkivknn neplpeiksi gdqiilksdn kdadqnhmsq nhqnipptnt errsksctil (SEQ ID NO: 113)
```

FIG. 8A

AAV4 capsid
GenBank NP_044927

```
      1 mtdgylpdwl ednlsegvre wwalqpgapk pkanqqhqdn arglvlpgyk ylgpgngldk
     61 gepvnaadaa alehdkaydq qlkagdnpyl kynhadaefq qrlqgdtsfg gnlgravfqa
    121 kkrvleplgl veqagetapg kkrpliespq qpdsstgigk kgkqpakkkl vfedetgagd
    181 gppegstsga msddsemraa aggaaveggq gadgvgnasg dwhcdstwse ghvtttstrt
    241 wvlptynnhl ykrlgeslqs ntyngfstpw gyfdfnrfhc hfsprdwqrl innnwgmrpk
    301 amrvkifniq vkevttsnge ttvannltst vqifadssye lpyvmdagqe gslppfpndv
    361 fmvpqygycg lvtgntsqqq tdrnafycle yfpsqmlrtg nnfeitysfe kvpfhsmyah
    421 sqsldrlmnp lidqylwglq stttgttlna gtattnftkl rptnfsnfkk nwlpgpsikq
    481 qgfsktanqn ykipatgsds likyethstl dgrwsaltpg ppmatagpad skfsnsqlif
    541 agpkqngnta tvpgtlifts eeelaatnat dtdmwgnlpg gdqsnsnlpt vdrltalgav
    601 pgmvwqnrdi yyqgpiwaki phtdghfhps pliggfglkh pppqifiknt pvpanpattf
    661 sstpvnsfit qystgqvsvq idweiqkers krwnpevqft snygqqnsll wapdaagkyt
    721 epraigtryl thhl (SEQ ID NO: 114)
```

FIG. 8B
Ancestral AAV capsid

