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(54) **Title:** VECTORIZED TNF-ALPHA ANTAGONISTS FOR OCULAR INDICATIONS

(57) **Abstract:** Provided are methods and compositions for the delivery of fully human post-translationally modified therapeutic TNF receptor Fc fusions. The fully human post-translationally modified therapeutic TNF receptor Fc fusions may be delivered by gene therapy methods, e.g., as a recombinant adeno-associated virus (rAAV) vector to the appropriate tissue. Also provided are methods of treating ocular indications such as non-infectious uveitis with the fully human post-translationally modified therapeutic TNF receptor Fc fusions.

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VECTORIZED TNF-ALPHA ANTAGONISTS FOR OCULAR INDICATIONS

1. INTRODUCTION

[0001] Compositions and methods are described for the delivery of a fully human post-translationally modified (HuPTM) therapeutic tumor necrosis factor receptor (TNFR) fusion protein that binds to tumor necrosis factor alpha (TNF-α) to a human subject diagnosed with non-infectious uveitis.

2. BACKGROUND OF THE INVENTION

[0002] Therapeutic anti-TNFα Fc fusion proteins have been shown to be effective in treating a number of diseases and conditions. However, because these agents are effective for only a short period of time, repeated injections for long durations are often required, thereby creating considerable treatment burden for patients.

[0003] Uveitis includes a group of heterogeneous diseases characterized by inflammation of the uveal tract. Uveitis may be generally classified by the etiology of inflammation as infectious or non-infectious (autoimmune disorders), which could be related or not to a systemic disease. In addition, uveitis can be anatomically classified as anterior, intermediate, posterior or panuveitis, and they may have an acute, chronic or recurrent course. The clinical presentation is variable, the symptoms may include blurred vision, photophobia, ocular pain and significant visual impairment (Valenzuela et al., Front Pharmacol. 2020; 11: 655).

[0004] Non-infectious uveitis is a serious, sight-threatening intraocular inflammatory condition characterized by inflammation of the uvea (iris, ciliary body, and choroid). Non-infectious uveitis is thought to result from an immune-mediated response to ocular antigens and is a leading cause of irreversible blindness in working-age population in the developed world. The goal of uveitis treatment is to control inflammation, prevent recurrences, and preserve vision, as well as minimize the adverse effects of medications. Currently, the standard of care for non-infectious uveitis includes the administration of corticosteroids as first-line agents, but in some cases a more aggressive therapy is required. This includes synthetic immunosuppressants, such as antimetabolites (methotrexate, mycophenolate mofetil, and azathioprine), calcineurinic inhibitors (cyclosporine, tacrolimus), and alkylating agents (cyclophosphamide, chlorambucil). In those patients who become intolerant or refractory to corticosteroids and conventional immunosuppressive treatment, biologic agents have arisen as an effective therapy in pediatric and adulthood uveitis, based on targeting relevant

immunological pathways involved in disease pathogenesis. Current immunomodulatory therapy includes the inhibition of TNFα, achieved with mAb, such as infliximab, adalimumab, golimumab, and certolizumab-pegol, or with TNF receptor fusion protein, etanercept. In this regard, anti-TNF agents (infliximab and adalimumab) have shown the strongest results in terms of favorable outcomes. Adalimumab has been approved for treatment of non-infectious uveitis by subcutaneous administration every other week. When conventional immunosuppressive treatments and/or anti-TNF-α therapies fail, other biological agents are recommended.

[0005] EYS606 encodes a recombinant fusion protein linking the TNFα p55 receptor 1 (TNFR1) to an Fc portion of an IgG1 immunoglobulin molecule. EYS606 is currently under investigation as non-viral gene therapy for the treatment of non-infectious posterior, intermediate or panuveitis. EYS606 is administered by electrotransfer in the ciliary muscle of patients.

[0006] Etanercept is a dimeric fusion protein consisting of two extracellular domains of human p75 TNFα receptor (TNFR2) fused to an Fc portion of an IgG1 immunoglobulin molecule (TNFR:Fc) and may be used for treatment of several autoimmune inflammatory diseases, including rheumatoid arthritis, Crohn's disease, and psoriatic arthritis. Etanercept is subcutaneously administrated at a dose of 50 mg once per week or 25 mg twice a week (Valenzuela et al., Front Pharmacol. 2020; 11: 655.).

[0007] There is a need for more effective treatments that reduce the treatment burden on patients suffering from non-infectious uveitis. Intravitreal medications have become a promising mode of drug administration in uveitis patients as they provide high volume of drug to the target tissues, eliminating the risk of systemic toxicity. Reducing or eliminating the need for periodic ocular administration would reduce patient burden and improve therapy.

3. SUMMARY OF THE INVENTION

[0008] Biologic inhibitors delivered by gene therapy have several advantages over injected or infused therapeutic biologic inhibitors that dissipate over time resulting in peak and trough levels. Sustained expression of the transgene product biologic inhibitor, as opposed to injecting a biologic inhibitors repeatedly, allows for a more consistent level of the biologic inhibitor to be present at the site of action, and is less risky and more convenient for patients, since fewer injections need to be made. Furthermore, biologic inhibitors expressed from transgenes are post-translationally modified

in a different manner than those that are directly injected because of the different microenvironment present during and after translation. Without being bound by any particular theory, this results in biologic inhibitors that have different diffusion, bioactivity, distribution, affinity, pharmacokinetic, and immunogenicity characteristics, such that the antibodies delivered to the site of action are "biobetters" in comparison with directly injected biologics. Systemic administration, such as expressed from a depot in the liver, or, in addition, localized delivery of the therapeutic to eye tissue could reduce exposure of the subject to the therapeutic and reduce the risk of potential adverse effects. Accordingly, provided herein are compositions and methods for anti-TNFα gene therapy, particularly recombinant AAV gene therapy, designed to target the eye and generate a depot of transgenes for expression of anti-TNFα Fc fusion proteins (TNFR:Fc), particularly etanercept (TNFR2:Fc) and EYS606 (TNFR1:Fc), that result in a therapeutically effective or prophylactic levels of the biologic inhibitor in the eye within 20 days, 30 days, 40 days, 50 days, 60 days, or 90 days of administration of the rAAV composition.

[0009] Compositions and methods are described for the systemic delivery of an anti-TNFα Fc fusion protein to a patient (human subject) diagnosed with non-infectious uveitis or other condition indicated for treatment with the therapeutic anti-TNFα Fc fusion protein. Delivery may be advantageously accomplished via gene therapy—*e.g.*, by administering a viral vector or other DNA expression construct encoding a therapeutic anti-TNFα Fc fusion protein to a subject diagnosed with a condition indicated for treatment with the therapeutic anti- TNFα Fc fusion protein—to create a permanent depot in the eye, or in alternative embodiments, liver and/or muscle, of the patient that continuously supplies the HuPTM anti-TNFα Fc fusion protein, *e.g.*, a human-glycosylated transgene product, to the appropriate eye tissue (including via the circulation circulation) of the subject where the anti-TNFα Fc fusion protein exerts its therapeutic or prophylactic effect.

[0010] The recombinant vector used for delivering the transgene includes non-replicating recombinant adeno-associated virus vectors ("rAAV"). In embodiments, the AAV type has a tropism for the eye, for example, AAV8 subtype, AAV3B subtype, AAV2.7m8, or AAVrh73 subtype of AAV. However, other viral vectors may be used, including but not limited to lentiviral vectors; vaccinia viral vectors, or non-viral expression vectors referred to as "naked DNA" constructs. Expression of the transgene can be controlled by constitutive or tissue-specific expression control elements, particularly elements that are ocular tissue-specific control elements, for example one or more elements of Table

1 or, alternatively, Table 1a. The constructs also may comprise a signal or leader peptide that directs secretion of the expressed anti-TNFα Fc fusion protein, for example, a peptide from Table 2, or Tables 3 or 4.

[0011] In certain embodiments, the HuPTM anti-TNFα Fc fusion protein encoded by the transgene can include, but is not limited to, a TNFR:Fc fusion proteins that binds to TNFα, particularly etanercept (or any biosimilar version thereof) or EYS606, see, for example **FIGS. 2A** and **2B**.

[0012] Gene therapy constructs for the therapeutic anti-TNFα Fc fusion protein are designed such that the soluble TNFR (TNFR1 or TNFR2) fused to the Fc portion are expressed as a dimeric fusion protein (SEQ ID NO: 10 and 12).

[0013] In addition, anti-TNFα Fc fusion proteins expressed from transgenes in vivo are not likely to contain degradation products associated with biologics produced by recombinant technologies, such as protein aggregation and protein oxidation. Aggregation is an issue associated with protein production and storage due to high protein concentration, surface interaction with manufacturing equipment and containers, and purification with certain buffer systems. These conditions, which promote aggregation, do not exist in transgene expression in gene therapy. Oxidation, such as methionine, tryptophan, and histidine oxidation, is also associated with protein production and storage, and is caused by stressed cell culture conditions, metal and air contact, and impurities in buffers and excipients. The proteins expressed from transgenes in vivo may also oxidize in a stressed condition. However, humans, and many other organisms, are equipped with an antioxidation defense system, which not only reduces the oxidation stress, but sometimes also repairs and/or reverses the oxidation. Thus, proteins produced in vivo are not likely to be in an oxidized form. Both aggregation and oxidation could affect the potency, pharmacokinetics (clearance), and immunogenicity.

[0014] The production of HuPTM anti-TNFα Fc fusion proteins in the eye of the human subject should result in a "biobetter" molecule for the treatment of disease accomplished via gene therapy – *e.g.*, by administering a viral vector or other DNA expression construct encoding a HuPTM anti-TNFα fusion protein to a patient (human subject) diagnosed with a disease indication for that Fc fusion protein, to create a permanent depot in the subject that continuously supplies the human-

glycosylated, sulfated transgene product produced by the subject's transduced cells. The cDNA construct for the HuPTM anti-TNFα Fc fusion protein should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced human cells.

[0015] As an alternative, or an additional treatment to gene therapy, the HuPTM anti-TNFα Fc fusion protein can be produced in human cell lines by recombinant DNA technology, and the glycoprotein can be administered to patients.

[0016] Combination therapies involving systemic delivery of the HuPTM anti-TNFα fusion protein to the patient accompanied by administration of other available treatments are encompassed by the methods provided herein. The additional treatments may be administered before, concurrently or subsequent to the gene therapy treatment. Such additional treatments can include but are not limited to co-therapy with the therapeutic anti-TNFα Fc fusion proteins or anti-TNFα mAbs.

[0017] Also provided are methods of manufacturing the viral vectors, particularly the AAV based viral vectors. In specific embodiments, provided are methods of producing recombinant AAVs comprising culturing a host cell containing an artificial genome comprising a cis expression cassette flanked by AAV ITRs, wherein the cis expression cassette comprises a transgene encoding a therapeutic antibody operably linked to expression control elements that will control expression of the transgene in human cells; a trans expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and capsid protein operably linked to expression control elements that drive expression of the AAV rep and capsid proteins in the host cell in culture and supply the rep and cap proteins in trans; sufficient adenovirus helper functions to permit replication and packaging of the artificial genome by the AAV capsid proteins; and recovering recombinant AAV encapsidating the artificial genome from the cell culture.

[0018] Provided are compositions comprising rAAV vectors which comprise an optimized expression cassette containing a photoreceptor-specific promoter or other suitable promoter, including a CAG promoter, Best1/GRK promoter (or other promoter as provided in Table 1 or Table 1a(and a codon optimized and CpG depleted transgene that express a transgene, for example, a soluble TNFR (TNFR1 or TNFR2) and Fc domain (including the hinge, CH2 and CH3 domains) of an anti-TNFα

therapeutic Fc fusion protein, including etanercept and EYS606. Methods of administration and manufacture are also provided. In particular, provided are compositions and methods comprising rAAV comprising the construct CAG.etanercept or U1a.Vh4i.etanercept.scAAV (see Table 7).

[0019] Pharmaceutical compositions suitable for administration to human subjects comprise a suspension of the recombinant vector in a formulation buffer comprising a physiologically compatible aqueous buffer, a surfactant and optional excipients.

3.1 ILLUSTRATIVE EMBODIMENTS

1. A pharmaceutical composition for treating non-infectious uveitis in a human subject in need thereof, comprising an adeno-associated virus (AAV) vector having:

(a) a viral capsid that has a tropism for ocular tissue cells; and

(b) an artificial genome comprising an expression cassette flanked by AAV internal tandem repeats (ITRs), wherein the expression cassette comprises a transgene encoding an anti-TNFα Fc fusion protein, operably linked to one or more regulatory sequences that control expression of the transgene in human ocular cells;

wherein said AAV vector is formulated for subretinal, intravitreal, intranasal, intracameral, suprachoroidal, or systemic administration to said human subject.

2. The pharmaceutical composition of paragraph 1, wherein the anti-TNFα Fc fusion protein comprises a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked through a peptide bond to a polypeptide comprising an Fc domain of an immunoglobulin heavy chain.
3. The pharmaceutical composition of paragraph 1 or 2, wherein the viral capsid is at least 95% identical to the amino acid sequence of AAV serotype 1 (AAV1), serotype 2 (AAV2), serotype AAV2.7m8 (AAV2.7m8), serotype 3 (AAV3), serotype 3B (AAV3B), serotype 4 (AAV4), serotype 5 (AAV5), serotype 6 (AAV6), serotype 7 (AAV7), serotype 8 (AAV8), serotype rh8 (AAVrh8), serotype 9 (AAV9), serotype 9e (AAV9e), serotype rh10 (AAVrh10), serotype rh20 (AAVrh20), serotype rh39 (AAVrh39), serotype hu.37 (AAVhu.37), serotype rh73 (AAVrh73), serotype rh74 (AAVrh74), serotype hu51 (AAV.hu51), serotype hu21 (AAV.hu21), serotype hu12 (AAV.hu12), or serotype hu26 (AAV.hu26).

4. The pharmaceutical composition of any of paragraphs 1 to 3, wherein the AAV capsid is AAV8, AAV3B, AAV2.7m8, or AAVrh73.
5. The pharmaceutical composition of paragraphs 1 to 4, wherein the ocular tissue cell is a cornea cell, an iris cell, a ciliary body cell, a schlemm's canal cell, a trabecular meshwork cell, a retinal cell, a RPE-choroid tissue cell, or an optic nerve cell.
6. The pharmaceutical composition of paragraphs 1 to 5, wherein the regulatory sequence includes a regulatory sequence from Table 1 or 1b.
7. The pharmaceutical composition of paragraph 5, wherein the regulatory sequence is a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:54 or 117), a mouse cone arresting (CAR) promoter (SEQ ID NOS:114-116), a human red opsin (RedO) promoter (SEQ ID NO:112) a CB promoter (SEQ ID NO: 159), a CBLong promoter (SEQ ID NO: 160) or Best1/GRK promoter (SEQ ID NO:161).
8. The pharmaceutical composition of any of paragraphs 1 to 7, wherein the transgene encodes a signal sequence at the N-terminus of the anti-TNFα Fc fusion protein that directs secretion and post translational modification in said human ocular cells.
9. The pharmaceutical composition of paragraph 8, wherein said signal sequence is MYRMQLLLLLIALSLALVTNS (SEQ ID NO:62) or a signal sequence from Table 2, 3 or 4.
10. The pharmaceutical composition of any of paragraphs 1 to 8, wherein transgene has the structure from the N-terminus to the C-terminus: Signal sequence–soluble TNFR extracellular domain – hinge region – Fc domain – PolyA.
11. The composition of paragraph 10, wherein the transgene further comprises a thrombin cleavage site of SEQ ID NO:8 at the C-terminus of the soluble TNFR extracellular domain.
12. The pharmaceutical composition of any of paragraphs 1 to 11, wherein anti-TNFα Fc fusion protein is expressed as a dimeric fusion protein.
13. The pharmaceutical composition of any of paragraphs 1 to 12, wherein the anti-TNFα Fc fusion protein is etanercept or EYS606.

14. The pharmaceutical composition of any of paragraphs 1 to 13, wherein said transgene comprises the nucleotide sequence of SEQ ID NO: 15-18.
15. The pharmaceutical composition of any of paragraphs 1 to 14, wherein the anti-TNFα Fc fusion protein has an amino acid sequence of SEQ ID NO: 10 or 12.
16. The pharmaceutical composition of any of paragraphs 1 to 15, wherein the anti-TNFα Fc fusion protein is a hyperglycosylated mutant or wherein the Fc polypeptide of the anti-TNFα Fc fusion protein is glycosylated or aglycosylated.
17. The pharmaceutical composition of any of paragraphs 1 to 16, wherein the Fc domain is an IgG1-Fc domain.
18. The pharmaceutical composition of any of paragraphs 1 to 17, wherein the artificial genome is self complementary.
19. The pharmaceutical composition of any of paragraphs 1 to 18 wherein the artificial genome is the construct CAG.etanercept (SEQ ID NO: 15 or 16) or mU1a.Vh4i.etanercept.scAAV (SEQ ID NO: 17or 18).
20. A composition comprising an adeno-associated virus (AAV) vector having:

a. a viral AAV capsid, that is optionally at least 95% identical to the amino acid sequence of AAV serotype 1 (AAV1), serotype 2 (AAV2), serotype AAV2.7m8 (AAV2.7m8), serotype 3 (AAV3), serotype 3B (AAV3B), serotype 4 (AAV4), serotype 5 (AAV5), serotype 6 (AAV6), serotype 7 (AAV7), serotype 8 (AAV8), serotype rh8 (AAVrh8), serotype 9 (AAV9), serotype 9e (AAV9e), serotype rh10 (AAVrh10), serotype rh20 (AAVrh20), serotype rh39 (AAVrh39), serotype hu.37 (AAVhu.37), serotype rh73 (AAVrh73), serotype rh74 (AAVrh74), serotype hu51 (AAV.hu51), serotype hu21 (AAV.hu21), serotype hu12 (AAV.hu12), or serotype hu26 (AAV.hu26).

b. an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding an anti-TNF-α Fc fusion protein comprising a human soluble TNFα receptor type I (TNFR1) or type II (TNFR2) extracellular domain covalently linked through a peptide bond to a polypeptide comprising an Fc domain of an immunoglobulin heavy chain, operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

wherein the transgene encodes a signal sequence at the N-terminus of said anti-TNFα Fc fusion protein that directs secretion and post translational modification of said anti-TNFα Fc fusion in ocular tissue cells.

21. The composition of paragraph 20, wherein the transgene further comprises a thrombin cleavage site of SEQ ID NO:8 at the C-terminus of soluble human TNFR extracellular domain.
22. The composition of any of paragraphs 20 or 21, wherein the anti-TNFα Fc fusion protein has an amino acid sequence of SEQ ID NO: 10 or 12.
23. The composition of paragraphs 20 to 22, wherein the anti-TNFα Fc fusion protein is etanercept or EYS606.
24. The composition of paragraphs 20 to 23, wherein the ocular tissue cell is a cornea cell, an iris cell, a ciliary body cell, a schlemm's canal cell, a trabecular meshwork cell, a retinal cell, a RPE-choroid tissue cell, or an optic nerve cell.
25. The composition of paragraphs 20 to 24, wherein said transgene comprises the nucleotide sequence of SEQ ID NO:13 or 14.
26. The composition of paragraphs 20 to 25, wherein said signal sequence is MYRMQLLLLLIALSLALVTNS (SEQ ID NO:62) or a signal sequence from Tables 2, 3 or 4.
27. The composition of any of paragraphs 20 to 26, wherein the artificial genome is self complementary.
28. The composition of any of paragraphs 20 to 27 wherein the artificial genome is the construct CAG.etanercept (SEQ ID NO: 15) or mU1a.Vh4i.etanercept.scAAV (SEQ ID NO: 17).

Method of Treatment

29. A method of treating non-infectious uveitis in a human subject in need thereof, comprising subretinally, intravitreally, intranasally, intracamerally, suprachoroidally, or systemically administering to the subject a therapeutically effective amount of a composition comprising a recombinant AAV comprising a transgene encoding an anti-TNFα Fc fusion protein operably linked to one or more regulatory sequences that control expression of the transgene in ocular tissue cells.

30. A method of treating non-infectious uveitis in a human subject in need thereof, comprising: subretinally, intravitreally, intranasally, intracamerally, suprachoroidally, or systemically administering to said subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding an anti-TNFα Fc fusion protein, operably linked to one or more regulatory sequences that control expression of the transgene in human ocular tissue cells, so that a depot is formed that releases a human post-translationally modified (HuPTM) form of anti-TNFα Fc fusion protein.

31. The method of paragraphs 29 and 30, wherein the ocular tissue cell is a cornea cell, an iris cell, a ciliary body cell, a schlemm's canal cell, a trabecular meshwork cell, a retinal cell, a RPE-choroid tissue cell, or an optic nerve cell.

32. The method of paragraphs 29 to 31, wherein said anti-TNFα Fc fusion protein comprises a human soluble TNFα receptor type I (TNFR1) or type II (TNFR2) extracellular domain covalently linked to an IgG Fc domain.

33. The method of paragraphs 29 to 32, wherein said transgene is etanercept or EYS606.

34. The method of paragraphs 29 to 33, wherein said transgene has the nucleotide sequence of SEQ ID NO: 15-17.

35. The method of paragraphs 29 to 34, wherein the recombinant nucleotide expression vector is packaged in an rAAV having a viral capsid, wherein viral capsid is at least 95% identical to the amino acid sequence of AAV serotype 1 (AAV1), serotype 2 (AAV2), serotype AAV2.7m8, serotype 3 (AAV3), serotype 3B (AAV3B), serotype 4 (AAV4), serotype 5 (AAV5), serotype 6 (AAV6), serotype 7 (AAV7), serotype 8 (AAV8), serotype rh8 (AAVrh8), serotype 9 (AAV9), serotype 9e (AAV9e), serotype rh10 (AAVrh10), serotype rh20 (AAVrh20), serotype rh39 (AAVrh39), serotype hu.37 (AAVhu.37), serotype rh73 (AAVrh73), or serotype rh74 (AAVrh74), serotype hu51 (AAV.hu51), serotype hu21 (AAV.hu21), serotype hu12 (AAV.hu12), or serotype hu26 (AAV.hu26).

36. The method of any of paragraphs 29, 31 to 35, wherein the AAV capsid is AAV8, AAV2.7m8, AAV3B, or AAVrh73.

37. The method of any of paragraphs 29 to 36, wherein the regulatory sequence includes a regulatory sequence from Table 1 or 1a.

38. The method of paragraph 37, wherein the regulatory sequence is a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:54 or 117), a mouse cone arresting (CAR) promoter (SEQ ID NOS:114-116), a human red opsin (RedO) promoter (SEQ ID NO:112), a CB promoter (SEQ ID NO: 159), a CBLong promoter (SEQ ID NO: 160) or Best1/GRK promoter (SEQ ID NO: 161).

39. The method of any of paragraphs 29 to 38, wherein the transgene encodes a signal sequence at the N-terminus of the anti-TNFα Fc fusion protein that directs secretion and post translational modification in said human ocular tissue cells.

40. The method of paragraph 39, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO:62) or a signal sequence from Tables 2, 3 or 4.

41. The method of any of paragraphs 25 to 40, wherein transgene has the structure: Signal sequence–9human soluble TNFR extracellular domain (type 1 or type 2) – hinge region - Fc domain – PolyA.

42. The method of paragraph 41, wherein the transgene further comprises a thrombin cleavage site having SEQ ID NO:8 at the C-terminus of the human soluble TNFR extracellular domain.

43. The method of any of paragraphs 29 to 42, wherein the anti-TNFα Fc fusion protein is a hyperglycosylated mutant or wherein the Fc domain of the anti-TNFα Fc fusion protein is glycosylated or aglycosylated.

44. The method of any of paragraphs 29 to 43, wherein anti-TNFα Fc fusion protein contains an alpha 2,6-sialylated glycan.

45. The method of any of paragraphs 29 to 44, wherein anti-TNFα Fc fusion protein is glycosylated but does not contain detectable NeuGc and/or α-Gal.

46. The method of any of paragraphs 29 to 45, wherein anti-TNFα Fc fusion protein contains a tyrosine sulfation.

47. The method of any of paragraphs 29 to 46 in which production of said HuPTM form of the anti-TNFα Fc fusion protein is confirmed by transducing human ocular cells in culture with said recombinant nucleotide expression vector and expressing said anti-TNFα Fc fusion protein.

48. The method of paragraphs 29 or 47, wherein the therapeutically effective amount is determined to be sufficient to improve best corrected visual acuity (BCVA) by >= 2 ETDRS lines or increase in logMAR, reduced inflammatory activity of the anterior and posterior chamber according to the SUN classification, and/ or reduction in grade of vitreous haze.

49. The method of any of paragraphs 29 to 48, wherein the rAAV is self complementary.

50. The method of any of paragraphs 29 to 49 wherein the transgene is within the construct CAG.etanercept (SEQ ID NO: 15 or 16) or mU1a.Vh4i.etanercept.scAAV (SEQ ID NO: 17 or 18).

Method of Manufacture

51. A method of producing recombinant AAVs comprising:

(a) culturing a host cell containing:

(i) an artificial genome comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises a transgene encoding an anti-TNFα Fc fusion protein, wherein the anti-TNFα Fc fusion protein comprises a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked through a peptide bond to a polypeptide comprising an Fc domain of an immunoglobulin heavy chain, operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

(ii) a *trans* expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and an AAV capsid protein operably linked to expression control elements that drive expression of the AAV rep and the AAV capsid protein in the host cell in culture and supply the AAV rep and the AAV capsid protein in *trans*, wherein the capsid has ocular tissue tropism;

(iii) sufficient adenovirus helper functions to permit replication and packaging of the artificial genome by the AAV capsid protein; and

(b) recovering recombinant AAV encapsidating the artificial genome from the cell culture.

52. The method of paragraph 51, wherein the ocular tissue cell is a cornea cell, an iris cell, a ciliary body cell, a schlemm's canal cell, a trabecular meshwork cell, a retinal cell, a RPE-choroid tissue cell, or an optic nerve cell.

53. The method of paragraphs 51 or 52, wherein the transgene encodes etanercept or EYS606, wherein the AAV capsid protein is The rAAV capsid protein of embodiment 1, wherein said capsid protein is from at least one AAV serotype of AAV serotype 1 (AAV1), serotype 2 (AAV2), serotype 2.7m8, serotype 3 (AAV3), serotype 3B (AAV3B), serotype 4 (AAV4), serotype 5 (AAV5), serotype 6 (AAV6), serotype 7 (AAV7), serotype 8 (AAV8), serotype rh8 (AAVrh8), serotype 9 (AAV9), serotype 9e (AAV9e), serotype rh10 (AAVrh10), serotype rh20 (AAVrh20), serotype rh39 (AAVrh39), serotype hu.37 (AAVhu.37), serotype rh73 (AAVrh73), serotype rh74 (AAVrh74), serotype hu51 (AAV.hu51), serotype hu21 (AAV.hu21), serotype hu12 (AAV.hu12), or serotype hu26 (AAV.hu26).

54. A host cell containing:

a. an artificial genome comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprising a transgene encoding an anti-TNFα fusion protein, wherein the anti-TNFα Fc fusion protein comprises a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked through a peptide bond to polypeptide comprising an Fc domain of an immunoglobulin heavy chain, operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

b. a *trans* expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and an AAV capsid protein operably linked to expression control elements that drive expression of the AAV rep and the AAV capsid protein in the host cell in culture and supply the AAV rep and the AAV capsid protein in *trans,* wherein the capsid has ocular tissue tropism;

c. sufficient adenovirus helper functions to permit replication and packaging of the artificial genome by the AAV capsid protein.

55. The host cell of paragraph 54, wherein the transgene encodes etanercept or EYS606.

56. The host cell of paragraphs 53 or 54, wherein the AAV capsid protein is AAV serotype 1 (AAV1), serotype 2 (AAV2), serotype 2.7m8 (AAV2.7m8), serotype 3 (AAV3), serotype 3B (AAV3B), serotype 4 (AAV4), serotype 5 (AAV5), serotype 6 (AAV6), serotype 7 (AAV7), serotype 8 (AAV8), serotype rh8 (AAVrh8), serotype 9 (AAV9), serotype 9e (AAV9e), serotype rh10 (AAVrh10), serotype rh20 (AAVrh20), serotype rh39 (AAVrh39), serotype hu.37 (AAVhu.37), serotype rh73 (AAVrh73), serotype rh74 (AAVrh74), serotype hu51 (AAV.hu51), serotype hu21 (AAV.hu21), serotype hu12 (AAV.hu12), or serotype hu26 (AAV.hu26).

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0020] **FIG. 1**. A schematic of an rAAV vector genome construct containing an expression cassette encoding etanercept controlled by expression elements, flanked by the AAV ITRs.

[0021] **FIGS. 2A** and **2B.** The amino acid sequence of anti-TNFα Fc fusion proteins etanercept (**A**) and EYS606 (**B**). Glycosylation sites are boldface or underlined. Glutamine glycosylation sites; asparaginal (N) glycosylation sites, canonical and non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (italics) are as indicated in the legend. The Fc domain (CH2 and CH3 domains) is highlighted in grey. Hinge region is indicated in italics. Thrombin cleavage site is underlined.

[0022] **FIG. 3**. Clustal Multiple Sequence Alignment of various capsids with ocular tissue tropism. Amino acid substitutions (shown in bold in the bottom rows) can be made to AAV8 capsids by "recruiting" amino acid residues from the corresponding position of other aligned AAV capsids. Sequence shown in gray = hypervariable regions. The amino acid sequences of the AAV capsids are assigned sequence ID numbers as indicated in **FIG. 3**.

[0023] **FIG. 4.** Clustal Multiple Sequence Alignment of constant heavy chain regions (CH2 and CH3) of IgG1 (SEQ ID NO:47), IgG2 (SEQ ID NO:48), and IgG4 (SEQ ID NO:49). The hinge region, from residue 219 to residue 230 of the heavy chain, is shown in italics. The numbering of the amino acids is in EU-format.

[0024] **FIGS. 5A and B**. **A**. Binding of TNFα across model species (mouse, rat, and human) by vectorized adalimumab IgG and Fab. Negative control included supernatant derived from non-transfected cells. Vectorized lanadelumab (pAAV.CAG.lanadelumab.IgG) functioned as a non-specific

antibody control. Data represented as mean±SEM. **B.** Binding of TNFα across model species (mouse, rat, and human) by vectorized adalimumab IgG and etanercept. Negative control included supernatant derived from non-transfected cells. Vectorized lanadelumab (pAAV.CAG.lanadelumab.IgG) functioned as a non-specific antibody control. Data represented as mean±SEM.

5. DETAILED DESCRIPTION OF THE INVENTION

[0025] Compositions and methods are described for the systemic for the delivery of a fully human post-translationally modified (HuPTM) therapeutic anti-TNFα Fc fusion protein that binds to TNFα to a human subject diagnosed with non-infectious uveitis. Delivery may be advantageously accomplished via gene therapy—*e.g.*, by administering a viral vector or other DNA expression construct encoding a therapeutic anti-TNFα Fc fusion protein (or a hyperglycosylated derivative of either) to a patient (human subject) diagnosed with non-infectious uveitis —to create a permanent depot in a tissue or organ of the patient, particularly ocular tissues such as the retina, that continuously supplies the HuPTM anti-TNFα Fc fusion protein, *e.g.*, a human-glycosylated transgene product, to where the anti-TNFα Fc fusion protein exerts its therapeutic effect.

[0026] In certain embodiments, the HuPTM anti-TNFα Fc fusion protein encoded by the transgene, but it not limited to, is a TNFR:Fc fusion protein that binds TNFα, particularly etanercept or EYS606 (see **FIGS. 2A** and **2B** for the amino acid sequence of the TNFR-Fc fusion protein etanercept and EYS606, respectively). In embodiments, when expressed, the TNFR Fc fusion protein is dimeric.

[0027] The HuPTM anti-TNFα Fc fusion protein encoded by the transgene can include, but is not limited to, a therapeutic anti-TNFα TNFR1:Fc fusion that binds to TNFα, including but not limited to, EYS606. The amino acid sequences of the foregoing are provided in Table 6, *infra*. The TNFR1 domain having an amino acid sequence of SEQ ID NO: 1 and Fc domain having an amino acid sequence of SEQ ID NO: 6 (or 7 without the hinge), and the EYS606 protein having an amino acid sequence of SEQ ID NO: 12. The HuPTM anti-TNFα TNFR1:Fc fusion encoded by the transgene can include, but is not limited to, a dimeric fusion protein engineered to contain additional glycosylation sites on the Fc domain.

[0028] The HuPTM anti-TNFα Fc fusion protein encoded by the transgene can include, but is not limited to, a therapeutic anti-TNFα TNFR2:Fc fusion that binds to TNFα, including but not limited to, etanercept. The amino acid sequences of the foregoing are provided in Table 6, *infra*. The TNFR2 domain having an amino acid sequence of SEQ ID NO: 2 and the Fc domain having an amino acid sequence of SEQ ID NO: 3 (SEQ ID NO 4 without the hinge region) and etanercept having the amino acid sequence of SEQ ID NO: 10 (SEQ ID NO: 11 including leader sequence) with a transgene nucleotide sequence of one of SEQ ID NOs: 13-18)The HuPTM anti-TNFα TNFR2:Fc fusion protein encoded by the transgene can include, but is not limited to, a dimeric fusion protein engineered to contain additional glycosylation sites on the Fc domain.

[0029] The compositions and methods provided herein systemically deliver the anti-TNFα Fc fusion protein, particularly, etanercept and EYS606, from a depot of viral genomes, for example, in the subject's eye, or liver/muscle, at a level either in the ocular tissue (e.g., in the vitreous or aqueous humor, or in the serum that is therapeutically or prophylactically effective to treat or ameliorate the symptoms of non-infectious uveitis or other indication that may be treated with an anti-TNFα Fc fusion protein. Identified herein are viral vectors for delivery of transgenes encoding the therapeutic anti-TNFα Fc fusion protein to cells in the human subject, including, in embodiments, one or more ocular tissue cells, and regulatory elements operably linked to the nucleotide sequence encoding the anti-TNFα Fc fusion protein that promote the expression of the antibody in the cells, in embodiments, in the ocular tissue cells. Such regulatory elements, including ocular tissue-specific regulatory elements, are provided in Table 1 and Table 1a herein. Accordingly, such viral vectors may be delivered to the human subject at appropriate dosages, such that at least 20, 30, 40, 50 or 60 days after administration, anti-TNFα Fc fusion protein is present at therapeutically effective levels in the serum or in ocular tissues of said human subject. In embodiments, the therapeutically effective level of the anti- anti-TNFα Fc fusion protein is determined (in human trials, animal models, such as those described herein, etc.) to improve best corrected visual acuity (BCVA) by >= 2 ETDRS lines or increase in logMAR, reduced inflammatory activity of the anterior and posterior chamber according to the SUN classification, and/ or reduction in grade of vitreous haze

[0030] The recombinant vector used for delivering the transgene includes non-replicating recombinant adeno-associated virus vectors ("rAAV"). rAAVs are particularly attractive vectors for a

number of reasons – they can transduce non-replicating cells, and therefore, can be used to deliver the transgene to tissues where cell division occurs at low levels, such as the retina; they can be modified to preferentially target a specific organ of choice; and there are hundreds of capsid serotypes to choose from to obtain the desired tissue specificity, and/or to avoid neutralization by pre-existing patient antibodies to some AAVs. Such rAAVs include but are not limited to AAV based vectors comprising capsid components from one or more of AAV1, AAV2, AAV2.7m8 AAV3, AAV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAV9, AAV9e, AAVrh10, AAVrh20, AAVrh39, AAVhu.37, AAVrh73, AAVrh74, AAV.hu51, AAV.hu21, AAV.hu12, or AAV.hu26. In certain embodiments, AAV based vectors provided herein comprise capsids from one or more of AAV2.7m8, AAV8, AAV9, AAV10, or AAVrh10 serotypes.

[0031] However, other viral vectors may be used, including but not limited to lentiviral vectors; vaccinia viral vectors, or non-viral expression vectors referred to as "naked DNA" constructs. Expression of the transgene can be controlled by constitutive or tissue-specific expression control elements.

[0032] Gene therapy constructs for the therapeutic anti-TNFα Fc fusion protein are designed such that the covalently linked TNFR and the Fc portion are expressed as a dimeric fusion protein. For example, the TNFR:Fc fusion may include all or a portion of a hinge region (*e.g.* SEQ ID NO: 5 or 9) that is linked to disulfide bond formation between heavy chains. Preferably, TNFR1: Fc is a biobetter or a biosimilar of EYS606, or more preferably, TNFR: Fc is EYS606. Preferably, TNFR2: Fc is a biobetter or a biosimilar of etanercept, or more preferably, TNFR: Fc is etanercept.

[0033] In certain embodiments, nucleic acids (e.g., polynucleotides) and nucleic acid sequences disclosed herein may be codon-optimized, for example, via any codon-optimization technique known to one of skill in the art (see, e.g., review by Quax et al., 2015, Mol Cell 59:149-161) and may also be optimized to reduce CpG dimers. Nucleotide sequences of the therapeutic anti-TNFα Fc fusion proteins, which may be codon optimized, are disclosed in Table 7. The anti-TNFα Fc fusion protein requires a N-terminal leader to ensure proper post-translation processing and secretion. Useful leader sequences for the expression of the therapeutic anti-TNFα Fc fusion protein in human cells are disclosed herein. An exemplary recombinant expression construct is shown in **FIG. 1**.

[0034] The production of HuPTM anti-TNFα Fc fusion proteins should result in a "biobetter" molecule for the treatment of disease accomplished via gene therapy – *e.g.*, by administering a viral vector or other DNA expression construct encoding an anti-TNFα Fc fusion protein, such as etanercept or EYS606, to a patient (human subject) diagnosed with a disease indication for that anti-TNFα Fc fusion protein, to create a permanent depot in the subject that continuously supplies the human-glycosylated, sulfated transgene product produced by the subject's transduced cells. The cDNA construct for the HuPTM anti-TNFα Fc fusion protein should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced human cells.

[0035] Pharmaceutical compositions suitable for administration to human subjects comprise a suspension of the recombinant vector in a formulation buffer comprising a physiologically compatible aqueous buffer, a surfactant and optional excipients. Such formulation buffer can comprise one or more of a polysaccharide, a surfactant, polymer, or oil.

[0036] As an alternative, or an additional treatment to gene therapy, the full-length HuPTM anti-TNFα Fc fusion protein can be produced in human cell lines by recombinant DNA technology, and the glycoprotein can be administered to patients. Human cell lines that can be used for such recombinant glycoprotein production include but are not limited to human embryonic kidney 293 cells (HEK293), fibrosarcoma HT-1080, HKB-11, CAP, HuH-7, and retinal cell lines, PER.C6, or RPE to name a few (*e.g.*, see Dumont et al., 2015, Crit. Rev. Biotechnol. 36(6):1110-1122, which is incorporated by reference in its entirety for a review of the human cell lines that could be used for the recombinant production of the HuPTM biologic). To ensure complete glycosylation, especially sialylation, and tyrosine-sulfation, the cell line used for production can be enhanced by engineering the host cells to co-express α-2,6-sialyltransferase (or both α-2,3- and α-2,6-sialyltransferases) and/or TPST-1 and TPST-2 enzymes responsible for tyrosine-O-sulfation in human cells.

[0037] It is not essential that every molecule produced either in the gene therapy or protein therapy approach be fully glycosylated and sulfated. Rather, the population of glycoproteins produced should have sufficient glycosylation (including 2,6-sialylation) and sulfation to demonstrate efficacy. The goal of gene therapy treatment of the invention is to slow or arrest the progression of disease.

[0038] Combination therapies involving delivery of the HuPTM anti-TNFα Fc fusion protein to the patient accompanied by administration of other available treatments are encompassed by the methods of the invention. The additional treatments may be administered before, concurrently or subsequent to the gene therapy treatment. Such additional treatments can include but are not limited to co-therapy with the therapeutic anti-TNFα Fc fusion protein.

[0039] Also provided are methods of manufacturing the viral vectors, particularly the AAV based viral vectors. In specific embodiments, provided are methods of producing recombinant AAVs comprising culturing a host cell containing an artificial genome comprising a cis expression cassette flanked by AAV ITRs, wherein the cis expression cassette comprises a transgene encoding a therapeutic anti-TNFα Fc fusion protein, operably linked to expression control elements that will control expression of the transgene in human cells; a trans expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and capsid protein operably linked to expression control elements that drive expression of the AAV rep and capsid proteins in the host cell in culture and supply the rep and cap proteins in trans; sufficient adenovirus helper functions to permit replication and packaging of the artificial genome by the AAV capsid proteins; and recovering recombinant AAV encapsidating the artificial genome from the cell culture.

5.1 DEFINITIONS

[0040] The phrase “Anti-TNFα Fc fusion protein” means a polypeptide comprising the soluble, extracellular domain or portion of a receptor for TNFα, including TNF-α receptor p55 or p75, covalently linked, for example, through a peptide bond, to an Fc domain of an immunoglobulin, particularly an IgG.

[0041] The term “regulatory element” or “nucleic acid regulatory element” are non-coding nucleic acid sequences that control the transcription of neighboring genes. Cis regulatory elements typically regulate gene transcription by binding to transcription factors. This includes “composite nucleic acid regulatory elements” comprising more than one enhancer or promoter elements as described herein.

[0042] The term “expression cassette” or "nucleic acid expression cassette" refers to nucleic acid molecules that include one or more transcriptional control elements including, but not limited to

promoters, enhancers and/or regulatory elements, introns and polyadenylation sequences. The enhancers and promoters typically function to direct (trans)gene expression in one or more desired cell types, tissues or organs.

[0043] The term “operably linked” and “operably linked to” refers to nucleic acid sequences being linked and typically contiguous, or substantially contiguous, and, where necessary to join two protein coding regions, contiguous and in reading frame. However, since enhancers generally function when separated from the promoter by several kilobases and intronic sequences may be of variable lengths, some polynucleotide elements may be operably linked and still be functional while not directly contiguous with a downstream promoter and transgene.

[0044] The term “AAV” or “adeno-associated virus” refers to a Dependoparvovirus within the Parvoviridae genus of viruses. The AAV can be an AAV derived from a naturally occurring “wild-type” virus, an AAV derived from a rAAV genome packaged into a capsid comprising capsid proteins encoded by a naturally occurring cap gene and/or from a rAAV genome packaged into a capsid comprising capsid proteins encoded by a non-naturally occurring capsid cap gene. An example of the latter includes a rAAV having a capsid protein comprising a peptide insertion into or modification of the amino acid sequence of the naturally-occurring capsid.

[0045] The term “rAAV” refers to a “recombinant AAV.” In some embodiments, a recombinant AAV has an AAV genome in which part or all of the rep and cap genes have been replaced with heterologous sequences.

[0046] The term “rep-cap helper plasmid” refers to a plasmid that provides the viral rep and cap gene function and aids the production of AAVs from rAAV genomes lacking functional rep and/or the cap gene sequences.

[0047] The term “cap gene” refers to the nucleic acid sequences that encode capsid proteins that form or help form the capsid coat of the virus. For AAV, the capsid protein may be VP1, VP2, or VP3.

[0048] The term “rep gene” refers to the nucleic acid sequences that encode the non-structural protein needed for replication and production of virus.

[0049] The terms "nucleic acids" and "nucleotide sequences" include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), combinations of DNA and RNA molecules or hybrid DNA/RNA molecules, and analogs of DNA or RNA molecules. Such analogs can be generated using, for example, nucleotide analogs, which include, but are not limited to, inosine or tritylated bases. Such analogs can also comprise DNA or RNA molecules comprising modified backbones that lend beneficial attributes to the molecules such as, for example, nuclease resistance or an increased ability to cross cellular membranes. The nucleic acids or nucleotide sequences can be single-stranded, double-stranded, may contain both single-stranded and double-stranded portions, and may contain triple-stranded portions, but preferably is double-stranded DNA.

[0050] The terms "subject", "host", and "patient" are used interchangeably. As used herein, a subject is preferably a mammal such as a non-primate (*e.g.*, cows, pigs, horses, cats, dogs, rats etc.) or a primate (*e.g.*, monkey and human), most preferably a human.

[0051] The terms "therapeutic agent" or "biotherapeutic agent" refer to any agent which can be used in treating, managing, or ameliorating symptoms associated with a disease or disorder, where the disease or disorder is associated with a function to be provided by a transgene. As used herein, a "therapeutically effective amount" refers to the amount of agent, (*e.g.*, an amount of product expressed by the transgene) that provides at least one therapeutic benefit in the treatment or management of the target disease or disorder, when administered to a subject suffering therefrom. Further, a therapeutically effective amount with respect to an agent of the invention means that amount of agent alone, or when in combination with other therapies, that provides at least one therapeutic benefit in the treatment or management of the disease or disorder.

[0052] The phrase "liver-specific" or "liver-directed" refers to nucleic acid elements that have adapted their activity in liver (hepatic) cells or tissue due to the interaction of such elements with the intracellular environment of the hepatic cells. The liver acts as a bioreactor or "depot" for the body in the context of a gene therapy delivered to the liver tissue and a gene cassette enhanced for expression in the liver will produce the biotherapeutic (translated protein) that is secreted into the circulation. As such, the biotherapeutic agent is delivered systemically to the subject by way of liver expression. Without being bound by any one theory, liver production of a biotherapeutic agent (such as produced by the delivered transgene) can provide immunotolerance to the agent such that endogenous T cells of

the subject producing the protein will recognize the protein as self-protein, and not induce an innate immune response.

5.2 CONSTRUCTS

[0053] Viral vectors or other DNA expression constructs encoding an HuPTM anti-TNFα Fc fusion protein are provided herein. The viral vectors and other DNA expression constructs provided herein include any suitable method for delivery of a transgene to a target cell. The means of delivery of a transgene include viral vectors, liposomes, other lipid-containing complexes, other macromolecular complexes, synthetic modified mRNA, unmodified mRNA, small molecules, non-biologically active molecules (*e.g.*, gold particles), polymerized molecules (*e.g.*, dendrimers), naked DNA, plasmids, phages, transposons, cosmids, or episomes. In some embodiments, the vector is a targeted vector, *e.g.*, a vector targeted to ocular tissue cells or a vector that has a tropism for ocular tissue cells.

[0054] In some aspects, the disclosure provides for a nucleic acid for use, wherein the nucleic acid comprises a nucleotide sequence that encodes a HuPTM anti-TNFα Fc fusion protein, as a transgene described herein, operatively linked to a promoter selected for expression in tissue targeted for expression of the transgene, for example, but not limited to the ubiquitous promoters, such as CB7/CAG promoter (SEQ ID NO:50) and associated upstream regulatory sequences, cytomegalovirus (CMV) promoter, EF-1 alpha promoter (SEQ ID NO:53), mU1a (SEQ ID NO:52), UB6 promoter, chicken beta-actin (CBA) promoter, and ocular-tissue specific promoters, such as human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:54 or 117), a mouse cone arresting (CAR) promoter (SEQ ID NOS:114-116), a human red opsin (RedO) promoter (SEQ ID NO:112), a CB promoter (SEQ ID NO: 159), a CBLong promoter (SEQ ID NO: 160), or a Best1/GRK promoter (SEQ ID NO: 161). See Tables 1 and 1a for a list of useful promoters.

[0055] In certain embodiments, provided herein are recombinant vectors that comprise one or more nucleic acids (*e.g.*, polynucleotides). The nucleic acids may comprise DNA, RNA, or a combination of DNA and RNA. In certain embodiments, the DNA comprises one or more of the sequences selected from the group consisting of promoter sequences, the sequence of the gene of interest (the transgene, *e.g.*, the nucleotide sequences encoding a HuPTM anti-TNFα Fc fusion

protein), untranslated regions, and termination sequences. In certain embodiments, viral vectors provided herein comprise a promoter operably linked to the gene of interest.

[0056] In certain embodiments, nucleic acids (*e.g.*, polynucleotides) and nucleic acid sequences disclosed herein may be codon-optimized, for example, via any codon-optimization technique known to one of skill in the art (*see, e.g.*, review by Quax et al., 2015, Mol Cell 59:149-161). Nucleotide sequences for expression of the anti-TNFα Fusion protein in human cells are provided herein in Table 7.

[0057] In a specific embodiment, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) one or more control elements, b) optionally, a chicken β-actin or other intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for a soluble extracellular domain of TNFR2 linked to the N-terminus of the human IgG1 Fc domain, wherein the Fc domain comprises from the N-terminus to the C-terminus: Hinge region- CH2 domain – CH3 domain (etanercept). An exemplary construct is shown in **FIG. 1 and in FIG. 2A**.

[0058] In a specific embodiment, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) one or more control elements, b) optionally, a chicken β-actin or other intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for a soluble extracellular domain of TNFR1 linked via a thrombin cleavage site to the N-terminus of the human IgG1 Fc domain, wherein the Fc domain comprises from the N-terminus to the C-terminus: Hinge region- CH2 domain – CH3 domain (EYS060). An exemplary construct is shown in **FIG. 2B**.

5.2.1 mRNA Vectors

[0059] In certain embodiments, as an alternative to DNA vectors, the vectors provided herein are modified mRNA encoding for the gene of interest (*e.g.*, the transgene, for example, HuPTM non-monoclonal antibody biologic). The synthesis of modified and unmodified mRNA for delivery of a transgene to retinal pigment epithelial cells is taught, for example, in Hansson et al., J. Biol. Chem., 2015, 290(9):5661-5672, which is incorporated by reference herein in its entirety. In certain embodiments, provided herein is a modified mRNA encoding for a HuPTM anti-TNFα Fc fusion protein.

5.2.2 Viral vectors

[0060] Viral vectors include adenovirus, adeno-associated virus (AAV, *e.g.*, AAV2.7m8, AAV3, AAV8, AAV9, AAVrh10, AAV2.7m8, and other serotypes), lentivirus, helper-dependent adenovirus, herpes simplex virus, poxvirus, hemagglutinin virus of Japan (HVJ), alphavirus, vaccinia virus, and retrovirus vectors. Retroviral vectors include murine leukemia virus (MLV) and human immunodeficiency virus (HIV)-based vectors. Alphavirus vectors include semliki forest virus (SFV) and sindbis virus (SIN). In certain embodiments, the viral vectors provided herein are recombinant viral vectors. In certain embodiments, the viral vectors provided herein are altered such that they are replication-deficient in humans. In certain embodiments, the viral vectors are hybrid vectors, *e.g.*, an AAV vector placed into a "helpless" adenoviral vector. In certain embodiments, provided herein are viral vectors comprising a viral capsid from a first virus and viral envelope proteins from a second virus. In specific embodiments, the second virus is vesicular stomatitus virus (VSV). In more specific embodiments, the envelope protein is VSV-G protein.

[0061] In certain embodiments, the viral vectors provided herein are HIV based viral vectors. In certain embodiments, HIV-based vectors provided herein comprise at least two polynucleotides, wherein the gag and pol genes are from an HIV genome and the env gene is from another virus.

[0062] In certain embodiments, the viral vectors provided herein are herpes simplex virus-based viral vectors. In certain embodiments, herpes simplex virus-based vectors provided herein are modified such that they do not comprise one or more immediately early (IE) genes, rendering them non-cytotoxic.

[0063] In certain embodiments, the viral vectors provided herein are MLV based viral vectors. In certain embodiments, MLV-based vectors provided herein comprise up to 8 kb of heterologous DNA in place of the viral genes.

[0064] In certain embodiments, the viral vectors provided herein are lentivirus-based viral vectors. In certain embodiments, lentiviral vectors provided herein are derived from human lentiviruses. In certain embodiments, lentiviral vectors provided herein are derived from non-human lentiviruses. In certain embodiments, lentiviral vectors provided herein are packaged into a lentiviral capsid. In certain embodiments, lentiviral vectors provided herein comprise one or more of the

following elements: long terminal repeats, a primer binding site, a polypurine tract, att sites, and an encapsidation site.

[0065] In certain embodiments, the viral vectors provided herein are alphavirus-based viral vectors. In certain embodiments, alphavirus vectors provided herein are recombinant, replication-defective alphaviruses. In certain embodiments, alphavirus replicons in the alphavirus vectors provided herein are targeted to specific cell types by displaying a functional heterologous ligand on their virion surface.

[0066] In certain embodiments, the viral vectors provided herein are AAV based viral vectors. In certain embodiments, the AAV-based vectors provided herein do not encode the AAV rep gene (required for replication) and/or the AAV cap gene (required for synthesis of the capsid proteins) (the rep and cap proteins may be provided by the packaging cells in *trans*). Multiple AAV serotypes have been identified. In certain embodiments, AAV-based vectors provided herein comprise components from one or more serotypes of AAV. In preferred embodiments, AAV-based vectors provided herein comprise components from one or more serotypes of AAV with tropism to ocular tissues, liver and/or muscle. Throughout the specification, AAV "serotype" refers to an AAV having an immunologically distinct capsid, a naturally-occurring capsid, or an engineered capsid. In certain embodiments, AAV based vectors provided herein comprise capsid components from one or more of AAV1, AAV2, AAV2.7m8, AAV3, AAV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAV9, AAV9e, AAVrh10, AAVrh20, AAVrh39, AAVhu.37, AAVrh73, AAVrh74, AAV.hu51, AAV.hu21, AAV.hu12, or AAV.hu26. In certain embodiments, AAV based vectors provided herein are or comprise components from one or more of AAV2.7m8, AAV8, AAV3B, AAV9, AAV10, AAVrh73, or AAVrh10 serotypes. Provided are viral vectors in which the capsid protein is a variant of the AAV8 capsid protein (SEQ ID NO:32), AAV3B capsid protein (SEQ ID NO:26), or AAVrh73 capsid protein (SEQ ID NO:38), and the capsid protein is e.g., at least 95%, 96%, 97%, 98%, 99% or 99.9% identical to the amino acid sequence of the AAV8 capsid protein (SEQ ID NO:32), AAV3B capsid protein (SEQ ID NO:26), or AAVrh73 capsid protein (SEQ ID NO:38), while retaining the biological function of the native capsid. In certain embodiments, the encoded AAV capsid has the sequence of SEQ ID NO:32 with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 amino acid substitutions and retaining the biological function of the AAV8, AAV3B, or AAVrh73 capsid.

FIG. 3 provides a comparative alignment of the amino acid sequences of the capsid proteins of different AAV serotypes with potential amino acids that may be substituted at certain positions in the aligned sequences based upon the comparison in the row labeled SUBS. Accordingly, in specific embodiments, the AAV vector comprises an AAV8, AAV3B, or AAVrh73, capsid variant that has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 amino acid substitutions that are not present at that position in the native AAV capsid sequence as identified in the SUBS row of **FIG. 3**. Amino acid sequence for AAV8, AAV3B, or AAVrh73 capsids are provided in **FIG. 3**.

[0067] In some embodiments, AAV-based vectors comprise components from one or more serotypes of AAV. In some embodiments, AAV based vectors provided herein comprise capsid components from one or more of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAV14, AAV15, AAV16, AAV.rh8, AAV.rh10, AAV.rh20, AAV.rh39, AAV.Rh74, AAV.RHM4-1, AAV.hu37, AAV.Anc80, AAV.Anc80L65, AAV.7m8, AAV.PHP.B, AAV.PHP.eB, AAV2.5, AAV2tYF, AAV3B, AAV.LK03, AAV.HSC1, AAV.HSC2, AAV.HSC3, AAV.HSC4, AAV.HSC5, AAV.HSC6, AAV.HSC7, AAV.HSC8, AAV.HSC9, AAV.HSC10, AAV.HSC11, AAV.HSC12, AAV.HSC13, AAV.HSC14, AAV.HSC15, or AAV.HSC16 or other rAAV particles, or combinations of two or more thereof. In some embodiments, AAV based vectors provided herein comprise components from one or more of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAV14, AAV15, AAV16, AAV.rh8, AAV.rh10, AAV.rh20, AAV.rh39, AAV.Rh74, AAV.RHM4-1, AAV.hu37, AAV.Anc80, AAV.Anc80L65, AAV.7m8, AAV.PHP.B, AAV.PHP.eB, AAV2.5, AAV2tYF, AAV3B, AAV.LK03, AAV.HSC1, AAV.HSC2, AAV.HSC3, AAV.HSC4, AAV.HSC5, AAV.HSC6, AAV.HSC7, AAV.HSC8, AAV.HSC9, AAV.HSC10, AAV.HSC11, AAV.HSC12, AAV.HSC13, AAV.HSC14, AAV.HSC15, or AAV.HSC16 or other rAAV particles, or combinations of two or more thereof serotypes. In some embodiments, rAAV particles comprise a capsid protein at least 80% or more identical, e.g., 85%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, etc., i.e. up to 100% identical, to e.g., VP1, VP2 and/or VP3 sequence of an AAV capsid serotype selected from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAV14, AAV15, AAV16, AAV.rh8, AAV.rh10, AAV.rh20, AAV.rh39, AAV.Rh74, AAV.RHM4-1, AAV.hu37, AAV.Anc80, rAAV.Anc80L65, AAV.7m8, AAV.PHP.B, AAV.PHP.eB, AAV2.5, AAV2tYF, AAV3B, AAV.LK03,

AAV.HSC1, AAV.HSC2, AAV.HSC3, AAV.HSC4, AAV.HSC5, AAV.HSC6, AAV.HSC7, AAV.HSC8, AAV.HSC9, AAV.HSC10, AAV.HSC11, AAV.HSC12, AAV.HSC13, AAV.HSC14, AAV.HSC15, or AAV.HSC16, or a derivative, modification, or pseudotype thereof.

[0068] In particular embodiments, the recombinant AAV for use in compositions and methods herein is Anc80 or Anc80L65 (see, e.g., Zinn et al., 2015, Cell Rep. 12(6): 1056-1068, which is incorporated by reference in its entirety). In particular embodiments, the recombinant AAV for use in compositions and methods herein is AAV.7m8 (including variants thereof) (see, e.g., US 9,193,956; US 9,458,517; US 9,587,282; US 2016/0376323, and WO 2018/075798, each of which is incorporated herein by reference in its entirety). In particular embodiments, the AAV for use in compositions and methods herein is any AAV disclosed in US 9,585,971, such as AAV-PHP.B. In particular embodiments, the AAV for use in compositions and methods herein is an AAV2/Rec2 or AAV2/Rec3 vector, which has hybrid capsid sequences derived from AAV8 and serotypes cy5, rh20 or rh39 (see, e.g., Issa et al., 2013, PLoS One 8(4): e60361, which is incorporated by reference herein for these vectors). In particular embodiments, the AAV for use in compositions and methods herein is an AAV disclosed in any of the following, each of which is incorporated herein by reference in its entirety: US 7,282,199; US 7,906,111; US 8,524,446; US 8,999,678; US 8,628,966; US 8,927,514; US 8,734,809; US9,284,357; US 9,409,953; US 9,169,299; US 9,193,956; US 9,458,517; US 9,587,282; US 2015/0374803; US 2015/0126588; US 2017/0067908; US 2013/0224836; US 2016/0215024; US 2017/0051257; PCT/US2015/034799; and PCT/EP2015/053335. In some embodiments, rAAV particles have a capsid protein at least 80% or more identical, e.g., 85%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, etc., i.e. up to 100% identical, to the VP1, VP2 and/or VP3 sequence of an AAV capsid disclosed in any of the following patents and patent applications, each of which is incorporated herein by reference in its entirety: United States Patent Nos. 7,282,199; 7,906,111; 8,524,446; 8,999,678; 8,628,966; 8,927,514; 8,734,809; US 9,284,357; 9,409,953; 9,169,299; 9,193,956; 9,458,517; and 9,587,282; US patent application publication nos. 2015/0374803; 2015/0126588; 2017/0067908; 2013/0224836; 2016/0215024; 2017/0051257; and International Patent Application Nos. PCT/US2015/034799; PCT/EP2015/053335.