```
MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADA
EFQERLQEDTSFGGNLGRAVFQAKKRVLEPLGLVEEGAKTAPGKKRPVEPSPQRSPDSSTGIGKKGQQPAKKRLNFGQTGDSESVPDPQPLGEPPAGP
SGLGSGTMAAGGGAPMADNNEGADGVGNASGNWHCDSTWLGDRVITTSTRTWALPTYNNHLYKQISSXSXGXTNDNHYFGYSTPWGYFDFNRFHCHFS
PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTTNDGVTTIANNLTSTVQVFSDSEYQLPYVLGSAHQGCLPPFPADVFMIPQYGYLTLNNGSQAVGRS
SFYCLEYFPSQMLRTGNNFTFSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLXRTQSTGGTAGXXELLFSQXGPXXMSXQAKNWLPGPCYRQQRV
SKTLXQNNNSNFAWTGATKYHLNGRXSLVNPGVAMATHKDDEXRFFPSSGVLIFGKXGAGXNNTXLXNVMXTXEEEIKTTNPVATEXYGVVAXNLQSS
NTAPXTGXVNSQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPVPANPPXXFXXAKFASFITQYSTGQVSVEIEW
ELQKENSKRWNPEIQYTSNYAKSXNVDFAVXXXGVYXEPRPIGTRYLTRNL (SEQ ID NO: 115)
```

(X is any amino acid)

FIG. 9 -- Table 1

	ONL Fold increase in reads	Insert	Source library	Region
(SEQ ID NO: 29)	63.79919679	LQRGVRIPSVLEVNGQ	LS588	Central
(SEQ ID NO: 30)	7.153386879	LQKADRQPGVVVVNCQ	LS588	Peripheral
(SEQ ID NO: 24)	2.181299886	TGLDATRDHGLSPVTGT	Anc-7mer	Central
(SEQ ID NO: 26)	1.975644028	NGAVADYTRGLSPATGT	Anc-7mer	Peripheral
	1.558702536	7m8	7m8	CONTROL
(SEQ ID NO: 28)	1.500800454	LQKNARPASTESVNFQ	LS588	Central
(SEQ ID NO: 27)	1.371471857	TGGDPTRGTGLSPVTGA	Anc-7mer	Peripheral
	1.181900886	k916	k916	CONTROL
	1.180138343	AAV24YF+	AAV24YF+	CONTROL
	1.096454525	AAV2	AAV2	CONTROL
(SEQ ID NO: 25)	1.040515096	TGSDGTRDHGLSPVTWT	Anc-7mer	Central
(SEQ ID NO: 30)	0.915832658	LQRGNRPVTTADVNTQ	LS588	Peripheral
(SEQ ID NO: 5)	0.821793827	QAHQDTTKNA	AAV2-7mer	Peripheral
	0.565046307	k912	k912	CONTROL
(SEQ ID NO: 21)	0.562635287	TGVMHSQASGLS	AAV5-7mer	Peripheral
	0.500833298	k91	k91	CONTROL
(SEQ ID NO: 35)	0.387792793	LALIQDSMRA	AAV2-7mer	Central
(SEQ ID NO: 20)	0.377253299	TVVSTQAGIGLS	AAV5-7mer	Peripheral
(SEQ ID NO: 23)	0.346854635	TGSDMAHGTGLS	AAV5-7mer most abundant	CONTROL
(SEQ ID NO: 22)	0.34669906	TGDGSPAAPGLS	RPE-AAV5-7mer	Central
(SEQ ID NO: 100)	0.324308359	TGMHVTMMAGLN	AAV5-7mer	Central
(SEQ ID NO: 2)	0.298540099	LANQEHVKNA	AAV2-7mer	Peripheral
	0.258738252	AAV5	AAV5	CONTROL
(SEQ ID NO: 4)	0.238979892	LTHQDTTKNA	AAV2-7mer	Central
(SEQ ID NO: 99)	0.161482878	TGGHGSAPDGLS	RPE-AAV4-7mer	Central
(SEQ ID NO: 9)	0.141133263	TGGHDSSLDGLS	AAV4-7mer	Peripheral
(SEQ ID NO: 98)	0.136923607	TGDGGTTMNGLS	AAV4-7mer most abundant	CONTROL
(SEQ ID NO: 8)	0.128082381	TSPYSGSSDGLS	AAV4-7mer	Peripheral
(SEQ ID NO: 6)	0.090871196	TGVMRSTNSGLN	AAV4-7mer	Central
	0.057446852	AAV4	AAV4	CONTROL

FIG. 10 – Table 2

RPE

	Fold increase in reads	Insert	Source library	Region
(SEQ ID NO: 29)	33.65598086	LQRGVRIPSVLEVNGQ	LS588	Central
(SEQ ID NO: 35)	4.627963274	LALIQDSMRA	AAV2-7mer	Central
(SEQ ID NO: 4)	4.155171929	LTHQDTTKNA	AAV2-7mer	Central
(SEQ ID NO: 5)	3.418111986	QAHQDTTKNA	AAV2-7mer	Peripheral
	3.307311067	k91	k91	CONTROL
(SEQ ID NO: 2)	2.250383296	LANQEHVKNA	AAV2-7mer	Peripheral
(SEQ ID NO: 26)	1.553340346	NGAVADYTRGLSPATGT	Anc-7mer	Peripheral
(SEQ ID NO: 24)	1.039956858	TGLDATRDHGLSPVTGT	Anc-7mer	Central
(SEQ ID NO: 31)	0.98426325	LQKADRQPGVVVVNCQ	LS588	Peripheral
(SEQ ID NO: 30)	0.691860699	LQRGNRPVTTADVNTQ	LS588	Peripheral
	0.584426815	k916	k916	CONTROL
	0.569675877	AAV24YF+	AAV24YF+	CONTROL
	0.563819035	AAV2	AAV2	CONTROL
(SEQ ID NO: 28)	0.515236441	LQKNARPASTESVNFQ	LS588	Central
(SEQ ID NO: 27)	0.475479014	TGGDPTRGTGLSPVTGA	Anc-7mer	Peripheral
(SEQ ID NO: 25)	0.474443207	TGSDGTRDHGLSPVTWT	Anc-7mer	Central
(SEQ ID NO: 21)	0.405199224	TGVMHSQASGLS	AAV5-7mer	Peripheral
(SEQ ID NO: 9)	0.337284091	TGGHDSSLDGLS	AAV4-7mer	Peripheral
(SEQ ID NO: 99)	0.334179068	TGGHGSAPDGLS	RPE-AAV4-7mer	Central
(SEQ ID NO: 8)	0.292104518	TSPYSGSSDGLS	AAV4-7mer	Peripheral
	0.25410362	AAV5	AAV5	CONTROL
(SEQ ID NO: 98)	0.208508888	TGDGGTTMNGLS	AAV4-7mer most abundant	CONTROL
	0.195373303	7m8	7m8	CONTROL
	0.175139543	k912	k912	CONTROL
	0.171857536	AAV4	AAV4	CONTROL
(SEQ ID NO: 23)	0.157923226	TGSDMAHGTGLS	AAV5-7mer most abundant	CONTROL
(SEQ ID NO: 20)	0.115992687	TVVSTQAGIGLS	AAV5-7mer	Peripheral
(SEQ ID NO: 6)	0.115792655	TGVMRSTNSGLN	AAV4-7mer	Central
(SEQ ID NO: 22)	0.046990066	TGDGSPAAPGLS	RPE-AAV5-7mer	Central
(SEQ ID NO: 100)	0.035004376	TGMHVTMMAGLN	AAV5-7mer	Central

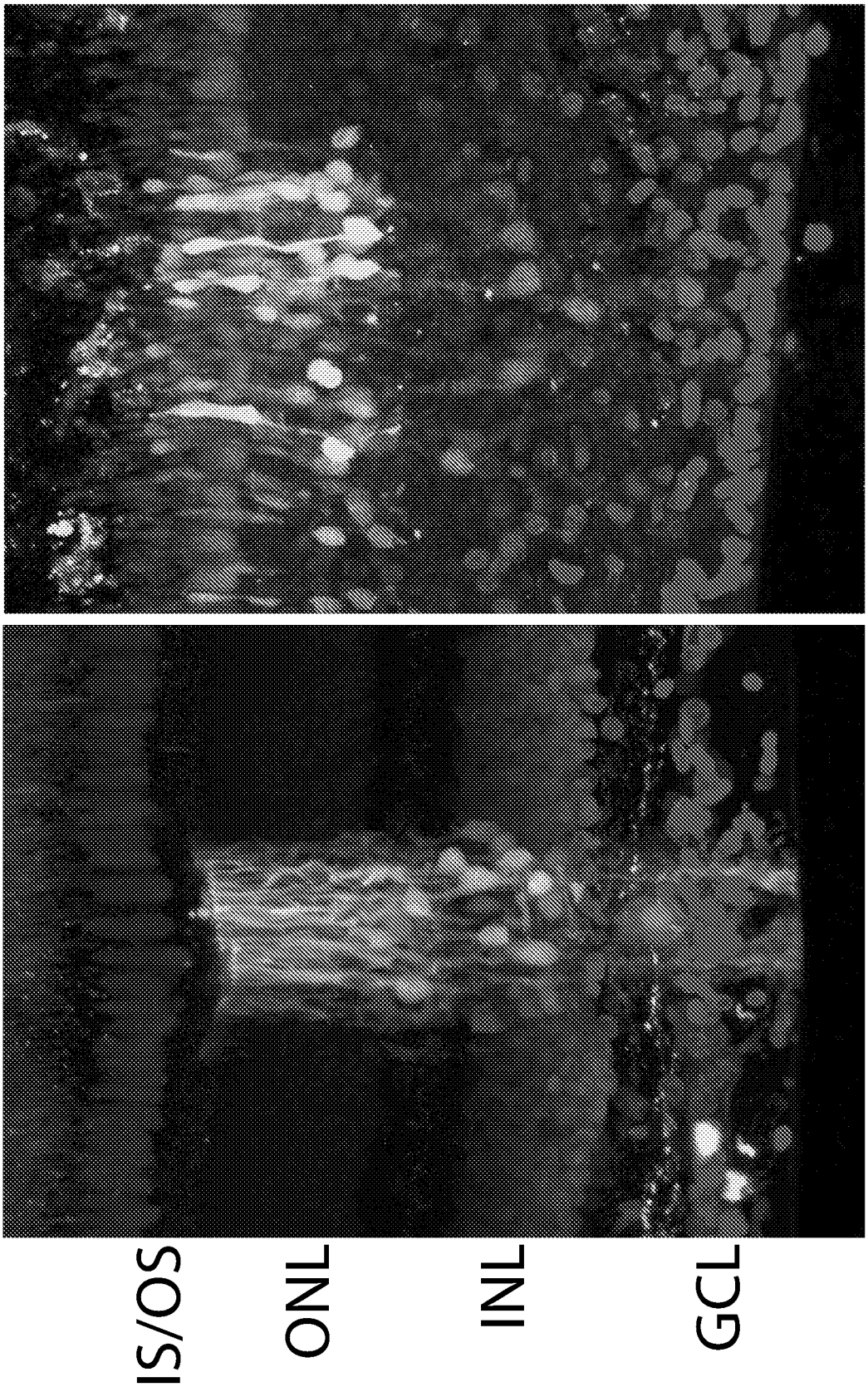


FIG. 11

FIG. 12A

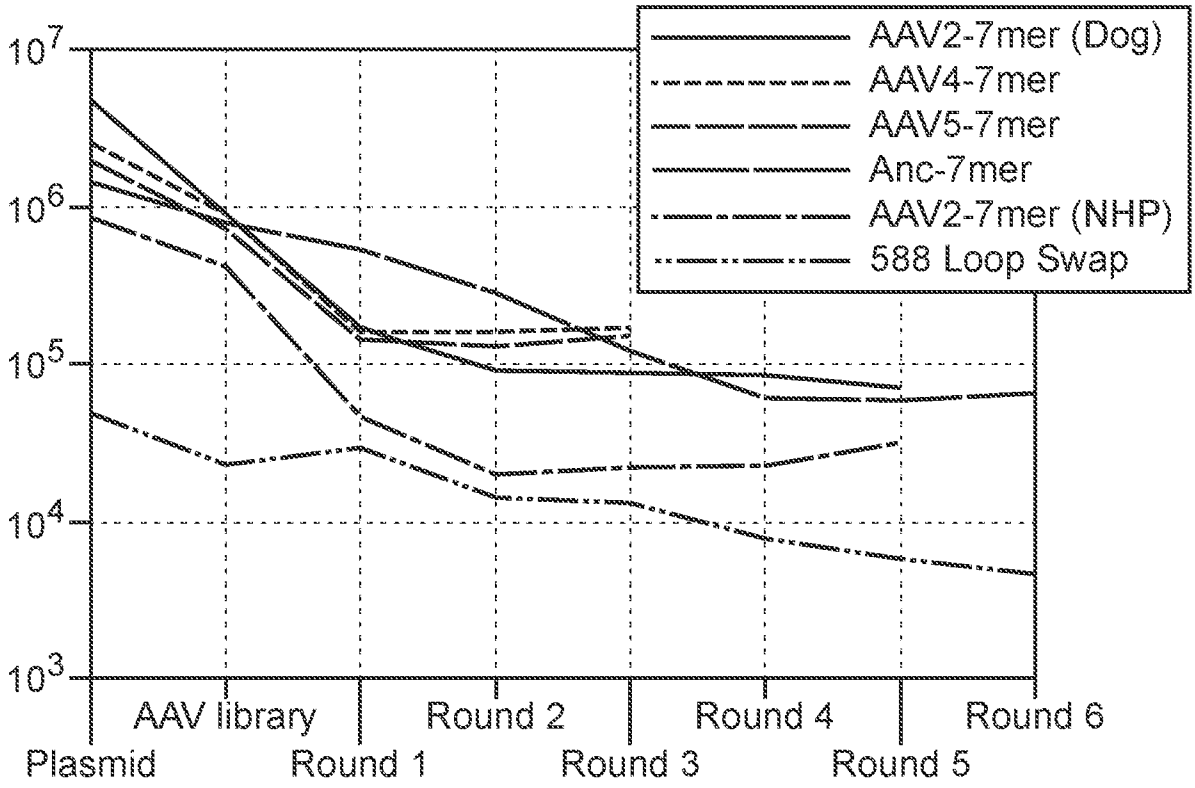


FIG. 12B

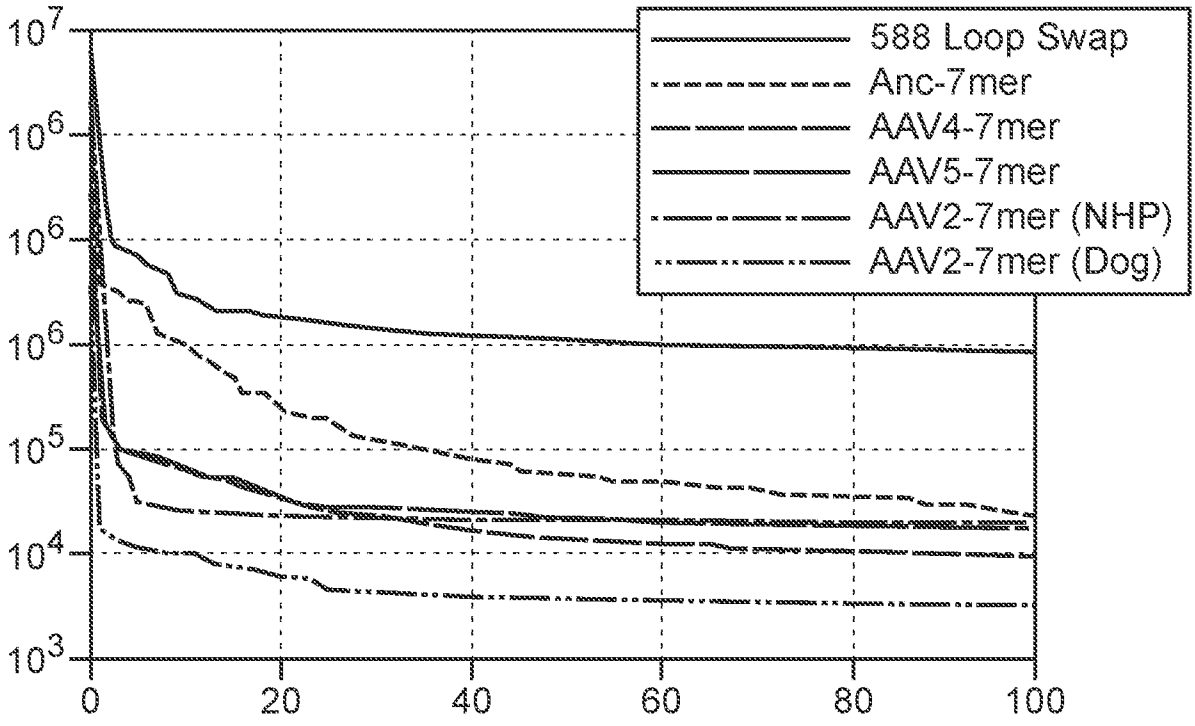
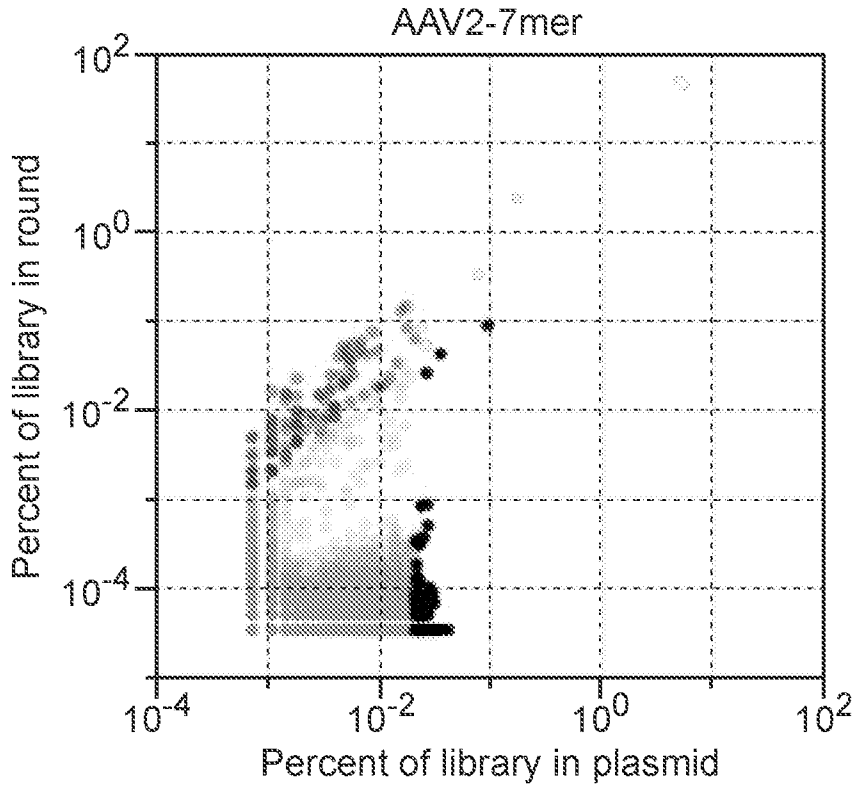


FIG. 12C


AAV2-7mer
Percent of library in round
10^{2}
10^{0}
10^{-2}
10^{-4}
10^{-4}
10^{-2}
10^{0}
10^{2}
Percent of library in plasmid

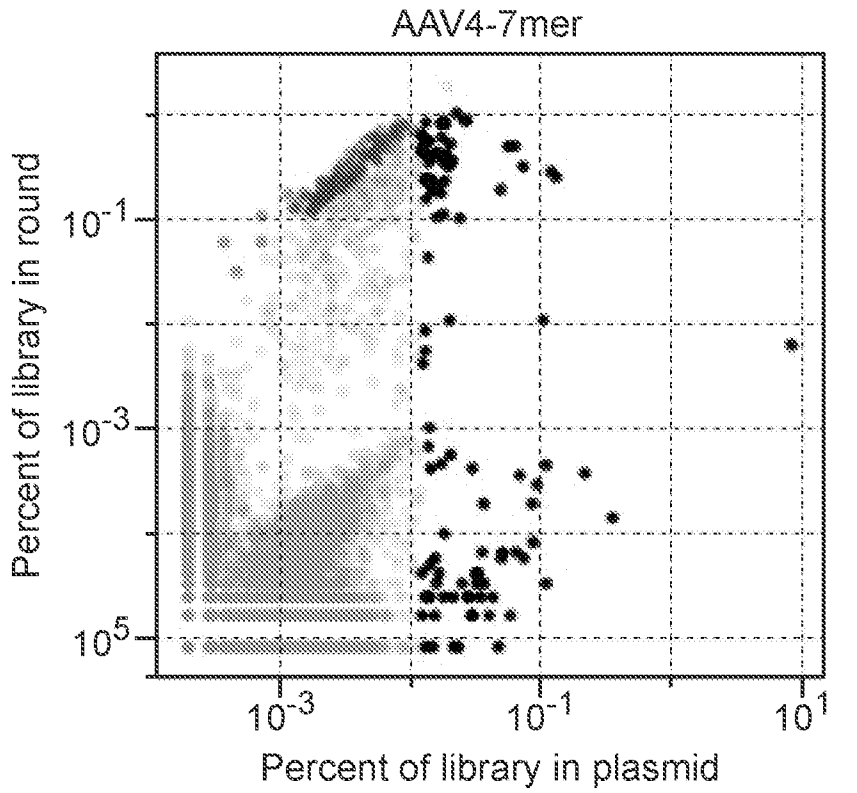
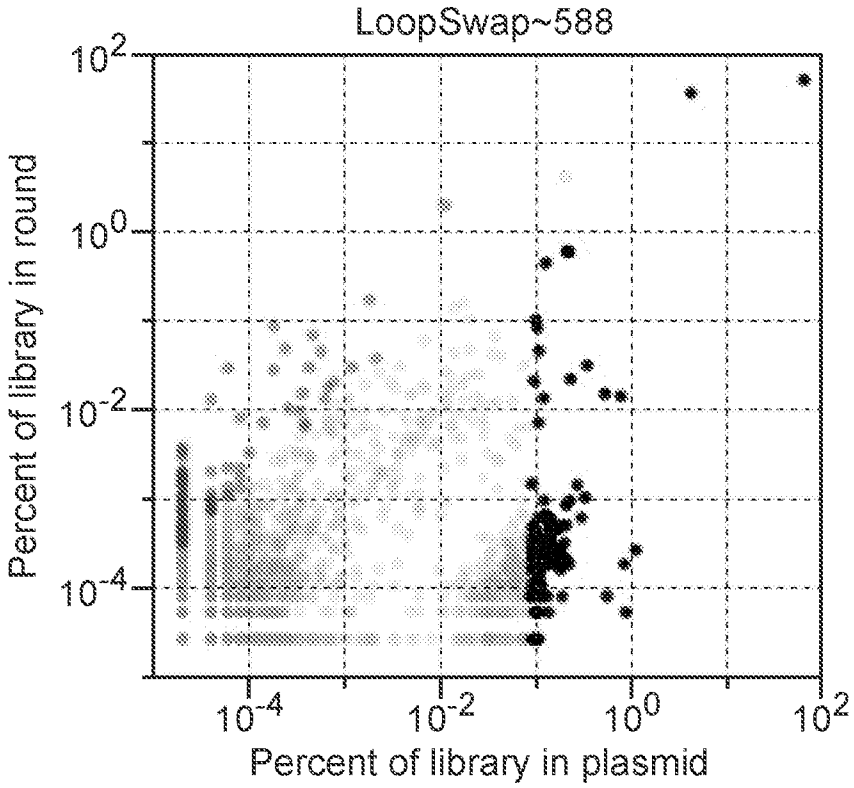

AAV4-7mer
Percent of library in round
10^{-1}
10^{-3}
10^{5}
10^{-3}
10^{-1}
10^{1}
Percent of library in plasmid

FIG. 12C (Cont.)


LoopSwap~588
Percent of library in round
Percent of library in plasmid
10^{2}
10^{0}
10^{-2}
10^{-4}

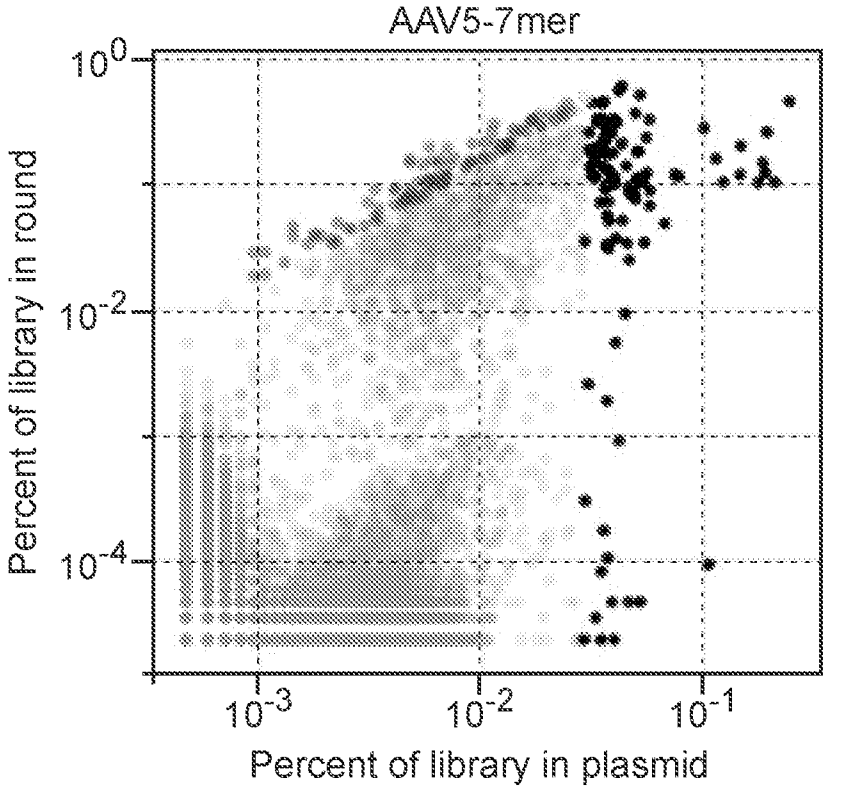

AAV5-7mer
Percent of library in round
Percent of library in plasmid
10^{0}
10^{-2}
10^{-4}
10^{-3}
10^{-2}
10^{-1}

FIG. 12C (Cont.)

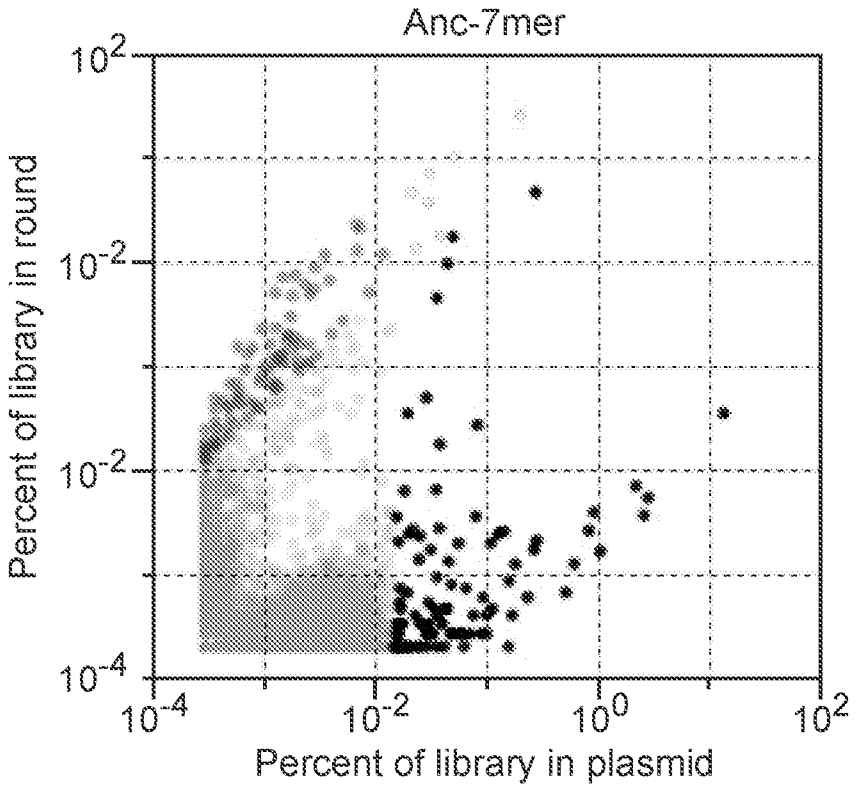


FIG. 12D

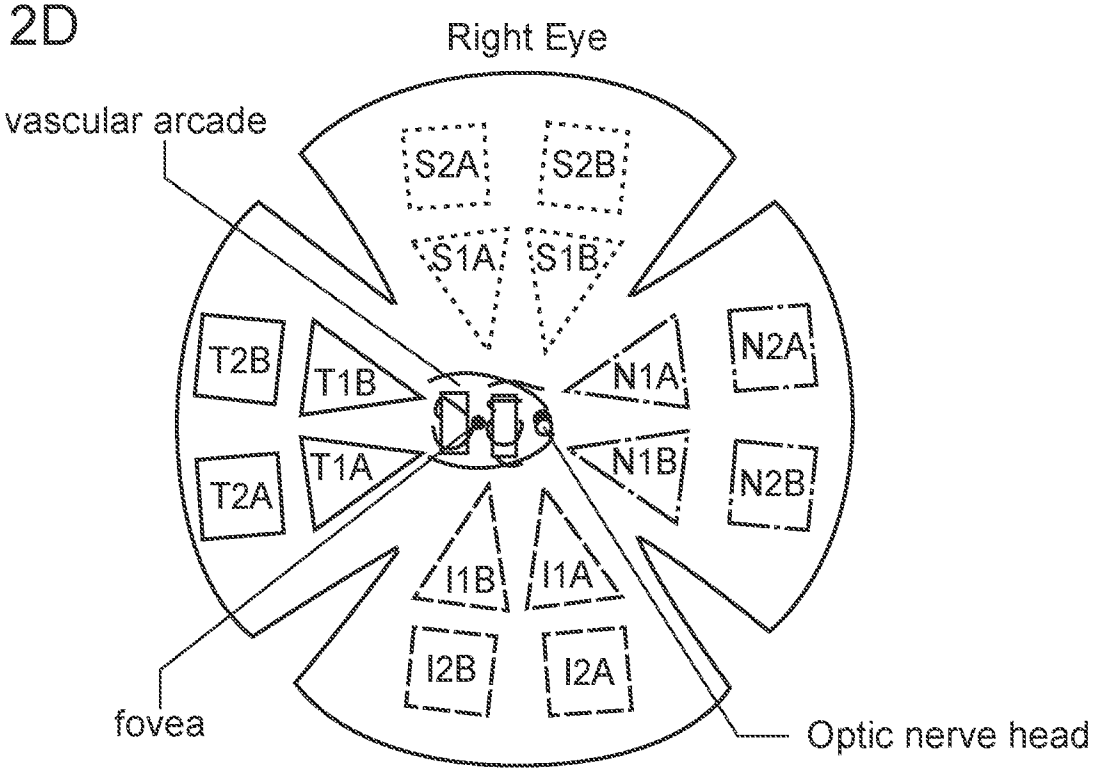


FIG. 12E

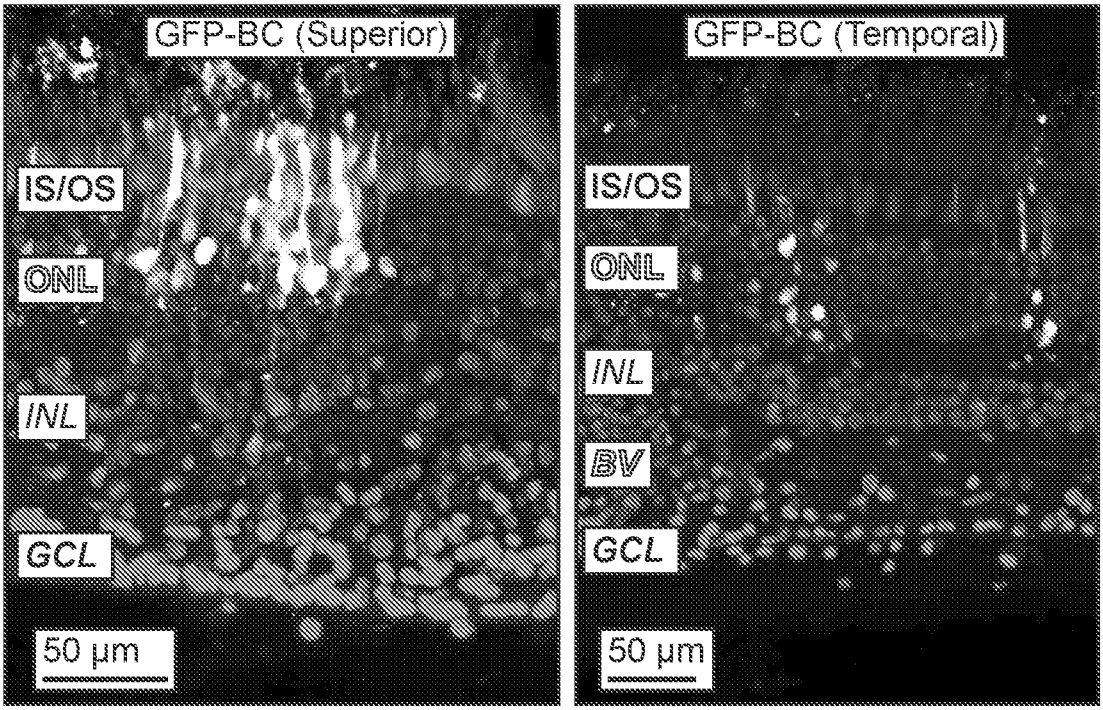


FIG. 12F

	NHP outer retina
(33.66)	LQRGVRIPSVLEVNGQ
(4.63)	LALIQDSMRA
(4.16)	LTHQDTTKNA
(3.42)	QAHQDTTKNA
(3.31)	LAHQDTTKNA
(2.25)	LANQEHVKNA
(1.55)	NGAVADYTRGLSPATGT
(1.04)	TGLDATRDHGLSPVTGT
(0.98)	LQKADRQPGVVVVNCQ
(0.69)	LQRGNRPVTTADVNTQ
(0.58)	PAPQDTTKKA
(0.57)	AAV24YF+
(0.56)	AAV2 control
(0.52)	LQKNARPASTESVNFQ
(0.48)	TGGDPTRGTGLSPVTGA
(0.47)	TGSDGTRDHGLSPVTWT
(0.41)	TGVMHSQASGLS
(0.34)	TGGHDSSLDGLS
(0.25)	AAV5 control
(0.20)	LALGETTRPA
(0.18)	LAPDSTTRSA
(0.17)	AAV4 control
(0.12)	TVVSTQAGIGLS

FIG. 13A

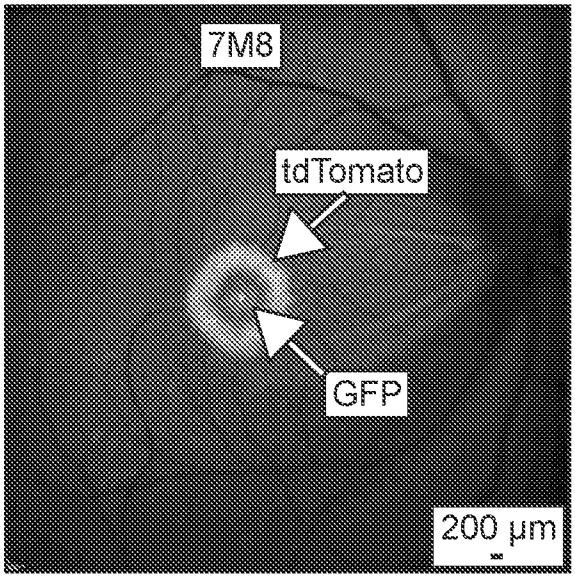


FIG. 13B

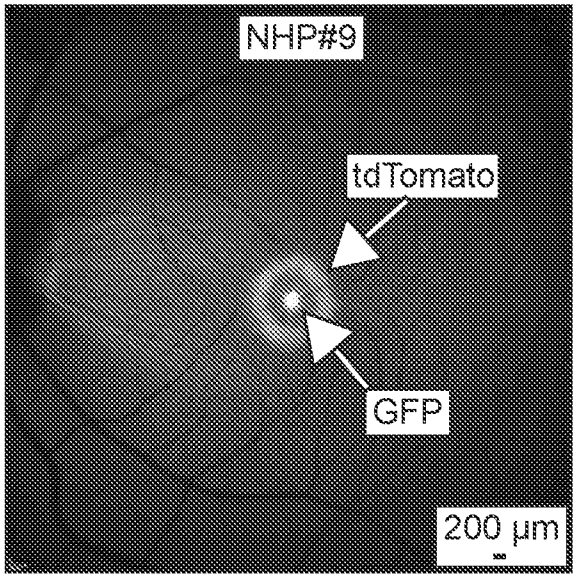


FIG. 13C

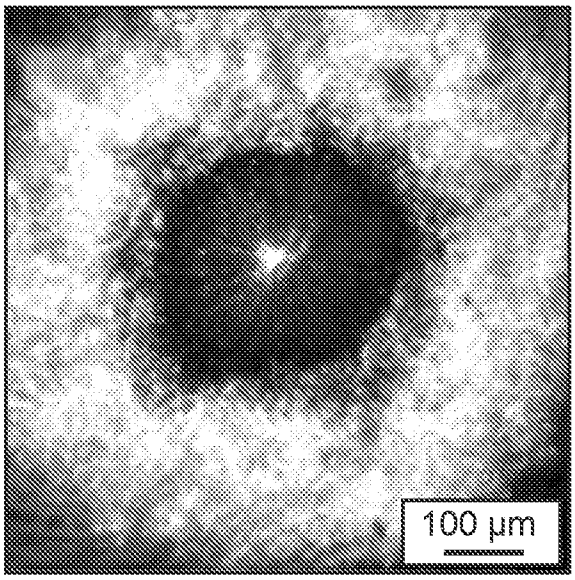


FIG. 13D

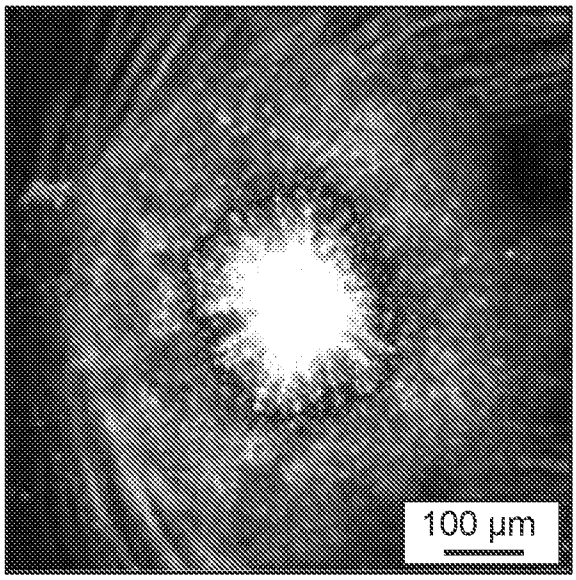


FIG. 13E

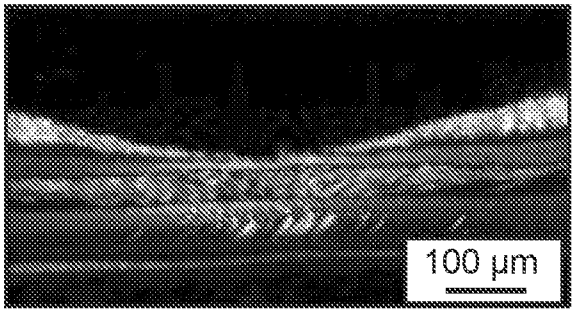


FIG. 13F

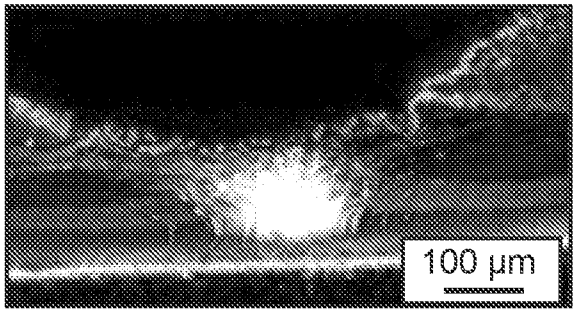


FIG. 13G

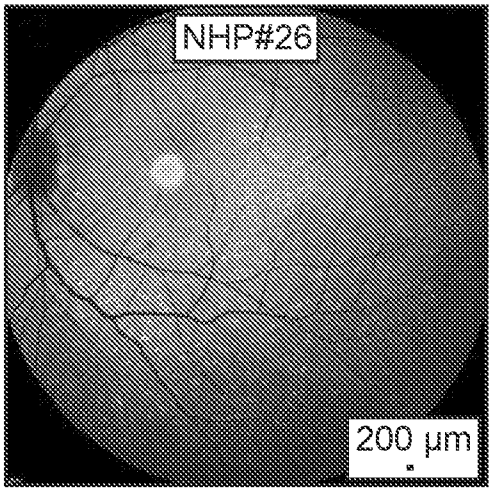


FIG. 13H

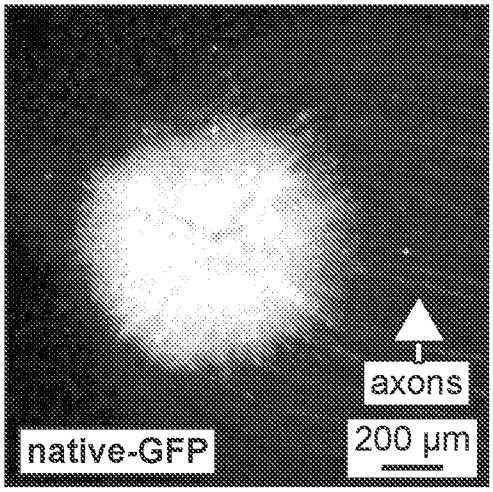


FIG. 13I

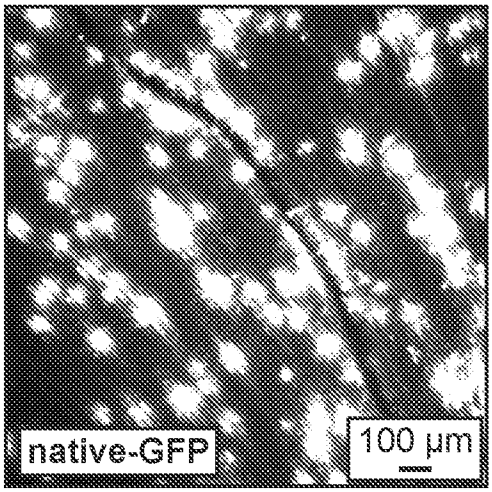


FIG. 13J

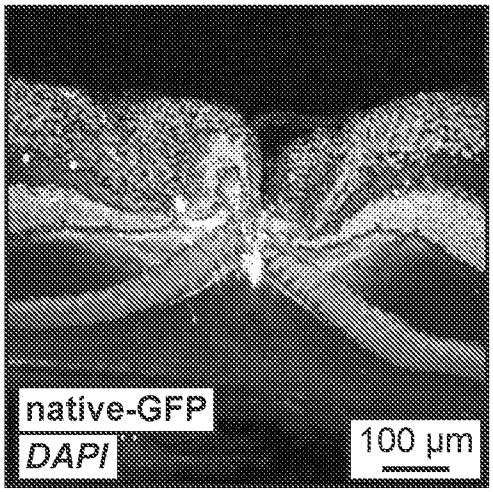


FIG. 13K

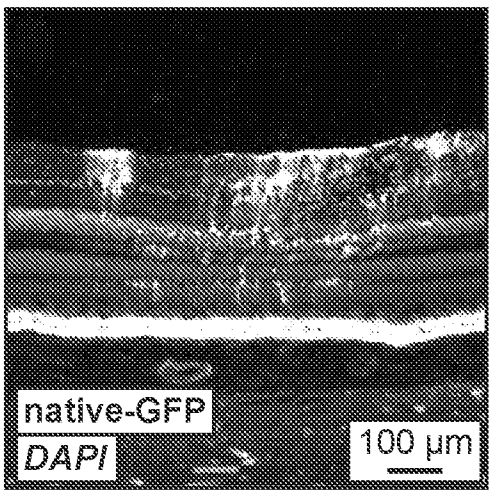


FIG. 13L

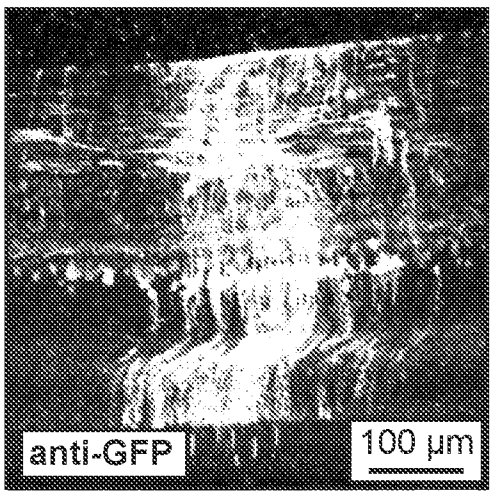


FIG. 13M

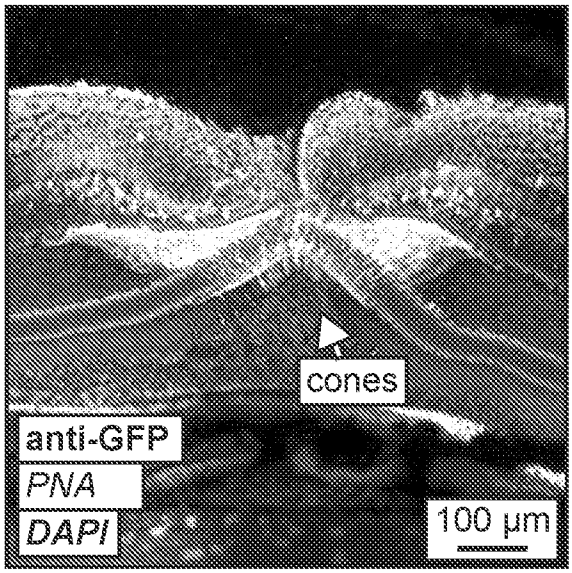


FIG. 13N

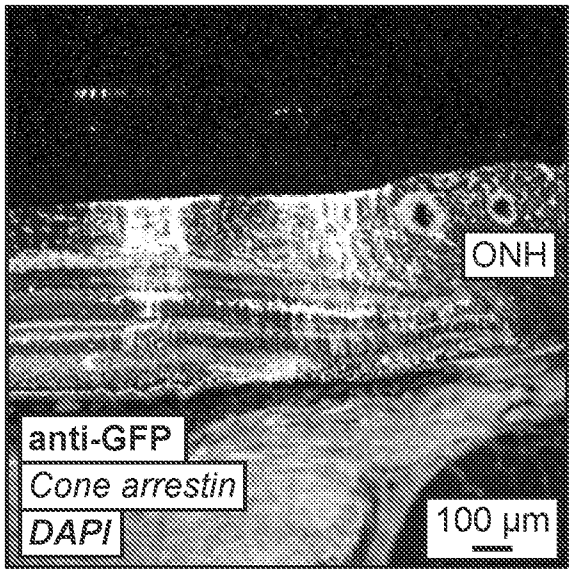


FIG. 13O

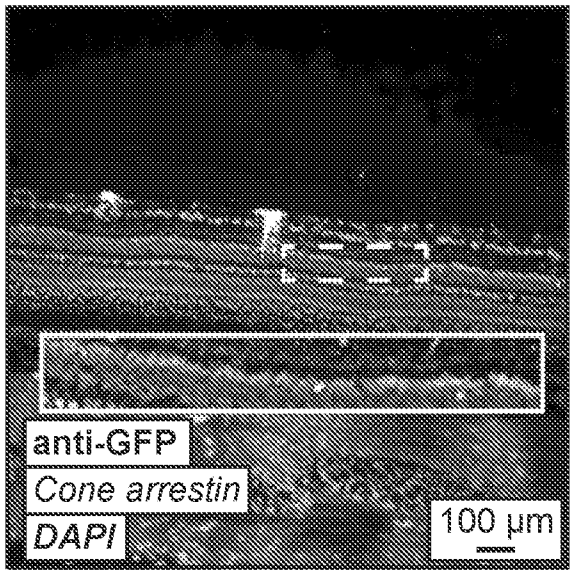


FIG. 13P

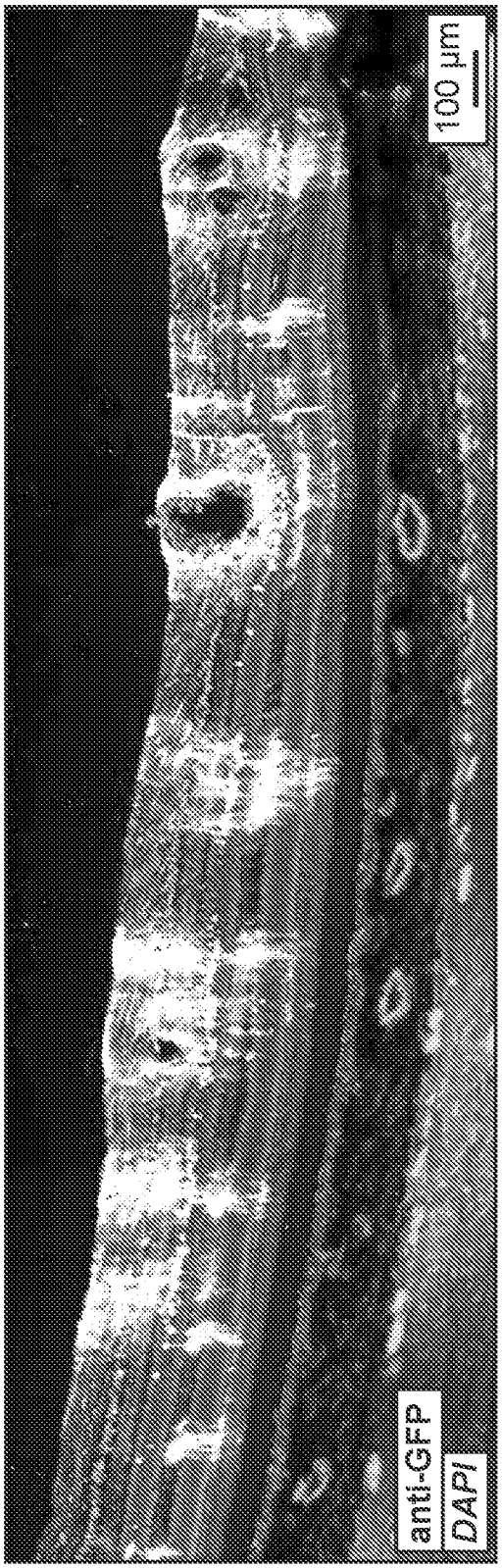
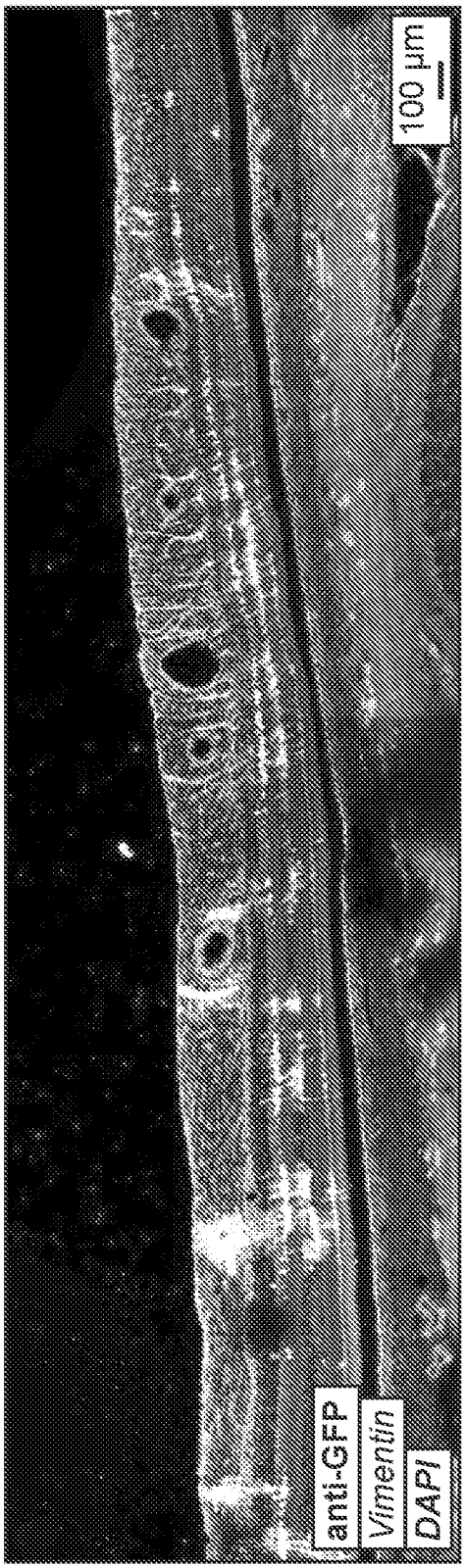


FIG. 13Q



SEQUENCE LISTING

<110> University of California - Berkeley
Schaffer, David V
Byrne, Leah C
Day, Timothy
Flannery, John G

<120> Adeno-Associated Virus Virions with Variant Capsid and Methods of Use Thereof

<130> BERK-355WO

<150> US 62/535,042
<151> 2017-07-20

<150> US 62/527,871
<151> 2017-06-30

<160> 143

<170> PatentIn version 3.5

<210> 1
<211> 733
<212> PRT
<213> Adeno-associated virus 2

<400> 1

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Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Thr Leu Ser
1               5                  10                  15


Glu Gly Ile Arg Gln Trp Trp Lys Leu Lys Pro Gly Pro Pro Pro Pro
            20                  25                  30


Lys Pro Ala Glu Arg His Lys Asp Asp Ser Arg Gly Leu Val Leu Pro
        35                  40                  45


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


Val Asn Glu Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80
```

```
Arg Gln Leu Asp Ser Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Pro Val Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu His Ser Pro Val Glu Pro Asp Ser Ser Ser Gly Thr Gly
145                 150                 155                 160

Lys Ala Gly Gln Gln Pro Ala Arg Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Ala Asp Ser Val Pro Asp Pro Gln Pro Leu Gly Gln Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Leu Gly Thr Asn Thr Met Ala Thr Gly Ser Gly
        195                 200                 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Met Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Ser Gln Ser Gly Ala Ser Asn Asp Asn His Tyr
            260                 265                 270
```

```
Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe His
        275                 280                 285

Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn Trp
    290                 295                 300

Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln Val
305                 310                 315                 320

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

Thr Ser Thr Val Gln Val Phe Thr Asp Ser Glu Tyr Gln Leu Pro Tyr
            340                 345                 350

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

Val Phe Met Val Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly Ser
    370                 375                 380

Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro Ser
385                 390                 395                 400

Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe Glu
                405                 410                 415

Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp Arg
            420                 425                 430

Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr
        435                 440                 445

Asn Thr Pro Ser Gly Thr Thr Thr Gln Ser Arg Leu Gln Phe Ser Gln
    450                 455                 460
```

```
Ala Gly Ala Ser Asp Ile Arg Asp Gln Ser Arg Asn Trp Leu Pro Gly
465                 470                 475                 480

Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Ser Ala Asp Asn Asn
                485                 490                 495

Asn Ser Glu Tyr Ser Trp Thr Gly Ala Thr Lys Tyr His Leu Asn Gly
            500                 505                 510

Arg Asp Ser Leu Val Asn Pro Gly Pro Ala Met Ala Ser His Lys Asp
        515                 520                 525

Asp Glu Glu Lys Phe Phe Pro Gln Ser Gly Val Leu Ile Phe Gly Lys
    530                 535                 540

Gln Gly Ser Glu Lys Thr Asn Val Asp Ile Glu Lys Val Met Ile Thr
545                 550                 555                 560

Asp Glu Glu Glu Ile Arg Thr Thr Asn Pro Val Ala Thr Glu Gln Tyr
                565                 570                 575

Gly Ser Val Ser Thr Asn Leu Gln Arg Gly Asn Arg Gln Ala Ala Thr
            580                 585                 590

Ala Asp Val Asn Thr Gln Gly Val Leu Pro Gly Met Val Trp Gln Asp
        595                 600                 605

Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr
    610                 615                 620

Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu Lys
625                 630                 635                 640

His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala Asn
                645                 650                 655
```

```
Pro Ser Thr Thr Phe Ser Ala Ala Lys Phe Ala Ser Phe Ile Thr Gln
            660                 665                 670


Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln Lys
        675                 680                 685


Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn Tyr
    690                 695                 700


Asn Lys Ser Val Asn Val Asp Phe Thr Val Asp Thr Asn Gly Val Tyr
705                 710                 715                 720


Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg
                725                 730


<210>  2
<211>  10
<212>  PRT
<213>  Artificial sequence

<220>
<223>  synthetic sequence

<400>  2

Leu Ala Asn Gln Glu His Val Lys Asn Ala
1               5                   10


<210>  3
<211>  20
<212>  DNA
<213>  Artificial sequence

<220>
<223>  synthetic sequence

<400>  3
cgcaacagga agcaacaccg                                                  20
```