[0069] In some embodiments, rAAV particles comprise any AAV capsid disclosed in United States Patent No. 9,840,719 and WO 2015/013313, such as AAV.Rh74 and RHM4-1, each of which is

incorporated herein by reference in its entirety. In some embodiments, rAAV particles comprise any AAV capsid disclosed in WO 2014/172669, such as AAV rh.74, which is incorporated herein by reference in its entirety. In some embodiments, rAAV particles comprise the capsid of AAV2/5, as described in Georgiadis et al., 2016, Gene Therapy 23: 857-862 and Georgiadis et al., 2018, Gene Therapy 25: 450, each of which is incorporated by reference in its entirety. In some embodiments, rAAV particles comprise any AAV capsid disclosed in WO 2017/070491, such as AAV2tYF, which is incorporated herein by reference in its entirety. In some embodiments, rAAV particles comprise the capsids of AAVLK03 or AAV3B, as described in Puzzo et al., 2017, Sci. Transl. Med. 29(9): 418, which is incorporated by reference in its entirety. In some embodiments, rAAV particles comprise any AAV capsid disclosed in US Pat Nos. 8,628,966; US 8,927,514; US 9,923,120 and WO 2016/049230, such as HSC1, HSC2, HSC3, HSC4, HSC5, HSC6, HSC7, HSC8, HSC9, HSC10, HSC11, HSC12, HSC13, HSC14, HSC15, or HSC16, each of which is incorporated by reference in its entirety.

[0070] In some embodiments, rAAV particles have a capsid protein disclosed in Intl. Appl. Publ. No. WO 2003/052051 (see, e.g., SEQ ID NO: 2 of ´051 publication), WO 2005/033321 (see, e.g., SEQ ID NOs: 123 and 88 of ´321 publication), WO 03/042397 (see, e.g., SEQ ID NOs: 2, 81, 85, and 97 of ´397 publication), WO 2006/068888 (see, e.g., SEQ ID NOs: 1 and 3-6 of ´888 publication), WO 2006/110689, (see, e.g., SEQ ID NOs: 5-38 of ´689 publication) WO2009/104964 (see, e.g., SEQ ID NOs: 1-5, 7, 9, 20, 22, 24 and 31 of ´964 publication), WO 2010/127097 (see, e.g., SEQ ID NOs: 5-38 of ´097 publication), and WO 2015/191508 (see, e.g., SEQ ID NOs: 80-294 of ´508 publication), and U.S. Appl. Publ. No. 20150023924 (see, e.g., SEQ ID NOs: 1, 5-10 of ´924 publication), the contents of each of which is herein incorporated by reference in its entirety. In some embodiments, rAAV particles have a capsid protein at least 80% or more identical, e.g., 85%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, etc., i.e. up to 100% identical, to the VP1, VP2 and/or VP3 sequence of an AAV capsid disclosed in Intl. Appl. Publ. No. WO 2003/052051 (see, e.g., SEQ ID NO: 2 of ´051 publication), WO 2005/033321 (see, e.g., SEQ ID NOs: 123 and 88 of ´321 publication), WO 03/042397 (see, e.g., SEQ ID NOs: 2, 81, 85, and 97 of ´397 publication), WO 2006/068888 (see, e.g., SEQ ID NOs: 1 and 3-6 of ´888 publication), WO 2006/110689 (see, e.g., SEQ ID NOs: 5-38 of ´689 publication) WO2009/104964 (see, e.g., SEQ ID NOs: 1-5, 7, 9, 20, 22, 24 and 31 of 964 publication), W0 2010/127097 (see, e.g., SEQ ID NOs: 5-38 of ´097 publication),

and WO 2015/191508 (see, e.g., SEQ ID NOs: 80-294 of ′508 publication), and U.S. Appl. Publ. No. 20150023924 (see, e.g., SEQ ID NOs: 1, 5-10 of ′924 publication).

[0071] In additional embodiments, rAAV particles comprise a pseudotyped AAV capsid. In some embodiments, the pseudotyped AAV capsids are rAAV2/8 or rAAV2/9 pseudotyped AAV capsids. Methods for producing and using pseudotyped rAAV particles are known in the art (see, e.g., Duan et al., J. Virol., 75:7662-7671 (2001); Halbert et al., J. Virol., 74:1524-1532 (2000); Zolotukhin et al., Methods 28:158-167 (2002); and Auricchio et al., Hum. Molec. Genet. 10:3075-3081, (2001).

[0072] AAV2.7m8-based, AAV8-based, AAV9-based, and AAVrh10-based viral vectors are used in certain of the methods described herein. Nucleotide sequences of AAV based viral vectors and methods of making recombinant AAV and AAV capsids are taught, for example, in United States Patent No. 9,193,956 B2, United States Patent No. 7,282,199 B2, United States Patent No. 7,790,449 B2, United States Patent No. 8,318,480 B2, United States Patent No. 8,962,332 B2 and International Patent Application No. PCT/EP2014/076466, each of which is incorporated herein by reference in its entirety. In one aspect, provided herein are AAV (*e.g.*, AAV2.7m8, AAV8, AAV9 or AAVrh10)-based viral vectors encoding a transgene (*e.g.*, an HuPTM dimeric fusion protein). The amino acid sequences of AAV capsids, including AAV2.7m8, AAV8, AAV9 and AAVrh10 are provided in FIG. 3.

[0073] In certain embodiments, a single-stranded AAV (ssAAV) may be used supra. In certain embodiments, a self-complementary vector, *e.g.*, scAAV, may be used (*see, e.g.*, Wu, 2007, Human Gene Therapy, 18(2):171-82, McCarty et al, 2001, Gene Therapy, Vol 8, Number 16, Pages 1248-1254; and U.S. Patent Nos. 6,596,535; 7,125,717; and 7,456,683, each of which is incorporated herein by reference in its entirety).

[0074] In certain embodiments, the viral vectors used in the methods described herein are adenovirus based viral vectors. A recombinant adenovirus vector may be used to transfer in the transgene encoding the HuPTM anti-TNFα Fc fusion protein. The recombinant adenovirus can be a first-generation vector, with an E1 deletion, with or without an E3 deletion, and with the expression cassette inserted into either deleted region. The recombinant adenovirus can be a second-generation vector, which contains full or partial deletions of the E2 and E4 regions. A helper-dependent adenovirus retains only the adenovirus inverted terminal repeats and the packaging signal (phi). The transgene is inserted between the packaging signal and the 3'ITR, with or without stuffer sequences

to keep the genome close to wild-type size of approximately 36 kb. An exemplary protocol for production of adenoviral vectors may be found in Alba et al., 2005, "Gutless adenovirus: last generation adenovirus for gene therapy," Gene Therapy 12:S18-S27, which is incorporated by reference herein in its entirety.

[0075] In certain embodiments, the viral vectors used in the methods described herein are lentivirus based viral vectors. A recombinant lentivirus vector may be used to transfer in the transgene encoding the HuPTM anti-TNFα Fc fusion protein. Four plasmids are used to make the construct: Gag/pol sequence containing plasmid, Rev sequence containing plasmids, Envelope protein containing plasmid (*e.g.*, VSV-G), and Cis plasmid with the packaging elements and the anti-TNFα Fc fusion protein.

[0076] For lentiviral vector production, the four plasmids are co-transfected into cells (*e.g.*, HEK293 based cells), whereby polyethylenimine or calcium phosphate can be used as transfection agents, among others. The lentivirus is then harvested in the supernatant (lentiviruses need to bud from the cells to be active, so no cell harvest needs/should be done). The supernatant is filtered (0.45 μm) and then magnesium chloride and benzonase added. Further downstream processes can vary widely, with using TFF and column chromatography being the most GMP compatible ones. Others use ultracentrifugation with/without column chromatography. Exemplary protocols for production of lentiviral vectors may be found in Lesch et al., 2011, "Production and purification of lentiviral vector generated in 293T suspension cells with baculoviral vectors," Gene Therapy 18:531-538, and Ausubel et al., 2012, "Production of CGMP-Grade Lentiviral Vectors," Bioprocess Int. 10(2):32-43, both of which are incorporated by reference herein in their entireties.

[0077] In a specific embodiment, a vector for use in the methods described herein is one that encodes an HuPTM anti-TNFα Fc fusion protein, such that, upon introduction of the vector into a relevant cell, a glycosylated and/or tyrosine sulfated variant of the HuPTM anti-TNFα Fc fusion protein is expressed by the cell.

5.2.3 Promoters and Modifiers of Gene Expression

[0078] In certain embodiments, the vectors provided herein comprise components that modulate gene delivery or gene expression (*e.g.*, "expression control elements"). In certain

embodiments, the vectors provided herein comprise components that modulate gene expression. In certain embodiments, the vectors provided herein comprise components that influence binding or targeting to cells. In certain embodiments, the vectors provided herein comprise components that influence the localization of the polynucleotide (*e.g.*, the transgene) within the cell after uptake. In certain embodiments, the vectors provided herein comprise components that can be used as detectable or selectable markers, *e.g.*, to detect or select for cells that have taken up the polynucleotide.

[0079] In certain embodiments, the viral vectors provided herein comprise one or more promoters that control expression of the transgene. These promoters (and other regulatory elements that control transcription, such as enhancers) may be constitutive (promote ubiquitous expression) or may specifically or selectively express in ocular tissues. In certain embodiments, the promoter is a constitutive promoter.

[0080] In certain embodiments, the promoter is a CB7 (also referred to as a CAG promoter) (see Dinculescu et al., 2005, Hum Gene Ther 16: 649-663, incorporated by reference herein in its entirety). In some embodiments, the CAG (SEQ ID NO:51) or CB7 promoter (SEQ ID NO:50) includes other expression control elements that enhance expression of the transgene driven by the vector. In certain embodiments, the other expression control elements include chicken β-actin intron and/or rabbit β-globin polyA signal (SEQ ID NO:55). In certain embodiments, the promoter comprises a TATA box. In certain embodiments, the promoter comprises one or more elements. In certain embodiments, the one or more promoter elements may be inverted or moved relative to one another. In certain embodiments, the elements of the promoter are positioned to function cooperatively. In certain embodiments, the elements of the promoter are positioned to function independently. In certain embodiments, the viral vectors provided herein comprise one or more promoters selected from the group consisting of the human CMV immediate early gene promoter, the SV40 early promoter, the Rous sarcoma virus (RS) long terminal repeat, and rat insulin promoter. In certain embodiments, the vectors provided herein comprise one or more long terminal repeat (LTR) promoters selected from the group consisting of AAV, MLV, MMTV, SV40, RSV, HIV-1, and HIV-2 LTRs.

[0081] In certain embodiments, the vectors provided herein comprise one or more tissue specific promoters (e.g., a retinal-specific promoter). In particular embodiments, the viral vectors provided herein comprises a ocular tissue cell specific promoter, such as, human rhodopsin kinase

(GRK1) promoter (SEQ ID NOS:54 or 117), a mouse cone arresting (CAR) promoter (SEQ ID NOS:114-116), a human red opsin (RedO) promoter (SEQ ID NO:112) or a Best1/GRK promoter (SEQ ID NO: 161).

[0082] Provided are nucleic acid regulatory elements that are chimeric with respect to arrangements of elements in tandem in the expression cassette. Regulatory elements, in general, have multiple functions as recognition sites for transcription initiation or regulation, coordination with cell-specific machinery to drive expression upon signaling, and to enhance expression of the downstream gene.

[0083] In certain embodiments, the promoter is an inducible promoter. In certain embodiments the promoter is a hypoxia-inducible promoter. In certain embodiments, the promoter comprises a hypoxia-inducible factor (HIF) binding site. In certain embodiments, the promoter comprises a HIF-1α binding site. In certain embodiments, the promoter comprises a HIF-2α binding site. In certain embodiments, the HIF binding site comprises an RCGTG motif. For details regarding the location and sequence of HIF binding sites, *see, e.g.*, Schödel, et al., Blood, 2011, 117(23):e207-e217, which is incorporated by reference herein in its entirety. In certain embodiments, the promoter comprises a binding site for a hypoxia induced transcription factor other than a HIF transcription factor. In certain embodiments, the viral vectors provided herein comprise one or more IRES sites that is preferentially translated in hypoxia. For teachings regarding hypoxia-inducible gene expression and the factors involved therein, *see, e.g.*, Kenneth and Rocha, Biochem J., 2008, 414:19-29, which is incorporated by reference herein in its entirety. In specific embodiments, the hypoxia-inducible promoter is the human N-WASP promoter, *see, e.g.*, Salvi, 2017, Biochemistry and Biophysics Reports 9:13-21 (incorporated by reference for the teaching of the N-WASP promoter) or is the hypoxia-induced promoter of human Epo, *see, e.g.*, Tsuchiya et al., 1993, J. Biochem. 113:395-400 (incorporated by reference for the disclosure of the Epo hypoxia-inducible promoter). In other embodiments, the promoter is a drug inducible promoter, for example, a promoter that is induced by administration of rapamycin or analogs thereof. See, *e.g.*, the disclosure of rapamycin inducible promoters in PCT publications WO94/18317, WO 96/20951, WO 96/41865, WO 99/10508, WO 99/10510, WO 99/36553, and WO 99/41258, and US 7,067,526, which are hereby incorporated by reference in their entireties for the disclosure of drug inducible promoters.

[0084] Provided herein are constructs containing certain ubiquitous and tissue-specific promoters. Such promoters include synthetic and tandem promoters. Examples and nucleotide sequences of promoters are provided in Tables 1 and 1a below. Table 1 also includes the nucleotide sequences of other regulatory elements useful for the expression cassettes provided herein.

Table 1. Promoter and Other Regulatory Element Sequences

Name/ SEQ ID NO.	Sequence
CAG/CB7 SEQ ID NO:50	gacattgattattgactagttattaatagtaatcaattacggggtcattagt tcatagcccatatatggagttccgcgttacataacttacggtaaatggcccg cctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatg ttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagta tttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagt acgcccccctattgacgtcaatgacggtaaatggcccgcctggcattatgccc agtacatgaccttatgggactttcctacttggcagtacatctacgtattagt catcgctattaccatggtcgaggtgagccccacgttctgcttcactctcccc atctccccccccctccccaccccaattttgtatttatttatttttttaattat tttgtgcagcgatgggggcgggggggggggggggcgcgcgccaggcggggc ggggcggggcgaggggcggggcggggcgaggcggagaggtgcggcggcagcc aatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggc ggcggccctataaaaagcgaagcgcgcggcgggcgggagtcgctgcgcgctg ccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgccccggctc tgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctc cgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggct gcgtgaaagccttgaggggctccgggagggccctttgtgcgggggggagcggc tcgggggggtgcgtgcgtgtgtgtgtgcgtggggagcgccgcgtgcggctccg cgctgcccggcggctgtgagcgctgcgggcgcggcgcggggctttgtgcgct ccgcagtgtgcgcgaggggagcgcggccgggggcggtgccccgcggtgcggg ggggggctgcgaggggaacaaaggctgcgtgcggggtgtgtgcgtgggggggt gagcaggggggtgtgggcgcgtcggtcgggctgcaaccccccctgcacccccc tccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacgggg cgtggcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgc cgggcggggcggggccgcctcgggccggggagggctcgggggaggggcgcgg cggcccccggagcgccggcggctgtcgaggcgcggcgagccgcagccattgc cttttatggtaatcgtgcgagagggcgcagggacttcctttgtcccaaatct gtgcggagccgaaatctgggaggcgccgccgcacccccctctagcgggcgcgg ggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagggccttcgt gcgtcgccgcgccgccgtcccccttctccctctccagcctcggggctgtccgc ggggggacggctgccttcgggggggacggggcagggcggggttcggcttctg gcgtgtgaccggcggctctagagcctctgctaaccatgttcatgccttcttc tttttcctacagctcctgggcaacgtgctggttattgtgctgtctcatcatt ttggcaaag

CAG (CMV-Chicken B-Actin Promoter-chimeric intron) SEQ ID NO:51	gacattgattattgactagttattaatagtaatcaattacggggtcattagt tcatagcccatatatggagttccgcgttacataacttacggtaaatggcccg cctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatg ttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagta tttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagt acgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgccc agtacatgaccttatgggactttcctacttggcagtacatctacgtattagt catcgctattaccatggtcgaggtgagccccacgttctgcttcactctcccc atctccccccccctccccaccccaattttgtatttatttatttttttaattat tttgtgcagcgatgggggcgggggggggggggggcgcgcgccaggcggggc ggggcggggcgaggggcggggcggggcgaggcggagaggtgcggcggcagcc aatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggc ggcggccctataaaaagcgaagcgcgcggcgggcgggagtcgctgcgcgctg ccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgccccggctc tgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctc cgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggct gcgtgaaagccttgaggggctccgggagggccctttgtgcgggggggagcggc tcgggggggtgcgtgcgtgtgtgtgtgcgtggggagcgccgcgtgcggctccg cgctgcccggcggctgtgagcgctgcgggcgcggcgcggggctttgtgcgct ccgcagtgtgcgcgaggggagcgcggccgggggcggtgccccgcggtgcggg gggggctgcgaggggaacaaaggctgcgtgcggggtgtgtgcgtgggggggt gagcaggggggtgtgggcgcgtcggtcgggctgcaacccccccctgcacccccc tccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacgggg cgtggcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgc cgggcggggcggggccgcctcgggccggggagggctcgggggagggggcgcgg cggcccccggagcgccggcggctgtcgaggcgcggcgagccgcagccattgc cttttatggtaatcgtgcgagagggcgcagggacttcctttgtcccaaatct gtgcggagccgaaatctgggaggcgccgccgcacccccctctagcgggcgcgg ggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagggccttcgt gcgtcgccgcgccgccgtcccccttctccctctccagcctcggggctgtccgc ggggggacggctgccttcgggggggacggggcagggcggggttcggcttctg gcgtgtgaccggcggctctagagcctctgctaaccatgttcatgccttcttc tttttcctacag

mU1a SEQ ID NO:52	atggaggcggtactatgtagatgagaattcaggagcaaactgggaaaagcaactgcttccaaa tatttgtgatttttacagtgtagttttggaaaaactcttagcctaccaattcttctaagtgtt ttaaaatgtgggagccagtacacatgaagttatagagtgttttaatgaggcttaaatatttac cgtaactatgaaatgctacgcatatcatgctgttcaggctccgtggccacgcaactcatact
EF-1α (core) SEQ ID NO:53	gggcagagcgcacatcgcccacagtccccgagaagttgggggggagggtcggcaattgaacgg gtgcctagagaaggtggcgcggggtaaactgggaaagtgatgtcgtgtactggctccgccttt ttcccgagggtgggggagaaccgtatataagtgcagtagtcgccgtgaacgttctttttcgca acgggtttgccgccagaacacag
Human UbC SEQ ID NO:111	GtctaacaaaaaagccaaaaacggccagaatttagcggacaatttactagtctaacactgaaA attacatattgacccaaatgattacatttcaaaaggtgcctaaaaaacttcacaaaacacact Cgccaaccccgagcgcatagttcaaaaccggagcttcagctacttaagaagataggtacataa Aaccgaccaaagaaactgacgcctcacttatccctcccctcaccagaggtccggcgcctgtcg aTtcaggagagcctaccctaggcccgaaccctgcgtcctgcgacggagaaaagcctaccgcac aCctaccggcaggtggccccaccctgcattataagccaacagaacgggtgacgtcacgacacg aCgagggcgcgcgctcccaaaggtacgggtgcactgcccaacggcaccgccataactgccgcc cCcgcaacagacgacaaaccgagttctccagtcagtgacaaacttcacgtcagggtccccaga tgGtgccccagcccatctcacccgaataagagctttcccgcattagcgaaggcctcaagacct tgggTtcttgccgcccaccatgccccccaccttgtttcaacgacctcacagcccgcctcacaa gcgtcttcCattcaagactcgggaacagccgccattttgctgcgctccccccaaccccccagtt cagggcaaccTtgctcgcggacccagactacagcccttggcggtctctccacacgcttccgtc ccaccgagcggccCggcggccacgaaagccccggccagcccagcagcccgctactcaccaagt gacgatcacagcgaTccacaaacaagaaccgcgacccaaatcccggctgcgacggaactagct gtgccacacccggcgCgtccttatataatcatcggcgttcaccgccccacggagatccctccg cagaatcgccgagaagggActacttttcctcgcctgttccgctctctggaaagaaaaccagtg ccctagagtcacccaagtcccgtCctaaaatgtccttctgctgatactggggttctaaggccg agtcttatgagcagcgggccgctgtcctGagcgtccgggcggaaggatcaggacgctcgctgc gcccttcgtctgacgtggcagcgctcgccgtgaggaggggggcgcccgcgggaggcgccaaaa cccggcgcggaggcc

Human red opsin (RedO) (photoreceptor-specific) SEQ ID NO: 112	ggaggctgaggggtggggaaagggcatgggtgtttcatgaggacagagcttccgtttcatgca atgaaaagagtttggagacggatggtggtgactggactatacacttacacacggtagcgatgg tacactttgtattatgtatattttaccacgatcttttaaagtgtcaaaggcaaatggccaaa tggttccttgtcctatagctgtagcagccatcggctgttagtgacaaagcccctgagtcaaga tgacagcagcccccataactcctaatcggctctcccgcgtggagtcatttaggagtagtcgca ttagagacaagtccaacatctaatcttccaccctggccagggccccagctggcagcgagggtg ggagactccgggcagagcagagggcgctgacattggggcccggcctggcttgggtccctctgg cctttccccaggggccctctttccttggggctttcttgggccgccactgctcccgctcctctc cccccatcccaccccctcaccccctcgttcttcatatccttctctagtgctccctccactttc atccaccttctgcaagagtgtgggaccacaaatgagttttcacctggcctggggacacacgt gcccccacaggtgctgagtgactttctaggacagtaatctgctttaggctaaaatgggacttg atcttctgttagccctaatcatcaattagcagagccggtgaaggtgcagaacctaccgccttt ccaggcctcctcccacctctgccacctccactctccttcctgggatgtgggggctggcacacg tgtggcccagggcattggtgggattgcactgagctgggtcattagcgtaatcctggacaaggg cagacagggcgagcggagggccagctccggggctcaggcaaggctgggggcttcccccagaca ccccactcctcctctgctggacccccacttcatagggcacttcgtgttctcaaagggcttcca aatagcatggtggccttggatgcccagggaagcctcagagttgcttatctccctctagacaga aggggaatctcggtcaagagggagaggtcgccctgttcaaggccacccagccagctcatggcg gtaatgggacaaggctggccagccatcccaccctcagaagggacccggtggggcaggtgatct cagaggaggctcacttctgggtctcacattcttggatccggttccaggcctcggccctaaata gtctccctgggctttcaagagaaccacatgagaaaggaggattcgggctctgagcagtttcac cacccacccccagtctgcaaatcctgacccgtgggtccacctgccccaaaggcggacgcagg acagtagaagggaacagagaacacataaacacagagagggccacagcggctcccacagtcacc gccaccttcctggcggggatgggtggggcgtctgagtttggttcccagcaaatccctctgagc cgcccttgcgggctcgcctcaggagcaggggagcaagaggtgggaggaggaggtctaagtccc aggcccaattaagagatcaggtagtgtagggtttgggagcttttaaggtgaagaggcccgggc tgatcccacaggccagtataaagcgccgtgaccctcaggtgatgcgccagggccggctgccgt cggggacagggctttccatagcc

Human rhodopsin (Rho) (photoreceptor-specific) SEQ ID NO:113	Agatcttcccc a cctagccacc tggcaaactg ctccttctct caaaggccca aacatggcct cccagactgc aacccccagg cagtcaggcc ctgtctccac aacctcacag ccaccctgga cggaatctgc ttcttcccac atttgagtcc tcctcagccc ctgagctcct ctgggcaggg ctgtttcttt ccatctttgt attcccaggg gcctgcaaat aaatgtttaa tgaacgaaca agagagtgaa ttccaattcc atgcaacaag gattgggctc ctgggcccta ggctatgtgt ctggcaccag aaacggaagc tgcaggttgc agcccctgcc ctcatggagc tcctcctgtc agaggagtgt ggggactgga tgactccaga ggtaacttgt gggggaacga acaggtaagg ggctgtgtga cgagatgaga gactgggaga ataaaccaga aagtctctag ctgtccagag gacatagcac agaggcccat ggtccctatt tcaaacccag gccaccagac tgagctggga ccttgggaca gacaagtcat gcagaagtta ggggaccttc tcctcccttt tcctggatgg atcctgagta ccttctcctc cctgacctca ggcttcctcc tagtgtcacc ttggcccctc ttagaagcca attaggccct cagtttctgc agcggggatt aatatgatta tgaacacccc caatctccca gatgctgatt cagccaggag cttaggaggg ggaggtcact ttataagggt ctgggggggt cagaacccag agtc (start of exon 1 at 5339; See also Bennett,J., Sun,D. and Kariko,K. Sequence analysis of the 5.34-kb 5' flanking region of the human rhodopsin-encoding gene. Gene 167 (1-2), 317-320 (1995))
Mouse cone arrestin promoter (CAR) *(photoreceptor-specific)* SEQ ID NO:114	TGGCCCTGGCATTCCCCTATACTGGGACATAGAACCTTCACAGGACCAAGGG CCTCTCCTCCCATTGATGACTGACTAGGCCATCCTCTAGCTACATAGGTGGT GGAGCCTAGAGTCCCTCCTTGTGTACTCTTTGGTGGTGGTTACTCTGGGGGT ACTAGGTTAGTTCGTATTGTTGTTCCTCCTAGGGGACTGCAAACCCCTTCAG CTCCTTGGGTCCTTTCTCTAGTTCCTTCTTTGGGGACCCTGTGCTCAGTTCA ATGGATGGCCAATTTCCTTCTTAAATGCCCCTAGCAGTAACTGTTAGGTCTC AATCCCAAGACAAATGTCTGAGGTGCCTATTTAACAGATCAAAGCGGACCTG TCCTCAGGTTAACCCAGTCACTCCCTGTACCTCAGTCCCTACCCATCACAAT TCTCCAGCCCATGAGCTTCGGGCTGTACTTCCCCAACGGGTTCTCCCATTTT GGGTACATGGCCTTTTTTTTTTACCTTTTTGGTTCCTTTGGCCTTTTGGCTT TTGGCTTCCAGGGCTTCTGGATCCCCCCCAACCCCTCCCATACACA TACACATGTGCACTCGTGCACTCAACCCAGCACAGGATAATGTTCATTCTTG ACCTTTCCACATACATCTGGCTATGTTCTCTCTCTTATCTACAATAAATCTC CTCCACTATACTTAGGAGCAGTTATGTTCTTCTTCTTTCTTTCTTTTTTTTT TTTTTTTCATTCAGTAACATCATCAGAATCCCCTAGCTCTGGCCTACCTCCT CAGTAACAATCAGC**TGATCCCTGGCCACTAATCTGTACTCACTAATCTGTTT TCCAAACTCTTGGCCCCTGAGCTAATTATAGCAGTGCTTCATGCCACCCACC CCAACCCTATCCTTGTTCTCTGACTCCCACTAATCTACACATTCAGAGGATT GTGGATATAAGAGGCTGGGAGGCCAGCTTAGCAACCAGAGCTCGAGGCTGAT GCGAGCTTCATCTCTTCCCTC**

Mouse cone arrestin promoter (CAR) *(photoreceptor-specific)* SEQ ID NO:115	TTTTTTTTTTACCTTTTTGGTTCCTTTGGCCTTTTGGCTTTTGGCTTCCAGG GCTTCTGGATCCCCCCCAACCCCTCCCATACACATACACATGTGCACTCGTG CACTCAACCCAGCACAGGATA ATGTTCATTCTTGACCTTTCCACATACATCTGGCTATGTTCTCTCTCTTATC TACAATAAATCTCCTCCACTATACTTAGGAGCAGTTATGTTCTTCTTCTTTC TTTCTTTTTTTTTTTTTTTTCATTCAGTAACATCATCAGAATCCCCTAGCTC TGGCCTACCTCCTCAGTAACAATCAGC**TGATCCCTGGCCACTAATCTGTACT CACTAATCTGTTTTCCAAACTCTTGGCCCCTGAGCTAATTATAGCAGTGCTT CATGCCACCCACCCCAACCCTATCCTTGTTCTCTGACTCCCACTAATCTACA** CATTCAGAGGATTGTGGATATAAGAGGCTGGGAGGCCAGCTTAGCAACCAGA GCTCGAGGCTGATGCGAGCTTCATCTCTTCCCTC
Mouse cone arrestin promoter (CAR) *(photoreceptor-specific)* SEQ ID NO:116	**TGATCCCTGGCCACTAATCTGTACTCACTAATCTGTTTTCCAAACTCTTGGC CCCTGAGCTAATTATAGCAGTGCTTCATGCCACCCACCCCAACCCTATCCTT GTTCTCTGACTCCCACTAATCTACACATTCAGAGGATTGTGGATATAAGAGG CTGGGAGGCCAGCTTAGCAACCAGAGCTCGAGGCTGATGCGAGCTTCATCTC TTCCCTC**
Human rhodopsin kinase (RK) or GRK1 *(photoreceptor-specific)* SEQ ID NO:117	gggcccca gaagcctggt ggttgtttgt ccttctcagg ggaaaagtga ggcggcccct tggaggaagg ggccgggcag aatgatctaa tcggattcca agcagctcag gggattgtct ttttctagca ccttcttgcc actcctaagc gtcctccgtg accccggctg ggatttagcc tggtgctgtg tcagccccgg
Human Bestrophin 1 (BEST1) promoter *(a.k.a. hVMD2 promoter)* SEQ ID NO:118	AAGG ACTCCTTTGT GGAGGTCCTG GCTTAGGGAG TCAAGTGACG GCGGCTCAGC ACTCACGTGG GCAGTGCCAG CCTCTAAGAG TGGGCAGGGG CACTGGCCAC AGAGTCCCAG GGAGTCCCAC CAGCCTAGTC GCCAGACC +38
Human Bestrophin 1 (BEST1) promoter *(a.k.a. hVMD2 promoter)* SEQ ID NO:119	GTCAAGTGACG GCGGCTCAGC ACTCACGTGG GCAGTGCCAG CCTCTAAGAG TGGGCAGGGG CACTGGCCAC AGAGTCCCAG GGAGTCCCAC CAGCCTAGTC GCCAGACC (transcriptional start site residue underlined at +1)