<210> 4
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 4

Leu Thr His Gln Asp Thr Thr Lys Asn Ala
1 5 10

<210> 5
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 5

Gln Ala His Gln Asp Thr Thr Lys Asn Ala
1 5 10

<210> 6
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 6

Thr Gly Val Met Arg Ser Thr Asn Ser Gly Leu Asn
1 5 10

<210> 7
<211> 12
<212> PRT
<213> Artificial sequence

<220>

<223> synthetic sequence

<400> 7

Thr Gly Glu Val Asp Leu Ala Gly Gly Gly Leu Ser
1 5 10

<210> 8
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 8

Thr Ser Pro Tyr Ser Gly Ser Ser Asp Gly Leu Ser
1 5 10

<210> 9
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 9

Thr Gly Gly His Asp Ser Ser Leu Asp Gly Leu Ser
1 5 10

<210> 10
<211> 224
<212> PRT
<213> Homo sapiens

<400> 10

Met Ser Arg Lys Ile Glu Gly Phe Leu Leu Leu Leu Leu Phe Gly Tyr
1 5 10 15

Glu Ala Thr Leu Gly Leu Ser Ser Thr Glu Asp Glu Gly Glu Asp Pro

```
            20                  25                  30

Trp Tyr Gln Lys Ala Cys Lys Cys Asp Cys Gln Gly Gly Pro Asn Ala
        35                  40                  45

Leu Trp Ser Ala Gly Ala Thr Ser Leu Asp Cys Ile Pro Glu Cys Pro
    50                  55                  60

Tyr His Lys Pro Leu Gly Phe Glu Ser Gly Glu Val Thr Pro Asp Gln
65                  70                  75                  80

Ile Thr Cys Ser Asn Pro Glu Gln Tyr Val Gly Trp Tyr Ser Ser Trp
                85                  90                  95

Thr Ala Asn Lys Ala Arg Leu Asn Ser Gln Gly Phe Gly Cys Ala Trp
            100                 105                 110

Leu Ser Lys Phe Gln Asp Ser Ser Gln Trp Leu Gln Ile Asp Leu Lys
        115                 120                 125

Glu Ile Lys Val Ile Ser Gly Ile Leu Thr Gln Gly Arg Cys Asp Ile
    130                 135                 140

Asp Glu Trp Met Thr Lys Tyr Ser Val Gln Tyr Arg Thr Asp Glu Arg
145                 150                 155                 160

Leu Asn Trp Ile Tyr Tyr Lys Asp Gln Thr Gly Asn Asn Arg Val Phe
                165                 170                 175

Tyr Gly Asn Ser Asp Arg Thr Ser Thr Val Gln Asn Leu Leu Arg Pro
            180                 185                 190

Pro Ile Ile Ser Arg Phe Ile Arg Leu Ile Pro Leu Gly Trp His Val
        195                 200                 205

Arg Ile Ala Ile Arg Met Glu Leu Leu Glu Cys Val Ser Lys Cys Ala
```

210 215 220

<210> 11
<211> 247
<212> PRT
<213> Homo sapiens

<400> 11

Met Thr Ile Leu Phe Leu Thr Met Val Ile Ser Tyr Phe Gly Cys Met
1 5 10 15

Lys Ala Ala Pro Met Lys Glu Ala Asn Ile Arg Gly Gln Gly Gly Leu
20 25 30

Ala Tyr Pro Gly Val Arg Thr His Gly Thr Leu Glu Ser Val Asn Gly
35 40 45

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

His Val Ile Glu Glu Leu Leu Asp Glu Asp His Lys Val Arg Pro Asn
65 70 75 80

Glu Glu Asn Asn Lys Asp Ala Asp Leu Tyr Thr Ser Arg Val Met Leu
85 90 95

Ser Ser Gln Val Pro Leu Glu Pro Pro Leu Leu Phe Leu Leu Glu Glu
100 105 110

Tyr Lys Asn Tyr Leu Asp Ala Ala Asn Met Ser Met Met Val Leu Arg
115 120 125

His Ser Asp Pro Ala Arg Arg Gly Glu Leu Ser Val Cys Asp Ser Ile
130 135 140

Ser Glu Trp Val Thr Ala Ala Asp Lys Lys Thr Ala Val Asp Met Ser
145 150 155 160

```
Gly Gly Thr Val Thr Val Leu Glu Lys Val Pro Val Ser Lys Gly Gln
                165                 170                 175


Leu Lys Gln Tyr Phe Tyr Glu Thr Lys Cys Asn Pro Met Gly Tyr Thr
            180                 185                 190


Lys Glu Gly Cys Arg Gly Ile Asp Lys Arg His Trp Asn Ser Gln Cys
        195                 200                 205


Arg Thr Thr Gln Ser Tyr Val Arg Ala Leu Thr Met Asp Ser Lys Lys
    210                 215                 220


Arg Ile Gly Trp Arg Phe Ile Arg Ile Asp Thr Ser Cys Val Cys Thr
225                 230                 235                 240


Leu Thr Ile Lys Arg Gly Arg
                245


<210>  12
<211>  533
<212>  PRT
<213>  Homo sapiens

<400>  12

Met Ser Ile Gln Val Glu His Pro Ala Gly Gly Tyr Lys Lys Leu Phe
1               5                   10                  15


Glu Thr Val Glu Glu Leu Ser Ser Pro Leu Thr Ala His Val Thr Gly
            20                  25                  30


Arg Ile Pro Leu Trp Leu Thr Gly Ser Leu Leu Arg Cys Gly Pro Gly
        35                  40                  45


Leu Phe Glu Val Gly Ser Glu Pro Phe Tyr His Leu Phe Asp Gly Gln
    50                  55                  60
```

```
Ala Leu Leu His Lys Phe Asp Phe Lys Glu Gly His Val Thr Tyr His
65                  70                  75                  80

Arg Arg Phe Ile Arg Thr Asp Ala Tyr Val Arg Ala Met Thr Glu Lys
                85                  90                  95

Arg Ile Val Ile Thr Glu Phe Gly Thr Cys Ala Phe Pro Asp Pro Cys
            100                 105                 110

Lys Asn Ile Phe Ser Arg Phe Phe Ser Tyr Phe Arg Gly Val Glu Val
        115                 120                 125

Thr Asp Asn Ala Leu Val Asn Val Tyr Pro Val Gly Glu Asp Tyr Tyr
    130                 135                 140

Ala Cys Thr Glu Thr Asn Phe Ile Thr Lys Ile Asn Pro Glu Thr Leu
145                 150                 155                 160

Glu Thr Ile Lys Gln Val Asp Leu Cys Asn Tyr Val Ser Val Asn Gly
                165                 170                 175

Ala Thr Ala His Pro His Ile Glu Asn Asp Gly Thr Val Tyr Asn Ile
            180                 185                 190

Gly Asn Cys Phe Gly Lys Asn Phe Ser Ile Ala Tyr Asn Ile Val Lys
        195                 200                 205

Ile Pro Pro Leu Gln Ala Asp Lys Glu Asp Pro Ile Ser Lys Ser Glu
    210                 215                 220

Ile Val Val Gln Phe Pro Cys Ser Asp Arg Phe Lys Pro Ser Tyr Val
225                 230                 235                 240

His Ser Phe Gly Leu Thr Pro Asn Tyr Ile Val Phe Val Glu Thr Pro
                245                 250                 255
```

```
Val Lys Ile Asn Leu Phe Lys Phe Leu Ser Ser Trp Ser Leu Trp Gly
            260                 265                 270

Ala Asn Tyr Met Asp Cys Phe Glu Ser Asn Glu Thr Met Gly Val Trp
        275                 280                 285

Leu His Ile Ala Asp Lys Lys Arg Lys Lys Tyr Leu Asn Asn Lys Tyr
    290                 295                 300

Arg Thr Ser Pro Phe Asn Leu Phe His His Ile Asn Thr Tyr Glu Asp
305                 310                 315                 320

Asn Gly Phe Leu Ile Val Asp Leu Cys Cys Trp Lys Gly Phe Glu Phe
                325                 330                 335

Val Tyr Asn Tyr Leu Tyr Leu Ala Asn Leu Arg Glu Asn Trp Glu Glu
            340                 345                 350

Val Lys Lys Asn Ala Arg Lys Ala Pro Gln Pro Glu Val Arg Arg Tyr
        355                 360                 365

Val Leu Pro Leu Asn Ile Asp Lys Ala Asp Thr Gly Lys Asn Leu Val
    370                 375                 380

Thr Leu Pro Asn Thr Thr Ala Thr Ala Ile Leu Cys Ser Asp Glu Thr
385                 390                 395                 400

Ile Trp Leu Glu Pro Glu Val Leu Phe Ser Gly Pro Arg Gln Ala Phe
                405                 410                 415

Glu Phe Pro Gln Ile Asn Tyr Gln Lys Tyr Cys Gly Lys Pro Tyr Thr
            420                 425                 430

Tyr Ala Tyr Gly Leu Gly Leu Asn His Phe Val Pro Asp Arg Leu Cys
        435                 440                 445
```

```
Lys Leu Asn Val Lys Thr Lys Glu Thr Trp Val Trp Gln Glu Pro Asp
    450                 455                 460


Ser Tyr Pro Ser Glu Pro Ile Phe Val Ser His Pro Asp Ala Leu Glu
465                 470                 475                 480


Glu Asp Asp Gly Val Val Leu Ser Val Val Val Ser Pro Gly Ala Gly
                485                 490                 495


Gln Lys Pro Ala Tyr Leu Leu Ile Leu Asn Ala Lys Asp Leu Ser Glu
            500                 505                 510


Val Ala Arg Ala Glu Val Glu Ile Asn Ile Pro Val Thr Phe His Gly
        515                 520                 525


Leu Phe Lys Lys Ser
    530


<210>  13
<211>  346
<212>  PRT
<213>  Homo sapiens

<400>  13

Met Ala Leu Leu Lys Val Lys Phe Asp Gln Lys Lys Arg Val Lys Leu
1               5                   10                  15


Ala Gln Gly Leu Trp Leu Met Asn Trp Phe Ser Val Leu Ala Gly Ile
            20                  25                  30


Ile Ile Phe Ser Leu Gly Leu Phe Leu Lys Ile Glu Leu Arg Lys Arg
        35                  40                  45


Ser Asp Val Met Asn Asn Ser Glu Ser His Phe Val Pro Asn Ser Leu
    50                  55                  60
```

```
Ile Gly Met Gly Val Leu Ser Cys Val Phe Asn Ser Leu Ala Gly Lys
65                  70                  75                  80


Ile Cys Tyr Asp Ala Leu Asp Pro Ala Lys Tyr Ala Arg Trp Lys Pro
                85                  90                  95


Trp Leu Lys Pro Tyr Leu Ala Ile Cys Val Leu Phe Asn Ile Ile Leu
            100                 105                 110


Phe Leu Val Ala Leu Cys Cys Phe Leu Leu Arg Gly Ser Leu Glu Asn
        115                 120                 125


Thr Leu Gly Gln Gly Leu Lys Asn Gly Met Lys Tyr Tyr Arg Asp Thr
    130                 135                 140


Asp Thr Pro Gly Arg Cys Phe Met Lys Lys Thr Ile Asp Met Leu Gln
145                 150                 155                 160


Ile Glu Phe Lys Cys Cys Gly Asn Asn Gly Phe Arg Asp Trp Phe Glu
                165                 170                 175


Ile Gln Trp Ile Ser Asn Arg Tyr Leu Asp Phe Ser Ser Lys Glu Val
            180                 185                 190


Lys Asp Arg Ile Lys Ser Asn Val Asp Gly Arg Tyr Leu Val Asp Gly
        195                 200                 205


Val Pro Phe Ser Cys Cys Asn Pro Ser Ser Pro Arg Pro Cys Ile Gln
    210                 215                 220


Tyr Gln Ile Thr Asn Asn Ser Ala His Tyr Ser Tyr Asp His Gln Thr
225                 230                 235                 240


Glu Glu Leu Asn Leu Trp Val Arg Gly Cys Arg Ala Ala Leu Leu Ser
                245                 250                 255
```

```
Tyr Tyr Ser Ser Leu Met Asn Ser Met Gly Val Val Thr Leu Leu Ile
            260                 265                 270


Trp Leu Phe Glu Val Thr Ile Thr Ile Gly Leu Arg Tyr Leu Gln Thr
        275                 280                 285


Ser Leu Asp Gly Val Ser Asn Pro Glu Glu Ser Glu Ser Glu Ser Gln
    290                 295                 300


Gly Trp Leu Leu Glu Arg Ser Val Pro Glu Thr Trp Lys Ala Phe Leu
305                 310                 315                 320


Glu Ser Val Lys Lys Leu Gly Lys Gly Asn Gln Val Glu Ala Glu Gly
                325                 330                 335


Ala Asp Ala Gly Gln Ala Pro Glu Ala Gly
            340                 345


<210>  14
<211>  470
<212>  PRT
<213>  Homo sapiens

<400>  14

Met Ser His His Pro Ser Gly Leu Arg Ala Gly Phe Ser Ser Thr Ser
1               5                   10                  15


Tyr Arg Arg Thr Phe Gly Pro Pro Pro Ser Leu Ser Pro Gly Ala Phe
            20                  25                  30


Ser Tyr Ser Ser Ser Ser Arg Phe Ser Ser Ser Arg Leu Leu Gly Ser
        35                  40                  45


Ala Ser Pro Ser Ser Ser Val Arg Leu Gly Ser Phe Arg Ser Pro Arg
    50                  55                  60


Ala Gly Ala Gly Ala Leu Leu Arg Leu Pro Ser Glu Arg Leu Asp Phe
```

```
65                  70                  75                  80

Ser Met Ala Glu Ala Leu Asn Gln Glu Phe Leu Ala Thr Arg Ser Asn
                85                  90                  95

Glu Lys Gln Glu Leu Gln Glu Leu Asn Asp Arg Phe Ala Asn Phe Ile
            100                 105                 110

Glu Lys Val Arg Phe Leu Glu Gln Gln Asn Ala Ala Leu Arg Gly Glu
        115                 120                 125

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

Gln Gln Glu Leu Arg Glu Leu Arg Arg Glu Leu Glu Leu Leu Gly Arg
145                 150                 155                 160

Glu Arg Asp Arg Val Gln Val Glu Arg Asp Gly Leu Ala Glu Asp Leu
                165                 170                 175

Ala Ala Leu Lys Gln Arg Leu Glu Glu Glu Thr Arg Lys Arg Glu Asp
            180                 185                 190

Ala Glu His Asn Leu Val Leu Phe Arg Lys Asp Val Asp Asp Ala Thr
        195                 200                 205

Leu Ser Arg Leu Glu Leu Glu Arg Lys Ile Glu Ser Leu Met Asp Glu
    210                 215                 220

Ile Glu Phe Leu Lys Lys Leu His Glu Glu Glu Leu Arg Asp Leu Gln
225                 230                 235                 240

Val Ser Val Glu Ser Gln Gln Val Gln Gln Val Glu Val Glu Ala Thr
                245                 250                 255

Val Lys Pro Glu Leu Thr Ala Ala Leu Arg Asp Ile Arg Ala Gln Tyr
```

```
            260                 265                 270

Glu Ser Ile Ala Ala Lys Asn Leu Gln Glu Ala Glu Glu Trp Tyr Lys
        275                 280                 285

Ser Lys Tyr Ala Asp Leu Ser Asp Ala Ala Asn Arg Asn His Glu Ala
    290                 295                 300

Leu Arg Gln Ala Lys Gln Glu Met Asn Glu Ser Arg Arg Gln Ile Gln
305                 310                 315                 320

Ser Leu Thr Cys Glu Val Asp Gly Leu Arg Gly Thr Asn Glu Ala Leu
                325                 330                 335

Leu Arg Gln Leu Arg Glu Leu Glu Glu Gln Phe Ala Leu Glu Ala Gly
            340                 345                 350

Gly Tyr Gln Ala Gly Ala Ala Arg Leu Glu Glu Glu Leu Arg Gln Leu
        355                 360                 365

Lys Glu Glu Met Ala Arg His Leu Arg Glu Tyr Gln Glu Leu Leu Asn
    370                 375                 380

Val Lys Met Ala Leu Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu
385                 390                 395                 400

Glu Gly Glu Glu Ser Arg Ile Ser Val Pro Val His Ser Phe Ala Ser
                405                 410                 415

Leu Asn Ile Lys Thr Thr Val Pro Glu Val Glu Pro Pro Gln Asp Ser
            420                 425                 430

His Ser Arg Lys Thr Val Leu Ile Lys Thr Ile Glu Thr Arg Asn Gly
        435                 440                 445

Glu Val Val Thr Glu Ser Gln Lys Glu Gln Arg Ser Glu Leu Asp Lys
```

450 455 460

Ser Ser Ala His Ser Tyr
465 470

<210> 15
<211> 1286
<212> PRT
<213> Homo sapiens

<400> 15

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

Ile Asp Ala Ile Pro Leu Val Leu Pro Ala Ser Lys Gly Lys Asn Met
20 25 30

Lys Thr Gln Pro Pro Leu Ser Arg Met Asn Arg Glu Glu Leu Glu Asp
35 40 45

Ser Phe Phe Arg Leu Arg Glu Asp His Met Leu Val Lys Glu Leu Ser
50 55 60

Trp Lys Gln Gln Asp Glu Ile Lys Arg Leu Arg Thr Thr Leu Leu Arg
65 70 75 80

Leu Thr Ala Ala Gly Arg Asp Leu Arg Val Ala Glu Glu Ala Ala Pro
85 90 95

Leu Ser Glu Thr Ala Arg Arg Gly Gln Lys Ala Gly Trp Arg Gln Arg
100 105 110

Leu Ser Met His Gln Arg Pro Gln Met His Arg Leu Gln Gly His Phe
115 120 125

His Cys Val Gly Pro Ala Ser Pro Arg Arg Ala Gln Pro Arg Val Gln
130 135 140

```
Val Gly His Arg Gln Leu His Thr Ala Gly Ala Pro Val Pro Glu Lys
145                 150                 155                 160

Pro Lys Arg Gly Pro Arg Asp Arg Leu Ser Tyr Thr Ala Pro Pro Ser
                165                 170                 175

Phe Lys Glu His Ala Thr Asn Glu Asn Arg Gly Glu Val Ala Ser Lys
            180                 185                 190

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

Val Ile Ser Met Ala Lys Pro Ile Gly Leu Cys Met Pro Asn Ser Ala
    210                 215                 220

His Ile Met Ala Ser Asn Thr Met Gln Val Glu Glu Pro Pro Lys Ser
225                 230                 235                 240

Pro Glu Lys Met Trp Pro Lys Asp Glu Asn Phe Glu Gln Arg Ser Ser
                245                 250                 255

Leu Glu Cys Ala Gln Lys Ala Ala Glu Leu Arg Ala Ser Ile Lys Glu
            260                 265                 270

Lys Val Glu Leu Ile Arg Leu Lys Lys Leu Leu His Glu Arg Asn Ala
        275                 280                 285

Ser Leu Val Met Thr Lys Ala Gln Leu Thr Glu Val Gln Glu Ala Tyr
    290                 295                 300

Glu Thr Leu Leu Gln Lys Asn Gln Gly Ile Leu Ser Ala Ala His Glu
305                 310                 315                 320

Ala Leu Leu Lys Gln Val Asn Glu Leu Arg Ala Glu Leu Lys Glu Glu
                325                 330                 335
```

```
Ser Lys Lys Ala Val Ser Leu Lys Ser Gln Leu Glu Asp Val Ser Ile
            340                 345                 350

Leu Gln Met Thr Leu Lys Glu Phe Gln Glu Arg Val Glu Asp Leu Glu
        355                 360                 365

Lys Glu Arg Lys Leu Leu Asn Asp Asn Tyr Asp Lys Leu Leu Glu Ser
    370                 375                 380

Met Leu Asp Ser Ser Asp Ser Ser Ser Gln Pro His Trp Ser Asn Glu
385                 390                 395                 400

Leu Ile Ala Glu Gln Leu Gln Gln Gln Val Ser Gln Leu Gln Asp Gln
                405                 410                 415

Leu Asp Ala Glu Leu Glu Asp Lys Arg Lys Val Leu Leu Glu Leu Ser
            420                 425                 430

Arg Glu Lys Ala Gln Asn Glu Asp Leu Lys Leu Glu Val Thr Asn Ile
        435                 440                 445

Leu Gln Lys His Lys Gln Glu Val Glu Leu Leu Gln Asn Ala Ala Thr
    450                 455                 460

Ile Ser Gln Pro Pro Asp Arg Gln Ser Glu Pro Ala Thr His Pro Ala
465                 470                 475                 480

Val Leu Gln Glu Asn Thr Gln Ile Glu Pro Ser Glu Pro Lys Asn Gln
                485                 490                 495

Glu Glu Lys Lys Leu Ser Gln Val Leu Asn Glu Leu Gln Val Ser His
            500                 505                 510

Ala Glu Thr Thr Leu Glu Leu Glu Lys Thr Arg Asp Met Leu Ile Leu
        515                 520                 525
```

```
Gln Arg Lys Ile Asn Val Cys Tyr Gln Glu Glu Leu Glu Ala Met Met
    530                 535                 540

Thr Lys Ala Asp Asn Asp Asn Arg Asp His Lys Glu Lys Leu Glu Arg
545                 550                 555                 560

Leu Thr Arg Leu Leu Asp Leu Lys Asn Asn Arg Ile Lys Gln Leu Glu
                565                 570                 575

Gly Ile Leu Arg Ser His Asp Leu Pro Thr Ser Glu Gln Leu Lys Asp
            580                 585                 590

Val Ala Tyr Gly Thr Arg Pro Leu Ser Leu Cys Leu Glu Thr Leu Pro
        595                 600                 605

Ala His Gly Asp Glu Asp Lys Val Asp Ile Ser Leu Leu His Gln Gly
    610                 615                 620

Glu Asn Leu Phe Glu Leu His Ile His Gln Ala Phe Leu Thr Ser Ala
625                 630                 635                 640

Ala Leu Ala Gln Ala Gly Asp Thr Gln Pro Thr Thr Phe Cys Thr Tyr
                645                 650                 655

Ser Phe Tyr Asp Phe Glu Thr His Cys Thr Pro Leu Ser Val Gly Pro
            660                 665                 670

Gln Pro Leu Tyr Asp Phe Thr Ser Gln Tyr Val Met Glu Thr Asp Ser
        675                 680                 685

Leu Phe Leu His Tyr Leu Gln Glu Ala Ser Ala Arg Leu Asp Ile His
    690                 695                 700

Gln Ala Met Ala Ser Glu His Ser Thr Leu Ala Ala Gly Trp Ile Cys
705                 710                 715                 720
```

```
Phe Asp Arg Val Leu Glu Thr Val Glu Lys Val His Gly Leu Ala Thr
                725                 730                 735

Leu Ile Gly Ala Gly Gly Glu Glu Phe Gly Val Leu Glu Tyr Trp Met
            740                 745                 750

Arg Leu Arg Phe Pro Ile Lys Pro Ser Leu Gln Ala Cys Asn Lys Arg
        755                 760                 765

Lys Lys Ala Gln Val Tyr Leu Ser Thr Asp Val Leu Gly Gly Arg Lys
    770                 775                 780

Ala Gln Glu Glu Glu Phe Arg Ser Glu Ser Trp Glu Pro Gln Asn Glu
785                 790                 795                 800

Leu Trp Ile Glu Ile Thr Lys Cys Cys Gly Leu Arg Ser Arg Trp Leu
                805                 810                 815

Gly Thr Gln Pro Ser Pro Tyr Ala Val Tyr Arg Phe Phe Thr Phe Ser
            820                 825                 830

Asp His Asp Thr Ala Ile Ile Pro Ala Ser Asn Asn Pro Tyr Phe Arg
        835                 840                 845

Asp Gln Ala Arg Phe Pro Val Leu Val Thr Ser Asp Leu Asp His Tyr
    850                 855                 860

Leu Arg Arg Glu Ala Leu Ser Ile His Val Phe Asp Asp Glu Asp Leu
865                 870                 875                 880

Glu Pro Gly Ser Tyr Leu Gly Arg Ala Arg Val Pro Leu Leu Pro Leu
                885                 890                 895

Ala Lys Asn Glu Ser Ile Lys Gly Asp Phe Asn Leu Thr Asp Pro Ala
            900                 905                 910
```

```
Glu Lys Pro Asn Gly Ser Ile Gln Val Gln Leu Asp Trp Lys Phe Pro
        915                 920                 925

Tyr Ile Pro Pro Glu Ser Phe Leu Lys Pro Glu Ala Gln Thr Lys Gly
    930                 935                 940

Lys Asp Thr Lys Asp Ser Ser Lys Ile Ser Ser Glu Glu Glu Lys Ala
945                 950                 955                 960

Ser Phe Pro Ser Gln Asp Gln Met Ala Ser Pro Glu Val Pro Ile Glu
                965                 970                 975

Ala Gly Gln Tyr Arg Ser Lys Arg Lys Pro Pro His Gly Gly Glu Arg
            980                 985                 990

Lys Glu Lys Glu His Gln Val Val  Ser Tyr Ser Arg Arg  Lys His Gly
        995                 1000                1005

Lys Arg  Ile Gly Val Gln Gly  Lys Asn Arg Met Glu  Tyr Leu Ser
    1010                1015                1020

Leu Asn  Ile Leu Asn Gly Asn  Thr Pro Glu Gln Val  Asn Tyr Thr
    1025                1030                1035

Glu Trp  Lys Phe Ser Glu Thr  Asn Ser Phe Ile Gly  Asp Gly Phe
    1040                1045                1050

Lys Asn  Gln His Glu Glu Glu  Glu Met Thr Leu Ser  His Ser Ala
    1055                1060                1065

Leu Lys  Gln Lys Glu Pro Leu  His Pro Val Asn Asp  Lys Glu Ser
    1070                1075                1080

Ser Glu  Gln Gly Ser Glu Val  Ser Glu Ala Gln Thr  Thr Asp Ser
    1085                1090                1095
```

```
Asp Asp  Val Ile Val Pro Pro  Met Ser Gln Lys Tyr  Pro Lys Ala
    1100                1105                1110

Asp Ser  Glu Lys Met Cys Ile  Glu Ile Val Ser Leu  Ala Phe Tyr
    1115                1120                1125

Pro Glu  Ala Glu Val Met Ser  Asp Glu Asn Ile Lys  Gln Val Tyr
    1130                1135                1140

Val Glu  Tyr Lys Phe Tyr Asp  Leu Pro Leu Ser Glu  Thr Glu Thr
    1145                1150                1155

Pro Val  Ser Leu Arg Lys Pro  Arg Ala Gly Glu Glu  Ile His Phe
    1160                1165                1170

His Phe  Ser Lys Val Ile Asp  Leu Asp Pro Gln Glu  Gln Gln Gly
    1175                1180                1185

Arg Arg  Arg Phe Leu Phe Asp  Met Leu Asn Gly Gln  Asp Pro Asp
    1190                1195                1200

Gln Gly  His Leu Lys Phe Thr  Val Val Ser Asp Pro  Leu Asp Glu
    1205                1210                1215

Glu Lys  Lys Glu Cys Glu Glu  Val Gly Tyr Ala Tyr  Leu Gln Leu
    1220                1225                1230

Trp Gln  Ile Leu Glu Ser Gly  Arg Asp Ile Leu Glu  Gln Glu Leu
    1235                1240                1245

Asp Ile  Val Ser Pro Glu Asp  Leu Ala Thr Pro Ile  Gly Arg Leu
    1250                1255                1260

Lys Val  Ser Leu Gln Ala Ala  Ala Val Leu His Ala  Ile Tyr Lys
    1265                1270                1275
```

Glu Met Thr Glu Asp Leu Phe Ser
1280 1285

<210> 16
<211> 653
<212> PRT
<213> Homo sapiens

<400> 16

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

Gly Leu Pro Glu Ser Ile Ile Ala Ala Ala Cys Ser Arg Ser Gly Arg
20 25 30

Arg Val Leu His Val Asp Ser Arg Ser Tyr Tyr Gly Gly Asn Trp Ala
35 40 45

Ser Phe Ser Phe Ser Gly Leu Leu Ser Trp Leu Lys Glu Tyr Gln Glu
50 55 60

Asn Ser Asp Ile Val Ser Asp Ser Pro Val Trp Gln Asp Gln Ile Leu
65 70 75 80

Glu Asn Glu Glu Ala Ile Ala Leu Ser Arg Lys Asp Lys Thr Ile Gln
85 90 95

His Val Glu Val Phe Cys Tyr Ala Ser Gln Asp Leu His Glu Asp Val
100 105 110

Glu Glu Ala Gly Ala Leu Gln Lys Asn His Ala Leu Val Thr Ser Ala
115 120 125

Asn Ser Thr Glu Ala Ala Asp Ser Ala Phe Leu Pro Thr Glu Asp Glu
130 135 140

```
Ser Leu Ser Thr Met Ser Cys Glu Met Leu Thr Glu Gln Thr Pro Ser
145                 150                 155                 160

Ser Asp Pro Glu Asn Ala Leu Glu Val Asn Gly Ala Glu Val Thr Gly
                165                 170                 175

Glu Lys Glu Asn His Cys Asp Asp Lys Thr Cys Val Pro Ser Thr Ser
            180                 185                 190

Ala Glu Asp Met Ser Glu Asn Val Pro Ile Ala Glu Asp Thr Thr Glu
        195                 200                 205

Gln Pro Lys Lys Asn Arg Ile Thr Tyr Ser Gln Ile Ile Lys Glu Gly
    210                 215                 220

Arg Arg Phe Asn Ile Asp Leu Val Ser Lys Leu Leu Tyr Ser Arg Gly
225                 230                 235                 240

Leu Leu Ile Asp Leu Leu Ile Lys Ser Asn Val Ser Arg Tyr Ala Glu
                245                 250                 255

Phe Lys Asn Ile Thr Arg Ile Leu Ala Phe Arg Glu Gly Arg Val Glu
            260                 265                 270

Gln Val Pro Cys Ser Arg Ala Asp Val Phe Asn Ser Lys Gln Leu Thr
        275                 280                 285

Met Val Glu Lys Arg Met Leu Met Lys Phe Leu Thr Phe Cys Met Glu
    290                 295                 300

Tyr Glu Lys Tyr Pro Asp Glu Tyr Lys Gly Tyr Glu Glu Ile Thr Phe
305                 310                 315                 320

Tyr Glu Tyr Leu Lys Thr Gln Lys Leu Thr Pro Asn Leu Gln Tyr Ile
                325                 330                 335
```

```
Val Met His Ser Ile Ala Met Thr Ser Glu Thr Ala Ser Ser Thr Ile
            340                 345                 350


Asp Gly Leu Lys Ala Thr Lys Asn Phe Leu His Cys Leu Gly Arg Tyr
        355                 360                 365


Gly Asn Thr Pro Phe Leu Phe Pro Leu Tyr Gly Gln Gly Glu Leu Pro
    370                 375                 380


Gln Cys Phe Cys Arg Met Cys Ala Val Phe Gly Gly Ile Tyr Cys Leu
385                 390                 395                 400


Arg His Ser Val Gln Cys Leu Val Val Asp Lys Glu Ser Arg Lys Cys
                405                 410                 415


Lys Ala Ile Ile Asp Gln Phe Gly Gln Arg Ile Ile Ser Glu His Phe
            420                 425                 430


Leu Val Glu Asp Ser Tyr Phe Pro Glu Asn Met Cys Ser Arg Val Gln
        435                 440                 445


Tyr Arg Gln Ile Ser Arg Ala Val Leu Ile Thr Asp Arg Ser Val Leu
    450                 455                 460


Lys Thr Asp Ser Asp Gln Gln Ile Ser Ile Leu Thr Val Pro Ala Glu
465                 470                 475                 480


Glu Pro Gly Thr Phe Ala Val Arg Val Ile Glu Leu Cys Ser Ser Thr
                485                 490                 495


Met Thr Cys Met Lys Gly Thr Tyr Leu Val His Leu Thr Cys Thr Ser
            500                 505                 510


Ser Lys Thr Ala Arg Glu Asp Leu Glu Ser Val Val Gln Lys Leu Phe
        515                 520                 525
```

```
Val Pro Tyr Thr Glu Met Glu Ile Glu Asn Glu Gln Val Glu Lys Pro
    530                 535                 540


Arg Ile Leu Trp Ala Leu Tyr Phe Asn Met Arg Asp Ser Ser Asp Ile
545                 550                 555                 560


Ser Arg Ser Cys Tyr Asn Asp Leu Pro Ser Asn Val Tyr Val Cys Ser
                565                 570                 575


Gly Pro Asp Cys Gly Leu Gly Asn Asp Asn Ala Val Lys Gln Ala Glu
            580                 585                 590


Thr Leu Phe Gln Glu Ile Cys Pro Asn Glu Asp Phe Cys Pro Pro Pro
        595                 600                 605


Pro Asn Pro Glu Asp Ile Ile Leu Asp Gly Asp Ser Leu Gln Pro Glu
    610                 615                 620


Ala Ser Glu Ser Ser Ala Ile Pro Glu Ala Asn Ser Glu Thr Phe Lys
625                 630                 635                 640


Glu Ser Thr Asn Leu Gly Asn Leu Glu Glu Ser Ser Glu
                645                 650


<210>  17
<211>  212
<212>  PRT
<213>  Homo sapiens

<400>  17

Met Ala Ser Leu Phe Ser Gly Arg Ile Leu Ile Arg Asn Asn Ser Asp
1               5                   10                  15


Gln Asp Glu Leu Asp Thr Glu Ala Glu Val Ser Arg Arg Leu Glu Asn
            20                  25                  30
```

```
Arg Leu Val Leu Leu Phe Phe Gly Ala Gly Ala Cys Pro Gln Cys Gln
        35                  40                  45

Ala Phe Val Pro Ile Leu Lys Asp Phe Phe Val Arg Leu Thr Asp Glu
    50                  55                  60

Phe Tyr Val Leu Arg Ala Ala Gln Leu Ala Leu Val Tyr Val Ser Gln
65                  70                  75                  80

Asp Ser Thr Glu Glu Gln Gln Asp Leu Phe Leu Lys Asp Met Pro Lys
                85                  90                  95

Lys Trp Leu Phe Leu Pro Phe Glu Asp Asp Leu Arg Arg Asp Leu Gly
            100                 105                 110

Arg Gln Phe Ser Val Glu Arg Leu Pro Ala Val Val Val Leu Lys Pro
        115                 120                 125

Asp Gly Asp Val Leu Thr Arg Asp Gly Ala Asp Glu Ile Gln Arg Leu
    130                 135                 140

Gly Thr Ala Cys Phe Ala Asn Trp Gln Glu Ala Ala Glu Val Leu Asp
145                 150                 155                 160

Arg Asn Phe Gln Leu Pro Glu Asp Leu Glu Asp Gln Glu Pro Arg Ser
                165                 170                 175

Leu Thr Glu Cys Leu Arg Arg His Lys Tyr Arg Val Glu Lys Ala Ala
            180                 185                 190

Arg Gly Gly Arg Asp Pro Gly Gly Gly Gly Gly Glu Glu Gly Gly Ala
        195                 200                 205

Gly Gly Leu Phe
    210
```

<210> 18
<211> 156
<212> PRT
<213> Homo sapiens

<400> 18

```
Met Val Asp Ile Leu Gly Glu Arg His Leu Val Thr Cys Lys Gly Ala
1               5                  10                  15


Thr Val Glu Ala Glu Ala Ala Leu Gln Asn Lys Val Val Ala Leu Tyr
            20                  25                  30


Phe Ala Ala Ala Arg Cys Ala Pro Ser Arg Asp Phe Thr Pro Leu Leu
        35                  40                  45


Cys Asp Phe Tyr Thr Ala Leu Val Ala Glu Ala Arg Arg Pro Ala Pro
    50                  55                  60


Phe Glu Val Val Phe Val Ser Ala Asp Gly Ser Ser Gln Glu Met Leu
65                  70                  75                  80


Asp Phe Met Arg Glu Leu His Gly Ala Trp Leu Ala Leu Pro Phe His
                85                  90                  95


Asp Pro Tyr Arg His Glu Leu Arg Lys Arg Tyr Asn Val Thr Ala Ile
            100                 105                 110


Pro Lys Leu Val Ile Val Lys Gln Asn Gly Glu Val Ile Thr Asn Lys
        115                 120                 125


Gly Arg Lys Gln Ile Arg Glu Arg Gly Leu Ala Cys Phe Gln Asp Trp
    130                 135                 140


Val Glu Ala Ala Asp Ile Phe Gln Asn Phe Ser Val
145                 150                 155
```

<210> 19

<211> 135
<212> PRT
<213> Homo sapiens

<400> 19

```
Met Val Asp Ile Leu Gly Glu Arg His Leu Val Thr Cys Lys Gly Ala
1               5                  10                  15


Thr Val Glu Ala Glu Ala Ala Leu Gln Asn Lys Val Val Ala Leu Tyr
            20                  25                  30


Phe Ala Ala Ala Arg Cys Ala Pro Ser Arg Asp Phe Thr Pro Leu Leu
        35                  40                  45


Cys Asp Phe Tyr Thr Ala Leu Val Ala Glu Ala Arg Arg Pro Ala Pro
    50                  55                  60


Phe Glu Val Val Phe Val Ser Ala Asp Gly Ser Ser Gln Glu Met Leu
65                  70                  75                  80


Asp Phe Met Arg Glu Leu His Gly Ala Trp Leu Ala Leu Pro Phe His
                85                  90                  95


Asp Pro Tyr Arg Gln Arg Ser Leu Ala Leu Leu Pro Arg Leu Glu Cys
            100                 105                 110


Ser Gly Val Ile Leu Ala His Cys Asn Leu Cys Leu Leu Gly Ser Ser
        115                 120                 125


Asp Ser Leu Ala Leu Ala Ser
    130                 135
```

<210> 20
<211> 12
<212> PRT
<213> Artificial sequence

<220>

<223> synthetic sequence

<400> 20

Thr Val Val Ser Thr Gln Ala Gly Ile Gly Leu Ser
1 5 10

<210> 21
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 21

Thr Gly Val Met His Ser Gln Ala Ser Gly Leu Ser
1 5 10

<210> 22
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 22

Thr Gly Asp Gly Ser Pro Ala Ala Pro Gly Leu Ser
1 5 10

<210> 23
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 23

Thr Gly Ser Asp Met Ala His Gly Thr Gly Leu Ser
1 5 10

<210> 24
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 24

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

Thr

<210> 25
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 25

Thr Gly Ser Asp Gly Thr Arg Asp His Gly Leu Ser Pro Val Thr Trp
1 5 10 15

Thr

<210> 26
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 26

Asn Gly Ala Val Ala Asp Tyr Thr Arg Gly Leu Ser Pro Ala Thr Gly
1 5 10 15

Thr

<210> 27
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 27

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

Ala

<210> 28
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 28

Leu Gln Lys Asn Ala Arg Pro Ala Ser Thr Glu Ser Val Asn Phe Gln
1 5 10 15

<210> 29
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 29

Leu Gln Arg Gly Val Arg Ile Pro Ser Val Leu Glu Val Asn Gly Gln
1 5 10 15

<210> 30
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 30

Leu Gln Arg Gly Asn Arg Pro Val Thr Thr Ala Asp Val Asn Thr Gln
1 5 10 15

<210> 31
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 31

Leu Gln Lys Ala Asp Arg Gln Pro Gly Val Val Val Val Asn Cys Gln
1 5 10 15

<210> 32
<211> 1368
<212> PRT
<213> Streptococcus pyogenes

<400> 32

Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp 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
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

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
            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


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>  33
<211>  1053
<212>  PRT
<213>  Staphylococcus aureus

<400>  33

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


Gly Tyr Gly Ile Ile Asp Tyr Glu Thr Arg Asp Val Ile Asp Ala Gly
            20                  25                  30


Val Arg Leu Phe Lys Glu Ala Asn Val Glu Asn Asn Glu Gly Arg Arg
        35                  40                  45


Ser Lys Arg Gly Ala Arg Arg Leu Lys Arg Arg Arg Arg His Arg Ile
    50                  55                  60


Gln Arg Val Lys Lys Leu Leu Phe Asp Tyr Asn Leu Leu Thr Asp His
65                  70                  75                  80


Ser Glu Leu Ser Gly Ile Asn Pro Tyr Glu Ala Arg Val Lys Gly Leu
                85                  90                  95


Ser Gln Lys Leu Ser Glu Glu Glu Phe Ser Ala Ala Leu Leu His Leu
            100                 105                 110


Ala Lys Arg Arg Gly Val His Asn Val Asn Glu Val Glu Glu Asp Thr
        115                 120                 125


Gly Asn Glu Leu Ser Thr Lys Glu Gln Ile Ser Arg Asn Ser Lys Ala
    130                 135                 140
```

```
Leu Glu Glu Lys Tyr Val Ala Glu Leu Gln Leu Glu Arg Leu Lys Lys
145                 150                 155                 160


Asp Gly Glu Val Arg Gly Ser Ile Asn Arg Phe Lys Thr Ser Asp Tyr
                165                 170                 175


Val Lys Glu Ala Lys Gln Leu Leu Lys Val Gln Lys Ala Tyr His Gln
            180                 185                 190


Leu Asp Gln Ser Phe Ile Asp Thr Tyr Ile Asp Leu Leu Glu Thr Arg
        195                 200                 205


Arg Thr Tyr Tyr Glu Gly Pro Gly Glu Gly Ser Pro Phe Gly Trp Lys
    210                 215                 220


Asp Ile Lys Glu Trp Tyr Glu Met Leu Met Gly His Cys Thr Tyr Phe
225                 230                 235                 240


Pro Glu Glu Leu Arg Ser Val Lys Tyr Ala Tyr Asn Ala Asp Leu Tyr
                245                 250                 255


Asn Ala Leu Asn Asp Leu Asn Asn Leu Val Ile Thr Arg Asp Glu Asn
            260                 265                 270


Glu Lys Leu Glu Tyr Tyr Glu Lys Phe Gln Ile Ile Glu Asn Val Phe
        275                 280                 285


Lys Gln Lys Lys Lys Pro Thr Leu Lys Gln Ile Ala Lys Glu Ile Leu
    290                 295                 300


Val Asn Glu Glu Asp Ile Lys Gly Tyr Arg Val Thr Ser Thr Gly Lys
305                 310                 315                 320


Pro Glu Phe Thr Asn Leu Lys Val Tyr His Asp Ile Lys Asp Ile Thr
                325                 330                 335
```

```
Ala Arg Lys Glu Ile Ile Glu Asn Ala Glu Leu Leu Asp Gln Ile Ala
            340                 345                 350


Lys Ile Leu Thr Ile Tyr Gln Ser Ser Glu Asp Ile Gln Glu Glu Leu
        355                 360                 365


Thr Asn Leu Asn Ser Glu Leu Thr Gln Glu Glu Ile Glu Gln Ile Ser
    370                 375                 380


Asn Leu Lys Gly Tyr Thr Gly Thr His Asn Leu Ser Leu Lys Ala Ile
385                 390                 395                 400


Asn Leu Ile Leu Asp Glu Leu Trp His Thr Asn Asp Asn Gln Ile Ala
                405                 410                 415


Ile Phe Asn Arg Leu Lys Leu Val Pro Lys Lys Val Asp Leu Ser Gln
            420                 425                 430


Gln Lys Glu Ile Pro Thr Thr Leu Val Asp Asp Phe Ile Leu Ser Pro
        435                 440                 445


Val Val Lys Arg Ser Phe Ile Gln Ser Ile Lys Val Ile Asn Ala Ile
    450                 455                 460


Ile Lys Lys Tyr Gly Leu Pro Asn Asp Ile Ile Ile Glu Leu Ala Arg
465                 470                 475                 480


Glu Lys Asn Ser Lys Asp Ala Gln Lys Met Ile Asn Glu Met Gln Lys
                485                 490                 495


Arg Asn Arg Gln Thr Asn Glu Arg Ile Glu Glu Ile Ile Arg Thr Thr
            500                 505                 510


Gly Lys Glu Asn Ala Lys Tyr Leu Ile Glu Lys Ile Lys Leu His Asp
        515                 520                 525
```

```
Met Gln Glu Gly Lys Cys Leu Tyr Ser Leu Glu Ala Ile Pro Leu Glu
    530                 535                 540

Asp Leu Leu Asn Asn Pro Phe Asn Tyr Glu Val Asp His Ile Ile Pro
545                 550                 555                 560

Arg Ser Val Ser Phe Asp Asn Ser Phe Asn Asn Lys Val Leu Val Lys
                565                 570                 575

Gln Glu Glu Asn Ser Lys Lys Gly Asn Arg Thr Pro Phe Gln Tyr Leu
            580                 585                 590

Ser Ser Ser Asp Ser Lys Ile Ser Tyr Glu Thr Phe Lys Lys His Ile
        595                 600                 605

Leu Asn Leu Ala Lys Gly Lys Gly Arg Ile Ser Lys Thr Lys Lys Glu
    610                 615                 620

Tyr Leu Leu Glu Glu Arg Asp Ile Asn Arg Phe Ser Val Gln Lys Asp
625                 630                 635                 640

Phe Ile Asn Arg Asn Leu Val Asp Thr Arg Tyr Ala Thr Arg Gly Leu
                645                 650                 655

Met Asn Leu Leu Arg Ser Tyr Phe Arg Val Asn Asn Leu Asp Val Lys
            660                 665                 670

Val Lys Ser Ile Asn Gly Gly Phe Thr Ser Phe Leu Arg Arg Lys Trp
        675                 680                 685

Lys Phe Lys Lys Glu Arg Asn Lys Gly Tyr Lys His His Ala Glu Asp
    690                 695                 700

Ala Leu Ile Ile Ala Asn Ala Asp Phe Ile Phe Lys Glu Trp Lys Lys
705                 710                 715                 720
```

```
Leu Asp Lys Ala Lys Lys Val Met Glu Asn Gln Met Phe Glu Glu Lys
               725                 730                 735

Gln Ala Glu Ser Met Pro Glu Ile Glu Thr Glu Gln Glu Tyr Lys Glu
            740                 745                 750

Ile Phe Ile Thr Pro His Gln Ile Lys His Ile Lys Asp Phe Lys Asp
        755                 760                 765

Tyr Lys Tyr Ser His Arg Val Asp Lys Lys Pro Asn Arg Glu Leu Ile
    770                 775                 780

Asn Asp Thr Leu Tyr Ser Thr Arg Lys Asp Asp Lys Gly Asn Thr Leu
785                 790                 795                 800

Ile Val Asn Asn Leu Asn Gly Leu Tyr Asp Lys Asp Asn Asp Lys Leu
               805                 810                 815

Lys Lys Leu Ile Asn Lys Ser Pro Glu Lys Leu Leu Met Tyr His His
            820                 825                 830

Asp Pro Gln Thr Tyr Gln Lys Leu Lys Leu Ile Met Glu Gln Tyr Gly
        835                 840                 845

Asp Glu Lys Asn Pro Leu Tyr Lys Tyr Tyr Glu Glu Thr Gly Asn Tyr
    850                 855                 860

Leu Thr Lys Tyr Ser Lys Lys Asp Asn Gly Pro Val Ile Lys Lys Ile
865                 870                 875                 880

Lys Tyr Tyr Gly Asn Lys Leu Asn Ala His Leu Asp Ile Thr Asp Asp
               885                 890                 895

Tyr Pro Asn Ser Arg Asn Lys Val Val Lys Leu Ser Leu Lys Pro Tyr
            900                 905                 910
```

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Arg Phe Asp Val Tyr Leu Asp Asn Gly Val Tyr Lys Phe Val Thr Val
        915                 920                 925


Lys Asn Leu Asp Val Ile Lys Lys Glu Asn Tyr Tyr Glu Val Asn Ser
    930                 935                 940


Lys Cys Tyr Glu Glu Ala Lys Lys Leu Lys Lys Ile Ser Asn Gln Ala
945                 950                 955                 960


Glu Phe Ile Ala Ser Phe Tyr Asn Asn Asp Leu Ile Lys Ile Asn Gly
                965                 970                 975


Glu Leu Tyr Arg Val Ile Gly Val Asn Asn Asp Leu Leu Asn Arg Ile
            980                 985                 990


Glu Val Asn Met Ile Asp Ile Thr  Tyr Arg Glu Tyr Leu  Glu Asn Met
        995                 1000                1005


Asn Asp  Lys Arg Pro Pro Arg  Ile Ile Lys Thr Ile  Ala Ser Lys
    1010                1015                1020


Thr Gln  Ser Ile Lys Lys Tyr  Ser Thr Asp Ile Leu  Gly Asn Leu
    1025                1030                1035


Tyr Glu  Val Lys Ser Lys Lys  His Pro Gln Ile Ile  Lys Lys Gly
    1040                1045                1050


<210>  34
<211>  1300
<212>  PRT
<213>  Francisella tularensis

<400>  34

Met Ser Ile Tyr Gln Glu Phe Val Asn Lys Tyr Ser Leu Ser Lys Thr
1               5                   10                  15


Leu Arg Phe Glu Leu Ile Pro Gln Gly Lys Thr Leu Glu Asn Ile Lys
```

```
            20                  25                  30

Ala Arg Gly Leu Ile Leu Asp Asp Glu Lys Arg Ala Lys Asp Tyr Lys
        35                  40                  45

Lys Ala Lys Gln Ile Ile Asp Lys Tyr His Gln Phe Phe Ile Glu Glu
    50                  55                  60

Ile Leu Ser Ser Val Cys Ile Ser Glu Asp Leu Leu Gln Asn Tyr Ser
65                  70                  75                  80

Asp Val Tyr Phe Lys Leu Lys Lys Ser Asp Asp Asp Asn Leu Gln Lys
                85                  90                  95

Asp Phe Lys Ser Ala Lys Asp Thr Ile Lys Lys Gln Ile Ser Glu Tyr
            100                 105                 110

Ile Lys Asp Ser Glu Lys Phe Lys Asn Leu Phe Asn Gln Asn Leu Ile
        115                 120                 125

Asp Ala Lys Lys Gly Gln Glu Ser Asp Leu Ile Leu Trp Leu Lys Gln
    130                 135                 140

Ser Lys Asp Asn Gly Ile Glu Leu Phe Lys Ala Asn Ser Asp Ile Thr
145                 150                 155                 160

Asp Ile Asp Glu Ala Leu Glu Ile Ile Lys Ser Phe Lys Gly Trp Thr
                165                 170                 175

Thr Tyr Phe Lys Gly Phe His Glu Asn Arg Lys Asn Val Tyr Ser Ser
            180                 185                 190

Asn Asp Ile Pro Thr Ser Ile Ile Tyr Arg Ile Val Asp Asp Asn Leu
        195                 200                 205

Pro Lys Phe Leu Glu Asn Lys Ala Lys Tyr Glu Ser Leu Lys Asp Lys
```

```
    210                 215                 220

Ala Pro Glu Ala Ile Asn Tyr Glu Gln Ile Lys Lys Asp Leu Ala Glu
225                 230                 235                 240

Glu Leu Thr Phe Asp Ile Asp Tyr Lys Thr Ser Glu Val Asn Gln Arg
                245                 250                 255

Val Phe Ser Leu Asp Glu Val Phe Glu Ile Ala Asn Phe Asn Asn Tyr
            260                 265                 270

Leu Asn Gln Ser Gly Ile Thr Lys Phe Asn Thr Ile Ile Gly Gly Lys
        275                 280                 285

Phe Val Asn Gly Glu Asn Thr Lys Arg Lys Gly Ile Asn Glu Tyr Ile
    290                 295                 300

Asn Leu Tyr Ser Gln Gln Ile Asn Asp Lys Thr Leu Lys Lys Tyr Lys
305                 310                 315                 320

Met Ser Val Leu Phe Lys Gln Ile Leu Ser Asp Thr Glu Ser Lys Ser
                325                 330                 335

Phe Val Ile Asp Lys Leu Glu Asp Asp Ser Asp Val Val Thr Thr Met
            340                 345                 350

Gln Ser Phe Tyr Glu Gln Ile Ala Ala Phe Lys Thr Val Glu Glu Lys
        355                 360                 365

Ser Ile Lys Glu Thr Leu Ser Leu Leu Phe Asp Asp Leu Lys Ala Gln
    370                 375                 380

Lys Leu Asp Leu Ser Lys Ile Tyr Phe Lys Asn Asp Lys Ser Leu Thr
385                 390                 395                 400

Asp Leu Ser Gln Gln Val Phe Asp Asp Tyr Ser Val Ile Gly Thr Ala
```

405 410 415

Val Leu Glu Tyr Ile Thr Gln Gln Ile Ala Pro Lys Asn Leu Asp Asn
420 425 430

Pro Ser Lys Lys Glu Gln Glu Leu Ile Ala Lys Lys Thr Glu Lys Ala
435 440 445

Lys Tyr Leu Ser Leu Glu Thr Ile Lys Leu Ala Leu Glu Glu Phe Asn
450 455 460

Lys His Arg Asp Ile Asp Lys Gln Cys Arg Phe Glu Glu Ile Leu Ala
465 470 475 480

Asn Phe Ala Ala Ile Pro Met Ile Phe Asp Glu Ile Ala Gln Asn Lys
485 490 495

Asp Asn Leu Ala Gln Ile Ser Ile Lys Tyr Gln Asn Gln Gly Lys Lys
500 505 510

Asp Leu Leu Gln Ala Ser Ala Glu Asp Asp Val Lys Ala Ile Lys Asp
515 520 525

Leu Leu Asp Gln Thr Asn Asn Leu Leu His Lys Leu Lys Ile Phe His
530 535 540

Ile Ser Gln Ser Glu Asp Lys Ala Asn Ile Leu Asp Lys Asp Glu His
545 550 555 560

Phe Tyr Leu Val Phe Glu Glu Cys Tyr Phe Glu Leu Ala Asn Ile Val
565 570 575

Pro Leu Tyr Asn Lys Ile Arg Asn Tyr Ile Thr Gln Lys Pro Tyr Ser
580 585 590

Asp Glu Lys Phe Lys Leu Asn Phe Glu Asn Ser Thr Leu Ala Asn Gly

```
        595                 600                 605

Trp Asp Lys Asn Lys Glu Pro Asp Asn Thr Ala Ile Leu Phe Ile Lys
    610                 615                 620

Asp Asp Lys Tyr Tyr Leu Gly Val Met Asn Lys Lys Asn Asn Lys Ile
625                 630                 635                 640

Phe Asp Asp Lys Ala Ile Lys Glu Asn Lys Gly Glu Gly Tyr Lys Lys
                645                 650                 655

Ile Val Tyr Lys Leu Leu Pro Gly Ala Asn Lys Met Leu Pro Lys Val
            660                 665                 670

Phe Phe Ser Ala Lys Ser Ile Lys Phe Tyr Asn Pro Ser Glu Asp Ile
        675                 680                 685

Leu Arg Ile Arg Asn His Ser Thr His Thr Lys Asn Gly Ser Pro Gln
    690                 695                 700

Lys Gly Tyr Glu Lys Phe Glu Phe Asn Ile Glu Asp Cys Arg Lys Phe
705                 710                 715                 720

Ile Asp Phe Tyr Lys Gln Ser Ile Ser Lys His Pro Glu Trp Lys Asp
                725                 730                 735

Phe Gly Phe Arg Phe Ser Asp Thr Gln Arg Tyr Asn Ser Ile Asp Glu
            740                 745                 750

Phe Tyr Arg Glu Val Glu Asn Gln Gly Tyr Lys Leu Thr Phe Glu Asn
        755                 760                 765

Ile Ser Glu Ser Tyr Ile Asp Ser Val Val Asn Gln Gly Lys Leu Tyr
    770                 775                 780

Leu Phe Gln Ile Tyr Asn Lys Asp Phe Ser Ala Tyr Ser Lys Gly Arg
```

```
785                 790                 795                 800

Pro Asn Leu His Thr Leu Tyr Trp Lys Ala Leu Phe Asp Glu Arg Asn
                805                 810                 815

Leu Gln Asp Val Val Tyr Lys Leu Asn Gly Glu Ala Glu Leu Phe Tyr
            820                 825                 830

Arg Lys Gln Ser Ile Pro Lys Lys Ile Thr His Pro Ala Lys Glu Ala
        835                 840                 845

Ile Ala Asn Lys Asn Lys Asp Asn Pro Lys Lys Glu Ser Val Phe Glu
    850                 855                 860

Tyr Asp Leu Ile Lys Asp Lys Arg Phe Thr Glu Asp Lys Phe Phe Phe
865                 870                 875                 880

His Cys Pro Ile Thr Ile Asn Phe Lys Ser Ser Gly Ala Asn Lys Phe
                885                 890                 895

Asn Asp Glu Ile Asn Leu Leu Leu Lys Glu Lys Ala Asn Asp Val His
            900                 905                 910

Ile Leu Ser Ile Asp Arg Gly Glu Arg His Leu Ala Tyr Tyr Thr Leu
        915                 920                 925

Val Asp Gly Lys Gly Asn Ile Ile Lys Gln Asp Thr Phe Asn Ile Ile
    930                 935                 940

Gly Asn Asp Arg Met Lys Thr Asn Tyr His Asp Lys Leu Ala Ala Ile
945                 950                 955                 960

Glu Lys Asp Arg Asp Ser Ala Arg Lys Asp Trp Lys Lys Ile Asn Asn
                965                 970                 975

Ile Lys Glu Met Lys Glu Gly Tyr Leu Ser Gln Val Val His Glu Ile
```

```
           980                 985                 990

Ala Lys Leu Val Ile Glu Tyr Asn  Ala Ile Val Val Phe  Glu Asp Leu
        995                1000                1005

Asn Phe  Gly Phe Lys Arg Gly  Arg Phe Lys Val Glu  Lys Gln Val
    1010                1015                1020

Tyr Gln  Lys Leu Glu Lys Met  Leu Ile Glu Lys Leu  Asn Tyr Leu
    1025                1030                1035

Val Phe  Lys Asp Asn Glu Phe  Asp Lys Thr Gly Gly  Val Leu Arg
    1040                1045                1050

Ala Tyr  Gln Leu Thr Ala Pro  Phe Glu Thr Phe Lys  Lys Met Gly
    1055                1060                1065

Lys Gln  Thr Gly Ile Ile Tyr  Tyr Val Pro Ala Gly  Phe Thr Ser
    1070                1075                1080

Lys Ile  Cys Pro Val Thr Gly  Phe Val Asn Gln Leu  Tyr Pro Lys
    1085                1090                1095

Tyr Glu  Ser Val Ser Lys Ser  Gln Glu Phe Phe Ser  Lys Phe Asp
    1100                1105                1110

Lys Ile  Cys Tyr Asn Leu Asp  Lys Gly Tyr Phe Glu  Phe Ser Phe
    1115                1120                1125

Asp Tyr  Lys Asn Phe Gly Asp  Lys Ala Ala Lys Gly  Lys Trp Thr
    1130                1135                1140

Ile Ala  Ser Phe Gly Ser Arg  Leu Ile Asn Phe Arg  Asn Ser Asp
    1145                1150                1155

Lys Asn  His Asn Trp Asp Thr  Arg Glu Val Tyr Pro  Thr Lys Glu
```

```
    1160                1165                1170

Leu Glu  Lys Leu Leu Lys Asp  Tyr Ser Ile Glu Tyr  Gly His Gly
    1175                1180                1185

Glu Cys  Ile Lys Ala Ala Ile  Cys Gly Glu Ser Asp  Lys Lys Phe
    1190                1195                1200

Phe Ala  Lys Leu Thr Ser Val  Leu Asn Thr Ile Leu  Gln Met Arg
    1205                1210                1215

Asn Ser  Lys Thr Gly Thr Glu  Leu Asp Tyr Leu Ile  Ser Pro Val
    1220                1225                1230

Ala Asp  Val Asn Gly Asn Phe  Phe Asp Ser Arg Gln  Ala Pro Lys
    1235                1240                1245

Asn Met  Pro Gln Asp Ala Asp  Ala Asn Gly Ala Tyr  His Ile Gly
    1250                1255                1260

Leu Lys  Gly Leu Met Leu Leu  Gly Arg Ile Lys Asn  Asn Gln Glu
    1265                1270                1275

Gly Lys  Lys Leu Asn Leu Val  Ile Lys Asn Glu Glu  Tyr Phe Glu
    1280                1285                1290

Phe Val  Gln Asn Arg Asn Asn
    1295                1300


<210>  35
<211>  10
<212>  PRT
<213>  Artificial sequence

<220>
<223>  synthetic sequence

<400>  35
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Leu Ala Leu Ile Gln Asp Ser Met Arg Ala
1               5                   10


<210>  36
<211>  42
<212>  PRT
<213>  Artificial sequence

<220>
<223>  synthetic sequence

<400>  36

Pro Val Ala Thr Glu Gln Tyr Gly Ser Val Ser Thr Asn Leu Gln Arg
1               5                   10                  15


Gly Asn Arg Gln Ala Ala Thr Ala Asp Val Asn Thr Gln Gly Val Leu
            20                  25                  30


Pro Gly Met Val Trp Gln Asp Arg Asp Val
        35                  40


<210>  37
<211>  42
<212>  PRT
<213>  Artificial sequence

<220>
<223>  synthetic sequence

<400>  37

Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Gln Ser
1               5                   10                  15


Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala Leu
            20                  25                  30


Pro Gly Met Val Trp Gln Asp Arg Asp Val
        35                  40
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<210> 38
<211> 42
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 38

Arg Val Ala Tyr Asn Val Gly Gly Gln Met Ala Thr Asn Asn Gln Ser
1 5 10 15

Ser Thr Thr Ala Pro Ala Thr Gly Thr Tyr Asn Leu Gln Glu Ile Val
20 25 30

Pro Gly Ser Val Trp Met Glu Arg Asp Val
35 40

<210> 39
<211> 42
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 39

Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Leu Gln Ser
1 5 10 15

Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Val Met Gly Ala Leu
20 25 30

Pro Gly Met Val Trp Gln Asp Arg Asp Val
35 40

<210> 40
<211> 42
<212> PRT

<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 40

Pro Val Ala Thr Glu Glu Tyr Gly Ile Val Ser Ser Asn Leu Gln Ala
1 5 10 15

Ala Asn Thr Ala Ala Gln Thr Gln Val Val Asn Asn Gln Gly Ala Leu
20 25 30

Pro Gly Met Val Trp Gln Asn Arg Asp Val
35 40

<210> 41
<211> 42
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 41

Pro Val Ala Thr Glu Glu Tyr Gly Ile Val Ala Asp Asn Leu Gln Gln
1 5 10 15

Gln Asn Thr Ala Pro Gln Ile Gly Thr Val Asn Ser Gln Gly Ala Leu
20 25 30

Pro Gly Met Val Trp Gln Asn Arg Asp Val
35 40

<210> 42
<211> 42
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 42

Pro Val Ala Thr Glu Ser Tyr Gly Gln Val Ala Thr Asn His Gln Ser
1 5 10 15

Ala Gln Ala Gln Ala Gln Thr Gly Trp Val Gln Asn Gln Gly Ile Leu
20 25 30

Pro Gly Met Val Trp Gln Asp Arg Asp Val
35 40

<210> 43
<211> 42
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 43

Pro Val Ala Thr Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln Gln
1 5 10 15

Ala Asn Thr Gly Pro Ile Val Gly Asn Val Asn Ser Gln Gly Ala Leu
20 25 30

Pro Gly Met Val Trp Gln Asn Arg Asp Val
35 40

<210> 44
<211> 42
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 44

Ala Thr Asp Thr Asp Met Trp Gly Asn Leu Pro Gly Gly Asp Gln Ser

1 5 10 15

Asn Ser Asn Leu Pro Thr Val Asp Arg Leu Thr Ala Leu Gly Ala Val
20 25 30

Pro Gly Met Val Trp Gln Asn Arg Asp Ile
35 40

<210> 45
<211> 42
<212> PRT
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<220>
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<220>
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<222> (6)..(6)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (12)..(12)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (22)..(22)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (25)..(25)
<223> Xaa can be any naturally occurring amino acid

<400> 45

Pro Val Ala Thr Glu Xaa Tyr Gly Val Val Ala Xaa Asn Leu Gln Ser
1 5 10 15

Ser Asn Thr Ala Pro Xaa Thr Gly Xaa Val Asn Ser Gln Gly Ala Leu
20 25 30