Human Bestrophin 1 (BEST1) promoter *(a.k.a. hVMD2 promoter)* SEQ ID NO:120	CTCAGC ACTCACGTGG GCAGTGCCAG CCTCTAAGAG TGGGCAGGGG CACTGGCCAC AGAGTCCCAG GGAGTCCCAC CAGCCTAGTC GCCAGAC (transcriptional start site residue underlined at +1)
Human Bestrophin 1 (BEST1) promoter *(a.k.a. hVMD2 promoter)* SEQ ID NO:121	TTAATAAACA TTTGGGCGAT TCTTACGGCC TCTAAAGACC AAGAACCACT GCTGCCTAGA GCTCTGCTCT CTTCATTGAA CAATACAAGA GGAGTGTGTA GGTAGACACC CACCACTTCC AACAGCTTAG GAGAGCCCTT GAGTATGGAT TGATGTATTA AAATTTATTG AATCACATGC TGAGATTTTC ACCAGCTGCC CGTGGGGATC TGGGCATTTA TTCCCATATT GCACTGGCTG GCTGGAAGCC AGCAGCATAA ACTCCAGGGC TGTTCTGTCA ACCCCCACCA GACTCACCCC GCTCCACCAG CCCCGGCAGG CTTCTCCTTC CATCTCTCTG AAGCAACTTA CTGATGGGCC CTGCCAGCCA ATCACAGCCA GAATAACGTA TGATGTCACC AGCAGCCAAT CAGAGCTCCT CGTCAGCATA TGCAGAATTC TGTCATTTTA CTAGGGTGAT GAAATTCCCA AGCAACACCA TCCTTTTCAGATAAGGGCAC TGAGGCTGAG AGAGGAGCTG AAACCTACCC GGCGTCACCA CACACAGGTG GCAAGGCTGG GACCAGAAAC CAGGACTGTT GACTGCAGCC CGGTATTCAT TCTTTCCATA GCCCACAGGG CTGTCAAAGA CCCCAGGGCC TAGTCAGAGG CTCCTCCTTC CTGGAGAGTT CCTGGCACAG AAGTTGAAGC TCAGCACAGC CCCCTAACCC CCAACTCTCT CTGCAAGGCC TCAGGGGTCA GAACACTGGT GGAGCAGATC CTTTAGCCTC TGGATTTTAG GGCCATGGTA GAGGGGGTGT TGCCCTAAAT TCCAGCCCTG GTCTCAGCCC AACACCCTCC AAGAAGAAAT TAGAGGGGCC ATGGCCAGGC TGTGCTAGCC GTTGCTTCTG AGCAGATTAC AAGAAGGGAC CAAGACAAGG ACTCCTTTGT GGAGGTCCTG GCTTAGGGAG TCAAGTGACG GCGG**CTCAGC ACTCACGTGG GCAGTGCCAG CCTCTAAGAG** **TGGGCAGGGG CACTGGCCAC AGAGTCCCAG GGAGTCCCAC** **CAGCCTAGTC GCCAGACC**TT CTGTGGGATC ATCGGACCCA (transcriptional start site residue underlined at +1; minimal active promoter region in bold)
GRK1 promoter SEQ ID NO:54	GGGCCCCAGAAGCCTGGTGGTTGTTTGTCCTTCTCAGGGGAAAAGTGAGGCGGCCCCTTGGAG GAAGGGGCCGGGCAGAATGATCTAATCGGATTCCAAGCAGCTCAGGGGATTGTCTTTTTCTAG CACCTTCTTGCCACTCCTAAGCGTCCTCCGTGACCCCGGCTGGGATTTAGCCTGGTGCTGTGT CAGCCCCGGGCTCCCAGGGGCTTCCCAGTGGTCCCCAGGAACCCTCGACAGGGCCAGGGCGTC TCTCTCGTCCAGCAAGGGCAGGGACGGGCCACAGGCCAAGGGC

Upstream Kozak sequence	GCCACC
Rabbit beta-globin polyA SEQ ID NO:55	gatcttttccctctgccaaaaattatggggacatcatgaagcccttgagcatctgacttctggctaataaaggaaatttattttcattgcaatagtgtgttggaatttttgtgtctctcactcg
Chimeric Intron SEQ ID NO:56	gtaagtatcaaggttacaagacaggtttaaggagaccaatagaaactgggcttgtcgagacagagaagactcttgcgtttctgataggcacctattggtcttactgacatccactttgcctttctctccacag
VH4 Intron SEQ ID NO:57	gtgagtatctcagggatccagacatggggatatgggaggtgcctctgatcccagggctcactgtgggtctctctgttcacag
SV40 Intron SEQ ID NO:157	gtaagtttagtcttttgtcttttatttcaggtcccggatccggtggtggtgcaaatcaaagaactgctcctcagtggatgttgcctttacttctag
5'ITR SEQ ID NO:58	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct
5'-ITR (Deleted D-sequence for self-complimentary AAV) SEQ ID NO:59	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagtgg
3'-ITR AAV SEQ ID NO:60	gaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagtggccaa
3'-ITR (Deleted D-sequence for self-complimentary AAV) SEQ ID NO:61	ttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcag

CB promoter SEQ ID NO:159	gacgacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcc catatatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgcccaacg acccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaatagggactttcc attgacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatcaagtgtatc atatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgccc agtacatgaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctatta ccatggtcgaggtgagccccacgttctgcttcactctccccatctccccccccctccccaccc caattttgtatttatttatttttaattattttgtgcagcgatgggggcgggggggggggggg ggcgcgcgccaggcggggcggggcggggcgaggggcggggcggggcgaggcggagaggtgcgg cggcagccaatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggcggc ggccctataaaaagcgaagcgcgcggcgggcgg
CB long promoter (CB+100) SEQ ID NO:160	gacgacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcc catatatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgcccaacg acccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaatagggactttcc attgacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatcaagtgtatc atatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgccc agtacatgaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctatta ccatggtcgaggtgagccccacgttctgcttcactctccccatctccccccccctccccaccc caattttgtatttatttatttttaattattttgtgcagcgatgggggcgggggggggggggg ggcgcgcgccaggcggggcggggcggggcgaggggcggggcggggcgaggcggagaggtgcgg cggcagccaatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggcggc ggccctataaaaagcgaagcgcgcggcgggcgggagtcgctgcgcgctgccttcgccccgtgc cccgctccgccgccgcctcgcgccgcccgccccggctctgactgaccgcgttactcccacagg tgagcg
Best1/GRK1 tandem promoter SEQ ID NO:161	GTCGACAAATTCTGTCATTTTACTAGGGTGATGAAATTCCCAAGCAACACCATCCTTTTCAGA TAAGGGCACTGAGGCTGAGAGAGGAGCTGAAACCTACCCGGGGTCACCACACACAGGTGGCAA GGCTGGGACCAGAAACCAGGACTGTTGACTGCAGCCCGGTATTCATTCTTTCCATAGCCCACA GGGCTGTCAAAGACCCCAGGGCCTAGTCAGAGGCTCCTCCTTCCTGGAGAGTTCCTGGCACAG AAGTTGAAGCTCAGCACAGCCCCCTAACCCCCAACTCTCTCTGCAAGGCCTCAGGGGTCAGAA CACTGGTGGAGCAGATCCTTTAGCCTCTGGATTTTAGGGCCATGGTAGAGGGGGTGTTGCCCT AAATTCCAGCCCTGGTCTCAGCCCAACACCCTCCAAGAAGAAATTAGAGGGGCCATGGCCAGG CTGTGCTAGCCGTTGCTTCTGAGCAGATTACAAGAAGGGACTAAGACAAGGACTCCTTTGTGG AGGTCCTGGCTTAGGGAGTCAAGTGACGGCGGCTCAGCACTCACGTGGGCAGTGCCAGCCTCT AAGAGTGGGCAGGGGCACTGGCCACAGAGTCCCAGGGAGTCCCACCAGCCTAGTCGCCAGAtC TAGAGGGCCCCAGAAGCCTGGTGGTTGTTTGTCCTTCTCAGGGGAAAAGTGAGGCGGCCCCTT GGAGGAAGGGGCCGGGCAGAAGATCTAATCGGATTCCAAGCAGCTCAGGGGATTGTCTTTTTC TAGCACCTTCTTGCCACTCCTAAGCGTCCTCCGTGACCCCGGCTGGGATTTAGCCTGGTGCTG TGTCAGCCCCGGGCTCCCAGGGGCTTCCCAGTGGTCCCCAGGAACCCTCGACAGGGCCAGGGC GTCTCTCTCGTCCAGCAAGGGCAGGGACGGGCCACAGGCCAAGGGCCTTAAGC

Table 1a. Other regulatory sequences

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Tandem (2) ApoE Enhancers SEQ ID NO:138	aggctcagaggcacacaggagtttctgggctcaccctgccccccttccaaccc ctcagttcccatcctccagcagctgtttgtgtgctgcctctgaagtccacac tgaacaaacttcagcctactcatgtccctaaaatgggcaaacattgcaagca gcaaacagcaaacacacagccctccctgcctgctgaccttggagctggggca gaggtcagagacctctctgggcccatgccacctccaacatccactcgacccc ttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagt gtgagagggtctagaaggctcagaggcacacaggagtttctgggctcaccct gccccccttccaaccccctcagttcccatcctccagcagctgtttgtgtgctgc ctctgaagtccacactgaacaaacttcagcctactcatgtccctaaaatggg

	caaacattgcaagcagcaaacagcaaacacacagccctccctgcctgctgac cttggagctggggcagaggtcagagacctctctg
hAAT Promoter SEQ ID NO:139	gatcttgctaccagtggaacagccactaaggattctgcagtgagagcagagg gccagctaagtggtactctcccagagactgtctgactcacgccacccccctcc accttggacacaggacgctgtggtttctgagccaggtacaatgactcctttc ggtaagtgcagtggaagctgtacactgcccaggcaaagcgtccgggcagcgt aggcgggcgactcagatcccagccagtggacttagcccctgtttgctcctcc gataactggggtgaccttggttaatattcaccagcagcctccccgttgccc ctctggatccactgcttaaatacggacgaggacagggccctgtctcctcagc ttcaggcaccaccactgacctgggacagt
hAAT(ΔATG) Promoter SEQ ID NO:140	gatcttgctaccagtggaacagccactaaggattctgcagtgagagcagagg gccagctaagtggtactctcccagagactgtctgactcacgccacccccctcc accttggacacaggacgctgtggtttctgagccaggtacagtgactcctttc ggtaagtgcagtggaagctgtacactgcccaggcaaagcgtccgggcagcgt aggcgggcgactcagatcccagccagtggacttagcccctgtttgctcctcc gataactggggtgaccttggttaatattcaccagcagcctccccgttgccc ctctggatccactgcttaaatacggacgaggacagggccctgtctcctcagc ttcaggcaccaccactgacctgggacagt
Mck Enhancer (MckE) SEQ ID NO:141	ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccg agatgcctggttataattaacccagacatgtggctgccccccccccccccccaa cacctgctgcctctaaaaataaccctgtccctggtggatc
Tandem (2) Mck Enhancers (2 MckE) SEQ ID NO:142	ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccg agatgcctggttataattaacccagacatgtggctgccccccccccccccccaa cacctgctgcctctaaaaataaccctgtccctggtggatcccactacgggtt taggctgcccatgtaaggaggcaaggcctggggacacccgagatgcctggtt ataattaacccagacatgtggctgccccccccccccccccaacacctgctgcct ctaaaaataaccctgtccctggtggatc
Tandem Mck (3) Enhancers (3 MckE) SEQ ID NO:143	ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccg agatgcctggttataattaacccagacatgtggctgccccccccccccccccaa cacctgctgcctctaaaaataaccctgtccctggtggatcccactacgggtt taggctgcccatgtaaggaggcaaggcctggggacacccgagatgcctggtt ataattaacccagacatgtggctgccccccccccccccccaacacctgctgcct ctaaaaataaccctgtccctggtggatcccactacgggtttaggctgcccat gtaaggaggcaaggcctggggacacccgagatgcctggttataattaaccca gacatgtggctgccccccccccccccccaacacctgctgcctctaaaaataacc ctgtccctggtggatc
Myosin heavy chain enhancer (MhcE) SEQ ID NO:144	cccttcagattaaaaataactgaggtaagggcctgggtaggggaggtggtgt gagacgctcctgtctctcctctatctgcccatcggcccttttggggaggagga atgtgcccaaggactaaaaaaaggccatggagccagaggggcgagggcaaca gacctttcatgggcaaaccttggggccctgctgaagctttggc

[0085] In certain embodiments, the viral vectors provided herein comprise one or more regulatory elements other than a promoter. In certain embodiments, the viral vectors provided herein comprise an enhancer. In certain embodiments, the viral vectors provided herein comprise a repressor. In certain embodiments, the viral vectors provided herein comprise an intron (e.g. VH4 intron (SEQ ID NO:57) or a chimeric intron (SEQ ID NO:56). The viral vectors may also include a Kozak sequence to promote translation of the transgene product, for example GCCACC.

[0086] In certain embodiments, the viral vectors provided herein comprise a polyadenylation sequence downstream of the coding region of the transgene. Any polyA site that signals termination of transcription and directs the synthesis of a polyA tail is suitable for use in AAV vectors of the present disclosure. Exemplary polyA signals are derived from, but not limited to, the following: the SV40 late gene, the rabbit β-globin gene (SEQ ID NO:55), the bovine growth hormone (BPH) gene, the human growth hormone (hGH) gene, the synthetic polyA (SPA) site, and the bovine growth hormone (bGH) gene. *See*, *e.g.*, Powell and Rivera-Soto, 2015, *Discov. Med.*, 19(102):49-57.

[0087] Provided are gene expression cassettes and rAAVs comprising gene expression cassettes in which expression of the transgene is controlled by engineered nucleic acid regulatory elements that have more than one regulatory element (promoter or enhancer).

5.2.4 Signal Peptides

[0088] In certain embodiments, the vectors provided herein comprise components that modulate protein delivery. In certain embodiments, the viral vectors provided herein comprise one or more signal peptide encoding nucleotide sequences that are fused to the nucleotide sequence encoding the anti-TNFα Fc fusion protein such that the protein expressed from the transgene has the signal sequence at the N-terminus to direct secretion. Signal peptides may also be referred to herein as "leader sequences" or "leader peptides". In certain embodiments, the signal peptides allow for the transgene product to achieve the proper packaging (*e.g.*, glycosylation) in the cell. In certain embodiments, the signal peptides allow for the transgene product to achieve the proper localization in the cell. In certain embodiments, the signal peptides allow for the transgene product to achieve secretion from the cell.

[0089] There are two general approaches to select a signal sequence for protein production in a gene therapy context or in cell culture. One approach is to use a signal peptide from proteins homologous to the protein being expressed. For example, a human antibody signal peptide may be used to express IgGs in CHO or other cells. Another approach is to identify signal peptides optimized for the particular host cells used for expression. Signal peptides may be interchanged between different proteins or even between proteins of different organisms, but usually the signal sequences of the most abundant secreted proteins of that cell type are used for protein expression. For example, the signal peptide of human albumin, the most abundant protein in plasma, was found to substantially increase protein production yield in CHO cells. However, certain signal peptides may retain function and exert activity after being cleaved from the expressed protein as "post-targeting functions". Thus, in specific embodiments, the signal peptide is selected from signal peptides of the most abundant proteins secreted by the cells used for expression to avoid the post-targeting functions. In a certain embodiment, the signal sequence is fused to both the heavy and light chain sequences. An exemplary sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO:62) which can be encoded by a nucleotide sequence of SEQ ID NO:63 (see Table 2, FIGs. 2A and B). Alternatively, signal sequences that are appropriate for expression, and may cause selective expression or directed expression of the HuPTM anti-TNFα Fc fusion protein in eye (ocular tissues) are provided in Table 2 below. Also provided are signal sequences active in liver (Table 3) and muscle (Table 4) cells.

Table 2. Signal peptides for expression in eye

Signal Peptide Origin	SEQ ID NO:	Sequence
Mutant interleukin 2 signal peptide	62	MYRMQLLLLIALSLALVTNS
Mutant interleukin 2 signal peptide coding sequence	63	atgtataggatgcaactgctcctcctgattgctctgagcctggctcttgtgaccaactct
VEGF-A signal peptide	64	MNFLLSWVHWSLALLLYLHHAKWSQA
Fibulin-1 signal peptide	65	MERAAPSRRVPLPLLLLGGLALLAAGVDA
Vitronectin signal peptide	66	MAPLRPLLILALLAWVALA
Complement Factor H signal peptide	67	MRLLAKIICLMLWAICVA
Opticin signal peptide	68	MRLLAFLSLLALVLQETGT
Albumin signal peptide	69	MKWVTFISLLFLFSSAYS
Chymotrypsinogen signal peptide	70	MAFLWLLSCWALLGTTFG
Interleukin-2 signal peptide	71	MYRMQLLSCIALILALVTNS
Trypsinogen-2 signal peptide	72	MNLLLILTFVAAAVA

Table 3. Signal peptides for expression in liver cells.

Signal Peptide Origin	SEQ ID NO:	Sequence
Human Serum albumin	73	MKWVTFISLLFLFSSAYS
Human α-1 Antitrypsin (SERPINA1)	74	MPSSVSWGILLLAGLCCLVPVSLA
Human Apolipoprotein A-1	75	MKAAVLTLAVLFLTGSQA
Human Apolipoprotein A-2	76	MKLLAATVLLLTICSLEG
Human Apolipoprotein B-100	77	MDPPRPALLALLALPALLLLLLAGARA

Signal Peptide Origin	SEQ ID NO:	Sequence
Human Coagulation Factor IX	78	MQRVNMIMAESPGLITICLLGYLLSAEC
Human Complement C2	79	MGPLMVLFCLLFLYPGLADS
Human Complement Factor H-related Protein 2 (CFHR2)	80	MWLLVSVILISRISSVGG
Human Complement Factor H-related Protein 5 (CFHR5)	81	MLLLFSVILISWVSTVGG
Human Fibrinogen α-chain (FGA)	82	MFSMRIVCLVLSVVGTAWT
Human Fibrinogen β-chain (FGB)	83	MKRMVSWSFHKLKTMKHLLLLLLCVFLVKS
Human Fibrinogen γ-chain (FGG)	84	MSWSLHPRNLILYFYALLFLSSTCVA
Human α-2-HS-Glycoprotein (AHSG)	85	MKSLVLLLCLAQLWGCHS
Human Hemopexin (HPX)	86	MARVLGAPVALGLWSLCWSLAIA
Human Kininogen-1	87	MKLITILFLCSRLLLSLT
Human Mannose-binding protein C (MBL2)	88	MSLFPSLPLLLLSMVAASYS
Human Plasminogen (PLMN)	89	MEHKEVVLLLLFLKSGQG
Human Prothrombin (Coagulation Factor II)	90	MAHVRGLQLPGCLALAALCSLVHS
Human Secreted Phosphoprotein 24	91	MISRMEKMTMMMKILIMFALGMNYWSCSG
Human Anti-thrombin-III (SERPINC1)	92	MYSNVIGTVTSGKRKVYLLSLLLIGFWDCVTC
Human Serotransferrin (TF)	93	MRLAVGALLVCAVLGLCLA

Table 4. Signal peptides for expression in muscle cells.

Signal Peptide Origin	**SEQ ID NO:**	**Sequence**
Human SPARC	94	MRAWIFFLLCLAGRALA
Human Collagen alpha-1(I) chain	95	MFSFVDLRLLLLLAATALLTHG
Human Lactotransferrin	96	MKLVFLVLLFLGALGLCLA
Human Complement C3	97	MGPTSGPSLLLLLLTHLPLALG
Human Lumican	98	MSLSAFTLFLALIGGTSG
Human Gelsolin isoform 1	99	MAPHRPAPALLCALSLALCALSLPVRA
Human Pro-cathepsin H	100	MWATLPLLCAGAWLLGVPVCGA
Human SERPINF1	101	MQALVLLLCIGALLGHSSC
Human SERPINE1	102	MQMSPALTCLVLGLALVFGEGSA
Human Cathepsin D	103	MQPSSLLPLALCLLAAPASA
Human TIMP1	104	MAPFEPLASGILLLLWLIAPSRA
Human Fibronectin	105	MLRGPGPGLLLLAVQCLGTAVPSTGASKSKR
Human Complement C1s subcomponent	106	MWCIVLFSLLAWVYA
Human Cathepsin L1	107	MNPTLILAAFCLGIASA
Human Cathepsin B	108	MWQLWASLCCLLVLANA
Human Salivary acidic proline-rich phosphoprotein ½	109	MLLILLSVALLAFSSA
Human Follistatin-related protein 1	110	MWKRWLALALALVAVAWVRA

5.2.5 Untranslated regions

[0090] In certain embodiments, the viral vectors provided herein comprise one or more untranslated regions (UTRs), *e.g.*, 3' and/or 5' UTRs. In certain embodiments, the UTRs are optimized for the desired level of protein expression. In certain embodiments, the UTRs are optimized for the mRNA half-life of the transgene. In certain embodiments, the UTRs are optimized for the stability of the mRNA of the transgene. In certain embodiments, the UTRs are optimized for the secondary structure of the mRNA of the transgene.

5.2.6 Inverted terminal repeats

[0091] In certain embodiments, the viral vectors provided herein comprise one or more inverted terminal repeat (ITR) sequences. ITR sequences may be used for packaging the recombinant

gene expression cassette into the virion of the viral vector. In certain embodiments, the ITR is from an AAV, *e.g.*, AAV8 or AAV2 (*see, e.g.*, Yan et al., 2005, J. Virol., 79(1):364-379; United States Patent No. 7,282,199 B2, United States Patent No. 7,790,449 B2, United States Patent No. 8,318,480 B2, United States Patent No. 8,962,332 B2 and International Patent Application No. PCT/EP2014/076466, each of which is incorporated herein by reference in its entirety). In preferred embodiments, nucleotide sequences encoding the ITRs may, for example, comprise the nucleotide sequences of SEQ ID NOS:58 (5'-ITR) or 60 (3'-ITR). In certain embodiments, the modified ITRs used to produce self-complementary vector, *e.g.*, scAAV, may be used (*see, e.g.*, Wu, 2007, Human Gene Therapy, 18(2):171-82, McCarty et al, 2001, Gene Therapy, Vol 8, Number 16, Pages 1248-1254; and U.S. Patent Nos. 6,596,535; 7,125,717; and 7,456,683, each of which is incorporated herein by reference in its entirety). In preferred embodiments, nucleotide sequences encoding the modified ITRs may, for example, comprise the nucleotide sequences of SEQ ID NOS:58 (5'-ITR) or 60 (3'-ITR) or modified for scAAV, SEQ ID NO:59 (m 5'ITR) or SEQ ID NO:61 (m 3' ITR).

5.2.7 Transgenes

[0092] The transgenes encode a HuPTM anti-TNFα Fc fusion protein, e.g. a TNFR1:Fc fusion protein or TNFR2:Fc fusion protein, based upon a therapeutic anti-TNFα Fc fusion protein disclosed herein. In specific embodiments, the HuPTM anti-TNFα Fc fusion protein is engineered to contain additional glycosylation sites on the TNFR and/or Fc domain. In addition, the Fc domain of the anti-TNFα Fc fusion protein may be engineered to alter the glycosylation site at N297 to prevent glycosylation at that site (for example, a substitution at N297 for another amino acid and/or a substitution at T297 for a residue that is not a T or S to knock out the glycosylation site). Such Fc domains are "aglycosylated".

5.2.7.1 Constructs for Expression of HuPTM TNFR:Fc Fusion Proteins

[0093] In certain embodiments, the transgene encodes an anti-TNFa fusion protein, wherein the anti-TNFα Fc fusion protein comprises a soluble, extracellular portion of human TNFα receptor

type I (TNFR1) or type II (TNFR2) covalently linked, such as through a peptide bond, to polypeptide containing an Fc domain of an immunoglobulin heavy chain.

[0094] In certain embodiments, the transgene encodes all or a TNFα-binding portion of the extracellular domain of the TNFR2 (SEQ ID NO: 2) fused to all or a portion of an Fc domain (including, for example, the hinge, CH2 and CH3 domains) of an immunoglobulin heavy chain (SEQ ID NO: 3 or 4). In preferred embodiments, the transgene encodes an anti-TNFα Fc fusion protein, wherein the anti-TNFα Fc fusion protein comprises human soluble, extracellular domain of TNFR2 covalently linked, such as through a peptide bond, to the Fc domain of human IgG1 (including heavy chain CH2, and heavy chain CH3, and the hinge region) that upon expression associate to form a dimeric TNFR2:Fc fusion protein. In particular, the anti-TNFα Fc fusion protein is etanercept (having the amino acid sequence of SEQ ID NO: 10 or 11 with leader sequence) or any biosimilar form of etanercept, including etanercept-szzs (ERELZI®) and etantercept-ykro (ETICOVO®).

[0095] In other embodiments, the transgene encodes all or part of the soluble extracellular domain of the TNFR1 (SEQ ID NO: 1) fused to all or part of an immunoglobulin heavy chain Fc domain (SEQ ID NO: 6 or 7). In preferred embodiments, the transgene encodes an anti-TNFα Fc fusion protein, wherein the anti-TNFα Fc fusion protein comprises human soluble, extracellular domain of TNFR1 covalently linked, such as through a peptide bond, to the Fc portion of human IgG1 (including heavy chain CH2, and heavy chain CH3, and the hinge region), that upon expression associate to form a dimeric TNFR1:Fc fusion protein (SEQ ID NO: 12). In some embodiments, TNFR1 is fused to the Fc domain via a thrombin cleavage site LVPRGS (SEQ ID NO:8). In certain embodiments the anti-TNFα Fc fusion protein is EYS060 (having an amino acid sequence of SEQ ID NO: 12). .

[0096] The recombinant AAV constructs express the HuPTM anti-TNFα Fc fusion protein in a cell, cell culture, or in a subject. The nucleotide sequences encoding the soluble extracellular domain of the TNFR and Fc domains may be codon optimized for expression in human cells and have reduced incidence of CpG dimers in the sequence to promote expression in human cells. In preferred embodiments, the transgenes encode any of the therapeutic anti-TNFα Fc fusion proteins disclosed

herein, for example, the TNFR:Fc fusion depicted in FIG. 1 or 2 (sequences provided in FIGS 2A and 2B) herein.

[0097] In certain embodiments, the Fc domain is an IgG Fc domain, but in other embodiments, the Fc region may be an IgA, IgD, IgE, or IgM. The Fc fusion protein expressed from the transgene may have an IgG1, IgG2, IgG3, or IgG4 Fc domain, but is preferably derived from human IgG1. The Fc domain can include some or all of the heavy chain CH1, hinge, CH2, and CH3 domains described herein (see FIG. 4 and Table 5) or fragments or variants thereof.

[0098] The Fc domain of the Fc fusion protein has one or more effector functions that vary with the antibody isotype. The effector functions can be the same as that of the wild-type or the therapeutic Fc fusion protein or can be modified therefrom to add, enhance, modify, or inhibit one or more effector functions using the Fc modifications disclosed in Section 5.2.8, infra. In certain embodiments, the HuPTM non-monoclonal antibody transgene encodes a fusion protein comprising an Fc polypeptide comprising an amino acid sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence set forth in the Fc domain polypeptides of the therapeutic fusion protein described herein as set forth in Table 6 for etanercept or an exemplary Fc domain of an IgG1, IgG2 or IgG4 isotype as set forth in Table 5. In some embodiments, the HuPTM fusion protein comprises an Fc polypeptide or a sequence that is a variant of the Fc polypeptide sequence in Table 5 in that the sequence has been modified with one or more of the techniques described in Section 5.2.8 *infra*, to alter the Fc polypeptide's effector function.

[0099] The recombinant AAV constructs express the HuPTM anti-TNFα Fc fusion protein in a cell, cell culture, or in a subject. The nucleotide sequences encoding the anti-TNFα Fc fusion protein may be codon optimized for expression in human cells and have reduced incidence of CpG dimers in the sequence to promote expression in human cells. In preferred embodiments, the transgene encodes any of the therapeutic anti-TNFα Fc fusion protein disclosed herein, for example, the therapeutic anti-TNFα Fc fusion protein etanercept or EYS606 depicted in **FIGS. 2A and 2B** herein and including, in certain embodiments, the associated Fc domain provided in Table 6 or, alternatively in Table 5. The Fc domain is further discussed in Section 5.2.8. Exemplary Fc domain sequences are provided in Table 6, as well as in FIG. 3 and Table 5. FIG. 2A provides the amino acid sequence of TNFR2:Fc fusion

etanercept and FIG. 2B provides the amino acid sequence of TNFR1:Fc fusion EYS606 (see also Table 6).

[0100] In some embodiments, the transgene for expression of an anti-TNFα Fc fusion protein may comprises a nucleotide sequence encoding a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked, such as through a peptide bond, to polypeptide containing an Fc domain of an immunoglobulin heavy chain as described further herein. In some embodiments, TNFR1 is fused to the Fc domain via a thrombin cleavage site (SEQ ID NO:8).

[0101] Nucleotide sequences encoding the soluble extracellular domain of TNFR1 or TNFR2, optionally the thrombin cleavage site, the hinge region, and the IgG1 Fc chain (CH2 + CH3) of a therapeutic anti-TNFα Fc fusion protein as disclosed herein are provided in Table 7. In certain embodiments, these nucleotide sequences are codon optimized for expression in human cells. See for example, the codon optimized sequences of etanercept (SEQ ID NOs 15-18) of Table 7.

[0102] The transgene may include the portion of the hinge region that forms interchain di-sulfide bonds (*e.g.*, the portion containing the sequence CPPCPA (SEQ ID NO:153). Fc domain sequences that do not contain portion of the hinge region comprising the sequence CCPCPA (SEQ ID NO:153) will not form intrachain disulfide bonds, whereas those Fc fusion domain sequences with a portion of the hinge region at the C-terminus containing the sequence CPPCPA (SEQ ID NO:153) will form intrachain disulfide bonds and, thus, will form dimeric fusion proteins fragments. In some embodiments, the hinge contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:145), and specifically, EPKSCDKTHL (SEQ ID NO:146), EPKSCDKTHT (SEQ ID NO:147), EPKSCDKTHTCPPCPA (SEQ ID NO:148), EPKSCDKTHLCPPCPA (SEQ ID NO:149), DKTHTCPPCPAPELLGG (SEQ ID NO:21), DKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:152), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:150) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:151) .

[0103] In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a constitutive or inducible (e.g., hypoxia-inducible or rifamycin-inducible) promoter sequence or a tissue specific promoter/regulatory region, for example, one of the regulatory regions provided in Table 1 or Table1a, particularly a promoter that promotes ocular tissue specific expression and b) a sequence encoding the transgene (*e.g.*, an anti-TNFα Fc fusion protein).

In certain embodiments, the sequence comprising the transgene encodes an anti-TNFα Fc fusion protein comprising a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked, such as through a peptide bond, to polypeptide containing an Fc domain of an immunoglobulin heavy chain. In certain embodiments, the sequence comprising the transgene encodes a signal sequence at the N-terminus of the anti-TNFα Fc fusion protein that directs secretion and post translational modification in said human ocular cells. In other embodiments, the sequence encodes for a transgene product having an amino acid sequence of SEQ ID NO: 10, 11 or 12. In preferred embodiments, the anti-TNFα fusion protein is etanercept or EYS606.

[0104] In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a constitutive or an inducible promoter sequence or a tissue specific promoter, such as one of the promoters or regulatory regions in Table 1 and 1a, and b) a sequence encoding the transgene (*e.g.*, an anti-TNFα Fc fusion protein), wherein the transgene comprises a signal peptide, a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked, such as through a peptide bond, to polypeptide comprising an Fc domain of an immunoglobulin heavy chain to form an anti-TNFα Fc fusion protein. In other embodiments, the viral vectors provided herein have the following elements in the following order: a) a ocular tissue-specific promoter listed in Table 1 and 1a, and b) a sequence encoding the transgene comprising a signal peptide, wherein the transgene comprises a signal peptide, a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked, such as through a peptide bond, to polypeptide containing an Fc domain of an immunoglobulin heavy chain to form anti-TNFα Fc fusion protein. In specific embodiments, the viral vectors provided herein comprise further a thrombin cleavage site linked to the C-terminus of the TNFR domain having amino acid sequence of LSPRGS (SEQ ID NO:158).

[0105] In specific embodiments, provided are AAV vectors comprising a viral capsid that is at least 95% identical to the amino acid sequence of an AAV2.7m8 capsid, AAV8 capsid, an AAV3B capsid, or an AAVrh73 capsid (see FIG. 3); and an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding an anti-TNFα Fc fusion protein; operably linked to one or more regulatory sequences that control expression of the transgene in one or more ocular tissues.

[0106] The rAAV vectors that encode and express the therapeutic fusion protein may be administered to treat or prevent or ameliorate symptoms of a disease or condition amenable to treatment, prevention or amelioration of symptoms with the therapeutic fusion protein. Also provided are methods of expressing HuPTM anti-TNFα Fc fusion protein in human cells using the rAAV vectors and constructs encoding them.

5.2.8 Fc Region Modifications

[0107] In certain embodiments, the transgenes encode anti-TNFα Fc fusion proteins that associate to form a dimeric Fc fusion protein. Accordingly, the transgenes comprise nucleotide sequences that encode, for example, the soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked, such as through a peptide bond, to polypeptide containing an Fc domain of an immunoglobulin heavy chain (FIGS. 2A and 2B), including all or a portion of the hinge region of the heavy chain and N-terminal of the Fc domain peptide. Table 6 provides the amino acid sequences of the Fc polypeptides for certain of the therapeutic anti-TNFα Fc fusion proteins described herein. Alternatively, an IgG2, or IgG4 Fc domain, the sequences of which are provided in FIG. 4 and provided in Table 5 may be utilized. As detailed, the transgene may comprise a nucleotide sequence encoding the Fc domain polypeptide for the therapeutic anti-TNFα Fc fusion protein linked to the nucleotide sequence encoding the soluble, extracellular portion of human TNFR at the N-terminus of the hinge region as provided herein (with the amino acid sequences provided in FIG. 2A and 2B and Table 6).

[0108] The term "Fc region" refers to a dimer of two "Fc polypeptides" (or “Fc domains”), each "Fc polypeptide" comprising the heavy chain constant region of an antibody excluding the first constant region immunoglobulin domain. In some embodiments, an "Fc region" includes two Fc polypeptides linked by one or more disulfide bonds, chemical linkers, or peptide linkers. "Fc polypeptide" refers to at least the last two constant region immunoglobulin domains of IgA, IgD, and IgG, or the last three constant region immunoglobulin domains of IgE and IgM and may also include part or all of the flexible hinge N-terminal to these domains. For IgG, e.g., "Fc polypeptide" comprises immunoglobulin domains Cgamma2 (Cγ2, often referred to as CH2 domain) and Cgamma3 (Cγ3, also referred to as CH3 domain) and may include the lower part of the hinge domain between Cgamma1 (Cγ1, also referred to as CH1 domain) and CH2 domain. Although the boundaries of the Fc

polypeptide may vary, the human IgG heavy chain Fc polypeptide is usually defined to comprise residues starting at T223 or C226 or P230, to its carboxyl-terminus, wherein the numbering is according to the EU index as in Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Services, Springfield, Va.). For IgA, e.g., Fc polypeptide comprises immunoglobulin domains Calpha2 (Cα2) and Calpha3 (Cα3) and may include the lower part of the hinge between Calpha1 (Cα1) and Cα2.

[0109] In certain embodiments, the Fc polypeptide is that of etanercept or EYS606 (see Table 6). In other embodiments, the Fc polypeptide is an IgG Fc polypeptide. The Fc polypeptide may be from the IgG1, IgG2, or IgG4 isotype (see FIG 4 for alignment of IgG1, IgG2 and IgG4 Fc domain sequences, numbered according to EU numbering) or may be an IgG3 Fc domain, depending, for example, upon the desired effector activity of the therapeutic antibody. In some embodiments, the engineered heavy chain constant region (CH), which includes the Fc domain, is chimeric. As such, a chimeric CH region combines CH domains derived from more than one immunoglobulin isotype and/or subtype. For example, the chimeric (or hybrid) CH region comprises part or all of an Fc region from IgG, IgA and/or IgM. In other examples, the chimeric CH region comprises part or all a CH2 domain derived from a human IgG1, human IgG2, or human IgG4 molecule, combined with part or all of a CH3 domain derived from a human IgG1, human IgG2, or human IgG4 molecule. In other embodiments, the chimeric CH region contains a chimeric hinge region.

TABLE 5. Table of Fc Domain Amino Acid Sequences

Fc domains	Chain/ SEQ ID NO.	Sequence
IgG1	47	*EPKSCDKTHTCPPCPAPELLGGPSVFL*FPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
IgG2	48	*ERKCCVECPPCPAPPVAGPSVFL*FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKT ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKT TPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
IgG4	49	*ESKYGPPCPSCPAPEFLGGPSVFL*FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

[0110] In some embodiments, the recombinant vectors encode therapeutic Fc fusions comprising an engineered (mutant) Fc regions, *e.g.* engineered Fc regions of an IgG constant region. Modifications to an antibody constant region, Fc region or Fc fragment of an IgG antibody may alter one or more effector functions such as Fc receptor binding or neonatal Fc receptor (FcRn) binding and thus half-life, CDC activity, ADCC activity, and/or ADPC activity, compared to a corresponding antibody having a wild-type IgG constant region, or an IgG heavy chain constant region without the recited modification(s). Accordingly, in some embodiments, the antibody may be engineered to provide an antibody constant region, Fc region or Fc fragment of an IgG antibody that exhibits altered binding (as compared to a reference or wild-type constant region without the recited modification(s)) to one or more Fc receptors (e.g., FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, FcγRIIIB, FcγRIV, or FcRn receptor). In some embodiments, the antibody an antibody constant region, Fc region or Fc fragment of an IgG antibody that exhibits a one or more altered effector functions such as CDC, ADCC, or ADCP activity, compared to a corresponding antibody having a wild-type IgG constant region, or an IgG constant without the recited modification(s).

[0111] "Effector function" refers to a biochemical event that results from the interaction of an antibody Fc region with an Fc receptor or ligand. Effector functions include FcγR-mediated effector functions such as ADCC and ADCP and complement-mediated effector functions such as CDC.

[0112] An "effector cell" refers to a cell of the immune system that expresses one or more Fc receptors and mediates one or more effector functions. Effector cells include but are not limited to monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and T cells, and may be from any organism including but not limited to humans, mice, rats, rabbits, and monkeys.

[0113] "ADCC" or "antibody dependent cell-mediated cytotoxicity" refers to the cell-mediated reaction wherein nonspecific cytotoxic effector (immune) cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell.

[0114] "ADCP" or “antibody dependent cell-mediated phagocytosis” refers to the cell-mediated reaction wherein nonspecific cytotoxic effector (immune) cells that express FcγRs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell.

[0115] "CDC" or "complement-dependent cytotoxicity" refers to the reaction wherein one or more complement protein components recognize bound antibody on a target cell and subsequently cause lysis of the target cell.

[0116] In some embodiments, the modifications of the Fc domain include, but are not limited to, the following modifications and combinations thereof, with reference to EU numbering of an IgG constant region (see FIG. 4): 233, 234, 235, 236, 237, 238, 239, 248, 249, 250, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 297, 298, 301, 303, 305, 307, 308, 309, 311, 312, 315, 318, 320, 322, 324, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 337, 338, 339, 340, 342, 344, 356, 358, 359, 360, 361, 362, 373, 375, 376, 378, 380, 382, 383, 384, 386, 388, 389, 398, 414, 416, 419, 428, 430, 433, 434, 435, 437, 438, and 439.

[0117] In certain embodiments, the Fc region comprises an amino acid addition, deletion, or substitution of one or more of amino acid residues 251-256, 285-290, 308-314, 385-389, and 428-436 of the IgG. In some embodiments, 251-256, 285-290, 308-314, 385-389, and 428-436 (EU numbering of Kabat; see FIG. 4) is substituted with histidine, arginine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, or glutamine. In some embodiments, a non-histidine residue is substituted with a histidine residue. In some embodiments, a histidine residue is substituted with a non-histidine residue.

[0118] Enhancement of FcRn binding by an antibody having an engineered Fc leads to preferential binding of the affinity-enhanced antibody to FcRn as compared to antibody having wild-type Fc, and thus leads to a net enhanced recycling of the FcRn-affinity-enhanced antibody, which results in further increased antibody half-life. An enhanced recycling approach allows highly effective targeting and clearance of antigens, including e.g. "high titer" circulating antigens, such as C5, cytokines, or bacterial or viral antigens.

[0119] Provided in certain embodiments are modified constant region, Fc region or Fc fragment of an IgG antibody with enhanced binding to FcRn in serum as compared to a wild-type Fc region (without engineered modifications). In some instances, antibodies, e.g. IgG antibodies, are engineered to bind to FcRn at a neutral pH, *e.g.*, at or above pH 7.4, to enhance pH-dependence of binding to FcRn as compared to a wild-type Fc region (without engineered modifications). In some

instances, antibodies, e.g. IgG antibodies, are engineered to exhibit enhanced binding (e.g. increased affinity or K_D) to FcRn in endosomes (*e.g.*, at an acidic pH, *e.g.*, at or below pH 6.0) relative to a wild-type IgG and/or reference antibody binding to FcRn at an acidic pH, as well as in comparison to binding to FcRn in serum (*e.g.*, at a neutral pH, e.g., at or above pH 7.4). Provided are antibodies with an engineered antibody constant region, Fc region or Fc fragment of an IgG antibody that exhibits an improved serum or resident tissue half-life, compared to a corresponding antibody having a wild-type IgG constant region, or an IgG constant without the recited modification(s);

[0120] Non-limiting examples of such Fc modifications include, *e.g.*, a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., LN/Y/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (e.g., H/F or Y); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (e.g., 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (e.g., M428L) and 434S (e.g., N434S) modification; a 428L, 2591 (e.g., V2591), and 308F (e.g., V308F) modification; a 433K (e.g., H433K) and a 434 (e.g., 434Y) modification; a 252, 254, and 256 (e.g., 252Y, 254T, and 256E) modification; a 250Q and 428L modification (e.g., T250Q and M428L); and a 307 and/or 308 modification (e.g., 308F or 308P) (EU numbering; see FIG 4).

[0121] In some embodiments, the Fc region can be a mutant form such as hIgG1 Fc including M252 mutations, e.g. M252Y and S254T and T256E ("YTE mutation") exhibit enhanced affinity for human FcRn (Dall'Acqua, et al., 2002, J Immunol 169:5171-5180) and subsequent crystal structure of this mutant antibody bound to hFcRn resulting in the creation of two salt bridges (Oganesyan, et al. 2014, JBC 289(11): 7812–7824). Antibodies having the YTE mutation have been administered to monkeys and humans, and have significantly improved pharmacokinetic properties (Haraya, et al., 2019, Drug Metabolism and Pharmacokinetics, 34(1):25-41).

[0122] In some embodiments, modifications to one or more amino acid residues in the Fc region may reduce half-life in systemic circulation (serum), however result in improved retainment in tissues (e.g. in the eye) by disabling FcRn binding (e.g. H435A, EU numbering of Kabat) (Ding et al., 2017, MAbs 9:269-284; and Kim, 1999, Eur J Immunol 29:2819).

[0123] In some embodiments, the Fc domain may be engineered to activate all, some, or none of the normal Fc effector functions, without affecting the Fc polypeptide's (e.g. antibody's) desired

pharmacokinetic properties. Fc polypeptides having altered effector function may be desirable as they may reduce unwanted side effects, such as activation of effector cells, by the therapeutic protein.

[0124] Methods to alter or even ablate effector function may include mutation(s) or modification(s) to the hinge region amino acid residues of an antibody. For example, IgG Fc domain mutants comprising 234A, 237A, and 238S substitutions, according to the EU numbering system, exhibit decreased complement dependent lysis and/or cell mediated destruction. Deletions and/or substitutions in the lower hinge, e.g. where positions 233-236 within a hinge domain (EU numbering) are deleted or modified to glycine, have been shown in the art to significantly reduce ADCC and CDC activity.

[0125] In specific embodiments, the Fc domain is an aglycosylated Fc domain that has a substitution at residue 297 or 299 to alter the glycosylation site at 297 such that the Fc domain is not glycosylated. Such aglycosylated Fc domains may have reduced ADCC or other effector activity.

[0126] Non-limiting examples of proteins comprising mutant and/or chimeric CH regions having altered effector functions, and methods of engineering and testing mutant antibodies, are described in the art, e.g. K.L. Amour, et al., Eur. J. Immunol. 1999, 29:2613–2624; Lazar et al., Proc. Natl. Acad. Sci. USA 2006, 103:4005; US Patent Application Publication No. 20070135620A1 published June 14, 2007; US Patent Application Publication No. 20080154025 A1, published June 26, 2008; US Patent Application Publication No. 20100234572 A1, published September 16, 2010; US Patent Application Publication No. 20120225058 A1, published September 6, 2012; US Patent Application Publication No. 20150337053 A1, published November 26, 2015; International Publication No. WO20/16161010A2 published October 6, 2016; U.S. 9,359,437, issued June 7,2016; and US Patent No. 10,053,517, issued August 21, 2018, all of which are herein incorporated by reference.

[0127] The C-terminal lysines (-K) conserved in the heavy chain genes of all human IgG subclasses are generally absent from antibodies circulating in serum – the C-terminal lysines are cleaved off in circulation, resulting in a heterogeneous population of circulating IgGs. (van den Bremer et al., 2015, mAbs 7:672-680). In the vectored constructs for full length mAbs, the DNA encoding the C-terminal lysine (-K) or glycine-lysine (-GK) of the Fc terminus can be deleted to

produce a more homogeneous antibody product *in situ*. (See, Hu et al., 2017 Biotechnol. Prog. 33: 786-794 which is incorporated by reference herein in its entirety).

5.2.9 Manufacture and testing of vectors

[0128] The viral vectors provided herein may be manufactured using host cells. The viral vectors provided herein may be manufactured using mammalian host cells, for example, A549, WEHI, 10T1/2, BHK, MDCK, COS1, COS7, BSC 1, BSC 40, BMT 10, VERO, W138, HeLa, 293, Saos, C2C12, L, HT1080, HepG2, primary fibroblast, hepatocyte, and myoblast cells. The viral vectors provided herein may be manufactured using host cells from human, monkey, mouse, rat, rabbit, or hamster.

[0129] The host cells are stably transformed with the sequences encoding the transgene and associated elements (*e.g.*, the vector genome), and the means of producing viruses in the host cells, for example, the replication and capsid genes (*e.g.*, the rep and cap genes of AAV). For a method of producing recombinant AAV vectors with AAV8 capsids, see Section IV of the Detailed Description of U.S. Patent No. 7,282,199 B2, which is incorporated herein by reference in its entirety. Genome copy titers of said vectors may be determined, for example, by TAQMAN® analysis. Virions may be recovered, for example, by $CsCl_2$ sedimentation.

[0130] Alternatively, baculovirus expression systems in insect cells may be used to produce AAV vectors. For a review, see Aponte-Ubillus et al., 2018, Appl. Microbiol. Biotechnol. 102:1045-1054 which is incorporated by reference herein in its entirety for manufacturing techniques.

[0131] In vitro assays, *e.g.*, cell culture assays, can be used to measure transgene expression from a vector described herein, thus indicating, *e.g.*, potency of the vector. For example, the PER.C6® Cell Line (Lonza), a cell line derived from human embryonic retinal cells, or retinal pigment epithelial cells, *e.g.*, the retinal pigment epithelial cell line hTERT RPE-1 (available from ATCC®), can be used to assess transgene expression. Once expressed, characteristics of the expressed product can be determined, including determination of the glycosylation and tyrosine sulfation patterns associated with the human glycosylated anti-TNFα Fc fusion protein. Glycosylation patterns and methods of determining the same are discussed in Section 5.4. In addition, benefits resulting from glycosylation/sulfation of the cell-expressed human glycosylated anti-TNFα Fc fusion proteins can be determined using assays known in the art, *e.g.*, the methods described in Section 5.4.

[0132] Vector genome concentration (GC) or vector genome copies can be evaluated using digital PCR (dPCR) or ddPCR™ (BioRad Technologies, Hercules, CA, USA). In one example, ocular tissue samples, such as aqueous and/or vitreous humor samples, are obtained at several timepoints. In another example, several mice are sacrificed at various timepoints post injection. Ocular tissue samples are subjected to total DNA extraction and dPCR assay for vector copy numbers. Copies of vector genome (transgene) per gram of tissue may be measured in a single biopsy sample, or measured in various tissue sections at sequential timepoints will reveal spread of AAV throughout the eye. Total DNA from collected ocular fluid or tissue is extracted with the DNeasy Blood & Tissue Kit and the DNA concentration measured using a Nanodrop spectrophotometer. To determine the vector copy numbers in each tissue sample, digital PCR is performed with Naica Crystal Digital PCR system (Stilla technologies). Two color multiplexing system is applied to simultaneously measure the transgene AAV and an endogenous control gene. In brief, the transgene probe can be labelled with FAM (6-carboxyfluorescein) dye while the endogenous control probe can be labelled with VIC fluorescent dye. The copy number of delivered vector in a specific tissue section per diploid cell is calculated as: (vector copy number)/(endogenous control)×2. Vector copy in specific cell types or tissues, such as cornea, iris, ciliary body, schlemm's canal cells, trabecular meshwork, retinal cells, RPE cells, RPE-choroid tissue, or optic nerve cells, over time may indicate sustained expression of the transgene by the tissue.

5.2.9 Compositions

[0133] Pharmaceutical compositions suitable for administration to human subjects comprise a suspension of the recombinant vector in a formulation buffer comprising a physiologically compatible aqueous buffer, a surfactant and optional excipients. Such formulation buffer can comprise one or more of a polysaccharide, a surfactant, polymer, or oil. In some embodiments, the pharmaceutical composition comprises rAAV combined with a pharmaceutically acceptable carrier for administration to a subject. In one embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant (*e.g.*, Freund's complete and incomplete adjuvant), excipient, or vehicle with which the agent is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, including, *e.g.*, peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a common carrier when the

pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Additional examples of pharmaceutically acceptable carriers, excipients, and stabilizers include, but are not limited to, buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight polypeptides; proteins, such as serum albumin and gelatin; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™ as known in the art. The pharmaceutical composition of the present invention can also include a lubricant, a wetting agent, a sweetener, a flavoring agent, an emulsifier, a suspending agent, and a preservative, in addition to the above ingredients. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like.

5.3 Methods of Treating Non-Infectious Uveitis

[0134] In another aspect, methods for treating non-infectious uveitis or other indication that can be treated with an anti-TNFα Fc Fusion protein in a subject in need thereof comprising the administration of recombinant AAV particles comprising an expression cassette encoding anti-TNFα Fc Fusion protein and variants thereof, are provided. A subject in need thereof includes a subject suffering from non-infectious uveitis, or a subject pre-disposed thereto, *e.g.*, a subject at risk of developing or having a recurrence of the non-infectious uveitis, or other indication that may be treated with anti-TNFα Fc Fusion protein. Subjects to whom such gene therapy is administered can be those responsive to anti-TNFα, e.g. etanercept, adalimumab, infliximab, or golimumab, In particular embodiments, the methods encompass treating patients who have been diagnosed with non-infectious uveitis, and, in certain embodiments, identified as responsive to treatment with an anti-TNFα Fc Fusion protein or considered a good candidate for therapy with an anti-TNFα Fc Fusion protein. In

specific embodiments, the patients have previously been treated with an anti-TNFα Fc Fusion protein. To determine responsiveness, the anti-TNFα Fc Fusion protein (e.g., produced in human cell culture, bioreactors, etc.) may be administered directly to the subject.

[0135] In specific embodiments, provided are methods of treating non-infectious uveitis or other indication amenable to treatment with an anti-TNFα Fc Fusion protein in a human subject in need thereof comprising: administering to the eye (or liver and/or muscle) of said subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding an anti-TNFα Fc Fusion protein an Fc region operably linked to one or more regulatory sequences that control expression of the transgene in human ocular tissue cells, so that a depot is formed that releases a HuPTM form of mAb or antigen-binding fragment thereof. Subretinal, intravitreal, intracamerally, or suprachoroidal administration should result in expression of the soluble transgene product in one or more of the following retinal cell types: human photoreceptor cells (cone cells, rod cells); horizontal cells; bipolar cells; amarcrine cells; retina ganglion cells (midget cell, parasol cell, bistratified cell, giant retina ganglion cell, photosensitive ganglion cell, and muller glia); and retinal pigment epithelial cells or other ocular tissue cell: cornea cells, iris cells, ciliary body cells, a schlemm's canal cells, a trabecular meshwork cells, RPE-choroid tissue cells, or optic nerve cells.

[0136] Recombinant vectors and pharmaceutical compositions for treating diseases or disorders in a subject in need thereof are described in Section 5.2. Such vectors should have a tropism for human ocular tissue, or liver and/or muscle cells and can include non-replicating rAAV, particularly those bearing an AAV2.7m8, AAV3B, AAV8, AAAV9, AAV10, AAVrh10, or AAVrh73 capsid. The recombinant vectors can be administered in any manner such that the recombinant vector enters ocular tissue cells, e.g., by introducing the recombinant vector into the eye. Such vectors should further comprise one or more regulatory sequences that control expression of the transgene in human ocular tissue cells and/or human liver and muscle cells include, but are not limited to, human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:54 or 117), a mouse cone arresting (CAR) promoter (SEQ ID NOS:114-116), a human red opsin (RedO) promoter (SEQ ID NO:112) or a Best1/GRK promoter (SEQ ID NO: 161) (see also Tables 1 and 1a).

5.4 N-GLYCOSYLATION, TYROSINE SULFATION, AND O-GLYCOSYLATION

[0137] The amino acid sequence (primary sequence) of HuPTM anti-TNFα Fc fusion proteins disclosed herein each comprises at least one site at which N-glycosylation or O-glycosylation takes place (see **FIGS. 2A and 2B**) for glycosylation positions within the amino acid sequences of the Fc fusion proteins). Post-translational modification also occurs in the Fc domain of full length antibodies, particularly at residue N297 (by EU numbering, see FIG. 4).

[0138] Alternatively, mutations may be introduced into the Fc domain to alter the glycosylation site at residue N297 (EU numbering, see FIG. 4), in particular substituting another amino acid for the asparagine at 297 or the threonine at 299 to remove the glycosylation site resulting in an aglycosylated Fc domain.

5.4.1 N-Glycosylation

Reverse Glycosylation Sites

[0139] The canonical N-glycosylation sequence is known in the art to be Asn-X-Ser (or Thr), wherein X can be any amino acid except Pro. However, it recently has been demonstrated that asparagine (Asn) residues of human antibodies can be glycosylated in the context of a reverse consensus motif, Ser(or Thr)-X-Asn, wherein X can be any amino acid except Pro. See Valliere-Douglass et al., 2009, J. Biol. Chem. 284:32493-32506; and Valliere-Douglass et al., 2010, J. Biol. Chem. 285:16012-16022. As disclosed herein, certain anti-TNFα Fc fusion proteins disclosed herein comprise canonical and/or reverse consensus sequences.

Non-Consensus Glycosylation Sites

[0140] In addition to reverse N-glycosylation sites, it recently has been demonstrated that glutamine (Gln) residues of human antibodies can be glycosylated in the context of a non-consensus motif, Gln-Gly-Thr. See Valliere-Douglass et al., 2010, J. Biol. Chem. 285:16012-16022. Surprisingly, certain of the HuGlyFab fragments disclosed herein comprise such non-consensus sequences. In addition, O-glycosylation comprises the addition of N-acetyl-galactosamine to serine or threonine residues by the enzyme. It has been demonstrated that amino acid residues present in the hinge region of antibodies can be O-glycosylated. The possibility of O-glycosylation confers another advantage to the therapeutic anti-TNFα Fc fusion proteins provided herein, as compared to, *e.g.*, antigen-binding fragments produced in *E. coli*, again because the *E. coli* naturally does not contain

machinery equivalent to that used in human O-glycosylation. (Instead, O-glycosylation in *E. coli* has been demonstrated only when the bacteria is modified to contain specific O-glycosylation machinery. See, e.g., Farid-Moayer et al., 2007, J. Bacteriol. 189:8088-8098.)

Engineered N-Glycosylation Sites

[0141] In certain embodiments, a nucleic acid encoding an anti-TNFα Fc Fusion protein is modified to include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more N-glycosylation sites (including the canonical N-glycosylation consensus sequence, reverse N-glycosylation site, and non-consensus N-glycosylation sites) than would normally be associated with the HuPTM anti-TNFα Fc Fusion protein (*e.g.*, relative to the number of N-glycosylation sites associated with the HuPTM anti-TNFα Fc Fusion protein in its unmodified state). In specific embodiments, introduction of glycosylation sites is accomplished by insertion of N-glycosylation sites (including the canonical N-glycosylation consensus sequence, reverse N-glycosylation site, and non-consensus N-glycosylation sites) anywhere in the primary structure of the antigen-binding fragment, so long as said introduction does not impact binding of the antibody or antigen-binding fragment to its antigen. Introduction of glycosylation sites can be accomplished by, *e.g.*, adding new amino acids to the primary structure of the soluble extracellular TNFR- domain or Fc domain (*e.g.*, the glycosylation sites are added, in full or in part), or by mutating existing amino acids in the soluble extracellular TNFR domain or Fc domain, in order to generate the N-glycosylation sites (*e.g.*, amino acids are not added but selected amino acids of the anti-TNFα Fc Fusion protein are mutated so as to form N-glycosylation sites). Those of skill in the art will recognize that the amino acid sequence of a protein can be readily modified using approaches known in the art, *e.g.*, recombinant approaches that include modification of the nucleic acid sequence encoding the protein.

[0142] In a specific embodiment, an anti-TNFα Fc Fusion protein is modified such that, when expressed in mammalian cells, such as retina, CNS, liver or muscle cells, it can be hyperglycosylated.

N-Glycosylation of HuPTM anti TNFα Fc fusion proteins

[0143] Unlike small molecule drugs, biologics usually comprise a mixture of many variants with different modifications or forms that could have a different potency, pharmacokinetics, and/or safety profile. It is not essential that every molecule produced either in the gene therapy or protein therapy approach be fully glycosylated and sulfated. Rather, the population of glycoproteins produced

should have sufficient glycosylation (including 2,6-sialylation) and sulfation to demonstrate efficacy. The goal of gene therapy treatment provided herein can be, for example, to slow or arrest the progression of a disease or abnormal condition or to reduce the severity of one or more symptoms associated with the disease or abnormal condition.

[0144] When a HuPTM anti-TNFα Fc fusion protein is expressed in a human cell, the N-glycosylation sites of the Fc fusion protein can be glycosylated with various different glycans. Glycosylation of the Fc domain has been characterized and is a single N-linked glycan at asparagine 297 (EU numbering; see FIG. 4). The glycan plays an integral structural and functional role, impacting antibody effector function, such as binding to Fc receptor (see, for example, Jennewein and Alter, 2017, Trends In Immunology 38:358 for a discussion of the role of Fc glycosylation in antibody function). Removal of the Fc region glycan almost completely ablates effector function (Jennewien and Alter at 362). The composition of the Fc glycan has been shown to impact effector function, for example hypergalactosylation and reduction in fucosylation have been shown to increase ADCC activity while sialylation correlates with anti-inflammatory effects (*Id.* at 364). Disease states, genetics and even diet can impact the composition of the Fc glycan *in vivo*. For recombinantly expressed antibodies and Fc fusion proteins, the glycan composition can differ significantly by the type of host cell used for recombinant expression and strategies are available to control and modify the composition of the glycan in therapeutic antibodies recombinantly expressed in cell culture, such as CHO to alter effector function (see, for example, US 2014/0193404 by Hansen et al.). Accordingly, the HuPTM anti-TNFα Fc fusion proteins provided herein may advantageously have a glycan at N297 that is more like the native, human glycan composition than antibodies expressed in non-human host cells.

[0145] Importantly, when the HuPTM anti-TNFα Fc fusion proteins are expressed in human cells, the need for *in vitro* production in prokaryotic host cells (*e.g.*, *E. coli*) or eukaryotic host cells (*e.g.*, CHO cells or NS0 cells) is circumvented. Instead, as a result of the methods described herein, N-glycosylation sites of the HuPTM anti-TNFα Fc fusion proteins are advantageously decorated with glycans relevant to and beneficial to treatment of humans. Such an advantage is unattainable when CHO cells, NS0 cells, or *E. coli* are utilized in antibody/antigen-binding fragment production, because *e.g.*, CHO cells (1) do not express 2,6 sialyltransferase and thus cannot add 2,6 sialic acid during N-

glycosylation; (2) can add Neu5Gc as sialic acid instead of Neu5Ac; and (3) can also produce an immunogenic glycan, the α-Gal antigen, which reacts with anti-α-Gal antibodies present in most individuals, which at high concentrations can trigger anaphylaxis; and because (4) *E. coli* does not naturally contain components needed for N-glycosylation.