```
Pro Gly Met Val Trp Gln Asn Arg Asp Val
        35                  40


<210>  46
<211>  60
<212>  PRT
<213>  Artificial sequence

<220>
<223>  synthetic sequence


<220>
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<222>  (1)..(2)
<223>  Xaa can be any naturally occurring amino acid

<220>
<221>  misc_feature
<222>  (43)..(43)
<223>  Xaa can be any naturally occurring amino acid

<400>  46

Xaa Xaa Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser
1               5                   10                  15


Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
            20                  25                  30


Gln Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Xaa Asn Gln Ser Gly Ser
        35                  40                  45


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


<210>  47
<211>  60
<212>  PRT
<213>  Artificial sequence
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<220>
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<220>
<221> misc_feature
<222> (1)..(2)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (43)..(43)
<223> Xaa can be any naturally occurring amino acid

<400> 47

Xaa Xaa Thr Phe Ser Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser
1 5 10 15

Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
20 25 30

Gln Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Xaa Asn Gln Ser Gly Ser
35 40 45

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

<210> 48
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<220>
<221> misc_feature
<222> (1)..(3)
<223> Xaa can be any naturally occurring amino acid

<400> 48

Xaa Xaa Xaa Phe Ser Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser
1 5 10 15

Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
            20 25 30

Gln Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Gly Thr Thr Ser Gly Thr
        35 40 45

Thr Asn Gln Ser Arg Leu Leu Phe Ser Gln Ala Gly
    50 55 60

<210> 49
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(3)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (43)..(43)
<223> Xaa can be any naturally occurring amino acid

<400> 49

Xaa Xaa Xaa Phe Ser Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser
1 5 10 15

Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
            20 25 30

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

Thr Thr Gln Ser Arg Leu Gln Phe Ser Gln Ala Gly
    50   55   60

<210> 50
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<220>
<221> misc_feature
<222> (45)..(45)
<223> Xaa can be any naturally occurring amino acid

<400> 50

Asn Phe Gln Phe Thr Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser
1   5   10   15

Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
            20   25   30

Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr Gln Thr Thr Xaa Gly Gly Thr
        35   40   45

Ala Asn Thr Gln Thr Leu Gly Phe Ser Gln Gly Gly
    50   55   60

<210> 51
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<220>
<221> misc_feature

<222> (45)..(45)
<223> Xaa can be any naturally occurring amino acid

<400> 51

Asn Phe Gln Phe Thr Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser
1 5 10 15

Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
20 25 30

Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr Gln Thr Thr Xaa Gly Gly Thr
35 40 45

Ala Asn Thr Gln Thr Leu Gly Phe Ser Gln Gly Gly
50 55 60

<210> 52
<211> 59
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 52

Phe Gln Phe Ser Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser Tyr
1 5 10 15

Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln
20 25 30

Tyr Leu Tyr Tyr Leu Val Arg Thr Gln Thr Thr Gly Thr Gly Gly Thr
35 40 45

Gln Thr Leu Ala Phe Ser Gln Ala Gly Pro Ser
50 55

<210> 53

<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (45)..(45)
<223> Xaa can be any naturally occurring amino acid

<400> 53

Asn Phe Glu Phe Ser Tyr Thr Phe Glu Asp Val Pro Phe His Ser Ser
1 5 10 15

Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
20 25 30

Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr Gln Ser Thr Xaa Gly Gly Thr
35 40 45

Gln Gly Thr Gln Gln Leu Leu Phe Ser Gln Ala Gly
50 55 60

<210> 54
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Xaa can be any naturally occurring amino acid

<400> 54

Xaa Phe Glu Phe Ser Tyr Ser Phe Glu Asp Val Pro Phe His Ser Ser

1 5 10 15

Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
20 25 30

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

Ala Gly Asn Arg Glu Leu Gln Phe Tyr Gln Gly Gly
50 55 60

<210> 55
<211> 60
<212> PRT
<213> Artificial sequence

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<220>
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<222> (1)..(1)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (43)..(44)
<223> Xaa can be any naturally occurring amino acid

<400> 55

Xaa Phe Gln Phe Ser Tyr Glu Phe Glu Asn Val Pro Phe His Ser Ser
1 5 10 15

Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
20 25 30

Gln Tyr Leu Tyr Tyr Leu Ser Lys Thr Ile Xaa Xaa Asn Gly Ser Gly
35 40 45

Gln Asn Gln Gln Thr Leu Lys Phe Ser Val Ala Gly
50 55 60

<210> 56
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (43)..(44)
<223> Xaa can be any naturally occurring amino acid

<400> 56

Xaa Phe Gln Phe Ser Tyr Glu Phe Glu Asn Val Pro Phe His Ser Ser
1 5 10 15

Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp
20 25 30

Gln Tyr Leu Tyr Tyr Leu Ser Lys Thr Ile Xaa Xaa Asn Gly Ser Gly
35 40 45

Gln Asn Gln Gln Thr Leu Lys Phe Ser Val Ala Gly
50 55 60

<210> 57
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> misc_feature
<222> (43)..(49)
<223> Xaa can be any naturally occurring amino acid

<400> 57

Asn Phe Glu Phe Thr Tyr Asn Phe Glu Glu Val Pro Phe His Ser Ser
1   5   10   15

Phe Ala Pro Ser Gln Asn Leu Phe Lys Leu Ala Asn Pro Leu Val Asp
            20   25   30

Gln Tyr Leu Tyr Arg Phe Val Ser Thr Asn Xaa Xaa Xaa Xaa Xaa Xaa
        35   40   45

Xaa Asn Thr Gly Gly Val Gln Phe Asn Lys Asn Leu
    50   55   60

<210> 58
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 58

Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys
1   5   10   15

Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser
            20   25   30

Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu
        35   40   45

Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His

50 55 60

<210> 59
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 59

Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys
1 5 10 15

Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser
20 25 30

Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu
35 40 45

Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His
50 55 60

<210> 60
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 60

Pro Gln Ser Met Ser Leu Gln Ala Arg Asn Trp Leu Pro Gly Pro Cys
1 5 10 15

Tyr Arg Gln Gln Arg Leu Ser Lys Thr Ala Asn Asp Asn Asn Asn Ser
20 25 30

Asn Phe Pro Trp Thr Ala Ala Ser Lys Tyr His Leu Asn Gly Arg Asp

35 40 45

Ser Leu Val Asn Pro Gly Pro Ala Met Ala Ser His
50 55 60

<210> 61
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 61

Ala Ser Asp Ile Arg Asp Gln Ser Arg Asn Trp Leu Pro Gly Pro Cys
1 5 10 15

Tyr Arg Gln Gln Arg Val Ser Lys Thr Ser Ala Asp Asn Asn Asn Ser
20 25 30

Glu Tyr Ser Trp Thr Gly Ala Thr Lys Tyr His Leu Asn Gly Arg Asp
35 40 45

Ser Leu Val Asn Pro Gly Pro Ala Met Ala Ser His
50 55 60

<210> 62
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 62

Pro Asn Thr Met Ala Asn Gln Ala Lys Asn Trp Leu Pro Gly Pro Cys
1 5 10 15

Tyr Arg Gln Gln Arg Val Ser Thr Thr Thr Gly Gln Asn Asn Asn Ser

20 25 30

Asn Phe Ala Trp Thr Ala Gly Thr Lys Tyr His Leu Asn Gly Arg Asn
35 40 45

Ser Leu Ala Asn Pro Gly Ile Ala Met Ala Thr His
50 55 60

<210> 63
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 63

Pro Asn Thr Met Ala Asn Gln Ala Lys Asn Trp Leu Pro Gly Pro Cys
1 5 10 15

Tyr Arg Gln Gln Arg Val Ser Thr Thr Thr Gly Gln Asn Asn Asn Ser
20 25 30

Asn Phe Ala Trp Thr Ala Gly Thr Lys Tyr His Leu Asn Gly Arg Asn
35 40 45

Ser Leu Ala Asn Pro Gly Ile Ala Met Ala Thr His
50 55 60

<210> 64
<211> 60
<212> PRT
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<220>
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<222> (2)..(3)
<223> Xaa can be any naturally occurring amino acid

<400> 64

Ser Xaa Xaa Met Ala Asn Gln Ala Arg Asn Trp Val Pro Gly Pro Cys
1 5 10 15

Tyr Arg Gln Gln Arg Val Ser Thr Thr Thr Asn Gln Asn Asn Asn Ser
20 25 30

Asn Phe Ala Trp Thr Gly Ala Ala Lys Phe Lys Leu Asn Gly Arg Asp
35 40 45

Ser Leu Met Asn Pro Gly Val Ala Met Ala Ser His
50 55 60

<210> 65
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 65

Pro Ala Asn Met Ser Ala Gln Ala Lys Asn Trp Leu Pro Gly Pro Cys
1 5 10 15

Tyr Arg Gln Gln Arg Val Ser Thr Thr Leu Ser Gln Asn Asn Asn Ser
20 25 30

Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His Leu Asn Gly Arg Asp
35 40 45

Ser Leu Val Asn Pro Gly Val Ala Met Ala Thr His
50 55 60

<210> 66

<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 66

Pro Ser Thr Met Ala Glu Gln Ala Lys Asn Trp Leu Pro Gly Pro Cys
1 5 10 15

Phe Arg Gln Gln Arg Val Ser Lys Thr Leu Asp Gln Asn Asn Asn Ser
20 25 30

Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His Leu Asn Gly Arg Asn
35 40 45

Ser Leu Val Asn Pro Gly Val Ala Met Ala Thr His
50 55 60

<210> 67
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 67

Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro Gly Pro Ser
1 5 10 15

Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn Asn Asn Ser
20 25 30

Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn Gly Arg Asn
35 40 45

Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His

50 55 60

<210> 68
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 68

Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro Gly Pro Ser
1 5 10 15

Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn Asn Asn Ser
20 25 30

Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn Gly Arg Asn
35 40 45

Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His
50 55 60

<210> 69
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 69

Ala Gly Arg Tyr Ala Asn Thr Tyr Lys Asn Trp Phe Pro Gly Pro Met
1 5 10 15

Gly Arg Thr Gln Gly Trp Asn Leu Gly Ser Gly Val Asn Arg Ala Ser
20 25 30

Val Ser Ala Phe Ala Thr Thr Asn Arg Met Glu Leu Glu Gly Ala Ser

35 40 45

Tyr Gln Val Pro Pro Gln Pro Asn Gly Met Thr Asn
50 55 60

<210> 70
<211> 60
<212> PRT
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<220>
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<220>
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<222> (19)..(20)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 70

Lys Asp Asp Glu Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe
1 5 10 15

Gly Lys Xaa Xaa Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Xaa
20 25 30

Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val
35 40 45

Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe
50 55 60

<210> 71
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (19)..(20)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 71

Lys Asp Asp Lys Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe
1   5   10   15

Gly Lys Xaa Xaa Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Xaa
            20   25   30

Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val
        35   40   45

Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Leu
    50   55   60

<210> 72
<211> 60
<212> PRT
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<220>
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<220>
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<220>

<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 72

Lys Asp Asp Glu Glu Lys Phe Phe Pro Met His Gly Asn Leu Ile Phe
1 5 10 15

Gly Lys Xaa Xaa Glu Gly Thr Thr Ala Ser Asn Ala Glu Leu Asp Xaa
20 25 30

Asn Val Met Ile Thr Asp Glu Glu Glu Ile Arg Thr Thr Asn Pro Val
35 40 45

Ala Thr Glu Gln Tyr Gly Thr Val Ala Asn Asn Leu
50 55 60

<210> 73
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 73

Lys Asp Asp Glu Glu Lys Phe Phe Pro Gln Ser Gly Val Leu Ile Phe
1 5 10 15

Gly Lys Xaa Xaa Gln Gly Ser Glu Lys Thr Asn Val Asp Ile Glu Xaa

20 25 30

Lys Val Met Ile Thr Asp Glu Glu Glu Ile Arg Thr Thr Asn Pro Val
35 40 45

Ala Thr Glu Gln Tyr Gly Ser Val Ser Thr Asn Leu
50 55 60

<210> 74
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (19)..(20)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 74

Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Asn Gly Ile Leu Ile Phe
1 5 10 15

Gly Lys Xaa Xaa Gln Asn Ala Ala Arg Asp Asn Ala Asp Tyr Ser Xaa
20 25 30

Asp Val Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val
35 40 45

Ala Thr Glu Glu Tyr Gly Ile Val Ala Asp Asn Leu
50 55 60

<210> 75
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (19)..(20)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 75

Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Asn Gly Ile Leu Ile Phe
1 5 10 15

Gly Lys Xaa Xaa Gln Asn Ala Ala Arg Asp Asn Ala Asp Tyr Ser Xaa
20 25 30

Asp Val Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val
35 40 45

Ala Thr Glu Glu Tyr Gly Ile Val Ala Asp Asn Leu
50 55 60

<210> 76
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (19)..(20)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 76

Lys Asp Asp Asp Asp Arg Phe Phe Pro Ser Ser Gly Val Leu Ile Phe
1 5 10 15

Gly Lys Xaa Xaa Gln Gly Ala Gly Asn Asp Gly Val Asp Tyr Ser Xaa
20 25 30

Gln Val Leu Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val
35 40 45

Ala Thr Glu Glu Tyr Gly Ala Val Ala Ile Asn Asn
50 55 60

<210> 77
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (19)..(20)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 77

Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Ser Gly Val Leu Met Phe

1 5 10 15

Gly Lys Xaa Xaa Gln Gly Ala Gly Arg Asp Asn Val Asp Tyr Ser Xaa
20 25 30

Ser Val Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val
35 40 45

Ala Thr Glu Gln Tyr Gly Val Val Ala Asp Asn Leu
50 55 60

<210> 78
<211> 60
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (19)..(20)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (25)..(25)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 78

Lys Asp Asp Glu Asp Arg Phe Phe Pro Ser Ser Gly Val Leu Ile Phe
1 5 10 15

Gly Lys Xaa Xaa Thr Gly Ala Thr Xaa Asn Lys Thr Thr Leu Glu Xaa
20 25 30

Asn Val Leu Met Thr Asn Glu Glu Glu Ile Arg Pro Thr Asn Pro Val
        35   40   45

Ala Thr Glu Glu Tyr Gly Ile Val Ser Ser Asn Leu
    50   55   60

<210> 79
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<220>
<221> misc_feature
<222> (19)..(20)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 79

Lys Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe
1   5   10   15

Gly Lys Xaa Xaa Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Xaa
            20   25   30

Lys Val Met Ile Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val
        35   40   45

Ala Thr Glu Ser Tyr Gly Gln Val Ala Thr Asn His
    50   55   60

<210> 80
<211> 60

<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (19)..(20)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<400> 80

Lys Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe
1 5 10 15

Gly Lys Xaa Xaa Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Xaa
20 25 30

Lys Val Met Ile Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val
35 40 45

Ala Thr Glu Ser Tyr Gly Gln Val Ala Thr Asn His
50 55 60

<210> 81
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 81

Asn Leu Gln Gly Ser Asn Thr Tyr Ala Leu Glu Asn Thr Met Ile Phe
1 5 10 15

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Asn Ser Gln Pro Ala Asn Pro Gly Thr Thr Ala Thr Tyr Leu Glu Gly
            20                  25                  30


Asn Met Leu Ile Thr Ser Glu Ser Glu Thr Gln Pro Val Asn Arg Val
        35                  40                  45


Ala Tyr Asn Val Gly Gly Gln Met Ala Thr Asn Asn
    50                  55                  60


<210>  82
<211>  60
<212>  PRT
<213>  Artificial sequence

<220>
<223>  synthetic sequence

<400>  82

Gln Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly
1               5                   10                  15


Ala Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly
            20                  25                  30


Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser
        35                  40                  45


Pro Leu Met Gly Gly Phe Gly Leu Lys Asn Pro Pro
    50                  55                  60


<210>  83
<211>  60
<212>  PRT
<213>  Artificial sequence

<220>
<223>  synthetic sequence

<400>  83
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Gln Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Val Met Gly
1 5 10 15

Ala Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly
            20 25 30

Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser
        35 40 45

Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro
    50 55 60

<210> 84
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 84

Gln Ser Ser Asn Thr Ala Pro Thr Thr Gly Thr Val Asn His Gln Gly
1 5 10 15

Ala Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly
            20 25 30

Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser
        35 40 45

Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro
    50 55 60

<210> 85
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 85

Gln Arg Gly Asn Arg Gln Ala Ala Thr Ala Asp Val Asn Thr Gln Gly
1 5 10 15

Val Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly
20 25 30

Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser
35 40 45

Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro
50 55 60

<210> 86
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 86

Gln Gln Gln Asn Thr Ala Pro Gln Ile Gly Thr Val Asn Ser Gln Gly
1 5 10 15

Ala Leu Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly
20 25 30

Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser
35 40 45

Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro
50 55 60

<210> 87

<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 87

Gln Gly Gln Arg Gln Ala Ala Gln Ile Gly Thr Val Asn Ser Gln Gly
1 5 10 15

Ala Leu Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly
20 25 30

Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser
35 40 45

Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro
50 55 60

<210> 88
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 88

Gln Ala Ala Asn Thr Gln Ala Gln Thr Gly Leu Val His Asn Gln Gly
1 5 10 15

Val Ile Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly
20 25 30

Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser
35 40 45

Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro

50 55 60

<210> 89
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 89

Gln Gln Ala Asn Thr Gly Pro Ile Val Gly Asn Val Asn Ser Gln Gly
1 5 10 15

Ala Leu Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly
20 25 30

Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser
35 40 45

Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro
50 55 60

<210> 90
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 90

Gln Ala Ala Asn Thr Ala Ala Gln Thr Gln Val Val Asn Asn Gln Gly
1 5 10 15

Ala Leu Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly
20 25 30

Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser

35 40 45

Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro
50 55 60

<210> 91
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 91

Gln Ser Ala Gln Ala Gln Ala Gln Thr Gly Trp Val Gln Asn Gln Gly
1 5 10 15

Ile Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly
20 25 30

Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser
35 40 45

Pro Leu Met Gly Gly Phe Gly Met Lys His Pro Pro
50 55 60

<210> 92
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 92

Gln Ser Gly Gln Ala Gln Ala Ala Thr Gly Trp Val Gln Asn Gln Gly
1 5 10 15

Ile Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly

20 25 30

Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser
35 40 45

Pro Leu Met Gly Gly Phe Gly Met Lys His Pro Pro
50 55 60

<210> 93
<211> 60
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 93

Gln Ser Ser Thr Thr Ala Pro Ala Thr Gly Thr Tyr Asn Leu Gln Glu
1 5 10 15

Ile Val Pro Gly Ser Val Trp Met Glu Arg Asp Val Tyr Leu Gln Gly
20 25 30

Pro Ile Trp Ala Lys Ile Pro Glu Thr Gly Ala His Phe His Pro Ser
35 40 45

Pro Ala Met Gly Gly Phe Gly Leu Lys His Pro Pro
50 55 60

<210> 94
<211> 7
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> misc_feature

<222> (7)..(7)
<223> Xaa can be any naturally occurring amino acid

<400> 94

Pro Gln Ile Leu Ile Lys Xaa
1 5

<210> 95
<211> 7
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> misc_feature
<222> (7)..(7)
<223> Xaa can be any naturally occurring amino acid

<400> 95

Pro Gln Ile Met Ile Lys Xaa
1 5

<210> 96
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 96

Pro Gln Ile Leu Ile Lys Asn
1 5

<210> 97
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 97

Pro Met Met Leu Ile Lys Asn
1 5

<210> 98
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 98

Thr Gly Asp Gly Gly Thr Thr Met Asn Gly Leu Ser
1 5 10

<210> 99
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 99

Thr Gly Gly His Gly Ser Ala Pro Asp Gly Leu Ser
1 5 10

<210> 100
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 100

Thr Gly Met His Val Thr Met Met Ala Gly Leu Asn

1 5 10

<210> 101
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 101

Thr Gly Ala Ser Tyr Leu Asp Asn Ser Gly Leu Ser
1 5 10

<210> 102
<211> 860
<212> PRT
<213> Homo sapiens

<400> 102

Met Gly Glu Val Thr Ala Glu Glu Val Glu Lys Phe Leu Asp Ser Asn
1 5 10 15

Ile Gly Phe Ala Lys Gln Tyr Tyr Asn Leu His Tyr Arg Ala Lys Leu
20 25 30

Ile Ser Asp Leu Leu Gly Ala Lys Glu Ala Ala Val Asp Phe Ser Asn
35 40 45

Tyr His Ser Pro Ser Ser Met Glu Glu Ser Glu Ile Ile Phe Asp Leu
50 55 60

Leu Arg Asp Phe Gln Glu Asn Leu Gln Thr Glu Lys Cys Ile Phe Asn
65 70 75 80

Val Met Lys Lys Leu Cys Phe Leu Leu Gln Ala Asp Arg Met Ser Leu
85 90 95

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Phe Met Tyr Arg Thr Arg Asn Gly Ile Ala Glu Leu Ala Thr Arg Leu
            100                 105                 110


Phe Asn Val His Lys Asp Ala Val Leu Glu Asp Cys Leu Val Met Pro
        115                 120                 125


Asp Gln Glu Ile Val Phe Pro Leu Asp Met Gly Ile Val Gly His Val
    130                 135                 140


Ala His Ser Lys Lys Ile Ala Asn Val Pro Asn Thr Glu Glu Asp Glu
145                 150                 155                 160


His Phe Cys Asp Phe Val Asp Ile Leu Thr Glu Tyr Lys Thr Lys Asn
                165                 170                 175


Ile Leu Ala Ser Pro Ile Met Asn Gly Lys Asp Val Val Ala Ile Ile
            180                 185                 190


Met Ala Val Asn Lys Val Asp Gly Ser His Phe Thr Lys Arg Asp Glu
        195                 200                 205


Glu Ile Leu Leu Lys Tyr Leu Asn Phe Ala Asn Leu Ile Met Lys Val
    210                 215                 220


Tyr His Leu Ser Tyr Leu His Asn Cys Glu Thr Arg Arg Gly Gln Ile
225                 230                 235                 240


Leu Leu Trp Ser Gly Ser Lys Val Phe Glu Glu Leu Thr Asp Ile Glu
                245                 250                 255


Arg Gln Phe His Lys Ala Leu Tyr Thr Val Arg Ala Phe Leu Asn Cys
            260                 265                 270


Asp Arg Tyr Ser Val Gly Leu Leu Asp Met Thr Lys Gln Lys Glu Phe
        275                 280                 285
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Phe Asp Val Trp Pro Val Leu Met Gly Glu Val Pro Pro Tyr Ser Gly
    290                 295                 300

Pro Arg Thr Pro Asp Gly Arg Glu Ile Asn Phe Tyr Lys Val Ile Asp
305                 310                 315                 320

Tyr Ile Leu His Gly Lys Glu Asp Ile Lys Val Ile Pro Asn Pro Pro
                325                 330                 335

Pro Asp His Trp Ala Leu Val Ser Gly Leu Pro Ala Tyr Val Ala Gln
            340                 345                 350

Asn Gly Leu Ile Cys Asn Ile Met Asn Ala Pro Ala Glu Asp Phe Phe
        355                 360                 365

Ala Phe Gln Lys Glu Pro Leu Asp Glu Ser Gly Trp Met Ile Lys Asn
    370                 375                 380

Val Leu Ser Met Pro Ile Val Asn Lys Lys Glu Glu Ile Val Gly Val
385                 390                 395                 400

Ala Thr Phe Tyr Asn Arg Lys Asp Gly Lys Pro Phe Asp Glu Met Asp
                405                 410                 415

Glu Thr Leu Met Glu Ser Leu Thr Gln Phe Leu Gly Trp Ser Val Leu
            420                 425                 430

Asn Pro Asp Thr Tyr Glu Ser Met Asn Lys Leu Glu Asn Arg Lys Asp
        435                 440                 445

Ile Phe Gln Asp Ile Val Lys Tyr His Val Lys Cys Asp Asn Glu Glu
    450                 455                 460

Ile Gln Lys Ile Leu Lys Thr Arg Glu Val Tyr Gly Lys Glu Pro Trp
465                 470                 475                 480
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Glu Cys Glu Glu Glu Glu Leu Ala Glu Ile Leu Gln Ala Glu Leu Pro
                485                 490                 495


Asp Ala Asp Lys Tyr Glu Ile Asn Lys Phe His Phe Ser Asp Leu Pro
            500                 505                 510


Leu Thr Glu Leu Glu Leu Val Lys Cys Gly Ile Gln Met Tyr Tyr Glu
        515                 520                 525


Leu Lys Val Val Asp Lys Phe His Ile Pro Gln Glu Ala Leu Val Arg
    530                 535                 540


Phe Met Tyr Ser Leu Ser Lys Gly Tyr Arg Lys Ile Thr Tyr His Asn
545                 550                 555                 560


Trp Arg His Gly Phe Asn Val Gly Gln Thr Met Phe Ser Leu Leu Val
                565                 570                 575


Thr Gly Lys Leu Lys Arg Tyr Phe Thr Asp Leu Glu Ala Leu Ala Met
            580                 585                 590


Val Thr Ala Ala Phe Cys His Asp Ile Asp His Arg Gly Thr Asn Asn
        595                 600                 605


Leu Tyr Gln Met Lys Ser Gln Asn Pro Leu Ala Lys Leu His Gly Ser
    610                 615                 620


Ser Ile Leu Glu Arg His His Leu Glu Phe Gly Lys Thr Leu Leu Arg
625                 630                 635                 640


Asp Glu Ser Leu Asn Ile Phe Gln Asn Leu Asn Arg Arg Gln His Glu
                645                 650                 655