[0146] Assays for determining the glycosylation pattern of anti-TNFα Fc fusion proteins are known in the art. For example, hydrazinolysis can be used to analyze glycans. First, polysaccharides are released from their associated protein by incubation with hydrazine (the Ludger Liberate Hydrazinolysis Glycan Release Kit, Oxfordshire, UK can be used). The nucleophile hydrazine attacks the glycosidic bond between the polysaccharide and the carrier protein and allows release of the attached glycans. N-acetyl groups are lost during this treatment and have to be reconstituted by re-N-acetylation. Glycans may also be released using enzymes such as glycosidases or endoglycosidases, such as PNGase F and Endo H, which cleave cleanly and with fewer side reactions than hydrazines. The free glycans can be purified on carbon columns and subsequently labeled at the reducing end with the fluorophor 2-amino benzamide. The labeled polysaccharides can be separated on a GlycoSep-N column (GL Sciences) according to the HPLC protocol of Royle et al, Anal Biochem 2002, 304(1):70-90. The resulting fluorescence chromatogram indicates the polysaccharide length and number of repeating units. Structural information can be gathered by collecting individual peaks and subsequently performing MS/MS analysis. Thereby the monosaccharide composition and sequence of the repeating unit can be confirmed and additionally in homogeneity of the polysaccharide composition can be identified. Specific peaks of low or high molecular weight can be analyzed by MALDI-MS/MS and the result used to confirm the glycan sequence. Each peak in the chromatogram corresponds to a polymer, *e.g.*, glycan, consisting of a certain number of repeat units and fragments, *e.g.*, sugar residues, thereof. The chromatogram thus allows measurement of the polymer, *e.g.*, glycan, length distribution. The elution time is an indication for polymer length, while fluorescence intensity correlates with molar abundance for the respective polymer, *e.g.*, glycan. Other methods for assessing glycans associated with anti-TNFα Fc fusion proteins include those described by Montacir et al., 2018, The Protein Journal, 37(2), 164–179.

[0147] Homogeneity or heterogeneity of the glycan patterns associated with anti-TNFα Fc fusion proteins, as it relates to both glycan length or size and numbers glycans present across

glycosylation sites, can be assessed using methods known in the art, *e.g.*, methods that measure glycan length or size and hydrodynamic radius. HPLC, such as size exclusion, normal phase, reversed phase, and anion exchange HPLC, as well as capillary electrophoresis, allows the measurement of the hydrodynamic radius. Higher numbers of glycosylation sites in a protein lead to higher variation in hydrodynamic radius compared to a carrier with less glycosylation sites. However, when single glycan chains are analyzed, they may be more homogenous due to the more controlled length. Glycan length can be measured by hydrazinolysis, SDS PAGE, and capillary gel electrophoresis. In addition, homogeneity can also mean that certain glycosylation site usage patterns change to a broader/narrower range. These factors can be measured by Glycopeptide LC-MS/MS.

[0148] In certain embodiments, the HuPTM anti-TNFα Fc fusion proteins also do not contain detectable NeuGc and/or α-Gal. By "detectable NeuGc" or "detectable α-Gal" or "does not contain or does not have NeuGc or α-Gal" means herein that the HuPTM anti-TNFα Fc fusion protein does not contain NeuGc or α-Gal moieties detectable by standard assay methods known in the art. For example, NeuGc may be detected by HPLC according to Hara et al., 1989, "Highly Sensitive Determination of *N*-Acetyl-and *N*-Glycolylneuraminic Acids in Human Serum and Urine and Rat Serum by Reversed-Phase Liquid Chromatography with Fluorescence Detection." J. Chromatogr., B: Biomed. 377, 111–119, which is hereby incorporated by reference for the method of detecting NeuGc. Alternatively, NeuGc may be detected by mass spectrometry. The α-Gal may be detected using an ELISA, see, for example, Galili et al., 1998, "A sensitive assay for measuring α-Gal epitope expression on cells by a monoclonal anti-Gal antibody." Transplantation. 65(8):1129-32, or by mass spectrometry, see, for example, Ayoub et al., 2013, "Correct primary structure assessment and extensive glyco-profiling of cetuximab by a combination of intact, middle-up, middle-down and bottom-up ESI and MALDI mass spectrometry techniques." Landes Bioscience. 5(5):699–710. See also the references cited in Platts-Mills et al., 2015, "Anaphylaxis to the Carbohydrate Side-Chain Alpha-gal" Immunol Allergy Clin North Am. 35(2): 247–260.

Benefits of N-Glycosylation

[0149] N-glycosylation confers numerous benefits on the HuPTM anti-TNFα Fc fusion proteins described herein. Such benefits are unattainable by production of anti-TNFα Fc fusion proteins in *E. coli*, because *E. coli* does not naturally possess components needed for N-glycosylation.

Further, some benefits are unattainable through antibody production in, *e.g.*, CHO cells (or murine cells such as NS0 cells), because CHO cells lack components needed for addition of certain glycans (*e.g.*, 2,6 sialic acid and bisecting GlcNAc) and because either CHO or murine cell lines add N-N-Glycolylneuraminic acid ("Neu5Gc" or "NeuGc") which is not natural to humans (and potentially immunogenic), instead of N-Acetylneuraminic acid ("Neu5Ac") the predominant human sialic acid. See, e.g., Dumont et al., 2015, Crit. Rev. Biotechnol. 36(6):1110-1122; Huang et al., 2006, Anal. Biochem. 349:197-207 (NeuGc is the predominant sialic acid in murine cell lines such as SP2/0 and NS0); and Song et al., 2014, Anal. Chem. 86:5661-5666, each of which is incorporated by reference herein in its entirety). Moreover, CHO cells can also produce an immunogenic glycan, the α-Gal antigen, which reacts with anti-α-Gal antibodies present in most individuals, which at high concentrations can trigger anaphylaxis. *See, e.g.*, Bosques, 2010, Nat. Biotech. 28:1153-1156. The human glycosylation pattern of the HuPTM anti-TNFα Fc fusion proteins described herein should reduce immunogenicity of the transgene product and improve efficacy.

[0150] While non-canonical glycosylation sites usually result in low level glycosylation (*e.g.*, 1-5%) of the anti-TNFα Fc fusion protein population, the functional benefits may be significant (*See, e.g.*, van de Bovenkamp et al., 2016, J. Immunol. 196:1435-1441). For example, glycosylation may affect the stability, half-life, and binding characteristics of an antibody. To determine the effects of anti-TNFα Fc fusion proteins glycosylation on the affinity of the fusion protein for its target, any technique known to one of skill in the art may be used, for example, enzyme linked immunosorbent assay (ELISA), or surface plasmon resonance (SPR). To determine the effects of glycosylation on the half-life of the anti-TNFα Fc fusion proteins, any technique known to one of skill in the art may be used, for example, by measurement of the levels of radioactivity in the blood or organs in a subject to whom a radiolabelled antibody has been administered. To determine the effects of glycosylation on the stability, for example, levels of aggregation or protein unfolding, of the anti-TNFα Fc fusion proteins, any technique known to one of skill in the art may be used, for example, differential scanning calorimetry (DSC), high performance liquid chromatography (HPLC), *e.g.*, size exclusion high performance liquid chromatography (SEC-HPLC), capillary electrophoresis, mass spectrometry, or turbidity measurement.

[0151] The presence of sialic acid on HuPTM anti-TNFα Fc fusion proteins used in the methods described herein can impact clearance rate of the HuPTM anti-TNFα Fc fusion proteins. Accordingly, sialic acid patterns of a HuPTM anti-TNFα Fc fusion proteins can be used to generate a therapeutic having an optimized clearance rate. Methods of assessing anti-TNFα Fc fusion proteins clearance rate are known in the art..

[0152] In another specific embodiment, a benefit conferred by N-glycosylation is reduced aggregation. Occupied N-glycosylation sites can mask aggregation prone amino acid residues, resulting in decreased aggregation. Such N-glycosylation sites can be native to an anti-TNFα Fc fusion protein used herein or engineered into an antigen-binding fragment used herein, resulting in HuPTM anti-TNFα Fc fusion proteins that is less prone to aggregation when expressed, *e.g.*, expressed in human cells. Methods of assessing aggregation of antibodies are known in the art. *See, e.g.*, Courtois et al., 2016, mAbs 8:99-112 which is incorporated by reference herein in its entirety.

[0153] In another specific embodiment, a benefit conferred by N-glycosylation is reduced immunogenicity. Such N-glycosylation sites can be native to an antigen-binding fragment used herein or engineered into an antigen-binding fragment used herein, resulting in an HuPTM anti-TNFα Fc fusion protein that is less prone to immunogenicity when expressed, *e.g.*, expressed in human ocular tissue cells.

[0154] In another specific embodiment, a benefit conferred by N-glycosylation is protein stability. N-glycosylation of proteins is well-known to confer stability on them, and methods of assessing protein stability resulting from N-glycosylation are known in the art. *See, e.g.*, Sola and Griebenow, 2009, J Pharm Sci., 98(4): 1223–1245.

[0155] In another specific embodiment, a benefit conferred by N-glycosylation is altered binding affinity. Assays for measuring binding affinity are known in the art.

5.4.2 O-Glycosylation

[0156] O-glycosylation comprises the addition of N-acetyl-galactosamine to serine or threonine residues by the enzyme. It has been demonstrated that amino acid residues present in the hinge region of anti-TNFα Fc fusion proteins can be O-glycosylated. In certain embodiments, the anti-TNFα Fc fusion proteins comprise all or a portion of their hinge region, and thus are capable of

being O-glycosylated when expressed in human cells. The possibility of O-glycosylation confers another advantage to the anti-TNFα Fc fusion proteins provided herein, as compared to, *e.g.*, anti-TNFα Fc fusion proteins produced in *E. coli*, again because the *E. coli* naturally does not contain machinery equivalent to that used in human O-glycosylation. (Instead, O-glycosylation in *E. coli* has been demonstrated only when the bacteria is modified to contain specific O-glycosylation machinery. *See, e.g.*, Farid-Moayer et al., 2007, J. Bacteriol. 189:8088-8098.) O-glycosylated anti-TNFα Fc fusion proteins, by virtue of possessing glycans, shares advantageous characteristics with N-glycosylated anti-TNFα Fc fusion proteins (as discussed above).

5.5 Vectored HuPTM anti-TNFα Fc Fusion Protein Constructs and Formulations for Non-Infectious Uveitis

[0157] Compositions and methods are described for the delivery of HuPTM anti-TNFα Fc fusion proteins, such as TNFR1:Fc fusion proteins or TNFR2:Fc fusion proteins, that bind to tumor necrosis factor-alpha (TNFα), such as etanercept or EYS606 (**FIGS. 2A and 2B**) and indicated for treating non-infectious uveitis. In certain embodiments, the HuPTM anti-TNFα Fc fusion protein has the amino acid sequence of etanercept or EYS606, or biosimilars or biobetters thereof. Amino acid sequences of the soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) and Fc domains of the fusion proteins are provided in FIGS. 2A and 2B and Table 6. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an therapeutic anti-TNFα Fc fusion protein (and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with one or more symptoms of non-infectious uveitis to create a permanent depot that continuously supplies the HuPTM, e.g., human-glycosylated, transgene product to ocular tissues.

Transgenes

[0158] Provided are recombinant vectors containing a transgene encoding a HuPTM anti-TNFα Fc fusion protein that binds to TNFα that can be administered to deliver the HuPTM anti-TNFα Fc fusion protein in a patient. The transgene is a nucleic acid comprising the nucleotide sequences encoding an anti-TNFα Fc fusion protein comprising a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) and a Fc domain, such as etanercept or EYS606, or

variants thereof as detailed herein. The transgene may also encode an anti-TNFα Fc fusion protein that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0159] In certain embodiments, the anti-TNFα transgene comprises the nucleotide sequence encoding the TNFR2:Fc fusion protein etanercept (having amino acid sequences of SEQ ID NO: 10 or 11, see Table 6 and FIG. 2A). The nucleotide sequences may be codon optimized for expression in human cells. Nucleotide sequences may, for example, comprise the nucleotide sequences of SEQ ID NO: 13-18 (encoding the etanercept transgene sequences as set forth in Table 7. The TNFR2:Fc fusion sequences has a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, one or more cells ocular tissue cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:62). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more ocular tissue cells. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0160] In addition to the soluble, extracellular protein of the TNFR type 2 domain and a Fc constant region including C_H2 and C_H3 domain sequences, the transgene may comprise, at the N-terminus of the heavy chain C_H2 domain sequence, all or a portion of the hinge region. In specific embodiments, the Fc domain has an amino acid sequence of SEQ ID NO: 4 with an additional hinge region sequence at the N-terminus (e.g. SEQ ID NO: 3 with hinge) or containing all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:145), and specifically, EPKSCDKTHL (SEQ ID NO:146), EPKSCDKTHT (SEQ ID NO:147), EPKSCDKTHTCPPCPA (SEQ ID NO:148), EPKSCDKTHLCPPCPA (SEQ ID NO:149), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:150) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:151). The Fc domain of the anti-TNFα Fc fusion protein may have an amino acid sequence of SEQ ID NO: 3 or 4 (Table 6) or an IgG1 Fc domain, such as depicted in FIG. 4, or a mutant or variant thereof. The Fc domain may be engineered for altered binding to one or more Fc receptors and/or effector function as disclosed in Section 5.2.8, infra.

[0161] Expression of the etanercept may be directed by a constitutive or a tissue specific promoter. In certain embodiments, the transgene contains a CAG promoter (SEQ ID NO:51), CB promoter (SEQ ID NO: 159), CBLong promoter (SEQ ID NO: 161), a GRK1 (SEQ ID NO:54) promoter or a Best1/GRK promoter (SEQ ID NO: 161). Alternatively, the promoter may be a tissue specific promoter (or regulatory sequence including promoter and enhancer elements) such as the GRK1 promoter (SEQ ID NO:54 or 117), (a mouse cone arresting (CAR) promoter (SEQ ID NOS:114-116), a human red opsin (RedO) promoter (SEQ ID NO:112) or a Best1/GRK promoter (SEQ ID NO: 161). See FIG. 1 for a schematic showing the genomic configuration. The transgenes may contain elements provided in Table 1. Exemplary transgenes encoding etanercept are provided in Table 7 and include CAG.etanercept (SEQ ID NO: 16) or mU1a.Vh4i.etanercept.scAAV (SEQ ID NO: 18). ITR sequences are added to the 5' and 3; ends of the constructs to generate the genomes resulting in CAG.etanercept (SEQ ID NO: 15) and U1a.Vh4i.etanercept.scAAV (SEQ ID NO: 17). In certain embodiments, the construct is a self-complementary construct. The transgenes may be packaged into AAV, particularly AAV2.7m8, AAV8, AAV3B, or AAVrh73.

[0162] In certain embodiments, the transgene encodes an anti-TNFα Fc fusion protein comprising a soluble, extracellular portion of the TNFR type 2 domain comprising an amino acid sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence set forth in SEQ ID NO: 2. In certain embodiments, the transgene encodes an anti-TNFα Fc fusion protein comprising a Fc domain comprising an amino acid sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence set forth in SEQ ID NO: 3. In certain embodiments, transgene encodes an anti-TNFα Fc fusion protein comprising an amino acid sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence set forth in SEQ ID NO: 10 or 11. In specific embodiments, the TNFR2:Fc fusion protein comprising an amino acid sequence of SEQ ID NO: 10 or 11 with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more amino acid substitutions, insertions or deletions, and the substitutions, insertions or deletions are made.

[0163] In certain embodiments, the anti-TNFα transgene comprises the nucleotide sequence encoding the TNFR1:Fc fusion protein EYS606 (having amino acid sequence of SEQ ID NO: 12, see

Table 6 and FIG. 2B). The nucleotide sequences may be codon optimized for expression in human cells. The TNFR1:Fc fusion protein has a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:62). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more ocular tissue cells. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0164] In addition to the soluble, extracellular protein of the TNFR type 1 domain and a Fc constant region including C_H2 and C_H3 domain sequences, the transgene may comprise, at the N-terminus of the heavy chain C_H2 domain sequence, a thrombin cleavage site LVPRGS (SEQ ID NO:8) and all or a portion of the hinge region. In specific embodiments, the Fc domain has an amino acid sequence of SEQ ID NO: 3 or has a hinge region sequence at the N-terminus containing all or a portion of the amino acid sequence DKTHTCPPCPAPELLGG (SEQ ID NO:21), and specifically, DKTHTCPPCPA (SEQ ID NO:154), DKTHLCPPCPA (SEQ ID NO:155), DKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:152) or DKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:156). The Fc domain of the anti-TNFα Fc fusion protein may have an amino acid sequence of SEQ ID NO: 10 (Table 6). The Fc domain may be engineered for altered binding to one or more Fc receptors and/or effector function as disclosed in Section 5.2.8, infra.

[0165] Expression of EYS606 may be directed by a constitutive or a tissue specific promoter. . In certain embodiments, the transgene contains a CAG promoter (SEQ ID NO:51) or a GRK1 (SEQ ID NO:54) promoter. Alternatively, the promoter may be a tissue specific promoter (or regulatory sequence including promoter and enhancer elements) such as the GRK1 promoter (SEQ ID NO:54 or 117), (a mouse cone arresting (CAR) promoter (SEQ ID NOS:114-116), a human red opsin (RedO) promoter (SEQ ID NO112) or a Best1/GRK promoter (SEQ ID NO:161). The transgenes may contain elements provided in Table 1. Exemplary transgenes encoding EYS606 may be generated using methods known in the art. ITR sequences are added to the 5' and 3; ends of the constructs to generate the genomes. The transgenes may be packaged into AAV, particularly AAV8, AAV3B, or AAVrh73.

[0166] In certain embodiments, the transgene encodes an anti-TNFα Fc fusion protein comprising a soluble, extracellular portion of the TNFR type 1 domain comprising an amino acid sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence set forth in SEQ ID NO: 1. In certain embodiments, the transgene encodes an anti-TNFα Fc fusion protein comprising a Fc domain comprising an amino acid sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence set forth in SEQ ID NO: 6. In certain embodiments, transgene encodes an anti-TNFα Fc fusion protein comprising an amino acid sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence set forth in SEQ ID NO: 12. In specific embodiments, the TNFR1:Fc fusion protein comprises a soluble, extracellular portion of the TNFR type 1 domain comprising an amino acid sequence of SEQ ID NO: 1 with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more amino acid substitutions, insertions or deletions, and the substitutions, insertions or deletions are made. In specific embodiments, the TNFR1:Fc fusion protein comprises an amino acid sequence of SEQ ID NO: 12 with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more amino acid substitutions, insertions or deletions, and the substitutions, insertions or deletions are made, e.g., in the framework regions.

Gene Therapy Methods

[0167] Provided are methods of treating human subjects for non-infectious uveitis by administration of a viral vector containing a transgene encoding an anti-TNFα fusion protein. The fusion protein may be etanercept or EYS606, or a biobetter or biosimilar thereof. In embodiments, the patient has been diagnosed with and/or has symptom(s) associated with non-infectious uveitis. Recombinant vector used for delivering the transgene are described in Section 5.2. Such vectors should have a tropism for human ocular tissue cells and can include non-replicating rAAV, particularly those bearing an AAV8 capsid, an AAV3B capsid, or an AAVr73 capsid. Alternatively, vectors bearing an AAV2.7m8 or AAV9 capsid can be used for ocular indications. The recombinant vector, such as the one shown in FIG. 1, can be administered in any manner such that the recombinant vector enters one or more ocular tissue cell types, e.g. by introducing the recombinant vector into the eye. See Section 5.3 for details regarding the methods of treatment.

[0168] Provided are methods of treating human subjects for non-infectious uveitis by administration of a viral vector containing a transgene encoding an anti-TNFα fusion protein. The fusion protein may be etanercept or EYS606. In embodiments, the patient has been diagnosed with and/or has symptoms associated with non-infectious uveitis. Recombinant vectors used for delivering the transgene are described in Section 5.2 and exemplary transgenes are provided above. Such vectors should have a tropism for human ocular tissue cells and can include non-replicating rAAV, particularly those bearing an AAV3B, AAV8, or AAVrh73 capsid. The recombinant vectors, such as shown in FIGS. 2A and 2B, can be administered in any manner such that the recombinant vector enters the ocular tissue. In particular embodiments, the transgene is SEQ ID NO: 13-18 in an AAV8 vector (see Table 7).

[0169] Subjects to whom such gene therapy is administered can be those responsive to anti-TNFα therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with non-infectious uveitis, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-TNFα antibody, anti-TNFα Fc fusion protein, or considered a good candidate for therapy with an anti-TNFα antibody or anti-TNFα Fc fusion protein. In specific embodiments, the patients have previously been treated with etanercept, adalimumab, infliximab, or golimumab, and have been found to be responsive to etanercept, adalimumab, infliximab, or golimumab. In other embodiments, the patients have been previously treated with an anti-TNF-alpha antibody or fusion protein such as etanercept, certolizumab, or other anti-TNF-alpha agent. To determine responsiveness, the anti-TNFα transgene product (e.g., produced in cell culture, bioreactors, etc.) may be administered directly to the subject.

Human Post Translationally Modified anti-TNFα fusion proteins

[0170] The production of the HuPTM anti-TNFα fusion protein, should result in a "biobetter" molecule for the treatment of non-infectious uveitis accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-TNFα HuPTM anti-TNFα fusion protein, subretinally, intravitreally, intranasally, intracamerally, suprachoroidally, or systemically to human subjects (patients) diagnosed with or having one or more symptoms of non-infectious uveitis, to create a permanent depot in one or more ocular tissues (or cell types) that

continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced ocular tissue cells.

[0171] In specific embodiments, the HuPTM anti-TNFα fusion protein has a soluble, extracellular portion of the TNFR2 domain fused to a Fc domain with the amino acid sequences of etanercept as set forth in FIG. 2A (asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions indicated in FIG. 2A, including N149 or N171 of the TNFR2 domain (SEQ ID NO: 2) and/or N317 of the Fc domain (SEQ ID NO: 3), and/or O-linked glycosylation sites at one or more of the amino acid positions T8, T184, S199, and/or T200 of the TNFR2 domain (SEQ ID NO: 2) and/or T245 of the hinge region (SEQ ID NO: 11). In other embodiments, the HuPTM anti-TNFα fusion protein does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties.

[0172] In specific embodiments, the HuPTM anti-TNFα fusion protein has a soluble, extracellular portion of the TNFR1 domain fused to a Fc domain with the amino acid sequences of ESY606 as set forth in FIG. 2B (asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions as indicated in FIG. 2B, including N54, N94 or N145 of the TNFR1 domain (SEQ ID NO: 1) and/or N294 or N358 of the Fc domain (SEQ ID NO: 12), and/or O-linked glycosylation sites at one or more of the amino acid positions T8, T184, S199, and/or T200 of the TNFR2 domain (SEQ ID NO: 1) and/or T245 of the hinge region (SEQ ID NO: 12). In other embodiments, the HuPTM anti-TNFα fusion protein does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties.

[0173] In certain embodiments, the HuPTM anti-TNFα Fc fusion protein is therapeutically effective and is at least 0.5%, 1% or 2% glycosylated and/or sulfated and may be at least 5%, 10% or even 50% or 100% glycosylated and/or sulfated. The goal of gene therapy treatment provided herein is to slow or arrest the progression of or relieve one or more symptoms of non-infectious uveitis, such as to reduce the levels of pain, redness of the eye, sensitivity to light, and/or other discomfort for the patient. Efficacy may be monitored by measuring a reduction in pain, redness of the eye, and/or photophobia and/or an improvement in vision.

[0174] Combinations of delivery of the HuPTM anti-TNFα Fc fusion protein to the eye accompanied by delivery of other available treatments are encompassed by the methods provided herein. The additional treatments may be administered before, concurrently, or subsequent to the gene therapy treatment. Available treatments for a subject with non-infectious uveitis that could be combined with the gene therapy provided herein include but are not limited to, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, cyclophosphamide, corticosteroids (local and/or systemic), and others and administration with anti-TNFα agents, including but not limited to etanercept, EYS606, adalimumab, infliximab, or golimumab.

TABLE 6. Anti-TNFα Fc Fusion Amino Acid Sequences

Domain	SEQ ID NO.	Sequence
TNFR1 *Human TNFRSF1A Extracellular domain, UniProtKB - P19438 amino acid 1-211*	SEQ ID NO: 1	MGLSTVPDLLLPLVLLELLVGIYPSGVIGLVPHLGDREKRDSV CPQGKYIHPQNNSICCTKCHKGTYLYNDCPGPGQDTDCRECES GSFTASENHLRHCLSCSKCRKEMGQVEISSCTVDRDTVCGCRK NQYRHYWSENLFQCFNCSLCLNGTVHLSCQEKQNTVCTCHAGF FLRENECVSCSNCKKSLECTKLCLPQIENVKGTEDSGTT
TNFR2 *Human TNFRSF1B Extracellular domain, UniProtKB - P20333 amino acid 23-257*	SEQ ID NO: 2	LPAQVAFTPY APEPGSTCRL REYYDQTAQM CCSKCSPGQH AKVFCTKTSD TVCDSCEDST YTQLWNWVPE CLSCGSRCSS DQVETQACTR EQNRICTCRP GWYCALSKQE GCRLCAPLRK CRPGFGVARP GTETSDVVCK PCAPGTFSNT TSSTDICRPH QICNVVAIPG NASMDAVCTS TSPTRSMAPG AVHLPQPVST RSQHTQPTPE PSTAPSTSFL LPMGPSPPAE GSTGD
Etanercept: Fc (including hinge)	SEQ ID NO:3	*EPKSCDKTHT CPPCPAPELL GGPSV*FLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
Etanercept: Fc (without hinge)	SEQ ID NO: 4	FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS

Domain	SEQ ID NO.	Sequence
		LSLSPGK
Etanercept: Hinge region	SEQ ID NO: 5	EPKSCDKTHTCPPCPAPELLGGPSV
EYS606: Fc (including hinge)	SEQ ID NO: 6	*DKTHTCPPCPAPELLGGPSV*FLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGS
EYS606: Fc (without hinge)	SEQ ID NO: 7	FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
EYS606: Thrombin cleavage site	SEQ ID NO:8	LVPRGS
EYS606: Hinge region	SEQ ID NO: 9	DKTHTCPPCPAPELLGGPSV
Etanercept TNFR2:Fc fusion	SEQ ID NO: 10	LPAQVAFTPY APEPGSTCRL REYYDQTAQM CCSKCSPGQH AKVFCTKTSD TVCDSCEDST YTQLWNWVPE CLSCGSRCSS DQVETQACTR EQNRICTCRP GWYCALSKQE GCRLCAPLRK CRPGFGVARP GTETSDVVCK PCAPGTFSNT TSSTDICRPH QICNVVAIPG NASMDAVCTS TSPTRSMAPG AVHLPQPVST RSQHTQPTPE PSTAPSTSFL LPMGPSPPAE GSTGD*EPKSC* *DKTHTCPPCP* *APELLGGPSV* FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK
Etanercept plus leader sequence	SEQ ID NO: 11	**MYRMQLLLLLIALSLALVTNS**LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCC SKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWNWVPECLSCGSRCSSDQVE TQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGTETSD VVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMA PGAVHLPQPVSTRSQHTQPTPEPSTAPSTSFLLPMGPSPPAEGSTGD*EPKSC* *DKTHTCPPCPAPELLGGPSV*FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK

Domain	SEQ ID NO.	Sequence
		Leader sequence is shown in bold. TNFR domain is underlined. Hinge region is shown in italic and Fc domain is highlighted in grey.
EYS606	SEQ ID NO:12	MGLSTVPDLLLPLVLLELLVGIYPSGVIGLVPHLGDREKRDSVCPQGKYIHP QNNSICCTKCHKGTYLYNDCPGPGQDTDCRECESGSFTASENHLRHCLSCSK CRKEMGQVEISSCTVDRDTVCGCRKNQYRHYWSENLFQCFNCSLCLNGTVHL SCQEKQNTVCTCHAGFFLRENECVSCSNCKKSLECTKLCLPQIENVKGTEDS GTT**LVPRGS***DKTHTCPPCPAPELLGGPSV*FLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS Thrombin cleavage site is bold/underlined. Hinge region is shown in italic and Fc domain is highlighted in grey.

TABLE 7. Anti-TNFα Fc Fusion Nucleotide Sequences

Protein	SEQ ID NO.	Sequence
Etanercept	SEQ ID NO: 13	CTGCCTGCACAGGTGGCTTTTACCCCATATGCTCCTGAGCCTGGATCCACTTGTAGGC TGAGGGAGTATTATGATCAGACAGCCCAGATGTGCTGTTCAAAATGTTCCCCTGGACA GCATGCTAAGGTGTTTTGTACCAAGACAAGTGACACTGTCTGTGACAGCTGTGAGGAT TCTACTTACACCCAGCTGTGGAATTGGGTGCCAGAATGTCTGTCATGTGGGAGCAGGT GTTCTAGTGACCAGGTGGAAACTCAGGCCTGTACAAGAGAGCAGAACAGGATTTGTAC ATGTAGACCAGGGTGGTACTGTGCCCTGAGCAAACAGGAAGGGTGTAGGCTCTGTGCT CCCCTGAGGAAATGTAGACCTGGGTTTGGGGTGGCCAGACCAGGAACAGAAACTTCTG ATGTGGTCTGTAAGCCCTGTGCACCAGGAACCTTTTCAAACACTACCAGCAGTACAGA CATCTGCAGACCCCATCAGATCTGTAATGTGGTGGCCATTCCTGGGAATGCAAGTATG GATGCTGTCTGTACTTCCACCAGCCCAACTAGATCCATGGCCCCAGGGGCAGTCCACC TGCCCCAGCCTGTCAGCACTAGAAGCCAGCATACTCAGCCCACACCTGAGCCTTCTAC AGCACCCTCCACCTCTTTCCTGCTGCCTATGGGGCCATCACCTCCAGCTGAGGGCAGT ACAGGG*GATGAACCTAAGTCATGTGACAAAACCCATACCTGTCCACCCTGCCCTGCTC CTGAGCTGCTGGGGGGACCCAGTGTCTTCCTG*TTTCCTCCCAAACCTAAAGATACTCT GATGATCAGCAGAACCCCAGAGGTCACATGCGTGGTAGTGGATGTCTCCCATGAAGAC CCTGAAGTGAAGTTTAATTGGTATGTAGATGGGGTGGAGGTCCATAATGCAAAGACCA AGCCCAGGGAAGAACAGTATAACAGTACTTACAGGGTGGTGTCTGTGCTGACAGTACT GCACCAGGACTGGCTGAATGGGAAGGAGTATAAGTGCAAAGTCAGCAATAAGGCACTG CCTGCCCCTATTGAAAAGACAATTAGTAAAGCTAAGGGGCAGCCCAGGGAACCACAGG TCTACACTCTGCCCCCTAGTAGAGAGGAAATGACAAAGAATCAGGTCAGTCTGACATG TCTGGTCAAGGGATTCTATCCAAGTGATATTGCAGTGGAGTGGGAAAGTAATGGCCAG CCAGAGAATAACTACAAGACTACCCCCCCAGTGCTGGACAGTGATGGATCTTTCTTTC TGTACTCCAAACTGACTGTGGATAAATCAAGATGGCAGCAGGGCAATGTCTTTTCCTG TTCAGTCATGCATGAAGCCCTGCATAATCACTACACTCAGAAGAGCCTGTCCCTGTCC CCTGGCAAATGA TNFR2 domain is highlighted in grey. Hinge region is shown in italic.

Protein	SEQ ID NO.	Sequence
Etanercept plus leader sequence	SEQ ID NO: 14	**ATGTATAGGATGCAGCTGCTGCTGCTGATTGCTCTGAGTCTGGCTCTGGTCACAAATA** **GT**CTGCCTGCACAGGTGGCTTTTACCCCATATGCTCCTGAGCCTGGATCCACTTGTAG GCTGAGGGAGTATTATGATCAGACAGCCCAGATGTGCTGTTCAAAATGTTCCCCTGGA CAGCATGCTAAGGTGTTTTGTACCAAGACAAGTGACACTGTCTGTGACAGCTGTGAGG ATTCTACTTACACCCAGCTGTGGAATTGGGTGCCAGAATGTCTGTCATGTGGGAGCAG GTGTTCTAGTGACCAGGTGGAAACTCAGGCCTGTACAAGAGAGCAGAACAGGATTTGT ACATGTAGACCAGGGTGGTACTGTGCCCTGAGCAAACAGGAAGGGTGTAGGCTCTGTG CTCCCCTGAGGAAATGTAGACCTGGGTTTGGGGTGGCCAGACCAGGAACAGAAACTTC TGATGTGGTCTGTAAGCCCTGTGCACCAGGAACCTTTTCAAACACTACCAGCAGTACA GACATCTGCAGACCCCATCAGATCTGTAATGTGGTGGCCATTCCTGGGAATGCAAGTA TGGATGCTGTCTGTACTTCCACCAGCCCAACTAGATCCATGGCCCCAGGGGCAGTCCA CCTGCCCCAGCCTGTCAGCACTAGAAGCCAGCATACTCAGCCCACACCTGAGCCTTCT ACAGCACCCTCCACCTCTTTCCTGCTGCCTATGGGGCCATCACCTCCAGCTGAGGGCA GTACAGGGGATGAACCTAAGTCATGTGACAAAACCCATACCTGTCCACCCTGCCCTGC TCCTGAGCTGCTGGGGGGACCCAGTGTCTTCCTGTTTCCTCCCAAACCTAAAGATACT CTGATGATCAGCAGAACCCCAGAGGTCACATGCGTGGTAGTGGATGTCTCCCATGAAG ACCCTGAAGTGAAGTTTAATTGGTATGTAGATGGGGTGGAGGTCCATAATGCAAAGAC CAAGCCCAGGGAAGAACAGTATAACAGTACTTACAGGGTGGTGTCTGTGCTGACAGTA CTGCACCAGGACTGGCTGAATGGGAAGGAGTATAAGTGCAAAGTCAGCAATAAGGCAC TGCCTGCCCCTATTGAAAAGACAATTAGTAAAGCTAAGGGGCAGCCCAGGGAACCACA GGTCTACACTCTGCCCCCTAGTAGAGAGGAAATGACAAAGAATCAGGTCAGTCTGACA TGTCTGGTCAAGGGATTCTATCCAAGTGATATTGCAGTGGAGTGGGAAAGTAATGGCC AGCCAGAGAATAACTACAAGACTACCCCCCCAGTGCTGGACAGTGATGGATCTTTCTT TCTGTACTCCAAACTGACTGTGGATAAATCAAGATGGCAGCAGGGCAATGTCTTTTCC TGTTCAGTCATGCATGAAGCCCTGCATAATCACTACACTCAGAAGAGCCTGTCCCTGT CCCCTGGCAAATGA Leader sequence is shown in bold
pAAV.CAG. Etanercept *(from 5'-ITR to 3-ITR)*	SEQ ID NO:15	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacct ttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccat cactaggggttccttgtagttaatgattaacccgccatgctacttatctaccagggta atggggatcctctagaactatagctagtcgacattgattattgactagttattaatag taatcaattacggggtcattagttcatagcccatatatggagttccgcgttacataac ttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaat aatgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtg gagtatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagta cgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagtacat gaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctattacc atggtcgaggtgagccccacgttctgcttcactctccccatctccccccccctccccac ccccaattttgtatttatttatttttaattattttgtgcagcgatgggggcgggggg ggggggggggcgcgccaggcggggcggggcggggcgaggggcggggcggggcgagg cggagaggtgcggcggcagccaatcagagcggcgcgctccgaaagtttccttttatgg cgaggcggcggcggcggcggccctataaaaagcgaagcgcgcggcgggcgggagtcgc tgcgcgctgccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgccccgg ctctgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctccgg gctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggctgcgtgaaag ccttgaggggctccgggagggccctttgtgcgggggggagcggctcgggggggtgcgtgc gtgtgtgtgtgcgtggggagcgccgcgtgcggctccgcgctgcccggcggctgtgagc gctgcgggcgcggcgcggggctttgtgcgctccgcagtgtgcgcgaggggagcgcggc cgggggcggtgccccgcggtgcgggggggggctgcgaggggaacaaaggctgcgtgcgg ggtgtgtgcgtgggggggtgagcagggggtgtgggcgcgtcggtcgggctgcaacccc ccctgcacccccctccccgagttgctgagcacggcccggcttcgggtgcggggctccg tacggggcgtggcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtg ccgggcggggcggggccgcctcgggccggggagggctcgggggaggggcgcggcggcc cccggagcgccggcggctgtcgaggcgcggcgagccgcagccattgccttttatggta atcgtgcgagagggcgcagggacttcctttgtcccaaatctgtgcggagccgaaatct gggaggcgccgccgcacccccctctagcgggcgcggggcgaagcggtgcggcgccggca ggaaggaaatgggcggggagggccttcgtgcgtcgccgcgccgccgtcccctttctccc tctccagcctcggggctgtccgcgggggggacggctgccttcgggggggacggggcagg

Protein	SEQ ID NO.	Sequence
		gcggggttcggcttctggcgtgtgaccggcggctctagagcctctgctaaccatgttc atgccttcttcttttcctacagctcctgggcaacgtgctggttattgtgctgtctca tcattttggcaaagAATTCGCCACCATGTATAGGATGCAGCTGCTGCTGCTGATTGCT CTGAGTCTGGCTCTGGTCACAAATAGTCTGCCTGCACAGGTGGCTTTTACCCCATATG CTCCTGAGCCTGGATCCACTTGTAGGCTGAGGGAGTATTATGATCAGACAGCCCAGAT GTGCTGTTCAAAATGTTCCCCTGGACAGCATGCTAAGGTGTTTTGTACCAAGACAAGT GACACTGTCTGTGACAGCTGTGAGGATTCTACTTACACCCAGCTGTGGAATTGGGTGC CAGAATGTCTGTCATGTGGGAGCAGGTGTTCTAGTGACCAGGTGGAAACTCAGGCCTG TACAAGAGAGCAGAACAGGATTTGTACATGTAGACCAGGGTGGTACTGTGCCCTGAGC AAACAGGAAGGGTGTAGGCTCTGTGCTCCCCTGAGGAAATGTAGACCTGGGTTTGGGG TGGCCAGACCAGGAACAGAAACTTCTGATGTGGTCTGTAAGCCCTGTGCACCAGGAAC CTTTTCAAACACTACCAGCAGTACAGACATCTGCAGACCCCATCAGATCTGTAATGTG GTGGCCATTCCTGGGAATGCAAGTATGGATGCTGTCTGTACTTCCACCAGCCCAACTA GATCCATGGCCCCAGGGGCAGTCCACCTGCCCCAGCCTGTCAGCACTAGAAGCCAGCA TACTCAGCCCACACCTGAGCCTTCTACAGCACCCTCCACCTCTTTCCTGCTGCCTATG GGGCCATCACCTCCAGCTGAGGGCAGTACAGGGGATGAACCTAAGTCATGTGACAAAA CCCATACCTGTCCACCCTGCCCTGCTCCTGAGCTGCTGGGGGGACCCAGTGTCTTCCT GTTTCCTCCCAAACCTAAAGATACTCTGATGATCAGCAGAACCCCAGAGGTCACATGC GTGGTAGTGGATGTCTCCCATGAAGACCCTGAAGTGAAGTTTAATTGGTATGTAGATG GGGTGGAGGTCCATAATGCAAAGACCAAGCCCAGGGAAGAACAGTATAACAGTACTTA CAGGGTGGTGTCTGTGCTGACAGTACTGCACCAGGACTGGCTGAATGGGAAGGAGTAT AAGTGCAAAGTCAGCAATAAGGCACTGCCTGCCCCTATTGAAAAGACAATTAGTAAAG CTAAGGGGCAGCCCAGGGAACCACAGGTCTACACTCTGCCCCCTAGTAGAGAGGAAAT GACAAAGAATCAGGTCAGTCTGACATGTCTGGTCAAGGGATTCTATCCAAGTGATATT GCAGTGGAGTGGGAAAGTAATGGCCAGCCAGAGAATAACTACAAGACTACCCCCCCAG TGCTGGACAGTGATGGATCTTTCTTTCTGTACTCCAAACTGACTGTGGATAAATCAAG ATGGCAGCAGGGCAATGTCTTTTCCTGTTCAGTCATGCATGAAGCCCTGCATAATCAC TACACTCAGAAGAGCCTGTCCCTGTCCCCTGGCAAATGATAACtcgaggacggggtga actacgcctgaggatccgatcttttccctctgccaaaaattatggggacatcatgaa gcccccttgagcatctgacttctggctaataaaggaaatttattttcattgcaatagtg tgttggaatttttgtgtctctcactcggaagcaattcgttgatctgaatttcgacca cccataatacccattaccctggtagataagtagcatggcgggttaatcattaactaca aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactga ggccgggcgaccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagc gagcgagcgcgcag
pAAV.CAG. Etanercept *(from promoter to polyA)*	SEQ ID NO: 16	acattgattattgactagttattaatagtaatcaattacggggtcattagttcatagc ccatatatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgc ccaacgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaat agggactttccattgacgtcaatgggtggagtatttacggtaaactgcccacttggca gtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaat ggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagta catctacgtattagtcatcgctattaccatggtcgaggtgagccccacgttctgcttc actctccccatctcccccccctccccacccccaattttgtatttatttatttttaat tattttgtgcagcgatgggggcgggggggggggggggcgcgcgccaggcggggcggg gcggggcgaggggcggggcggggcgaggcggagaggtgcggcggcagccaatcagagc ggcgcgctccgaaagtttccttttatggcgaggcggcggcggcggcggccctataaaa agcgaagcgcgcggcgggcgggagtcgctgcgcgctgccttcgccccgtgccccgctc cgccgccgcctcgcgccgcccgccccggctctgactgaccgcgttactcccacaggtg agcgggcgggacggcccttctcctccgggctgtaattagcgcttggtttaatgacggc ttgtttcttttctgtggctgcgtgaaagccttgaggggctccgggagggccctttgtg cgggggggagcggctcgggggggtgcgtgcgtgtgtgtgtgcgtggggagcgccgcgtgc ggctccgcgctgcccggcggctgtgagcgctgcgggcgcggcgcggggctttgtgcgc tccgcagtgtgcgcgaggggagcgcggccgggggcggtgccccgcggtgcgggggggg ctgcgaggggaacaaaggctgcgtgcggggtgtgtgcgtgggggggtgagcagggggt gtgggcgcgtcggtcgggctgcaacccccccctgcacccccctccccgagttgctgagc acggcccggcttcgggtgcggggctccgtacggggcgtggcgcggggctcgccgtgcc gggcgggggggtggcggcaggtgggggtgccgggcgggggcggggccgcctcgggccggg gagggctcgggggagggggcgcggcggccccccggagcgccggcggctgtcgaggcgcgg

Protein	SEQ ID NO.	Sequence
		cgagccgcagccattgcctttatggtaatcgtgcgagagggcgcagggacttcctttgtcccaaatctgtgcggagccgaaatctgggaggcgccgccgcacccccctctagcgggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagggccttcgtgcgtcgccgcgccgccgtccccttctccctctccagcctcggggctgtccgcgggggggacggctgccttcgggggggacggggcagggcggggttcggcttctggcgtgtgaccggcggctctagagcctctgctaaccatgttcatgccttcttcttttttcctacagctcctgggcaacgtgctggttattgtgctgtctcatcattttggcaaagAATTCGCCACCATGTATAGGATGCAGCTGCTGCTGCTGATTGCTCTGAGTCTGGCTCTGGTCACAAATAGTCTGCCTGCACAGGTGGCTTTTACCCCATATGCTCCTGAGCCTGGATCCACTTGTAGGCTGAGGGAGTATTATGATCAGACAGCCCAGATGTGCTGTTCAAAATGTTCCCCTGGACAGCATGCTAAGGTGTTTTGTACCAAGACAAGTGACACTGTCTGTGACAGCTGTGAGGATTCTACTTACACCCAGCTGTGGAATTGGGTGCCAGAATGTCTGTCATGTGGGAGCAGGTGTTCTAGTGACCAGGTGGAAACTCAGGCCTGTACAAGAGAGCAGAACAGGATTTGTACATGTAGACCAGGGTGGTACTGTGCCCTGAGCAAACAGGAAGGGTGTAGGCTCTGTGCTCCCCTGAGGAAATGTAGACCTGGGTTTGGGGTGGCCAGACCAGGAACAGAAACTTCTGATGTGGTCTGTAAGCCCTGTGCACCAGGAACCTTTTCAAACACTACCAGCAGTACAGACATCTGCAGACCCCATCAGATCTGTAATGTGGTGGCCATTCCTGGGAATGCAAGTATGGATGCTGTCTGTACTTCCACCAGCCCAACTAGATCCATGGCCCCAGGGGCAGTCCACCTGCCCCAGCCTGTCAGCACTAGAAGCCAGCATACTCAGCCCACACCTGAGCCTTCTACAGCACCCTCCACCTCTTTCCTGCTGCCTATGGGGCCATCACCTCCAGCTGAGGGCAGTACAGGGGATGAACCTAAGTCATGTGACAAAACCCATACCTGTCCACCCTGCCCTGCTCCTGAGCTGCTGGGGGGACCCAGTGTCTTCCTGTTTCCTCCCAAACCTAAAGATACTCTGATGATCAGCAGAACCCCAGAGGTCACATGCGTGGTAGTGGATGTCTCCCATGAAGACCCTGAAGTGAAGTTTAATTGGTATGTAGATGGGGTGGAGGTCCATAATGCAAAGACCAAGCCCAGGGAAGAACAGTATAACAGTACTTACAGGGTGGTGTCTGTGCTGACAGTACTGCACCAGGACTGGCTGAATGGGAAGGAGTATAAGTGCAAAGTCAGCAATAAGGCACTGCCTGCCCCTATTGAAAAGACAATTAGTAAAGCTAAGGGGCAGCCCAGGGAACCACAGGTCTACACTCTGCCCCCTAGTAGAGAGGAAATGACAAAGAATCAGGTCAGTCTGACATGTCTGGTCAAGGGATTCTATCCAAGTGATATTGCAGTGGAGTGGGAAAGTAATGGCCAGCCAGAGAATAACTACAAGACTACCCCCCCAGTGCTGGACAGTGATGGATCTTTCTTTCTGTACTCCAAACTGACTGTGGATAAATCAAGATGGCAGCAGGGCAATGTCTTTTCCTGTTCAGTCATGCATGAAGCCCTGCATAATCACTACACTCAGAAGAGCCTGTCCCTGTCCCCTGGCAAATGATAACtcgaggacggggtgaactacgcctgaggatccgatcttttccctctgccaaaaattatggggacatcatgaagcccccttgagcatctgacttctggctaataaaggaaatttattttcattgcaatagtgtgttggaatttttgtgtctctcactcg
pAAV.sc.**mU1a**.Vh4i.**Etanercept** (5’-ITR to 3’-ITR) (2259 bp)	SEQ ID NO: 17	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagtggaattcaCGCGTATGGAGGCGGTACTATGTAGATGAGAATTCAGGAGCAAACTGGGAAAAGCAACTGCTTCCAAATATTTGTGATTTTTACAGTGTAGTTTTGGAAAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATGTGGGAGCCAGTACACATGAAGTTATAGAGTGTTTTAATGAGGCTTAAATATTTACCGTAACTATGAAATGCTACGCATATCATGCTGTTCAGGCTCCGTGGCCACGCAACTCATACTCAGGTGAGTATCTCAGGGATCCAGACATGGGGATATGGGAGGTGCCTCTGATCCCAGGGCTCACTGTGGGTCTCTCTGTTCACAGGTTAccggtGCCACCATGTATAGGATGCAGCTGCTGCTGCTGATTGCTCTGAGTCTGGCTCTGGTCACAAATAGTCTGCCTGCACAGGTGGCTTTTACCCCATATGCTCCTGAGCCTGGATCCACTTGTAGGCTGAGGGAGTATTATGATCAGACAGCCCAGATGTGCTGTTCAAAATGTTCCCCTGGACAGCATGCTAAGGTGTTTTGTACCAAGACAAGTGACACTGTCTGTGACAGCTGTGAGGATTCTACTTACACCCAGCTGTGGAATTGGGTGCCAGAATGTCTGTCATGTGGGAGCAGGTGTTCTAGTGACCAGGTGGAAACTCAGGCCTGTACAAGAGAGCAGAACAGGATTTGTACATGTAGACCAGGGTGGTACTGTGCCCTGAGCAAACAGGAAGGGTGTAGGCTCTGTGCTCCCCTGAGGAAATGTAGACCTGGGTTTGGGGTGGCCAGACCAGGAACAGAAACTTCTGATGTGGTCTGTAAGCCCTGTGCACCAGGAACCTTTTCAAACACTACCAGCAGTACAGACATCTGCAGACCCCATCAGATCTGTAATGTGGTGGCCATTCCTGGGAATGCAAGTATGGATGCTGTCTGTACTTCCACCAGCCCAACTAGATCCATGGCCCCAGGGGCAGTCCACCTGCCCCAGCCTGTCAGCACTAGAAGCCAGCATACTCAGCCCACACCTGAGCCTTCTACAGCACCCTCCACCTCTTTCCTGCTGCCTATGGGGCCATCACCTCCAGCTGAGGGCAGTACAGGGGATGAACCTAAGTCATGTGACAAAACCCATACCTGTCCACCCTGCCCTGCTCCTGAGCTGCTGGGGGGACCCAGTGTCTTCCTGTTTCCTCCCAAACCTAAAGA

Protein	SEQ ID NO.	Sequence
		TACTCTGATGATCAGCAGAACCCCAGAGGTCACATGCGTGGTAGTGGATGTCTCCCAT GAAGACCCTGAAGTGAAGTTTAATTGGTATGTAGATGGGGTGGAGGTCCATAATGCAA AGACCAAGCCCAGGGAAGAACAGTATAACAGTACTTACAGGGTGGTGTCTGTGCTGAC AGTACTGCACCAGGACTGGCTGAATGGGAAGGAGTATAAGTGCAAAGTCAGCAATAAG GCACTGCCTGCCCCTATTGAAAAGACAATTAGTAAAGCTAAGGGGCAGCCCAGGGAAC CACAGGTCTACACTCTGCCCCCTAGTAGAGAGGAAATGACAAAGAATCAGGTCAGTCT GACATGTCTGGTCAAGGGATTCTATCCAAGTGATATTGCAGTGGAGTGGGAAAGTAAT GGCCAGCCAGAGAATAACTACAAGACTACCCCCCCAGTGCTGGACAGTGATGGATCTT TCTTTCTGTACTCCAAACTGACTGTGGATAAATCAAGATGGCAGCAGGGCAATGTCTT TTCCTGTTCAGTCATGCATGAAGCCCTGCATAATCACTACACTCAGAAGAGCCTGTCC CTGTCCCCTGGCAAATGATAAaagcttgatcttttccctctgccaaaaattatgggg acatcatgaagcccttgagcatctgacttctggctaataaaggaaatttattttcat tgcaatagtgtgttggaatttttgtgtctctcactcggctagcgaagcaattctagc aggcatgctggggagagatcgatctgaggaaccctagtgatggagttggccactccc tctctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcga cctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagtggccaa
pAAV.sc.**mU1a**.Vh4i.**Etanercept** (promoter to polyA) (1951 bp)	SEQ ID NO: 18	ATGGAGGCGGTACTATGTAGATGAGAATTCAGGAGCAAACTGGGAAAAGCAACTGCTT CCAAATATTTGTGATTTTTACAGTGTAGTTTTGGAAAAACTCTTAGCCTACCAATTCT TCTAAGTGTTTTAAAATGTGGGAGCCAGTACACATGAAGTTATAGAGTGTTTTAATGA GGCTTAAATATTTACCGTAACTATGAAATGCTACGCATATCATGCTGTTCAGGCTCCG TGGCCACGCAACTCATACTCAGGTGAGTATCTCAGGGATCCAGACATGGGGATATGGG AGGTGCCTCTGATCCCAGGGCTCACTGTGGGTCTCTCTGTTCACAGGTTAccggtGCC ACCATGTATAGGATGCAGCTGCTGCTGCTGATTGCTCTGAGTCTGGCTCTGGTCACAA ATAGTCTGCCTGCACAGGTGGCTTTTACCCCATATGCTCCTGAGCCTGGATCCACTTG TAGGCTGAGGGAGTATTATGATCAGACAGCCCAGATGTGCTGTTCAAAATGTTCCCCT GGACAGCATGCTAAGGTGTTTTGTACCAAGACAAGTGACACTGTCTGTGACAGCTGTG AGGATTCTACTTACACCCAGCTGTGGAATTGGGTGCCAGAATGTCTGTCATGTGGGAG CAGGTGTTCTAGTGACCAGGTGGAAACTCAGGCCTGTACAAGAGAGCAGAACAGGATT TGTACATGTAGACCAGGGTGGTACTGTGCCCTGAGCAAACAGGAAGGGTGTAGGCTCT GTGCTCCCCTGAGGAAATGTAGACCTGGGTTTGGGGTGGCCAGACCAGGAACAGAAAC TTCTGATGTGGTCTGTAAGCCCTGTGCACCAGGAACCTTTTCAAACACTACCAGCAGT ACAGACATCTGCAGACCCCATCAGATCTGTAATGTGGTGGCCATTCCTGGGAATGCAA GTATGGATGCTGTCTGTACTTCCACCAGCCCAACTAGATCCATGGCCCCAGGGGCAGT CCACCTGCCCCAGCCTGTCAGCACTAGAAGCCAGCATACTCAGCCCACACCTGAGCCT TCTACAGCACCCTCCACCTCTTTCCTGCTGCCTATGGGGCCATCACCTCCAGCTGAGG GCAGTACAGGGGATGAACCTAAGTCATGTGACAAAACCCATACCTGTCCACCCTGCCC TGCTCCTGAGCTGCTGGGGGGACCCAGTGTCTTCCTGTTTCCTCCCAAACCTAAAGAT ACTCTGATGATCAGCAGAACCCCAGAGGTCACATGCGTGGTAGTGGATGTCTCCCATG AAGACCCTGAAGTGAAGTTTAATTGGTATGTAGATGGGGTGGAGGTCCATAATGCAAA GACCAAGCCCAGGGAAGAACAGTATAACAGTACTTACAGGGTGGTGTCTGTGCTGACA GTACTGCACCAGGACTGGCTGAATGGGAAGGAGTATAAGTGCAAAGTCAGCAATAAGG CACTGCCTGCCCCTATTGAAAAGACAATTAGTAAAGCTAAGGGGCAGCCCAGGGAACC ACAGGTCTACACTCTGCCCCCTAGTAGAGAGGAAATGACAAAGAATCAGGTCAGTCTG ACATGTCTGGTCAAGGGATTCTATCCAAGTGATATTGCAGTGGAGTGGGAAAGTAATG GCCAGCCAGAGAATAACTACAAGACTACCCCCCCAGTGCTGGACAGTGATGGATCTTT CTTTCTGTACTCCAAACTGACTGTGGATAAATCAAGATGGCAGCAGGGCAATGTCTTT TCCTGTTCAGTCATGCATGAAGCCCTGCATAATCACTACACTCAGAAGAGCCTGTCCC TGTCCCCTGGCAAATGATAAaagcttgatcttttccctctgccaaaaattatgggga catcatgaagcccttgagcatctgacttctggctaataaaggaaatttattttcatt gcaatagtgtgttggaatttttgtgtctctcactcg

5.6 Dose Administration of anti-TNFα Fc Fusion Proteins

[0175] Therapeutically effective doses of any such recombinant vector should be administered in any manner such that the recombinant vector enters ocular tissue cells (e.g., retinal cells), e.g. by introducing the recombinant vector into the bloodstream. Alternatively, the vector may be administered directly to the eye, e.g., via subretinal, intravitreal, intracameral, suprachoroidal injection. In specific, embodiments, the vector is administered subretinally, intravitreally, intracamerally, suprachoroidally, subcutaneously, intramuscularly or intravenously. Subretinal, intravitreal, intracamerally, or suprachoroidal administration should result in expression of the soluble transgene product in one or more of the following retinal cell types: human photoreceptor cells (cone cells, rod cells); horizontal cells; bipolar cells; amarcrine cells; retina ganglion cells (midget cell, parasol cell, bistratified cell, giant retina ganglion cell, photosensitive ganglion cell, and muller glia); and retinal pigment epithelial cells or other ocular tissue cell: cornea cells, iris cells, ciliary body cells, a schlemm's canal cells, a trabecular meshwork cells, RPE-choroid tissue cells, or optic nerve cells.

[0176] The expression of the transgene product results in delivery and maintenance of the transgene product in one or more ocular issues or ocular tissue cell types, e.g. retinal cells. Pharmaceutical compositions suitable for administration comprise a suspension of the recombinant vector comprising the transgene encoding anti-TNFα Fc fusion protein in a formulation buffer comprising a physiologically compatible aqueous buffer. The formulation buffer can comprise one or more of a polysaccharide, a surfactant, polymer, or oil.

[0177] Alternatively, vector encoding the recombinant vector encoding the anti-TNFα Fc fusion is delivered to the liver and the anti-TNFα Fc fusion is expressed and secreted into the circulation. In specific embodiments, doses and routes of administration of a vector comprising the transgene encoding an etanercept Fc fusion protein should result in expression of the etanercept Fc fusion protein that achieve and maintain an intravitreal concentration of the etanercept fusion protein at an equivalent level to the intravitreal concentration achieved by monthly injections of etanercept (Amgen) at a dose of 40 mg.

5.7 Monitoring of Efficacy

[0178] The compositions and methods described herein may be assessed for efficacy using any method for assessing efficacy in treating, preventing, or ameliorating NIU. The assessment may be determined in animal models or in human subjects. The efficacy on visual deficits may be measured

by best corrected visual acuity (BCVA), for example, assessing the increase in numbers of letters or lines and where efficacy may be assessed as an increase in greater than or equal to 2 ETDRS lines or an increase in logMAR, reduced inflammatory activity of the anterior and posterior chamber according to the SUN classification, and/ or reduction in grade of vitreous haze. Physical changes to the eye may be measured by Optical Coherence Tomography, using methods known in the aft.

[0179] The compositions and methods described herein may be assessed for efficacy using any method for assessing efficacy in treating, preventing, or ameliorating NIU. The assessment may be determined in animal models or in human subjects. The efficacy on visual deficits may be measured by best corrected visual acuity (BCVA), for example, assessing the increase in numbers of letters or lines and where efficacy may be assessed as an increase in greater than or equal to 2 ETDRS lines or an increase in logMAR, reduced inflammatory activity of the anterior and posterior chamber according to the SUN classification, and/ or reduction in grade of vitreous haze. Physical changes to the eye may be measured by Optical Coherence Tomography, using methods known in the aft. Efficacy may further be monitored by determining flare and/or relapse rates, anterior chamber cell, vitreous cell, and vitreous haze grades (e.g. grade of ≤0.5+), and/or number of active retinal or choroidal (inflammatory) lesions (*e.g.* see Kim J.S. et al, Int Ophthalmol Clin. 2015 Summer; 55(3): 79–110 or Rosenbaum J.T. et al Volume 49, Issue 3, December 2019, Pages 438-445; which are incorporated by reference herein in its entirety).

[0180] Endpoints may include, but are not limited to, mean change in vitreous haze grade in the study eye from baseline to 12, 16, 20, 24, or 28 weeks or at time of rescue, if earlier, proportion of responders with no recurrence of active intermediate, posterior, or panuveitis in the study eye at 12, 16, 20, 24, or 28 weeks, mean change in best corrected visual acuity from baseline to 12, 16, 20, 24, or 28 weeks, change from baseline in quality of life/patient reported outcome assessments, mean change in vitreous haze grade and anterior chamber cell grade from baseline to 12, 16, 20, 24, or 28 weeks, or change in immunosuppressive medication score from baseline to 12, 16, 20, 24, or 28 weeks.