His Ala Ile His Met Met Asp Ile Ala Ile Ile Ala Thr Asp Leu Ala
            660                 665                 670
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Leu Tyr Phe Lys Lys Arg Thr Met Phe Gln Lys Ile Val Asp Gln Ser
        675                 680                 685

Lys Thr Tyr Glu Ser Glu Gln Glu Trp Thr Gln Tyr Met Met Leu Glu
    690                 695                 700

Gln Thr Arg Lys Glu Ile Val Met Ala Met Met Met Thr Ala Cys Asp
705                 710                 715                 720

Leu Ser Ala Ile Thr Lys Pro Trp Glu Val Gln Ser Gln Val Ala Leu
                725                 730                 735

Leu Val Ala Ala Glu Phe Trp Glu Gln Gly Asp Leu Glu Arg Thr Val
            740                 745                 750

Leu Gln Gln Asn Pro Ile Pro Met Met Asp Arg Asn Lys Ala Asp Glu
        755                 760                 765

Leu Pro Lys Leu Gln Val Gly Phe Ile Asp Phe Val Cys Thr Phe Val
    770                 775                 780

Tyr Lys Glu Phe Ser Arg Phe His Glu Glu Ile Thr Pro Met Leu Asp
785                 790                 795                 800

Gly Ile Thr Asn Asn Arg Lys Glu Trp Lys Ala Leu Ala Asp Glu Tyr
                805                 810                 815

Asp Ala Lys Met Lys Val Gln Glu Glu Lys Lys Gln Lys Gln Gln Ser
            820                 825                 830

Ala Lys Ser Ala Ala Ala Gly Asn Gln Pro Gly Gly Asn Pro Ser Pro
        835                 840                 845

Gly Gly Ala Thr Thr Ser Lys Ser Cys Cys Ile Gln
    850                 855                 860
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<210> 103
<211> 854
<212> PRT
<213> Homo sapiens

<400> 103

```
Met Ser Leu Ser Glu Glu Gln Ala Arg Ser Phe Leu Asp Gln Asn Pro
1               5                  10                  15


Asp Phe Ala Arg Gln Tyr Phe Gly Lys Lys Leu Ser Pro Glu Asn Val
            20                  25                  30


Ala Ala Ala Cys Glu Asp Gly Cys Pro Pro Asp Cys Asp Ser Leu Arg
        35                  40                  45


Asp Leu Cys Gln Val Glu Glu Ser Thr Ala Leu Leu Glu Leu Val Gln
    50                  55                  60


Asp Met Gln Glu Ser Ile Asn Met Glu Arg Val Val Phe Lys Val Leu
65                  70                  75                  80


Arg Arg Leu Cys Thr Leu Leu Gln Ala Asp Arg Cys Ser Leu Phe Met
                85                  90                  95


Tyr Arg Gln Arg Asn Gly Val Ala Glu Leu Ala Thr Arg Leu Phe Ser
            100                 105                 110


Val Gln Pro Asp Ser Val Leu Glu Asp Cys Leu Val Pro Pro Asp Ser
        115                 120                 125


Glu Ile Val Phe Pro Leu Asp Ile Gly Val Val Gly His Val Ala Gln
    130                 135                 140


Thr Lys Lys Met Val Asn Val Glu Asp Val Ala Glu Cys Pro His Phe
145                 150                 155                 160


Ser Ser Phe Ala Asp Glu Leu Thr Asp Tyr Lys Thr Lys Asn Met Leu
```

```
                165                 170                 175

Ala Thr Pro Ile Met Asn Gly Lys Asp Val Val Ala Val Ile Met Ala
            180                 185                 190

Val Asn Lys Leu Asn Gly Pro Phe Phe Thr Ser Glu Asp Glu Asp Val
        195                 200                 205

Phe Leu Lys Tyr Leu Asn Phe Ala Thr Leu Tyr Leu Lys Ile Tyr His
    210                 215                 220

Leu Ser Tyr Leu His Asn Cys Glu Thr Arg Arg Gly Gln Val Leu Leu
225                 230                 235                 240

Trp Ser Ala Asn Lys Val Phe Glu Glu Leu Thr Asp Ile Glu Arg Gln
                245                 250                 255

Phe His Lys Ala Phe Tyr Thr Val Arg Ala Tyr Leu Asn Cys Glu Arg
            260                 265                 270

Tyr Ser Val Gly Leu Leu Asp Met Thr Lys Glu Lys Glu Phe Phe Asp
        275                 280                 285

Val Trp Ser Val Leu Met Gly Glu Ser Gln Pro Tyr Ser Gly Pro Arg
    290                 295                 300

Thr Pro Asp Gly Arg Glu Ile Val Phe Tyr Lys Val Ile Asp Tyr Ile
305                 310                 315                 320

Leu His Gly Lys Glu Glu Ile Lys Val Ile Pro Thr Pro Ser Ala Asp
                325                 330                 335

His Trp Ala Leu Ala Ser Gly Leu Pro Ser Tyr Val Ala Glu Ser Gly
            340                 345                 350

Phe Ile Cys Asn Ile Met Asn Ala Ser Ala Asp Glu Met Phe Lys Phe
```

```
        355                 360                 365

Gln Glu Gly Ala Leu Asp Asp Ser Gly Trp Leu Ile Lys Asn Val Leu
    370                 375                 380

Ser Met Pro Ile Val Asn Lys Lys Glu Glu Ile Val Gly Val Ala Thr
385                 390                 395                 400

Phe Tyr Asn Arg Lys Asp Gly Lys Pro Phe Asp Glu Gln Asp Glu Val
                405                 410                 415

Leu Met Glu Ser Leu Thr Gln Phe Leu Gly Trp Ser Val Met Asn Thr
            420                 425                 430

Asp Thr Tyr Asp Lys Met Asn Lys Leu Glu Asn Arg Lys Asp Ile Ala
        435                 440                 445

Gln Asp Met Val Leu Tyr His Val Lys Cys Asp Arg Asp Glu Ile Gln
    450                 455                 460

Leu Ile Leu Pro Thr Arg Ala Arg Leu Gly Lys Glu Pro Ala Asp Cys
465                 470                 475                 480

Asp Glu Asp Glu Leu Gly Glu Ile Leu Lys Glu Glu Leu Pro Gly Pro
                485                 490                 495

Thr Thr Phe Asp Ile Tyr Glu Phe His Phe Ser Asp Leu Glu Cys Thr
            500                 505                 510

Glu Leu Asp Leu Val Lys Cys Gly Ile Gln Met Tyr Tyr Glu Leu Gly
        515                 520                 525

Val Val Arg Lys Phe Gln Ile Pro Gln Glu Val Leu Val Arg Phe Leu
    530                 535                 540

Phe Ser Ile Ser Lys Gly Tyr Arg Arg Ile Thr Tyr His Asn Trp Arg
```

```
545                 550                 555                 560

His Gly Phe Asn Val Ala Gln Thr Met Phe Thr Leu Leu Met Thr Gly
                565                 570                 575

Lys Leu Lys Ser Tyr Tyr Thr Asp Leu Glu Ala Phe Ala Met Val Thr
            580                 585                 590

Ala Gly Leu Cys His Asp Ile Asp His Arg Gly Thr Asn Asn Leu Tyr
        595                 600                 605

Gln Met Lys Ser Gln Asn Pro Leu Ala Lys Leu His Gly Ser Ser Ile
    610                 615                 620

Leu Glu Arg His His Leu Glu Phe Gly Lys Phe Leu Leu Ser Glu Glu
625                 630                 635                 640

Thr Leu Asn Ile Tyr Gln Asn Leu Asn Arg Arg Gln His Glu His Val
                645                 650                 655

Ile His Leu Met Asp Ile Ala Ile Ile Ala Thr Asp Leu Ala Leu Tyr
            660                 665                 670

Phe Lys Lys Arg Ala Met Phe Gln Lys Ile Val Asp Glu Ser Lys Asn
        675                 680                 685

Tyr Gln Asp Lys Lys Ser Trp Val Glu Tyr Leu Ser Leu Glu Thr Thr
    690                 695                 700

Arg Lys Glu Ile Val Met Ala Met Met Met Thr Ala Cys Asp Leu Ser
705                 710                 715                 720

Ala Ile Thr Lys Pro Trp Glu Val Gln Ser Lys Val Ala Leu Leu Val
                725                 730                 735

Ala Ala Glu Phe Trp Glu Gln Gly Asp Leu Glu Arg Thr Val Leu Asp
```

```
            740                 745                 750

Gln Gln Pro Ile Pro Met Met Asp Arg Asn Lys Ala Ala Glu Leu Pro
        755                 760                 765

Lys Leu Gln Val Gly Phe Ile Asp Phe Val Cys Thr Phe Val Tyr Lys
    770                 775                 780

Glu Phe Ser Arg Phe His Glu Glu Ile Leu Pro Met Phe Asp Arg Leu
785                 790                 795                 800

Gln Asn Asn Arg Lys Glu Trp Lys Ala Leu Ala Asp Glu Tyr Glu Ala
                805                 810                 815

Lys Val Lys Ala Leu Glu Glu Lys Glu Glu Glu Glu Arg Val Ala Ala
            820                 825                 830

Lys Lys Val Gly Thr Glu Ile Cys Asn Gly Gly Pro Ala Pro Lys Ser
        835                 840                 845

Ser Thr Cys Cys Ile Leu
    850


<210>  104
<211>  853
<212>  PRT
<213>  Homo sapiens

<400>  104

Met Ser Leu Ser Glu Glu Gln Ala Arg Ser Phe Leu Asp Gln Asn Pro
1               5                   10                  15

Asp Phe Ala Arg Gln Tyr Phe Gly Lys Lys Leu Ser Pro Glu Asn Val
            20                  25                  30

Ala Ala Ala Cys Glu Asp Gly Cys Pro Pro Asp Cys Asp Ser Leu Arg
        35                  40                  45
```

```
Asp Leu Cys Gln Val Glu Glu Ser Thr Ala Leu Leu Glu Leu Val Gln
    50                  55                  60

Asp Met Gln Glu Ser Ile Asn Met Glu Arg Val Val Phe Lys Val Leu
65                  70                  75                  80

Arg Arg Leu Cys Thr Leu Leu Gln Ala Asp Arg Cys Ser Leu Phe Met
                85                  90                  95

Tyr Arg Gln Arg Asn Gly Val Ala Glu Leu Ala Thr Arg Leu Phe Ser
            100                 105                 110

Val Gln Pro Asp Ser Val Leu Glu Asp Cys Leu Val Pro Pro Asp Ser
        115                 120                 125

Glu Ile Val Phe Pro Leu Asp Ile Gly Val Val Gly His Val Ala Gln
    130                 135                 140

Thr Lys Lys Met Val Asn Val Glu Asp Val Ala Glu Cys Pro His Phe
145                 150                 155                 160

Ser Ser Phe Ala Asp Glu Leu Thr Asp Tyr Lys Thr Lys Asn Met Leu
                165                 170                 175

Ala Thr Pro Ile Met Asn Gly Lys Asp Val Val Ala Val Ile Met Ala
            180                 185                 190

Val Asn Lys Leu Asn Gly Pro Phe Phe Thr Ser Glu Asp Glu Asp Val
        195                 200                 205

Phe Leu Lys Tyr Leu Asn Phe Ala Thr Leu Tyr Leu Lys Ile Tyr His
    210                 215                 220

Leu Ser Tyr Leu His Asn Cys Glu Thr Arg Arg Gly Gln Val Leu Leu
225                 230                 235                 240
```

```
Trp Ser Ala Asn Lys Val Phe Glu Glu Leu Thr Asp Ile Glu Arg Gln
                245                 250                 255

Phe His Lys Ala Phe Tyr Thr Val Arg Ala Tyr Leu Asn Cys Glu Arg
            260                 265                 270

Tyr Ser Val Gly Leu Leu Asp Met Thr Lys Glu Lys Glu Phe Phe Asp
        275                 280                 285

Val Trp Ser Val Leu Met Gly Glu Ser Gln Pro Tyr Ser Gly Pro Arg
    290                 295                 300

Thr Pro Asp Gly Arg Glu Ile Val Phe Tyr Lys Val Ile Asp Tyr Ile
305                 310                 315                 320

Leu His Gly Lys Glu Glu Ile Lys Val Ile Pro Thr Pro Ser Ala Asp
                325                 330                 335

His Trp Ala Leu Ala Ser Gly Leu Pro Ser Tyr Val Ala Glu Ser Gly
            340                 345                 350

Phe Ile Cys Asn Ile Met Asn Ala Ser Ala Asp Glu Met Phe Lys Phe
        355                 360                 365

Gln Glu Gly Ala Leu Asp Asp Ser Gly Trp Leu Ile Lys Asn Val Leu
    370                 375                 380

Ser Met Pro Ile Val Asn Lys Lys Glu Glu Ile Val Gly Val Ala Thr
385                 390                 395                 400

Phe Tyr Asn Arg Lys Asp Gly Lys Pro Phe Asp Glu Gln Asp Glu Val
                405                 410                 415

Leu Met Glu Ser Leu Thr Gln Phe Leu Gly Trp Ser Val Met Asn Thr
            420                 425                 430
```

```
Asp Thr Tyr Asp Lys Met Asn Lys Leu Glu Asn Arg Lys Asp Ile Ala
        435                 440                 445

Gln Asp Met Val Leu Tyr His Val Lys Cys Asp Arg Asp Glu Ile Gln
    450                 455                 460

Leu Ile Leu Pro Thr Arg Ala Arg Leu Gly Lys Glu Pro Ala Asp Cys
465                 470                 475                 480

Asp Glu Asp Glu Leu Gly Glu Ile Leu Lys Glu Glu Leu Pro Gly Pro
                485                 490                 495

Thr Thr Phe Asp Ile Tyr Glu Phe His Phe Ser Asp Leu Glu Cys Thr
            500                 505                 510

Glu Leu Asp Leu Val Lys Cys Gly Ile Gln Met Tyr Tyr Glu Leu Gly
        515                 520                 525

Val Val Arg Lys Phe Gln Ile Pro Gln Glu Val Leu Val Arg Phe Leu
    530                 535                 540

Phe Ser Ile Ser Lys Gly Tyr Arg Arg Ile Thr Tyr His Asn Trp Arg
545                 550                 555                 560

His Gly Phe Asn Val Ala Gln Thr Met Phe Thr Leu Leu Met Thr Gly
                565                 570                 575

Lys Leu Lys Ser Tyr Tyr Thr Asp Leu Glu Ala Phe Ala Met Val Thr
            580                 585                 590

Ala Gly Leu Cys His Asp Ile Asp His Arg Gly Thr Asn Asn Leu Tyr
        595                 600                 605

Gln Met Lys Ser Gln Asn Pro Leu Ala Lys Leu His Gly Ser Ser Ile
    610                 615                 620
```

```
Leu Glu Arg His His Leu Glu Phe Gly Lys Phe Leu Leu Ser Glu Glu
625                 630                 635                 640

Thr Leu Asn Ile Tyr Gln Asn Leu Asn Arg Arg Gln His Glu His Val
                645                 650                 655

Ile His Leu Met Asp Ile Ala Ile Ile Ala Thr Asp Leu Ala Leu Tyr
            660                 665                 670

Phe Lys Lys Arg Ala Met Phe Gln Lys Ile Val Asp Glu Ser Lys Asn
        675                 680                 685

Tyr Gln Asp Lys Lys Ser Trp Val Glu Tyr Leu Ser Leu Glu Thr Thr
    690                 695                 700

Arg Lys Glu Ile Val Met Ala Met Met Met Thr Ala Cys Asp Leu Ser
705                 710                 715                 720

Ala Ile Thr Lys Pro Trp Glu Val Gln Ser Lys Val Ala Leu Leu Val
                725                 730                 735

Ala Ala Glu Phe Trp Glu Gln Gly Asp Leu Glu Arg Thr Val Leu Asp
            740                 745                 750

Gln Gln Pro Ile Pro Met Met Asp Arg Asn Lys Ala Ala Glu Leu Pro
        755                 760                 765

Lys Leu Gln Val Gly Phe Ile Asp Phe Val Cys Thr Phe Val Tyr Lys
    770                 775                 780

Glu Phe Ser Arg Phe His Glu Glu Ile Leu Pro Met Phe Asp Arg Leu
785                 790                 795                 800

Gln Asn Asn Arg Lys Glu Trp Lys Ala Leu Ala Asp Glu Tyr Glu Ala
                805                 810                 815
```

Lys Val Lys Ala Leu Glu Glu Lys Glu Glu Glu Glu Arg Val Ala Ala
820 825 830

Lys Lys Gly Thr Glu Ile Cys Asn Gly Gly Pro Ala Pro Lys Ser Ser
835 840 845

Thr Cys Cys Ile Leu
850

<210> 105
<211> 575
<212> PRT
<213> Homo sapiens

<400> 105

Met Thr Lys Glu Lys Glu Phe Phe Asp Val Trp Ser Val Leu Met Gly
1 5 10 15

Glu Ser Gln Pro Tyr Ser Gly Pro Arg Thr Pro Asp Gly Arg Glu Ile
20 25 30

Val Phe Tyr Lys Val Ile Asp Tyr Ile Leu His Gly Lys Glu Glu Ile
35 40 45

Lys Val Ile Pro Thr Pro Ser Ala Asp His Trp Ala Leu Ala Ser Gly
50 55 60

Leu Pro Ser Tyr Val Ala Glu Ser Gly Phe Ile Cys Asn Ile Met Asn
65 70 75 80

Ala Ser Ala Asp Glu Met Phe Lys Phe Gln Glu Gly Ala Leu Asp Asp
85 90 95

Ser Gly Trp Leu Ile Lys Asn Val Leu Ser Met Pro Ile Val Asn Lys
100 105 110

```
Lys Glu Glu Ile Val Gly Val Ala Thr Phe Tyr Asn Arg Lys Asp Gly
        115                 120                 125

Lys Pro Phe Asp Glu Gln Asp Glu Val Leu Met Glu Ser Leu Thr Gln
    130                 135                 140

Phe Leu Gly Trp Ser Val Met Asn Thr Asp Thr Tyr Asp Lys Met Asn
145                 150                 155                 160

Lys Leu Glu Asn Arg Lys Asp Ile Ala Gln Asp Met Val Leu Tyr His
                165                 170                 175

Val Lys Cys Asp Arg Asp Glu Ile Gln Leu Ile Leu Pro Thr Arg Ala
            180                 185                 190

Arg Leu Gly Lys Glu Pro Ala Asp Cys Asp Glu Asp Glu Leu Gly Glu
        195                 200                 205

Ile Leu Lys Glu Glu Leu Pro Gly Pro Thr Thr Phe Asp Ile Tyr Glu
    210                 215                 220

Phe His Phe Ser Asp Leu Glu Cys Thr Glu Leu Asp Leu Val Lys Cys
225                 230                 235                 240

Gly Ile Gln Met Tyr Tyr Glu Leu Gly Val Val Arg Lys Phe Gln Ile
                245                 250                 255

Pro Gln Glu Val Leu Val Arg Phe Leu Phe Ser Ile Ser Lys Gly Tyr
            260                 265                 270

Arg Arg Ile Thr Tyr His Asn Trp Arg His Gly Phe Asn Val Ala Gln
        275                 280                 285

Thr Met Phe Thr Leu Leu Met Thr Gly Lys Leu Lys Ser Tyr Tyr Thr
    290                 295                 300
```

```
Asp Leu Glu Ala Phe Ala Met Val Thr Ala Gly Leu Cys His Asp Ile
305                 310                 315                 320


Asp His Arg Gly Thr Asn Asn Leu Tyr Gln Met Lys Ser Gln Asn Pro
                325                 330                 335


Leu Ala Lys Leu His Gly Ser Ser Ile Leu Glu Arg His His Leu Glu
            340                 345                 350


Phe Gly Lys Phe Leu Leu Ser Glu Glu Thr Leu Asn Ile Tyr Gln Asn
        355                 360                 365


Leu Asn Arg Arg Gln His Glu His Val Ile His Leu Met Asp Ile Ala
    370                 375                 380


Ile Ile Ala Thr Asp Leu Ala Leu Tyr Phe Lys Lys Arg Ala Met Phe
385                 390                 395                 400


Gln Lys Ile Val Asp Glu Ser Lys Asn Tyr Gln Asp Lys Lys Ser Trp
                405                 410                 415


Val Glu Tyr Leu Ser Leu Glu Thr Thr Arg Lys Glu Ile Val Met Ala
            420                 425                 430


Met Met Met Thr Ala Cys Asp Leu Ser Ala Ile Thr Lys Pro Trp Glu
        435                 440                 445


Val Gln Ser Lys Val Ala Leu Leu Val Ala Ala Glu Phe Trp Glu Gln
    450                 455                 460


Gly Asp Leu Glu Arg Thr Val Leu Asp Gln Gln Pro Ile Pro Met Met
465                 470                 475                 480


Asp Arg Asn Lys Ala Ala Glu Leu Pro Lys Leu Gln Val Gly Phe Ile
                485                 490                 495
```

```
Asp Phe Val Cys Thr Phe Val Tyr Lys Glu Phe Ser Arg Phe His Glu
            500                 505                 510


Glu Ile Leu Pro Met Phe Asp Arg Leu Gln Asn Asn Arg Lys Glu Trp
        515                 520                 525


Lys Ala Leu Ala Asp Glu Tyr Glu Ala Lys Val Lys Ala Leu Glu Glu
    530                 535                 540


Lys Glu Glu Glu Glu Arg Val Ala Ala Lys Lys Val Gly Thr Glu Ile
545                 550                 555                 560


Cys Asn Gly Gly Pro Ala Pro Lys Ser Ser Thr Cys Cys Ile Leu
                565                 570                 575


<210>  106
<211>  694
<212>  PRT
<213>  Homo sapiens

<400>  106

Met Ala Lys Ile Asn Thr Gln Tyr Ser His Pro Ser Arg Thr His Leu
1               5                   10                  15


Lys Val Lys Thr Ser Asp Arg Asp Leu Asn Arg Ala Glu Asn Gly Leu
            20                  25                  30


Ser Arg Ala His Ser Ser Ser Glu Glu Thr Ser Ser Val Leu Gln Pro
        35                  40                  45


Gly Ile Ala Met Glu Thr Arg Gly Leu Ala Asp Ser Gly Gln Gly Ser
    50                  55                  60


Phe Thr Gly Gln Gly Ile Ala Arg Leu Ser Arg Leu Ile Phe Leu Leu
65                  70                  75                  80
```

```
Arg Arg Trp Ala Ala Arg His Val His His Gln Asp Gln Gly Pro Asp
                85                  90                  95

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

Gln Glu Ser Asn Ala Gln Ala Asn Val Gly Ser Gln Glu Pro Ala Asp
        115                 120                 125

Arg Gly Arg Ser Ala Trp Pro Leu Ala Lys Cys Asn Thr Asn Thr Ser
    130                 135                 140

Asn Asn Thr Glu Glu Glu Lys Lys Thr Lys Lys Lys Asp Ala Ile Val
145                 150                 155                 160

Val Asp Pro Ser Ser Asn Leu Tyr Tyr Arg Trp Leu Thr Ala Ile Ala
                165                 170                 175

Leu Pro Val Phe Tyr Asn Trp Tyr Leu Leu Ile Cys Arg Ala Cys Phe
            180                 185                 190

Asp Glu Leu Gln Ser Glu Tyr Leu Met Leu Trp Leu Val Leu Asp Tyr
        195                 200                 205

Ser Ala Asp Val Leu Tyr Val Leu Asp Val Leu Val Arg Ala Arg Thr
    210                 215                 220

Gly Phe Leu Glu Gln Gly Leu Met Val Ser Asp Thr Asn Arg Leu Trp
225                 230                 235                 240

Gln His Tyr Lys Thr Thr Thr Gln Phe Lys Leu Asp Val Leu Ser Leu
                245                 250                 255

Val Pro Thr Asp Leu Ala Tyr Leu Lys Val Gly Thr Asn Tyr Pro Glu
            260                 265                 270
```

```
Val Arg Phe Asn Arg Leu Leu Lys Phe Ser Arg Leu Phe Glu Phe Phe
        275                 280                 285

Asp Arg Thr Glu Thr Arg Thr Asn Tyr Pro Asn Met Phe Arg Ile Gly
    290                 295                 300

Asn Leu Val Leu Tyr Ile Leu Ile Ile Ile His Trp Asn Ala Cys Ile
305                 310                 315                 320

Tyr Phe Ala Ile Ser Lys Phe Ile Gly Phe Gly Thr Asp Ser Trp Val
                325                 330                 335

Tyr Pro Asn Ile Ser Ile Pro Glu His Gly Arg Leu Ser Arg Lys Tyr
            340                 345                 350

Ile Tyr Ser Leu Tyr Trp Ser Thr Leu Thr Leu Thr Thr Ile Gly Glu
        355                 360                 365

Thr Pro Pro Pro Val Lys Asp Glu Glu Tyr Leu Phe Val Val Val Asp
    370                 375                 380

Phe Leu Val Gly Val Leu Ile Phe Ala Thr Ile Val Gly Asn Val Gly
385                 390                 395                 400

Ser Met Ile Ser Asn Met Asn Ala Ser Arg Ala Glu Phe Gln Ala Lys
                405                 410                 415

Ile Asp Ser Ile Lys Gln Tyr Met Gln Phe Arg Lys Val Thr Lys Asp
            420                 425                 430

Leu Glu Thr Arg Val Ile Arg Trp Phe Asp Tyr Leu Trp Ala Asn Lys
        435                 440                 445

Lys Thr Val Asp Glu Lys Glu Val Leu Lys Ser Leu Pro Asp Lys Leu
    450                 455                 460
```

```
Lys Ala Glu Ile Ala Ile Asn Val His Leu Asp Thr Leu Lys Lys Val
465                 470                 475                 480


Arg Ile Phe Gln Asp Cys Glu Ala Gly Leu Leu Val Glu Leu Val Leu
                485                 490                 495


Lys Leu Arg Pro Thr Val Phe Ser Pro Gly Asp Tyr Ile Cys Lys Lys
            500                 505                 510


Gly Asp Ile Gly Lys Glu Met Tyr Ile Ile Asn Glu Gly Lys Leu Ala
        515                 520                 525


Val Val Ala Asp Asp Gly Val Thr Gln Phe Val Val Leu Ser Asp Gly
    530                 535                 540


Ser Tyr Phe Gly Glu Ile Ser Ile Leu Asn Ile Lys Gly Ser Lys Ser
545                 550                 555                 560


Gly Asn Arg Arg Thr Ala Asn Ile Arg Ser Ile Gly Tyr Ser Asp Leu
                565                 570                 575


Phe Cys Leu Ser Lys Asp Asp Leu Met Glu Ala Leu Thr Glu Tyr Pro
            580                 585                 590


Glu Ala Lys Lys Ala Leu Glu Glu Lys Gly Arg Gln Ile Leu Met Lys
        595                 600                 605


Asp Asn Leu Ile Asp Glu Glu Leu Ala Arg Ala Gly Ala Asp Pro Lys
    610                 615                 620


Asp Leu Glu Glu Lys Val Glu Gln Leu Gly Ser Ser Leu Asp Thr Leu
625                 630                 635                 640


Gln Thr Arg Phe Ala Arg Leu Leu Ala Glu Tyr Asn Ala Thr Gln Met
                645                 650                 655
```

Lys Met Lys Gln Arg Leu Ser Gln Leu Glu Ser Gln Val Lys Gly Gly
660 665 670

Gly Asp Lys Pro Leu Ala Asp Gly Glu Val Pro Gly Asp Ala Thr Lys
675 680 685

Thr Glu Asp Lys Gln Gln
690

<210> 107
<211> 676
<212> PRT
<213> Homo sapiens

<400> 107

Met Ala Lys Ile Asn Thr Gln Tyr Ser His Pro Ser Arg Thr His Leu
1 5 10 15

Lys Val Lys Thr Ser Asp Arg Asp Leu Asn Arg Ala Glu Asn Gly Leu
20 25 30

Ser Arg Ala His Ser Ser Ser Glu Glu Thr Ser Ser Val Leu Gln Pro
35 40 45

Gly Ile Ala Met Glu Thr Arg Gly Leu Ala Asp Ser Gly Gln Gly Ser
50 55 60

Phe Thr Gly Gln Gly Ile Ala Arg Leu Ser Arg Leu Ile Phe Leu Leu
65 70 75 80

Arg Arg Trp Ala Ala Arg His Val His His Gln Asp Gln Gly Pro Asp
85 90 95

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

Gln Glu Ser Asn Ala Gln Ala Asn Val Gly Ser Gln Glu Pro Ala Asp

```
        115                 120                 125

Arg Gly Arg Arg Lys Lys Thr Lys Lys Lys Asp Ala Ile Val Val Asp
    130                 135                 140

Pro Ser Ser Asn Leu Tyr Tyr Arg Trp Leu Thr Ala Ile Ala Leu Pro
145                 150                 155                 160

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

Leu Gln Ser Glu Tyr Leu Met Leu Trp Leu Val Leu Asp Tyr Ser Ala
            180                 185                 190

Asp Val Leu Tyr Val Leu Asp Val Leu Val Arg Ala Arg Thr Gly Phe
        195                 200                 205

Leu Glu Gln Gly Leu Met Val Ser Asp Thr Asn Arg Leu Trp Gln His
    210                 215                 220

Tyr Lys Thr Thr Thr Gln Phe Lys Leu Asp Val Leu Ser Leu Val Pro
225                 230                 235                 240

Thr Asp Leu Ala Tyr Leu Lys Val Gly Thr Asn Tyr Pro Glu Val Arg
                245                 250                 255

Phe Asn Arg Leu Leu Lys Phe Ser Arg Leu Phe Glu Phe Phe Asp Arg
            260                 265                 270

Thr Glu Thr Arg Thr Asn Tyr Pro Asn Met Phe Arg Ile Gly Asn Leu
        275                 280                 285

Val Leu Tyr Ile Leu Ile Ile Ile His Trp Asn Ala Cys Ile Tyr Phe
    290                 295                 300

Ala Ile Ser Lys Phe Ile Gly Phe Gly Thr Asp Ser Trp Val Tyr Pro
```

```
305                 310                 315                 320

Asn Ile Ser Ile Pro Glu His Gly Arg Leu Ser Arg Lys Tyr Ile Tyr
                325                 330                 335

Ser Leu Tyr Trp Ser Thr Leu Thr Leu Thr Thr Ile Gly Glu Thr Pro
            340                 345                 350

Pro Pro Val Lys Asp Glu Glu Tyr Leu Phe Val Val Val Asp Phe Leu
        355                 360                 365

Val Gly Val Leu Ile Phe Ala Thr Ile Val Gly Asn Val Gly Ser Met
    370                 375                 380

Ile Ser Asn Met Asn Ala Ser Arg Ala Glu Phe Gln Ala Lys Ile Asp
385                 390                 395                 400

Ser Ile Lys Gln Tyr Met Gln Phe Arg Lys Val Thr Lys Asp Leu Glu
                405                 410                 415

Thr Arg Val Ile Arg Trp Phe Asp Tyr Leu Trp Ala Asn Lys Lys Thr
            420                 425                 430

Val Asp Glu Lys Glu Val Leu Lys Ser Leu Pro Asp Lys Leu Lys Ala
        435                 440                 445

Glu Ile Ala Ile Asn Val His Leu Asp Thr Leu Lys Lys Val Arg Ile
    450                 455                 460

Phe Gln Asp Cys Glu Ala Gly Leu Leu Val Glu Leu Val Leu Lys Leu
465                 470                 475                 480

Arg Pro Thr Val Phe Ser Pro Gly Asp Tyr Ile Cys Lys Lys Gly Asp
                485                 490                 495

Ile Gly Lys Glu Met Tyr Ile Ile Asn Glu Gly Lys Leu Ala Val Val
```

```
            500                 505                 510

Ala Asp Asp Gly Val Thr Gln Phe Val Val Leu Ser Asp Gly Ser Tyr
        515                 520                 525

Phe Gly Glu Ile Ser Ile Leu Asn Ile Lys Gly Ser Lys Ser Gly Asn
    530                 535                 540

Arg Arg Thr Ala Asn Ile Arg Ser Ile Gly Tyr Ser Asp Leu Phe Cys
545                 550                 555                 560

Leu Ser Lys Asp Asp Leu Met Glu Ala Leu Thr Glu Tyr Pro Glu Ala
                565                 570                 575

Lys Lys Ala Leu Glu Glu Lys Gly Arg Gln Ile Leu Met Lys Asp Asn
            580                 585                 590

Leu Ile Asp Glu Glu Leu Ala Arg Ala Gly Ala Asp Pro Lys Asp Leu
        595                 600                 605

Glu Glu Lys Val Glu Gln Leu Gly Ser Ser Leu Asp Thr Leu Gln Thr
    610                 615                 620

Arg Phe Ala Arg Leu Leu Ala Glu Tyr Asn Ala Thr Gln Met Lys Met
625                 630                 635                 640

Lys Gln Arg Leu Ser Gln Leu Glu Ser Gln Val Lys Gly Gly Gly Asp
                645                 650                 655

Lys Pro Leu Ala Asp Gly Glu Val Pro Gly Asp Ala Thr Lys Thr Glu
            660                 665                 670

Asp Lys Gln Gln
        675

<210>  108
```

<211> 809
<212> PRT
<213> Homo sapiens

<400> 108

```
Met Phe Lys Ser Leu Thr Lys Val Asn Lys Val Lys Pro Ile Gly Glu
1               5                  10                  15

Asn Asn Glu Asn Glu Gln Ser Ser Arg Arg Asn Glu Glu Gly Ser His
            20                  25                  30

Pro Ser Asn Gln Ser Gln Gln Thr Thr Ala Gln Glu Glu Asn Lys Gly
        35                  40                  45

Glu Glu Lys Ser Leu Lys Thr Lys Ser Thr Pro Val Thr Ser Glu Glu
    50                  55                  60

Pro His Thr Asn Ile Gln Asp Lys Leu Ser Lys Lys Asn Ser Ser Gly
65                  70                  75                  80

Asp Leu Thr Thr Asn Pro Asp Pro Gln Asn Ala Ala Glu Pro Thr Gly
                85                  90                  95

Thr Val Pro Glu Gln Lys Glu Met Asp Pro Gly Lys Glu Gly Pro Asn
            100                 105                 110

Ser Pro Gln Asn Lys Pro Pro Ala Ala Pro Val Ile Asn Glu Tyr Ala
        115                 120                 125

Asp Ala Gln Leu His Asn Leu Val Lys Arg Met Arg Gln Arg Thr Ala
    130                 135                 140

Leu Tyr Lys Lys Lys Leu Val Glu Gly Asp Leu Ser Ser Pro Glu Ala
145                 150                 155                 160

Ser Pro Gln Thr Ala Lys Pro Thr Ala Val Pro Pro Val Lys Glu Ser
                165                 170                 175
```

```
Asp Asp Lys Pro Thr Glu His Tyr Tyr Arg Leu Leu Trp Phe Lys Val
            180                 185                 190

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

Ser Ile Asp Ser Tyr Thr Asp Arg Leu Tyr Leu Leu Trp Leu Leu Leu
    210                 215                 220

Val Thr Leu Ala Tyr Asn Trp Asn Cys Cys Phe Ile Pro Leu Arg Leu
225                 230                 235                 240

Val Phe Pro Tyr Gln Thr Ala Asp Asn Ile His Tyr Trp Leu Ile Ala
                245                 250                 255

Asp Ile Ile Cys Asp Ile Ile Tyr Leu Tyr Asp Met Leu Phe Ile Gln
            260                 265                 270

Pro Arg Leu Gln Phe Val Arg Gly Gly Asp Ile Ile Val Asp Ser Asn
        275                 280                 285

Glu Leu Arg Lys His Tyr Arg Thr Ser Thr Lys Phe Gln Leu Asp Val
    290                 295                 300

Ala Ser Ile Ile Pro Phe Asp Ile Cys Tyr Leu Phe Phe Gly Phe Asn
305                 310                 315                 320

Pro Met Phe Arg Ala Asn Arg Met Leu Lys Tyr Thr Ser Phe Phe Glu
                325                 330                 335

Phe Asn His His Leu Glu Ser Ile Met Asp Lys Ala Tyr Ile Tyr Arg
            340                 345                 350

Val Ile Arg Thr Thr Gly Tyr Leu Leu Phe Ile Leu His Ile Asn Ala
        355                 360                 365
```

```
Cys Val Tyr Tyr Trp Ala Ser Asn Tyr Glu Gly Ile Gly Thr Thr Arg
    370                 375                 380

Trp Val Tyr Asp Gly Glu Gly Asn Glu Tyr Leu Arg Cys Tyr Tyr Trp
385                 390                 395                 400

Ala Val Arg Thr Leu Ile Thr Ile Gly Gly Leu Pro Glu Pro Gln Thr
                405                 410                 415

Leu Phe Glu Ile Val Phe Gln Leu Leu Asn Phe Phe Ser Gly Val Phe
            420                 425                 430

Val Phe Ser Ser Leu Ile Gly Gln Met Arg Asp Val Ile Gly Ala Ala
        435                 440                 445

Thr Ala Asn Gln Asn Tyr Phe Arg Ala Cys Met Asp Asp Thr Ile Ala
    450                 455                 460

Tyr Met Asn Asn Tyr Ser Ile Pro Lys Leu Val Gln Lys Arg Val Arg
465                 470                 475                 480

Thr Trp Tyr Glu Tyr Thr Trp Asp Ser Gln Arg Met Leu Asp Glu Ser
                485                 490                 495

Asp Leu Leu Lys Thr Leu Pro Thr Thr Val Gln Leu Ala Leu Ala Ile
            500                 505                 510

Asp Val Asn Phe Ser Ile Ile Ser Lys Val Asp Leu Phe Lys Gly Cys
        515                 520                 525

Asp Thr Gln Met Ile Tyr Asp Met Leu Leu Arg Leu Lys Ser Val Leu
    530                 535                 540

Tyr Leu Pro Gly Asp Phe Val Cys Lys Lys Gly Glu Ile Gly Lys Glu
545                 550                 555                 560
```

```
Met Tyr Ile Ile Lys His Gly Glu Val Gln Val Leu Gly Gly Pro Asp
                565                 570                 575

Gly Thr Lys Val Leu Val Thr Leu Lys Ala Gly Ser Val Phe Gly Glu
            580                 585                 590

Ile Ser Leu Leu Ala Ala Gly Gly Gly Asn Arg Arg Thr Ala Asn Val
        595                 600                 605

Val Ala His Gly Phe Ala Asn Leu Leu Thr Leu Asp Lys Lys Thr Leu
    610                 615                 620

Gln Glu Ile Leu Val His Tyr Pro Asp Ser Glu Arg Ile Leu Met Lys
625                 630                 635                 640

Lys Ala Arg Val Leu Leu Lys Gln Lys Ala Lys Thr Ala Glu Ala Thr
                645                 650                 655

Pro Pro Arg Lys Asp Leu Ala Leu Leu Phe Pro Pro Lys Glu Glu Thr
            660                 665                 670

Pro Lys Leu Phe Lys Thr Leu Leu Gly Gly Thr Gly Lys Ala Ser Leu
        675                 680                 685

Ala Arg Leu Leu Lys Leu Lys Arg Glu Gln Ala Ala Gln Lys Lys Glu
    690                 695                 700

Asn Ser Glu Gly Gly Glu Glu Glu Gly Lys Glu Asn Glu Asp Lys Gln
705                 710                 715                 720

Lys Glu Asn Glu Asp Lys Gln Lys Glu Asn Glu Asp Lys Gly Lys Glu
                725                 730                 735

Asn Glu Asp Lys Asp Lys Gly Arg Glu Pro Glu Glu Lys Pro Leu Asp
            740                 745                 750
```

```
Arg Pro Glu Cys Thr Ala Ser Pro Ile Ala Val Glu Glu Glu Pro His
        755                 760                 765


Ser Val Arg Arg Thr Val Leu Pro Arg Gly Thr Ser Arg Gln Ser Leu
    770                 775                 780


Ile Ile Ser Met Ala Pro Ser Ala Glu Gly Gly Glu Glu Val Leu Thr
785                 790                 795                 800


Ile Glu Val Lys Glu Lys Ala Lys Gln
                805
```

<210> 109
<211> 354
<212> PRT
<213> Homo sapiens

<400> 109

```
Met Gly Ser Gly Ala Ser Ala Glu Asp Lys Glu Leu Ala Lys Arg Ser
1               5                   10                  15


Lys Glu Leu Glu Lys Lys Leu Gln Glu Asp Ala Asp Lys Glu Ala Lys
            20                  25                  30


Thr Val Lys Leu Leu Leu Leu Gly Ala Gly Glu Ser Gly Lys Ser Thr
        35                  40                  45


Ile Val Lys Gln Met Lys Ile Ile His Gln Asp Gly Tyr Ser Pro Glu
    50                  55                  60


Glu Cys Leu Glu Phe Lys Ala Ile Ile Tyr Gly Asn Val Leu Gln Ser
65                  70                  75                  80


Ile Leu Ala Ile Ile Arg Ala Met Thr Thr Leu Gly Ile Asp Tyr Ala
                85                  90                  95
```

```
Glu Pro Ser Cys Ala Asp Asp Gly Arg Gln Leu Asn Asn Leu Ala Asp
            100                 105                 110

Ser Ile Glu Glu Gly Thr Met Pro Pro Glu Leu Val Glu Val Ile Arg
        115                 120                 125

Arg Leu Trp Lys Asp Gly Gly Val Gln Ala Cys Phe Glu Arg Ala Ala
    130                 135                 140

Glu Tyr Gln Leu Asn Asp Ser Ala Ser Tyr Tyr Leu Asn Gln Leu Glu
145                 150                 155                 160

Arg Ile Thr Asp Pro Glu Tyr Leu Pro Ser Glu Gln Asp Val Leu Arg
                165                 170                 175

Ser Arg Val Lys Thr Thr Gly Ile Ile Glu Thr Lys Phe Ser Val Lys
            180                 185                 190

Asp Leu Asn Phe Arg Met Phe Asp Val Gly Gly Gln Arg Ser Glu Arg
        195                 200                 205

Lys Lys Trp Ile His Cys Phe Glu Gly Val Thr Cys Ile Ile Phe Cys
    210                 215                 220

Ala Ala Leu Ser Ala Tyr Asp Met Val Leu Val Glu Asp Asp Glu Val
225                 230                 235                 240

Asn Arg Met His Glu Ser Leu His Leu Phe Asn Ser Ile Cys Asn His
                245                 250                 255

Lys Phe Phe Ala Ala Thr Ser Ile Val Leu Phe Leu Asn Lys Lys Asp
            260                 265                 270

Leu Phe Glu Glu Lys Ile Lys Lys Val His Leu Ser Ile Cys Phe Pro
        275                 280                 285
```

```
Glu Tyr Asp Gly Asn Asn Ser Tyr Asp Asp Ala Gly Asn Tyr Ile Lys
    290                 295                 300


Ser Gln Phe Leu Asp Leu Asn Met Arg Lys Asp Val Lys Glu Ile Tyr
305                 310                 315                 320


Ser His Met Thr Cys Ala Thr Asp Thr Gln Asn Val Lys Phe Val Phe
                325                 330                 335


Asp Ala Val Thr Asp Ile Ile Ile Lys Glu Asn Leu Lys Asp Cys Gly
            340                 345                 350


Leu Phe



<210>  110
<211>  815
<212>  PRT
<213>  Homo sapiens

<400>  110

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


Phe Gly Lys Ser Lys Phe Ala Glu Asn Asn Pro Gly Lys Phe Trp Phe
            20                  25                  30


Lys Asn Asp Val Pro Val His Leu Ser Cys Gly Asp Glu His Ser Ala
        35                  40                  45


Val Val Thr Gly Asn Asn Lys Leu Tyr Met Phe Gly Ser Asn Asn Trp
    50                  55                  60


Gly Gln Leu Gly Leu Gly Ser Lys Ser Ala Ile Ser Lys Pro Thr Cys
65                  70                  75                  80
```

```
Val Lys Ala Leu Lys Pro Glu Lys Val Lys Leu Ala Ala Cys Gly Arg
                85                  90                  95

Asn His Thr Leu Val Ser Thr Glu Gly Gly Asn Val Tyr Ala Thr Gly
            100                 105                 110

Gly Asn Asn Glu Gly Gln Leu Gly Leu Gly Asp Thr Glu Glu Arg Asn
        115                 120                 125

Thr Phe His Val Ile Ser Phe Phe Thr Ser Glu His Lys Ile Lys Gln
    130                 135                 140

Leu Ser Ala Gly Ser Asn Thr Ser Ala Ala Leu Thr Glu Asp Gly Arg
145                 150                 155                 160

Leu Phe Met Trp Gly Asp Asn Ser Glu Gly Gln Ile Gly Leu Lys Asn
                165                 170                 175

Val Ser Asn Val Cys Val Pro Gln Gln Val Thr Ile Gly Lys Pro Val
            180                 185                 190

Ser Trp Ile Ser Cys Gly Tyr Tyr His Ser Ala Phe Val Thr Thr Asp
        195                 200                 205

Gly Glu Leu Tyr Val Phe Gly Glu Pro Glu Asn Gly Lys Leu Gly Leu
    210                 215                 220

Pro Asn Gln Leu Leu Gly Asn His Arg Thr Pro Gln Leu Val Ser Glu
225                 230                 235                 240

Ile Pro Glu Lys Val Ile Gln Val Ala Cys Gly Gly Glu His Thr Val
                245                 250                 255

Val Leu Thr Glu Asn Ala Val Tyr Thr Phe Gly Leu Gly Gln Phe Gly
            260                 265                 270
```

```
Gln Leu Gly Leu Gly Thr Phe Leu Phe Glu Thr Ser Glu Pro Lys Val
        275                 280                 285

Ile Glu Asn Ile Arg Asp Gln Thr Ile Ser Tyr Ile Ser Cys Gly Glu
    290                 295                 300

Asn His Thr Ala Leu Ile Thr Asp Ile Gly Leu Met Tyr Thr Phe Gly
305                 310                 315                 320

Asp Gly Arg His Gly Lys Leu Gly Leu Gly Leu Glu Asn Phe Thr Asn
                325                 330                 335

His Phe Ile Pro Thr Leu Cys Ser Asn Phe Leu Arg Phe Ile Val Lys
            340                 345                 350

Leu Val Ala Cys Gly Gly Cys His Met Val Val Phe Ala Ala Pro His
        355                 360                 365

Arg Gly Val Ala Lys Glu Ile Glu Phe Asp Glu Ile Asn Asp Thr Cys
    370                 375                 380

Leu Ser Val Ala Thr Phe Leu Pro Tyr Ser Ser Leu Thr Ser Gly Asn
385                 390                 395                 400

Val Leu Gln Arg Thr Leu Ser Ala Arg Met Arg Arg Arg Glu Arg Glu
                405                 410                 415

Arg Ser Pro Asp Ser Phe Ser Met Arg Arg Thr Leu Pro Pro Ile Glu
            420                 425                 430

Gly Thr Leu Gly Leu Ser Ala Cys Phe Leu Pro Asn Ser Val Phe Pro
        435                 440                 445

Arg Cys Ser Glu Arg Asn Leu Gln Glu Ser Val Leu Ser Glu Gln Asp
    450                 455                 460
```

```
Leu Met Gln Pro Glu Glu Pro Asp Tyr Leu Leu Asp Glu Met Thr Lys
465                 470                 475                 480


Glu Ala Glu Ile Asp Asn Ser Ser Thr Val Glu Ser Leu Gly Glu Thr
                485                 490                 495


Thr Asp Ile Leu Asn Met Thr His Ile Met Ser Leu Asn Ser Asn Glu
            500                 505                 510


Lys Ser Leu Lys Leu Ser Pro Val Gln Lys Gln Lys Lys Gln Gln Thr
        515                 520                 525


Ile Gly Glu Leu Thr Gln Asp Thr Ala Leu Thr Glu Asn Asp Asp Ser
    530                 535                 540


Asp Glu Tyr Glu Glu Met Ser Glu Met Lys Glu Gly Lys Ala Cys Lys
545                 550                 555                 560


Gln His Val Ser Gln Gly Ile Phe Met Thr Gln Pro Ala Thr Thr Ile
                565                 570                 575


Glu Ala Phe Ser Asp Glu Glu Val Glu Ile Pro Glu Glu Lys Glu Gly
            580                 585                 590


Ala Glu Asp Ser Lys Gly Asn Gly Ile Glu Glu Gln Glu Val Glu Ala
        595                 600                 605


Asn Glu Glu Asn Val Lys Val His Gly Gly Arg Lys Glu Lys Thr Glu
    610                 615                 620


Ile Leu Ser Asp Asp Leu Thr Asp Lys Ala Glu Asp His Glu Phe Ser
625                 630                 635                 640


Lys Thr Glu Glu Leu Lys Leu Glu Asp Val Asp Glu Glu Ile Asn Ala
                645                 650                 655
```

```
Glu Asn Val Glu Ser Lys Lys Lys Thr Val Gly Asp Asp Glu Ser Val
            660                 665                 670


Pro Thr Gly Tyr His Ser Lys Thr Glu Gly Ala Glu Arg Thr Asn Asp
        675                 680                 685


Asp Ser Ser Ala Glu Thr Ile Glu Lys Lys Glu Lys Ala Asn Leu Glu
    690                 695                 700


Glu Arg Ala Ile Cys Glu Tyr Asn Glu Asn Pro Lys Gly Tyr Met Leu
705                 710                 715                 720


Asp Asp Ala Asp Ser Ser Ser Leu Glu Ile Leu Glu Asn Ser Glu Thr
                725                 730                 735


Thr Pro Ser Lys Asp Met Lys Lys Thr Lys Lys Ile Phe Leu Phe Lys
            740                 745                 750


Arg Val Pro Ser Ile Asn Gln Lys Ile Val Lys Asn Asn Asn Glu Pro
        755                 760                 765


Leu Pro Glu Ile Lys Ser Ile Gly Asp Gln Ile Ile Leu Lys Ser Asp
    770                 775                 780


Asn Lys Asp Ala Asp Gln Asn His Met Ser Gln Asn His Gln Asn Ile
785                 790                 795                 800


Pro Pro Thr Asn Thr Glu Arg Arg Ser Lys Ser Cys Thr Ile Leu
                805                 810                 815


<210>  111
<211>  646
<212>  PRT
<213>  Homo sapiens

<400>  111

Met Arg Glu Pro Glu Glu Leu Met Pro Asp Ser Gly Ala Val Phe Thr
```

```
1               5                   10                  15

Phe Gly Lys Ser Lys Phe Ala Glu Asn Asn Pro Gly Lys Phe Trp Phe
            20                  25                  30

Lys Asn Asp Val Pro Val His Leu Ser Cys Gly Asp Glu His Ser Ala
        35                  40                  45

Val Val Thr Gly Asn Asn Lys Leu Tyr Met Phe Gly Ser Asn Asn Trp
    50                  55                  60

Gly Gln Leu Gly Leu Gly Ser Lys Ser Ala Ile Ser Lys Pro Thr Cys
65                  70                  75                  80

Val Lys Ala Leu Lys Pro Glu Lys Val Lys Leu Ala Ala Cys Gly Arg
                85                  90                  95

Asn His Thr Leu Val Ser Thr Glu Gly Gly Asn Val Tyr Ala Thr Gly
            100                 105                 110

Gly Asn Asn Glu Gly Gln Leu Gly Leu Gly Asp Thr Glu Glu Arg Asn
        115                 120                 125

Thr Phe His Val Ile Ser Phe Phe Thr Ser Glu His Lys Ile Lys Gln
    130                 135                 140

Leu Ser Ala Gly Ser Asn Thr Ser Ala Ala Leu Thr Glu Asp Gly Arg
145                 150                 155                 160

Leu Phe Met Trp Gly Asp Asn Ser Glu Gly Gln Ile Gly Leu Lys Asn
                165                 170                 175

Val Ser Asn Val Cys Val Pro Gln Gln Val Thr Ile Gly Lys Pro Val
            180                 185                 190

Ser Trp Ile Ser Cys Gly Tyr Tyr His Ser Ala Phe Val Thr Thr Asp
```

195 200 205

Gly Glu Leu Tyr Val Phe Gly Glu Pro Glu Asn Gly Lys Leu Gly Leu
210 215 220

Pro Asn Gln Leu Leu Gly Asn His Arg Thr Pro Gln Leu Val Ser Glu
225 230 235 240

Ile Pro Glu Lys Val Ile Gln Val Ala Cys Gly Gly Glu His Thr Val
245 250 255

Val Leu Thr Glu Asn Ala Val Tyr Thr Phe Gly Leu Gly Gln Phe Gly
260 265 270

Gln Leu Gly Leu Gly Thr Phe Leu Phe Glu Thr Ser Glu Pro Lys Val
275 280 285

Ile Glu Asn Ile Arg Asp Gln Thr Ile Ser Tyr Ile Ser Cys Gly Glu
290 295 300

Asn His Thr Ala Leu Ile Thr Asp Ile Gly Leu Met Tyr Thr Phe Gly
305 310 315 320

Asp Gly Arg His Gly Lys Leu Gly Leu Gly Leu Glu Asn Phe Thr Asn
325 330 335

His Phe Ile Pro Thr Leu Cys Ser Asn Phe Leu Arg Phe Ile Val Lys
340 345 350

Leu Val Ala Cys Gly Gly Cys His Met Val Val Phe Ala Ala Pro His
355 360 365

Arg Gly Val Ala Lys Glu Ile Glu Phe Asp Glu Ile Asn Asp Thr Cys
370 375 380

Leu Ser Val Ala Thr Phe Leu Pro Tyr Ser Ser Leu Thr Ser Gly Asn

385 390 395 400

Val Leu Gln Arg Thr Leu Ser Ala Arg Met Arg Arg Arg Glu Arg Glu
405 410 415

Arg Ser Pro Asp Ser Phe Ser Met Arg Arg Thr Leu Pro Pro Ile Glu
420 425 430

Gly Thr Leu Gly Leu Ser Ala Cys Phe Leu Pro Asn Ser Val Phe Pro
435 440 445

Arg Cys Ser Glu Arg Asn Leu Gln Glu Ser Val Leu Ser Glu Gln Asp
450 455 460

Leu Met Gln Pro Glu Glu Pro Asp Tyr Leu Leu Asp Glu Met Thr Lys
465 470 475 480

Glu Ala Glu Ile Asp Asn Ser Ser Thr Val Glu Ser Leu Gly Glu Thr
485 490 495

Thr Asp Ile Leu Asn Met Thr His Ile Met Ser Leu Asn Ser Asn Glu
500 505 510

Lys Ser Leu Lys Leu Ser Pro Val Gln Lys Gln Lys Lys Gln Gln Thr
515 520 525

Ile Gly Glu Leu Thr Gln Asp Thr Ala Leu Thr Glu Asn Asp Asp Ser
530 535 540

Asp Glu Tyr Glu Glu Met Ser Glu Met Lys Glu Gly Lys Ala Cys Lys
545 550 555 560

Gln His Val Ser Gln Gly Ile Phe Met Thr Gln Pro Ala Thr Thr Ile
565 570 575

Glu Ala Phe Ser Asp Glu Glu Val Glu Ile Pro Glu Glu Lys Glu Gly

580 585 590

Ala Glu Asp Ser Lys Gly Asn Gly Ile Glu Glu Gln Glu Val Glu Ala
595 600 605

Asn Glu Glu Asn Val Lys Val His Gly Gly Arg Lys Glu Lys Thr Glu
610 615 620

Ile Leu Ser Asp Asp Leu Thr Asp Lys Ala Glu Tyr Ser Ala Ser His
625 630 635 640

Ser Gln Ile Val Ser Val
645

<210> 112
<211> 1152
<212> PRT
<213> Homo sapiens

<400> 112

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

Phe Gly Lys Ser Lys Phe Ala Glu Asn Asn Pro Gly Lys Phe Trp Phe
20 25 30

Lys Asn Asp Val Pro Val His Leu Ser Cys Gly Asp Glu His Ser Ala
35 40 45

Val Val Thr Gly Asn Asn Lys Leu Tyr Met Phe Gly Ser Asn Asn Trp
50 55 60

Gly Gln Leu Gly Leu Gly Ser Lys Ser Ala Ile Ser Lys Pro Thr Cys
65 70 75 80

Val Lys Ala Leu Lys Pro Glu Lys Val Lys Leu Ala Ala Cys Gly Arg
85 90 95

```
Asn His Thr Leu Val Ser Thr Glu Gly Gly Asn Val Tyr Ala Thr Gly
            100                 105                 110

Gly Asn Asn Glu Gly Gln Leu Gly Leu Gly Asp Thr Glu Glu Arg Asn
        115                 120                 125

Thr Phe His Val Ile Ser Phe Phe Thr Ser Glu His Lys Ile Lys Gln
    130                 135                 140

Leu Ser Ala Gly Ser Asn Thr Ser Ala Ala Leu Thr Glu Asp Gly Arg
145                 150                 155                 160

Leu Phe Met Trp Gly Asp Asn Ser Glu Gly Gln Ile Gly Leu Lys Asn
                165                 170                 175

Val Ser Asn Val Cys Val Pro Gln Gln Val Thr Ile Gly Lys Pro Val
            180                 185                 190

Ser Trp Ile Ser Cys Gly Tyr Tyr His Ser Ala Phe Val Thr Thr Asp
        195                 200                 205

Gly Glu Leu Tyr Val Phe Gly Glu Pro Glu Asn Gly Lys Leu Gly Leu
    210                 215                 220

Pro Asn Gln Leu Leu Gly Asn His Arg Thr Pro Gln Leu Val Ser Glu
225                 230                 235                 240

Ile Pro Glu Lys Val Ile Gln Val Ala Cys Gly Gly Glu His Thr Val
                245                 250                 255

Val Leu Thr Glu Asn Ala Val Tyr Thr Phe Gly Leu Gly Gln Phe Gly
            260                 265                 270

Gln Leu Gly Leu Gly Thr Phe Leu Phe Glu Thr Ser Glu Pro Lys Val
        275                 280                 285
```

```
Ile Glu Asn Ile Arg Asp Gln Thr Ile Ser Tyr Ile Ser Cys Gly Glu
    290                 295                 300

Asn His Thr Ala Leu Ile Thr Asp Ile Gly Leu Met Tyr Thr Phe Gly
305                 310                 315                 320

Asp Gly Arg His Gly Lys Leu Gly Leu Gly Leu Glu Asn Phe Thr Asn
                325                 330                 335

His Phe Ile Pro Thr Leu Cys Ser Asn Phe Leu Arg Phe Ile Val Lys
            340                 345                 350

Leu Val Ala Cys Gly Gly Cys His Met Val Val Phe Ala Ala Pro His
        355                 360                 365

Arg Gly Val Ala Lys Glu Ile Glu Phe Asp Glu Ile Asn Asp Thr Cys
    370                 375                 380

Leu Ser Val Ala Thr Phe Leu Pro Tyr Ser Ser Leu Thr Ser Gly Asn
385                 390                 395                 400

Val Leu Gln Arg Thr Leu Ser Ala Arg Met Arg Arg Arg Glu Arg Glu
                405                 410                 415

Arg Ser Pro Asp Ser Phe Ser Met Arg Arg Thr Leu Pro Pro Ile Glu
            420                 425                 430

Gly Thr Leu Gly Leu Ser Ala Cys Phe Leu Pro Asn Ser Val Phe Pro
        435                 440                 445

Arg Cys Ser Glu Arg Asn Leu Gln Glu Ser Val Leu Ser Glu Gln Asp
    450                 455                 460

Leu Met Gln Pro Glu Glu Pro Asp Tyr Leu Leu Asp Glu Met Thr Lys
465                 470                 475                 480
```

```
Glu Ala Glu Ile Asp Asn Ser Ser Thr Val Glu Ser Leu Gly Glu Thr
                485                 490                 495

Thr Asp Ile Leu Asn Met Thr His Ile Met Ser Leu Asn Ser Asn Glu
            500                 505                 510

Lys Ser Leu Lys Leu Ser Pro Val Gln Lys Gln Lys Lys Gln Gln Thr
        515                 520                 525

Ile Gly Glu Leu Thr Gln Asp Thr Ala Leu Thr Glu Asn Asp Asp Ser
    530                 535                 540

Asp Glu Tyr Glu Glu Met Ser Glu Met Lys Glu Gly Lys Ala Cys Lys
545                 550                 555                 560

Gln His Val Ser Gln Gly Ile Phe Met Thr Gln Pro Ala Thr Thr Ile
                565                 570                 575

Glu Ala Phe Ser Asp Glu Glu Val Glu Ile Pro Glu Glu Lys Glu Gly
            580                 585                 590

Ala Glu Asp Ser Lys Gly Asn Gly Ile Glu Glu Gln Glu Val Glu Ala
        595                 600                 605

Asn Glu Glu Asn Val Lys Val His Gly Gly Arg Lys Glu Lys Thr Glu
    610                 615                 620

Ile Leu Ser Asp Asp Leu Thr Asp Lys Ala Glu Val Ser Glu Gly Lys
625                 630                 635                 640

Ala Lys Ser Val Gly Glu Ala Glu Asp Gly Pro Glu Gly Arg Gly Asp
                645                 650                 655

Gly Thr Cys Glu Glu Gly Ser Ser Gly Ala Glu His Trp Gln Asp Glu
            660                 665                 670
```

```
Glu Arg Glu Lys Gly Glu Lys Asp Lys Gly Arg Gly Glu Met Glu Arg
        675                 680                 685

Pro Gly Glu Gly Glu Lys Glu Leu Ala Glu Lys Glu Glu Trp Lys Lys
    690                 695                 700

Arg Asp Gly Glu Glu Gln Glu Gln Lys Glu Arg Glu Gln Gly His Gln
705                 710                 715                 720

Lys Glu Arg Asn Gln Glu Met Glu Glu Gly Gly Glu Glu Glu His Gly
                725                 730                 735

Glu Gly Glu Glu Glu Glu Gly Asp Arg Glu Glu Glu Glu Glu Lys Glu
            740                 745                 750

Gly Glu Gly Lys Glu Glu Gly Glu Gly Glu Glu Val Glu Gly Glu Arg
        755                 760                 765

Glu Lys Glu Glu Gly Glu Arg Lys Lys Glu Glu Arg Ala Gly Lys Glu
    770                 775                 780

Glu Lys Gly Glu Glu Glu Gly Asp Gln Gly Glu Gly Glu Glu Glu Glu
785                 790                 795                 800

Thr Glu Gly Arg Gly Glu Glu Lys Glu Glu Gly Gly Glu Val Glu Gly
                805                 810                 815

Gly Glu Val Glu Glu Gly Lys Gly Glu Arg Glu Glu Glu Glu Glu Glu
            820                 825                 830

Gly Glu Gly Glu Glu Glu Glu Gly Glu Gly Glu Glu Glu Glu Gly Glu
        835                 840                 845

Gly Glu Glu Glu Glu Gly Glu Gly Lys Gly Glu Glu Glu Gly Glu Glu
    850                 855                 860
```

```
Gly Glu Gly Glu Glu Glu Gly Glu Glu Gly Glu Gly Glu Gly Glu Glu
865                 870                 875                 880


Glu Glu Gly Glu Gly Glu Gly Glu Glu Glu Gly Glu Gly Glu Gly Glu
                885                 890                 895


Glu Glu Glu Gly Glu Gly Glu Gly Glu Glu Glu Gly Glu Gly Glu Gly
            900                 905                 910


Glu Glu Glu Glu Gly Glu Gly Lys Gly Glu Glu Glu Gly Glu Glu Gly
        915                 920                 925


Glu Gly Glu Gly Glu Glu Glu Glu Gly Glu Gly Glu Gly Glu Asp Gly
    930                 935                 940


Glu Gly Glu Gly Glu Glu Glu Glu Gly Glu Trp Glu Gly Glu Glu Glu
945                 950                 955                 960


Glu Gly Glu Gly Glu Gly Glu Glu Glu Gly Glu Gly Glu Gly Glu Glu
                965                 970                 975


Gly Glu Gly Glu Gly Glu Glu Glu Glu Gly Glu Gly Glu Gly Glu Glu
            980                 985                 990


Glu Glu Gly Glu Glu Glu Gly Glu  Glu Glu Gly Glu Gly  Glu Glu Glu
        995                 1000                1005


Gly Glu  Gly Glu Gly Glu Glu  Glu Glu Glu Gly Glu  Val Glu Gly
    1010                1015                1020


Glu Val  Glu Gly Glu Glu Gly  Glu Gly Glu Gly Glu  Glu Glu Glu
    1025                1030                1035


Gly Glu  Glu Glu Gly Glu Glu  Arg Glu Lys Glu Gly  Glu Gly Glu
    1040                1045                1050
```

```
Glu Asn  Arg Arg Asn Arg Glu  Glu Glu Glu Glu Glu  Glu Gly Lys
    1055                1060                1065


Tyr Gln  Glu Thr Gly Glu Glu  Glu Asn Glu Arg Gln  Asp Gly Glu
    1070                1075                1080


Glu Tyr  Lys Lys Val Ser Lys  Ile Lys Gly Ser Val  Lys Tyr Gly
    1085                1090                1095


Lys His  Lys Thr Tyr Gln Lys  Lys Ser Val Thr Asn  Thr Gln Gly
    1100                1105                1110


Asn Gly  Lys Glu Gln Arg Ser  Lys Met Pro Val Gln  Ser Lys Arg
    1115                1120                1125


Leu Leu  Lys Asn Gly Pro Ser  Gly Ser Lys Lys Phe  Trp Asn Asn
    1130                1135                1140


Val Leu  Pro His Tyr Leu Glu  Leu Lys
    1145                1150


<210>  113
<211>  1020
<212>  PRT
<213>  Homo sapiens

<400>  113

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


Phe Gly Lys Ser Lys Phe Ala Glu Asn Asn Pro Gly Lys Phe Trp Phe
            20                  25                  30


Lys Asn Asp Val Pro Val His Leu Ser Cys Gly Asp Glu His Ser Ala
        35                  40                  45
```

```
Val Val Thr Gly Asn Asn Lys Leu Tyr Met Phe Gly Ser Asn Asn Trp
    50                  55                  60

Gly Gln Leu Gly Leu Gly Ser Lys Ser Ala Ile Ser Lys Pro Thr Cys
65                  70                  75                  80

Val Lys Ala Leu Lys Pro Glu Lys Val Lys Leu Ala Ala Cys Gly Arg
                85                  90                  95

Asn His Thr Leu Val Ser Thr Glu Gly Gly Asn Val Tyr Ala Thr Gly
            100                 105                 110

Gly Asn Asn Glu Gly Gln Leu Gly Leu Gly Asp Thr Glu Glu Arg Asn
        115                 120                 125

Thr Phe His Val Ile Ser Phe Phe Thr Ser Glu His Lys Ile Lys Gln
    130                 135                 140

Leu Ser Ala Gly Ser Asn Thr Ser Ala Ala Leu Thr Glu Asp Gly Arg
145                 150                 155                 160

Leu Phe Met Trp Gly Asp Asn Ser Glu Gly Gln Ile Gly Leu Lys Asn
                165                 170                 175

Val Ser Asn Val Cys Val Pro Gln Gln Val Thr Ile Gly Lys Pro Val
            180                 185                 190

Ser Trp Ile Ser Cys Gly Tyr Tyr His Ser Ala Phe Val Thr Thr Asp
        195                 200                 205

Gly Glu Leu Tyr Val Phe Gly Glu Pro Glu Asn Gly Lys Leu Gly Leu
    210                 215                 220

Pro Asn Gln Leu Leu Gly Asn His Arg Thr Pro Gln Leu Val Ser Glu
225                 230                 235                 240
```

```
Ile Pro Glu Lys Val Ile Gln Val Ala Cys Gly Gly Glu His Thr Val
                245                 250                 255


Val Leu Thr Glu Asn Ala Val Tyr Thr Phe Gly Leu Gly Gln Phe Gly
            260                 265                 270


Gln Leu Gly Leu Gly Thr Phe Leu Phe Glu Thr Ser Glu Pro Lys Val
        275                 280                 285


Ile Glu Asn Ile Arg Asp Gln Thr Ile Ser Tyr Ile Ser Cys Gly Glu
    290                 295                 300


Asn His Thr Ala Leu Ile Thr Asp Ile Gly Leu Met Tyr Thr Phe Gly
305                 310                 315                 320


Asp Gly Arg His Gly Lys Leu Gly Leu Gly Leu Glu Asn Phe Thr Asn
                325                 330                 335


His Phe Ile Pro Thr Leu Cys Ser Asn Phe Leu Arg Phe Ile Val Lys
            340                 345                 350


Leu Val Ala Cys Gly Gly Cys His Met Val Val Phe Ala Ala Pro His
        355                 360                 365


Arg Gly Val Ala Lys Glu Ile Glu Phe Asp Glu Ile Asn Asp Thr Cys
    370                 375                 380


Leu Ser Val Ala Thr Phe Leu Pro Tyr Ser Ser Leu Thr Ser Gly Asn
385                 390                 395                 400


Val Leu Gln Arg Thr Leu Ser Ala Arg Met Arg Arg Arg Glu Arg Glu
                405                 410                 415


Arg Ser Pro Asp Ser Phe Ser Met Arg Arg Thr Leu Pro Pro Ile Glu
            420                 425                 430
```

```
Gly Thr Leu Gly Leu Ser Ala Cys Phe Leu Pro Asn Ser Val Phe Pro
        435                 440                 445


Arg Cys Ser Glu Arg Asn Leu Gln Glu Ser Val Leu Ser Glu Gln Asp
    450                 455                 460


Leu Met Gln Pro Glu Glu Pro Asp Tyr Leu Leu Asp Glu Met Thr Lys
465                 470                 475                 480


Glu Ala Glu Ile Asp Asn Ser Ser Thr Val Glu Ser Leu Gly Glu Thr
                485                 490                 495


Thr Asp Ile Leu Asn Met Thr His Ile Met Ser Leu Asn Ser Asn Glu
            500                 505                 510


Lys Ser Leu Lys Leu Ser Pro Val Gln Lys Gln Lys Lys Gln Gln Thr
        515                 520                 525


Ile Gly Glu Leu Thr Gln Asp Thr Ala Leu Thr Glu Asn Asp Asp Ser
    530                 535                 540


Asp Glu Tyr Glu Glu Met Ser Glu Met Lys Glu Gly Lys Ala Cys Lys
545                 550                 555                 560


Gln His Val Ser Gln Gly Ile Phe Met Thr Gln Pro Ala Thr Thr Ile
                565                 570                 575


Glu Ala Phe Ser Asp Glu Glu Val Gly Asn Asp Thr Gly Gln Val Gly
            580                 585                 590


Pro Gln Ala Asp Thr Asp Gly Glu Gly Leu Gln Lys Glu Val Tyr Arg
        595                 600                 605


His Glu Asn Asn Asn Gly Val Asp Gln Leu Asp Ala Lys Glu Ile Glu
    610                 615                 620
```

```
Lys Glu Ser Asp Gly Gly His Ser Gln Lys Glu Ser Glu Ala Glu Glu
625                 630                 635                 640


Ile Asp Ser Glu Lys Glu Thr Lys Leu Ala Glu Ile Ala Gly Met Lys
                645                 650                 655


Asp Leu Arg Glu Arg Glu Lys Ser Thr Lys Lys Met Ser Pro Phe Phe
            660                 665                 670


Gly Asn Leu Pro Asp Arg Gly Met Asn Thr Glu Ser Glu Glu Asn Lys
        675                 680                 685


Asp Phe Val Lys Lys Arg Glu Ser Cys Lys Gln Asp Val Ile Phe Asp
    690                 695                 700


Ser Glu Arg Glu Ser Val Glu Lys Pro Asp Ser Tyr Met Glu Gly Ala
705                 710                 715                 720


Ser Glu Ser Gln Gln Gly Ile Ala Asp Gly Phe Gln Gln Pro Glu Ala
                725                 730                 735


Ile Glu Phe Ser Ser Gly Glu Lys Glu Asp Asp Glu Val Glu Thr Asp
            740                 745                 750


Gln Asn Ile Arg Tyr Gly Arg Lys Leu Ile Glu Gln Gly Asn Glu Lys
        755                 760                 765


Glu Thr Lys Pro Ile Ile Ser Lys Ser Met Ala Lys Tyr Asp Phe Lys
    770                 775                 780


Cys Asp Arg Leu Ser Glu Ile Pro Glu Glu Lys Glu Gly Ala Glu Asp
785                 790                 795                 800


Ser Lys Gly Asn Gly Ile Glu Glu Gln Glu Val Glu Ala Asn Glu Glu
                805                 810                 815
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```
Asn Val Lys Val His Gly Gly Arg Lys Glu Lys Thr Glu Ile Leu Ser
            820                 825                 830

Asp Asp Leu Thr Asp Lys Ala Glu Asp His Glu Phe Ser Lys Thr Glu
        835                 840                 845

Glu Leu Lys Leu Glu Asp Val Asp Glu Glu Ile Asn Ala Glu Asn Val
    850                 855                 860

Glu Ser Lys Lys Lys Thr Val Gly Asp Asp Glu Ser Val Pro Thr Gly
865                 870                 875                 880

Tyr His Ser Lys Thr Glu Gly Ala Glu Arg Thr Asn Asp Asp Ser Ser
                885                 890                 895

Ala Glu Thr Ile Glu Lys Lys Glu Lys Ala Asn Leu Glu Glu Arg Ala
            900                 905                 910

Ile Cys Glu Tyr Asn Glu Asn Pro Lys Gly Tyr Met Leu Asp Asp Ala
        915                 920                 925

Asp Ser Ser Ser Leu Glu Ile Leu Glu Asn Ser Glu Thr Thr Pro Ser
    930                 935                 940

Lys Asp Met Lys Lys Thr Lys Lys Ile Phe Leu Phe Lys Arg Val Pro
945                 950                 955                 960

Ser Ile Asn Gln Lys Ile Val Lys Asn Asn Asn Glu Pro Leu Pro Glu
                965                 970                 975

Ile Lys Ser Ile Gly Asp Gln Ile Ile Leu Lys Ser Asp Asn Lys Asp
            980                 985                 990

Ala Asp Gln Asn His Met Ser Gln  Asn His Gln Asn Ile  Pro Pro Thr
        995                 1000                1005
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Asn Thr  Glu Arg Arg Ser Lys  Ser Cys Thr Ile Leu
    1010                1015                1020


<210>  114
<211>  734
<212>  PRT
<213>  Adeno-associated virus - 4

<400>  114

Met Thr Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser Glu
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Gly Val Arg Glu Trp Trp Ala Leu Gln Pro Gly Ala Pro Lys Pro Lys
            20                  25                  30


Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro Gly
        35                  40                  45


Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro Val
    50                  55                  60


Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp Gln
65                  70                  75                  80


Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala Asp
                85                  90                  95


Ala Glu Phe Gln Gln Arg Leu Gln Gly Asp Thr Ser Phe Gly Gly Asn
            100                 105                 110


Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro Leu
        115                 120                 125


Gly Leu Val Glu Gln Ala Gly Glu Thr Ala Pro Gly Lys Lys Arg Pro
    130                 135                 140
```

```
Leu Ile Glu Ser Pro Gln Gln Pro Asp Ser Ser Thr Gly Ile Gly Lys
145                 150                 155                 160


Lys Gly Lys Gln Pro Ala Lys Lys Lys Leu Val Phe Glu Asp Glu Thr
                165                 170                 175


Gly Ala Gly Asp Gly Pro Pro Glu Gly Ser Thr Ser Gly Ala Met Ser
            180                 185                 190


Asp Asp Ser Glu Met Arg Ala Ala Ala Gly Gly Ala Ala Val Glu Gly
        195                 200                 205


Gly Gln Gly Ala Asp Gly Val Gly Asn Ala Ser Gly Asp Trp His Cys
    210                 215                 220


Asp Ser Thr Trp Ser Glu Gly His Val Thr Thr Thr Ser Thr Arg Thr
225                 230                 235                 240


Trp Val Leu Pro Thr Tyr Asn Asn His Leu Tyr Lys Arg Leu Gly Glu
                245                 250                 255


Ser Leu Gln Ser Asn Thr Tyr Asn Gly Phe Ser Thr Pro Trp Gly Tyr
            260                 265                 270


Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp Gln
        275                 280                 285


Arg Leu Ile Asn Asn Asn Trp Gly Met Arg Pro Lys Ala Met Arg Val
    290                 295                 300


Lys Ile Phe Asn Ile Gln Val Lys Glu Val Thr Thr Ser Asn Gly Glu
305                 310                 315                 320


Thr Thr Val Ala Asn Asn Leu Thr Ser Thr Val Gln Ile Phe Ala Asp
                325                 330                 335
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Ser Ser Tyr Glu Leu Pro Tyr Val Met Asp Ala Gly Gln Glu Gly Ser
            340                 345                 350

Leu Pro Pro Phe Pro Asn Asp Val Phe Met Val Pro Gln Tyr Gly Tyr
        355                 360                 365

Cys Gly Leu Val Thr Gly Asn Thr Ser Gln Gln Gln Thr Asp Arg Asn
    370                 375                 380

Ala Phe Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly
385                 390                 395                 400

Asn Asn Phe Glu Ile Thr Tyr Ser Phe Glu Lys Val Pro Phe His Ser
                405                 410                 415

Met Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile
            420                 425                 430

Asp Gln Tyr Leu Trp Gly Leu Gln Ser Thr Thr Thr Gly Thr Thr Leu
        435                 440                 445

Asn Ala Gly Thr Ala Thr Thr Asn Phe Thr Lys Leu Arg Pro Thr Asn
    450                 455                 460

Phe Ser Asn Phe Lys Lys Asn Trp Leu Pro Gly Pro Ser Ile Lys Gln
465                 470                 475                 480

Gln Gly Phe Ser Lys Thr Ala Asn Gln Asn Tyr Lys Ile Pro Ala Thr
                485                 490                 495

Gly Ser Asp Ser Leu Ile Lys Tyr Glu Thr His Ser Thr Leu Asp Gly
            500                 505                 510

Arg Trp Ser Ala Leu Thr Pro Gly Pro Pro Met Ala Thr Ala Gly Pro
        515                 520                 525
```

```
Ala Asp Ser Lys Phe Ser Asn Ser Gln Leu Ile Phe Ala Gly Pro Lys
    530                 535                 540

Gln Asn Gly Asn Thr Ala Thr Val Pro Gly Thr Leu Ile Phe Thr Ser
545                 550                 555                 560

Glu Glu Glu Leu Ala Ala Thr Asn Ala Thr Asp Thr Asp Met Trp Gly
                565                 570                 575

Asn Leu Pro Gly Gly Asp Gln Ser Asn Ser Asn Leu Pro Thr Val Asp
            580                 585                 590

Arg Leu Thr Ala Leu Gly Ala Val Pro Gly Met Val Trp Gln Asn Arg
        595                 600                 605

Asp Ile Tyr Tyr Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr Asp
    610                 615                 620

Gly His Phe His Pro Ser Pro Leu Ile Gly Gly Phe Gly Leu Lys His
625                 630                 635                 640

Pro Pro Pro Gln Ile Phe Ile Lys Asn Thr Pro Val Pro Ala Asn Pro
                645                 650                 655

Ala Thr Thr Phe Ser Ser Thr Pro Val Asn Ser Phe Ile Thr Gln Tyr
            660                 665                 670

Ser Thr Gly Gln Val Ser Val Gln Ile Asp Trp Glu Ile Gln Lys Glu
        675                 680                 685

Arg Ser Lys Arg Trp Asn Pro Glu Val Gln Phe Thr Ser Asn Tyr Gly
    690                 695                 700

Gln Gln Asn Ser Leu Leu Trp Ala Pro Asp Ala Ala Gly Lys Tyr Thr
705                 710                 715                 720
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Glu Pro Arg Ala Ile Gly Thr Arg Tyr Leu Thr His His Leu
725 730

<210> 115
<211> 737
<212> PRT
<213> Ancestral Adeno-associated virus

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<220>
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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

<400> 115

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1 5 10 15

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Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
            20                  25                  30

Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
        35                  40                  45

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

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Pro Ser Pro Gln Arg Ser Pro Asp Ser Ser Thr Gly Ile
145                 150                 155                 160

Gly Lys Lys Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln
                165                 170                 175

Thr Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro
            180                 185                 190

Pro Ala Gly Pro Ser Gly Leu Gly Ser Gly Thr Met Ala Ala Gly Gly
        195                 200                 205
```

```
Gly Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn
    210                 215                 220

Ala Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val
225                 230                 235                 240

Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His
                245                 250                 255

Leu Tyr Lys Gln Ile Ser Ser Xaa Ser Xaa Gly Xaa Thr Asn Asp Asn
            260                 265                 270

His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400
```

```
Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr
                405                 410                 415

Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Xaa
        435                 440                 445

Arg Thr Gln Ser Thr Gly Gly Thr Ala Gly Xaa Xaa Glu Leu Leu Phe
    450                 455                 460

Ser Gln Xaa Gly Pro Xaa Xaa Met Ser Xaa Gln Ala Lys Asn Trp Leu
465                 470                 475                 480

Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Leu Xaa Gln
                485                 490                 495

Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His Leu
            500                 505                 510

Asn Gly Arg Xaa Ser Leu Val Asn Pro Gly Val Ala Met Ala Thr His
        515                 520                 525

Lys Asp Asp Glu Xaa Arg Phe Phe Pro Ser Ser Gly Val Leu Ile Phe
    530                 535                 540

Gly Lys Xaa Gly Ala Gly Xaa Asn Asn Thr Xaa Leu Xaa Asn Val Met
545                 550                 555                 560

Xaa Thr Xaa Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu
                565                 570                 575

Xaa Tyr Gly Val Val Ala Xaa Asn Leu Gln Ser Ser Asn Thr Ala Pro
            580                 585                 590
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```
Xaa Thr Gly Xaa Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val Trp
        595                 600                 605

Gln Asn Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro
    610                 615                 620

His Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly
625                 630                 635                 640

Leu Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro
                645                 650                 655

Ala Asn Pro Pro Xaa Xaa Phe Xaa Xaa Ala Lys Phe Ala Ser Phe Ile
            660                 665                 670

Thr Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu
        675                 680                 685

Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser
    690                 695                 700

Asn Tyr Ala Lys Ser Xaa Asn Val Asp Phe Ala Val Xaa Xaa Xaa Gly
705                 710                 715                 720

Val Tyr Xaa Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn
                725                 730                 735

Leu
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<210> 116
<211> 16
<212> PRT
<213> Artificial sequence

<220>

<223> synthetic sequence

<400> 116

Leu Gln Arg Gly Val Arg Ile Pro Ser Val Leu Glu Val Asn Gly Gln
1 5 10 15

<210> 117
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 117

Leu Ala Leu Ile Gln Asp Ser Met Arg Ala
1 5 10

<210> 118
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 118

Leu Gln Arg Gly Val Arg Ile Pro Ser Val Leu Glu Val Asn Gly Gln
1 5 10 15

<210> 119
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<400> 119

Leu Thr His Gln Asp Thr Thr Lys Asn Ala
1 5 10

<210> 120
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 120

Gln Ala His Gln Asp Thr Thr Lys Asn Ala
1 5 10

<210> 121
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<400> 121

Leu Ala His Gln Asp Thr Thr Lys Asn Ala
1 5 10

<210> 122
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<400> 122

Leu Ala Asn Gln Glu His Val Lys Asn Ala
1 5 10

<210> 123
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 123

Asn Gly Ala Val Ala Asp Tyr Thr Arg Gly Leu Ser Pro Ala Thr Gly
1   5   10   15

Thr

<210> 124
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 124

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

Thr

<210> 125
<211> 16
<212> PRT
<213> Artificial sequence

<220>
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<400> 125

Leu Gln Lys Ala Asp Arg Gln Pro Gly Val Val Val Val Asn Cys Gln
1   5   10   15

<210> 126
<211> 16

<212> PRT
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<220>
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<400> 126

Leu Gln Arg Gly Asn Arg Pro Val Thr Thr Ala Asp Val Asn Thr Gln
1 5 10 15

<210> 127
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 127

Pro Ala Pro Gln Asp Thr Thr Lys Lys Ala
1 5 10

<210> 128
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 128

Leu Gln Lys Asn Ala Arg Pro Ala Ser Thr Glu Ser Val Asn Phe Gln
1 5 10 15

<210> 129
<211> 17
<212> PRT
<213> Artificial sequence

<220>
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<400> 129

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

Ala

<210> 130
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 130

Thr Gly Ser Asp Gly Thr Arg Asp His Gly Leu Ser Pro Val Thr Trp
1 5 10 15

Thr

<210> 131
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<400> 131

Thr Gly Val Met His Ser Gln Ala Ser Gly Leu Ser
1 5 10

<210> 132
<211> 12
<212> PRT
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<220>

<223> synthetic sequence

<400> 132

Thr Gly Gly His Asp Ser Ser Leu Asp Gly Leu Ser
1 5 10

<210> 133
<211> 10
<212> PRT
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<400> 133

Leu Ala Leu Gly Glu Thr Thr Arg Pro Ala
1 5 10

<210> 134
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<220>
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<400> 134

Leu Ala Pro Asp Ser Thr Thr Arg Ser Ala
1 5 10

<210> 135
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<212> PRT
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<400> 135

Thr Val Val Ser Thr Gln Ala Gly Ile Gly Leu Ser
1 5 10

<210> 136
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<212> PRT
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<220>
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<223> The amino acid at position 3 is Leu or Asn.

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> The amino acid at position 4 is Ile or Gln.

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> The amino acid at position 5 is Gln or Glu.

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> The amino acid at position 6 is Asp or His.

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> The amino acid at position 7 is Ser or Val.

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> The amino acid at position 8 is Met or Lys.

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> The amino acid at position 9 is Arg or Asn.

<400> 136

Leu Ala Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ala
1   5   10

<210> 137
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<220>
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<223> Xaa at position 2 is G, V or S.

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa at position 3 is V, E, P, G, D, M, A, or S

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa at position 4 is M, V, Y, H, G, S, or D

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is R, D, S, G, V, Y, T, H, or M

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa at position 6 is S, L, G, T, Q, P, or A

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa at position 7 is T, A, S, M, D, Q, or H

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa at position 8 is N, G, S, L, M, P, G, or A

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa at position 9 is S, G, D, N, A, I, P, or T

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<222> (10)..(10)
<223> Xaa at position 10 is S or N.

<220>
<221> misc_feature
<222> (12)..(12)
<223> Xaa can be any naturally occurring amino acid

<400> 137

Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Leu Xaa
1 5 10

<210> 138
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<223> Xaa at position 3 is V, E, P, G, D, M, A, or S.

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa at position 4 is M, V, Y, H, G, S, or D.

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is R, D, S, G, V, Y, T, H, or M.

<220>
<221> MISC_FEATURE
<222> (6)..(6)

<223> Xaa at position 6 is S, L, G, T, Q, P, or A

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa at position 7 is T, A, S, M, D, Q, or H

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa at position 8 is N, G, S, L, M, P, G, or A

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa at position 9 is S, G, D, N, A, I, P, or T

<400> 138

Thr Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Leu Ser
1 5 10

<210> 139
<211> 17
<212> PRT
<213> Artificial sequence

<220>
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<223> Xaa at position 3 is L, S, A, or G.

<220>
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<222> (4)..(4)
<223> Xaa at position 4 is D or V.

<220>

<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is A, G, or P.

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa at position 6 is T or D.

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa at position 7 is R or Y

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa at position 8 is D, T, or G

<220>
<221> misc_feature
<222> (9)..(9)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (10)..(10)
<223> Xaa at position 10 is V or A

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> Xaa at position 11 is G or W

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa at position 12 is T or A

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa at position 4 is T or A.

<220>
<221> misc_feature
<222> (14)..(14)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (16)..(17)
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<400> 139

Xaa Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Leu Ser Pro Xaa Thr Xaa
1 5 10 15

Xaa

<210> 140
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<212> PRT
<213> Artificial sequence

<220>
<223> synthetic sequence

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa at position 3 is L, S, A, or G.

<220>
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<222> (5)..(5)
<223> Xaa at position 5 is A, G, or P.

<220>
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<222> (8)..(8)
<223> Xaa at position 8 is D, T, or G.

<220>
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<222> (9)..(9)
<223> Xaa at position 9 is H, R, or T.

<400> 140

Thr Gly Xaa Asp Xaa Thr Arg Xaa Xaa Gly Leu Ser Pro Val Thr Gly

1 5 10 15

Thr

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<211> 17
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (3)..(3)
<223> Xaa at position 3 is K or R.

<220>
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<222> (4)..(4)
<223> Xaa at position 4 is N, G, or A.

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa at position 5 is A, V, N, or D.

<220>
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<222> (7)..(7)
<223> Xaa at position 7 is P, I, or Q.

<220>
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<222> (8)..(8)
<223> Xaa at position 8 is A, P, or V.

<220>
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<222> (9)..(9)
<223> Xaa at position 9 is S, T, or G.

<220>
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<222> (10)..(10)
<223> Xaa at position 10 is T or V.

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> Xaa at position 11 is E, L, A, or V.

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa at position 12 is S, E, D, or V.

<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (15)..(15)
<223> Xaa at position 15 is F, G, T, or C.

<220>
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<400> 141

Leu Gln Xaa Xaa Xaa Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Val Asn Xaa
1 5 10 15

Gln

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Thr Gly Gly Leu Ser
1 5

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<400> 143

Leu Ala Ala
1