6. EXAMPLES

6.1 EXAMPLE 1: Etanercept cDNA-Based Vector

[0181] A etanercept cDNA-based vector was constructed comprising a transgene comprising nucleotide sequences encoding the TNFR:Fc fusion etanercept (amino acid sequences being SEQ ID NO: 10 or 11). Nucleotide sequences are the nucleotide sequence of SEQ ID NO: 13 or 14. The transgene also included nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLLIALSLALVTNS (SEQ ID NO:62). See FIG. 2A for amino acid sequence of the transgene product. The vector additionally includes a constitutive promoter, such as CAG and mU1a, and can include alternative promoters such as EF1a or CB7 or CB (SEQ ID NO: 159) or CB long (SEQ ID NO: 160) promoter, or a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:54), or a Best1/GRK promoter (SEQ ID NO: 161) or an inducible promoter, such as a hypoxia-inducible promoter.

6.2 EXAMPLE 2: EYS060 cDNA-Based Vector

[0182] A EYS060 cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the TNFR:Fc fusion EYS060 (amino acid sequences being SEQ ID NO: 12). The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLLIALSLALVTNS (SEQ ID NO:62). See FIG. 2B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CAG, mU1a, and can include alternative promoters such as EF1a or CB7 or CB (SEQ ID NO: 159) or CB long (SEQ ID NO: 160) promoter, or a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:54), or a Best1/GRK promoter (SEQ ID NO: 161), or an inducible promoter, such as a hypoxia-inducible promoter.

6.3 EXAMPLE 3: TNFα binding across model species with vectorized adalimumab IgG and Fab and vectorized etanercept

[0183] A. Vectorized adalimumab candidates isolated from model species including human, mouse, and rat were tested for their binding capacity for TNFα. Vectorized antibodies were expressed and secreted into cell supernatant following cis plasmid transfection into 293T cells. The cell supernatant was tested in an ELISA where the plates were coated with recombinant TNFα derived from the aforementioned species (**FIG. 5A**). Adalimumab IgG effectively bound human and mouse

derived TNFα. The Fab demonstrates a similar binding profile to human TNFα as the IgG. However, the Fab displays poor binding to mouse TNFα compared to adalimumab IgG. Both IgG and Fab display far reduced binding to rat TNFα.

[0184] B. Vectorized etanercept was assayed in the same manner for binding to human, mouse and rat TNFα. Etanercept bound all of human, mouse and rat derived TNFα and binds rat TNFα better than adalimumab. See FIG. 5B.

6.4 EXAMPLE 4: AAV-mediated Ocular Gene Therapy for Non-infectious Posterior Uveitis

[0185] Non-infectious posterior uveitis is a form of ocular inflammation that affects the retina and choroid of the eye and leads to blindness. It afflicts approximately 38,000 Americans per year. Patients are usually treated with systemic steroids or corticosteroids therapy, which results in high risks of systemic complications. In 2016, Humira (adalimumab), a human monoclonal antibody that targets tumor necrosis factor-alpha (TNFα), was approved by FDA and became the only systemic noncorticosteroid agent for the treatment of non-infectious uveitis (NIU) and has been widely used since then. In this study, a vectorized anti-TNFα Fc fusion protein, including CAG.etanercept or mU1a.Vh4i.etanercept.scAAV, or a vectorized EYS606, as well as AAV8.CAG.GFP, will be evaluated for AAV-mediated anti-TNFα Fc Fusion protein expression *in vivo* in mouse ocular tissues via local administration. AAV8.NUL will serve as a control vector. Efficacy studies in rodent EAU model will also be performed to investigate therapeutic potential of AAV-mediated anti-TNFα treatment for NIU.

[0186] Vectorized etanercept and EYS606 sequences will be constructed and tested in vitro. The transduction efficiency and cell type specificity in wild type mouse will further be evaluated. Young adult C57BL/6 and B10.RIII mice (8-10 weeks old) will be used for this study. Vectors including CAG.etanercept (SEQ ID NO: 15 or 16 (with and without flanking ITRs)) or mU1a.Vh4i.etanercept.scAAV (SEQ ID NO: 17 or 18 (with or without flanking ITR sequences)), or a vectorized EYS606, as well as, AAV8.CAG.GFP and AAV8.NUL will be delivered in mouse eyes via subretinal (SR) injection at different doses ($1x10^7$, $1x10^8$ and $1x10^9$ vg/eye) in 1μl of formulation buffer. Fundus and OCT imaging will be performed at 1, 2 and 4 weeks after SR injection. Ocular samples will be collected at 5 weeks post administration. Levels of antibody or fusion protein expression in ocular tissues will be quantified by ELISA. Cell type specificity will be determined by

immunofluorescent staining with various retinal cell markers. Test vector(s) will be selected for efficacy study. Different routes of administration (ROA) including suprachoroidal, intracameral and intravitreal injections will also be explored. The preferred ROA will be used for efficacy study.

[0187] Efficacy studies will be conducted by inducing experimental autoimmune uveitis (EAU) in B10.RIII mice by immunization with the human IRBP peptide. T-cell mediated ocular autoimmune response will occur in this model with a peak from approximately 11 to 18 days post-induction. Test vector will be administrated in mouse eye via preferred ROA at 2 weeks before or 1 week after induction of EAU. Contralateral eye will be delivered with AAV.NUL vector and serve as a control. Fundus and OCT imaging, electroretinography (ERG) and Optokinetic nystagmus (OKN) will be tested at 10, 17 and 30 days following induction of EAU to monitor the progress of the disease. Ocular tissues or whole eyeballs will be collected at 5 weeks post EAU induction. Levels of or fusion protein expression in ocular tissues will be detected and quantified by ELISA. Retina structure changes and neuron survival will be evaluated by histology and immunofluorescent staining.

6.5 EXAMPLE 5: In vivo Study

[0188] In this study, full length and Fab adalimumab antibody in an adeno-associated virus (AAV) vector (AAV8.CAG.adalimumab.IgG (NIU001) and AAV8.CAG.adalimumab.Fab (NIU002)), as well as etanercept Fc fusion protein (AAV8.CAG.etanercept), will be evaluated for AAV-mediated antibody expression *in vivo* in mouse ocular tissues via local administration (subretinal (SR), **Table 8**).

Table 8. Study Layout

Group	Vector	ROA	Inj. Volume (uL)	Dose (vg/eye)	N (animals)	N (eyes)
1	AAV8.CAG.Adalimumab.IgG	SR	1	1.00E+09	2	4
2		SR	1	1.00E+08	2	4
3	AAV8.CAG.Adalimumab.Fab	SR	1	1.00E+09	3	6
4		SR	1	1.00E+08	3	6
5	AAV8.CAG.Etanercept	SR	1	1.00E+09	3	6
6		SR	1	1.00E+08	3	6
7	Vehicle	SR	1	1.00E+09	2	4

[0189] Vectorized adalimumab and etanercept sequences have been constructed and tested in vitro. Young adult B10.RIII mice (6-8 weeks old) were used for this study. Vectors including AAV8.CAG.adalimumab.IgG, AAV8.CAG.adalimumab.Fab, AAV8.CAG.etanercept, and vehicle are delivered in mouse eyes via subretinal (SR) injection at two different doses ($1x10^8$ and $1x10^9$ vg/eye) in 1µl of formulation buffer (**Table 8**).

[0190] Fundus and OCT imaging were performed at 2 and 4 weeks after SR injection. Ocular samples were collected at 4 weeks post administration. Levels of antibody or fusion protein expression in ocular tissues are quantified by ELISA. Cell type specificity was determined by immunofluorescent staining with various retinal cell markers. Retina structure changes and neuron survival are evaluated by histology and immunofluorescent staining at 2 and 4 weeks post administration.

6.6 EXAMPLE 6: Evaluation of Vector-expressed Etanercept Binding Kinetics

[0191] Expression and purification of vectorized etanercept from AAV produced from cis plasmids will be assessed. The purified vectorized etanercept kinetics of binding to various species of TNFα protein will be compared to commercially produced etanercept in various ligand binding assays.

[0192] Binding affinity using Biacore™ (surface plasmon resonance (SPR)) assays: A study is performed to measure the binding affinity of different TNF-alpha (TNFα) molecules to purified TNFR-fusion proteins using BiacoreT200. First, binding affinity of TNFα to pAAV.CAG.Etanercept-produced fusion protein is compared to binding of TNFα to commercial etanercept. Second, binding affinity of TNFα from different species are tested in order to determine the suitability of various species TNFα proteins for later animal model studies. The Biacore assay is performed at 25°C using HBS-EP+ as the running buffer. Diluted fusion proteins are captured on the sensor chip through Fc capture method (15-20 minutes capture time). Different species TNFα proteins (human, macaque, porcine, mouse, canine, rabbit and rat) can be tested individually as the analyte, followed by injecting running buffer in the dissociation phase. Dissociation rates are calculated [Koff= Kd= protein dissociation rate; Kon= Ka= protein association rate; K¬D = Koff/Kon], and smaller (lower) KD values indicated the greater the affinity of the TNFR-fusion protein for its target.

Table 9. Assay setup

Ligand	Analyte
Etanercept	Human TNFα
pAAV.CAG.Etanercept	Human TNFα
Etanercept	Macaque TNFα
pAAV.CAG.Etanercept	Macaque TNFα
Etanercept	Porcine TNFα
pAAV.CAG.Etanercept	Porcine TNFα
Etanercept	Mouse TNFα
pAAV.CAG.Etanercept	Mouse TNFα
Etanercept	Canine TNFα
pAAV.CAG.Etanercept	Canine TNFα
Etanercept	Rabbit TNFα
pAAV.CAG.Etanercept	Rabbit TNFα
Etanercept	Rat TNFα
pAAV.CAG.Etanercept	Rat TNFα

[0193] Binding affinity (KD) of different species TNFα to vectorized etanercept vs. commercial etanercept will be ranked according to their KD value.

6.7 Example 7: Measurement of TNF-Fusion Protein Effector Function

[0194] Effector functions, antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), of the vector-produced etanercept will be evaluated by in vitro assays and compared to commercially produced etanercept (ENBREL). Effector functions are elicited through the Fc domain of antibodies and thus, fusion proteins containing an Fc domain, such as etanercept.

Materials and Methods

[0195] Target cells (CHO/DG44-tm TNFα; GenScript Cat. #RD00746) are maintained with corresponding complete culture medium at 37°C with 5% CO2. Effector cells (peripheral blood mononuclear cells, PBMCs; Saily Bio Cat. # XFB-HP100B) are thawed at 37°C and maintained with 1640 complete culture medium at 37°C with 5% CO2.

[0196] For the ADCC dose-response assay, CHO/DG44-tm TNFα and PBMCs can be used as target and effector cells, respectively. With a E/T (effector cell to target cell) ratio set at 25:1, etanercept (commercial) and human IgG1 against CHO/DG44-tm TNFα re used as positive and negative control, respectively. Briefly, the method steps are:

CHO/DG44-tm TNFα (target cells)

+

Samples

+

PBMC (effector cells)

↓

% target cell lysis

[0197] Effector cells (PBMCs) are thawed and resuspended with assay buffer (CellTiter-Glo®Detection Kit (Promega, Cat.#G7573). Target cells are also thawed and resuspended with ADCC assay buffer, then transferred in suspension to an assay plate following a plate map. Controls and test samples in solution are transferred to the assay plate as well, and the assay plate incubated at RT for 30 minutes. The effector cell density is adjusted according to the E/T ratio, then the effector cell suspension is transferred to the assay plate. The assay plate is then incubated in a cell incubator (37°C/5%CO2) for 6 hours, removed, then the supernatant of corresponding wells of the assay plate are transferred to another 96-well assay plate. LDH Mixture (LDH Cytotoxicity Detection Kit, Roche Cat# 11644793001) is transferred to the corresponding wells of the second 96-well assay plate and luminescence/ absorbance is read with a PHERAStar® (BMG LABTECH) plate reader.

[0198] For the CDC dose-response study, CHO/DG44-tm TNFα can be used as the target cell. With 5% NHSC (normal human serum complement), etanercept and human IgG1 against CHO/DG44-

tm TNFα can be used as positive and negative control, respectively. Briefly, the CDC assay method steps are:

CHO/DG44-tm TNFα (target cells)

+

Samples

+

NHSC

↓

% target cell lysis

[0199] Target cells are harvested by centrifugation and resuspended with assay buffer (CellTiter-Glo®Detection Kit (Promega, Cat.#G7573). Samples and controls are prepared in solution with CDC assay buffer. Target cell density was adjusted and then cell suspension transferred to the assay plate. Controls and test samples in working solution are also transferred to the assay plate, and then assay plate is incubated at RT for 30 minutes, before the Normal Human Serum Complement (NHSC) working solution (Quidel, Cat. # A113) is added to the assay plate. The assay plate is incubated in the cell incubator (37°C/5%CO2) for 4 hours, removed, and the Cell Titer-Glo® working solution is added to the corresponding wells and the plate incubated for about 10-30 minutes at RT. Luminescence data is read on a PHERAStar® FSX (BMG LABTECH) plate reader to determine the number of viable cells. Raw data of ADCC and CDC study are exported from the PHERAStar® FSX system and analyzed using Microsoft Office Excel 2016 and GraphPad Prism 6 software. The formula of ADCC % Target cell lysis = 100*(ODSamples - ODTumor cells plus effector cells) / (ODMaximum release - ODMinimum release). The formula of CDC % Target cell lysis = 100*(1-(RLUSamples - RLUNHSC) / (RLUCell+NHSC - RLUNHSC)). Relative EC50 values are obtained using four-parameter function as follows, characterizing sigmoid curve where %target cell lysis is against the concentration of the test samples: Y = Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope)) = Percentage of target cell lysis; and X = Concentration.

[0200] With an E/T ratio at 25:1, CHO/DG44-tm TNFα cells can be used as the target cells in a ADCC dose-response study. Dose-responses and Best-fit values of positive control (commercial etanercept), samples and negative control (Human IgG1) are calculated (e.g. EC50).

[0201] With 5% NHSC, CHO/DG44-tm TNFα cells are used as the target cells in CDC dose-response study. Dose-responses and Best-fit values of positive control (etanercept), samples and negative control (Human IgG1) are calculated (e.g. EC50).

[0202] AAV-etanercept ADCC and CDC activity will be compared to commercial etanercept. Without being bound to any one theory, differences may be observed due to the post-translational modification, such as glycosylation, which is expected to differ due to manufacturing cell culture of commercial etanercept.

EQUIVALENTS

[0203] Although the invention is described in detail with reference to specific embodiments thereof, it will be understood that variations which are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims. Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

[0204] All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference in their entireties.

What is claimed is:

1. A pharmaceutical composition for treating non-infectious uveitis in a human subject in need thereof, comprising an adeno-associated virus (AAV) vector having:

(a) a viral capsid that has a tropism for ocular tissue cells; and

(b) an artificial genome comprising an expression cassette flanked by AAV internal tandem repeats (ITRs), wherein the expression cassette comprises a transgene encoding an anti-TNFα Fc fusion protein, operably linked to one or more regulatory sequences that control expression of the transgene in human ocular cells;

wherein said AAV vector is formulated for subretinal, intravitreal, intranasal, intracameral, suprachoroidal, or systemic administration to said human subject.

2. The pharmaceutical composition of claim 1, wherein the anti-TNFα Fc fusion protein comprises a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked through a peptide bond to a polypeptide comprising an Fc domain of an immunoglobulin heavy chain.

3. The pharmaceutical composition of claim 1 or 2, wherein the viral capsid is at least 95% identical to the amino acid sequence of AAV serotype 1 (AAV1), serotype 2 (AAV2), serotype AAV2.7m8 (AAV2.7m8), serotype 3 (AAV3), serotype 3B (AAV3B), serotype 4 (AAV4), serotype 5 (AAV5), serotype 6 (AAV6), serotype 7 (AAV7), serotype 8 (AAV8), serotype rh8 (AAVrh8), serotype 9 (AAV9), serotype 9e (AAV9e), serotype rh10 (AAVrh10), serotype rh20 (AAVrh20), serotype rh39 (AAVrh39), serotype hu.37 (AAVhu.37), serotype rh73 (AAVrh73), or serotype rh74 (AAVrh74), serotype hu51 (AAV.hu51), serotype hu21 (AAV.hu21), serotype hu12 (AAV.hu12), or serotype hu26 (AAV.hu26).

4. The pharmaceutical composition of any of claims 1 to 3, wherein the AAV capsid is AAV8, AAV3B, AAV2.7m8, or AAVrh73.

5. The pharmaceutical composition of claims 1 to 4, wherein the ocular tissue cell is a cornea cell, an iris cell, a ciliary body cell, a schlemm's canal cell, a trabecular meshwork cell, a retinal cell, a RPE-choroid tissue cell, or an optic nerve cell.

6. The pharmaceutical composition of claims 1 to 5, wherein the regulatory sequence includes a regulatory sequence from Table 1 or 1a.

7. The pharmaceutical composition of claim 5, wherein the regulatory sequence is a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:54 or 117), a mouse cone arresting (CAR) promoter (SEQ ID NOS:114-116), a human red opsin (RedO) promoter (SEQ ID NO:112), a CB promoter (SEQ ID NO: 159), CBLong promoter (SEQ ID NO: 160), or Best1/GRK promoter (SEQ ID NO: 161).

8. The pharmaceutical composition of any of claims 1 to 7, wherein the transgene encodes a signal sequence at the N-terminus of the anti-TNFα Fc fusion protein that directs secretion and post translational modification in said human ocular cells.

9. The pharmaceutical composition of claim 8, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO:62) or a signal sequence from Table 2.

10. The pharmaceutical composition of any of claims 1 to 8, wherein transgene has the structure from the N-terminus to the C-terminus: Signal sequence–soluble TNFR extracellular domain – hinge region – Fc domain – PolyA.

11. The composition of claim 10, wherein the transgene further comprises a thrombin cleavage site of SEQ ID NO:8 at the C-terminus of the soluble TNFR extracellular domain.

12. The pharmaceutical composition of any of claims 1 to 11, wherein anti-TNFα Fc fusion protein is expressed as a dimeric fusion protein.

13. The pharmaceutical composition of any of claims 1 to 12, wherein the anti-TNFα Fc fusion protein is etanercept or EYS606.

14. The pharmaceutical composition of any of claims 1 to 13, wherein said transgene comprises the nucleotide sequence of SEQ ID NO: 13-18.

15. The pharmaceutical composition of any of claims 1 to 14, wherein the anti-TNFα Fc fusion protein has an amino acid sequence of SEQ ID NO: 10, 11 or 12.

16. The pharmaceutical composition of any of claims 1 to 15, wherein the anti-TNFα Fc fusion protein is a hyperglycosylated mutant or wherein the Fc polypeptide of the anti-TNFα Fc fusion protein is glycosylated or aglycosylated.
17. The pharmaceutical composition of any of claims 1 to 16, wherein the Fc domain is an IgG1-Fc domain.
18. The pharmaceutical composition of any of claims 1 to 17, wherein the artificial genome is self complementary.
19. The pharmaceutical composition of any of claims 1 to 18 wherein the artificial genome is the construct CAG.etanercept (SEQ ID NO: 15) or mU1a.Vh4i.etanercept.scAAV (SEQ ID NO: 17).
20. A composition comprising an adeno-associated virus (AAV) vector having:

a. a viral AAV capsid, that is optionally at least 95% identical to the amino acid sequence of AAV serotype 1 (AAV1), serotype 2 (AAV2), serotype AAV2.7m8 (AAV2.7m8), serotype 3 (AAV3), serotype 3B (AAV3B), serotype 4 (AAV4), serotype 5 (AAV5), serotype 6 (AAV6), serotype 7 (AAV7), serotype 8 (AAV8), serotype rh8 (AAVrh8), serotype 9 (AAV9), serotype 9e (AAV9e), serotype rh10 (AAVrh10), serotype rh20 (AAVrh20), serotype rh39 (AAVrh39), serotype hu.37 (AAVhu.37), serotype rh73 (AAVrh73), or serotype rh74 (AAVrh74), serotype hu51 (AAV.hu51), serotype hu21 (AAV.hu21), serotype hu12 (AAV.hu12), or serotype hu26 (AAV.hu26).

b. an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding an anti-TNF-α Fc fusion protein comprising a human soluble TNFα receptor type I (TNFR1) or type II (TNFR2) extracellular domain covalently linked through a peptide bond to a polypeptide comprising an Fc domain of an immunoglobulin heavy chain, operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

wherein the transgene encodes a signal sequence at the N-terminus of said anti-TNFα Fc fusion protein that directs secretion and post translational modification of said anti-TNFα Fc fusion in ocular tissue cells.

21. The composition of claim 20, wherein the transgene further comprises a thrombin cleavage site of SEQ ID NO:8 at the C-terminus of soluble human TNFR extracellular domain.
22. The composition of any of claims 20 or 21, wherein the anti-TNFα Fc fusion protein has an amino acid sequence of SEQ ID NO: 10, 11, or 12.
23. The composition of claims 20 to 22, wherein the anti-TNFα Fc fusion protein is etanercept or EYS606.
24. The composition of claims 20 to 23, wherein the ocular tissue cell is a cornea cell, an iris cell, a ciliary body cell, a schlemm's canal cell, a trabecular meshwork cell, a retinal cell, a RPE-choroid tissue cell, or an optic nerve cell.
25. The composition of claims 20 to 24, wherein said transgene comprises the nucleotide sequence of SEQ ID NO:13 or 14.
26. The composition of claims 20 to 25, wherein said signal sequence is MYRMQLLLLLIALSLALVTNS (SEQ ID NO:62) or a signal sequence from Tables 2 or 3.
27. The composition of any of claims 20 to 26, wherein the artificial genome is self complementary.
28. The composition of any of claims 20 to 27 wherein the artificial genome is the construct CAG.etanercept (SEQ ID NO: 15 or 16) or mU1a.Vh4i.etanercept.scAAV (SEQ ID NO: 17 or 18).
29. A method of treating non-infectious uveitis in a human subject in need thereof, comprising subretinally, intravitreally, intranasally, intracamerally, suprachoroidally, or systemically administering to the subject a therapeutically effective amount of a composition comprising a recombinant AAV comprising a transgene encoding an anti-TNFα Fc fusion protein operably linked to one or more regulatory sequences that control expression of the transgene in ocular tissue cells.
30. A method of treating non-infectious uveitis in a human subject in need thereof, comprising: subretinally, intravitreally, intranasally, intracamerally, suprachoroidally, or systemically administering to said subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding an anti-TNFα Fc fusion protein, operably linked to one or more regulatory sequences that control expression of the transgene in human

ocular tissue cells, so that a depot is formed that releases a human post-translationally modified (HuPTM) form of anti-TNFα Fc fusion protein.

31. The method of claims 29 and 30, wherein the ocular tissue cell is a cornea cell, an iris cell, a ciliary body cell, a schlemm's canal cell, a trabecular meshwork cell, a retinal cell, a RPE-choroid tissue cell, or an optic nerve cell.
32. The method of claims 29 to 31, wherein said anti-TNF-α Fc fusion protein comprises a human soluble TNFα receptor type I (TNFR1) or type II (TNFR2) extracellular domain covalently linked to an IgG Fc domain.
33. The method of claims 29 to 32, wherein said transgene is etanercept or EYS606.
34. The method of claims 29 to 33, wherein said transgene has the nucleotide sequence of SEQ ID NO: 13-18.
35. The method of claims 29 to 34, wherein the viral capsid is at least 95% identical to the amino acid sequence of AAV serotype 1 (AAV1), serotype 2 (AAV2), serotype AAV2.7m8, serotype 3 (AAV3), serotype 3B (AAV3B), serotype 4 (AAV4), serotype 5 (AAV5), serotype 6 (AAV6), serotype 7 (AAV7), serotype 8 (AAV8), serotype rh8 (AAVrh8), serotype 9 (AAV9), serotype 9e (AAV9e), serotype rh10 (AAVrh10), serotype rh20 (AAVrh20), serotype rh39 (AAVrh39), serotype hu.37 (AAVhu.37), serotype rh73 (AAVrh73), or serotype rh74 (AAVrh74), serotype hu51 (AAV.hu51), serotype hu21 (AAV.hu21), serotype hu12 (AAV.hu12), or serotype hu26 (AAV.hu26).
36. The method of any of claims 29 to 35, wherein the AAV capsid is AAV8, AAV2.7m8, AAV3B, or AAVrh73.
37. The method of any of claims 29 to 36, wherein the regulatory sequence includes a regulatory sequence from Table 1 or 1a.
38. The method of claim 37, wherein the regulatory sequence is a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:54 or 117), a mouse cone arresting (CAR) promoter (SEQ ID NOS:114-116), or a human red opsin (RedO) promoter (SEQ ID NO:112).
39. The method of any of claims 29 to 38, wherein the transgene encodes a signal sequence at the N-terminus of the anti-TNFα Fc fusion protein that directs secretion and post translational modification in said human ocular tissue cells.

40. The method of claim 39, wherein said signal sequence is MYRMQLLLLLIALSLALVTNS (SEQ ID NO:62) or a signal sequence from Tables 2 or 3.

41. The method of any of claims 25 to 40, wherein transgene has the structure: Signal sequence–9human soluble TNFR extracellular domain (type 1 or type 2) – hinge region - Fc domain – PolyA.

42. The method of claim 41, wherein the transgene further comprises a thrombin cleavage site having SEQ ID NO:8 at the C-terminus of the human soluble TNFR extracellular domain.

43. The method of any of claims 29 to 42, wherein the anti-TNFα Fc fusion protein is a hyperglycosylated mutant or wherein the Fc domain of the anti-TNFα Fc fusion protein is glycosylated or aglycosylated.

44. The method of any of claims 29 to 43, wherein anti-TNFα Fc fusion protein contains an alpha 2,6-sialylated glycan.

45. The method of any of claims 29 to 44, wherein anti-TNFα Fc fusion protein is glycosylated but does not contain detectable NeuGc and/or α-Gal.

46. The method of any of claims 29 to 45, wherein anti-TNFα Fc fusion protein contains a tyrosine sulfation.

47. The method of any of claims 29 to 46 in which production of said HuPTM form of the anti-TNFα Fc fusion protein is confirmed by transducing human ocular cells in culture with said recombinant nucleotide expression vector and expressing said anti-TNFα Fc fusion protein.

48. The method of claims 29 or 47, wherein the therapeutically effective amount is determined to be sufficient to improve best corrected visual acuity (BCVA) by >= 2 ETDRS lines or increase in logMAR, reduced inflammatory activity of the anterior and posterior chamber according to the SUN classification, and/ or reduction in grade of vitreous haze.

49. The method of any of claims 29 to 48, wherein the rAAV is self complementary.

50. The method of any of claims 29 to 49 wherein the transgene within the construct CAG.etanercept or mU1a.Vh4i.etanercept.scAAV.

51. A method of producing recombinant AAVs comprising:

(c) culturing a host cell containing:

(i) an artificial genome comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises a transgene encoding an anti-TNFα Fc fusion protein, wherein the anti-TNFα Fc fusion protein comprises a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked through a peptide bond to a polypeptide comprising an Fc domain of an immunoglobulin heavy chain, operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

(ii) a *trans* expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and an AAV capsid protein operably linked to expression control elements that drive expression of the AAV rep and the AAV capsid protein in the host cell in culture and supply the AAV rep and the AAV capsid protein in *trans*, wherein the capsid has ocular tissue tropism;

(iii) sufficient adenovirus helper functions to permit replication and packaging of the artificial genome by the AAV capsid protein; and

(d) recovering recombinant AAV encapsidating the artificial genome from the cell culture.

52. The method of claim 51, wherein the ocular tissue cell is a cornea cell, an iris cell, a ciliary body cell, a schlemm's canal cell, a trabecular meshwork cell, a retinal cell, a RPE-choroid tissue cell, or an optic nerve cell.

53. The method of claims 51 or 52, wherein the transgene encodes etanercept or EYS606, wherein the AAV capsid protein is The rAAV capsid protein of embodiment 1, wherein said capsid protein is from at least one AAV serotype of AAV serotype 1 (AAV1), serotype 2 (AAV2), serotype 2.7m8, serotype 3 (AAV3), serotype 3B (AAV3B), serotype 4 (AAV4), serotype 5 (AAV5), serotype 6 (AAV6), serotype 7 (AAV7), serotype 8 (AAV8), serotype rh8 (AAVrh8), serotype 9 (AAV9), serotype 9e (AAV9e), serotype rh10 (AAVrh10), serotype rh20 (AAVrh20), serotype rh39 (AAVrh39), serotype hu.37 (AAVhu.37), serotype rh73 (AAVrh73), or serotype

rh74 (AAVrh74), serotype hu51 (AAV.hu51), serotype hu21 (AAV.hu21), serotype hu12 (AAV.hu12), or serotype hu26 (AAV.hu26).

54. A host cell containing:

d. an artificial genome comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprising a transgene encoding an anti-TNFα fusion protein, wherein the anti-TNFα Fc fusion protein comprises a soluble, extracellular portion of human TNFα receptor type I (TNFR1) or type II (TNFR2) covalently linked through a peptide bond to polypeptide comprising an Fc domain of an immunoglobulin heavy chain, operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

e. a *trans* expression cassette lacking AAV ITRs, wherein the trans expression cassette encodes an AAV rep and an AAV capsid protein operably linked to expression control elements that drive expression of the AAV rep and the AAV capsid protein in the host cell in culture and supply the AAV rep and the AAV capsid protein in *trans,* wherein the capsid has ocular tissue tropism;

f. sufficient adenovirus helper functions to permit replication and packaging of the artificial genome by the AAV capsid protein.

55. The host cell of claim 54, wherein the transgene encodes etanercept or EYS606.

56. The host cell of claims 53 or 54, wherein the AAV capsid protein is AAV serotype 1 (AAV1), serotype 2 (AAV2), serotype 2.7m8 (AAV2.7m8), serotype 3 (AAV3), serotype 3B (AAV3B), serotype 4 (AAV4), serotype 5 (AAV5), serotype 6 (AAV6), serotype 7 (AAV7), serotype 8 (AAV8), serotype rh8 (AAVrh8), serotype 9 (AAV9), serotype 9e (AAV9e), serotype rh10 (AAVrh10), serotype rh20 (AAVrh20), serotype rh39 (AAVrh39), serotype hu.37 (AAVhu.37), serotype rh73 (AAVrh73), or serotype rh74 (AAVrh74), serotype hu51 (AAV.hu51), serotype hu21 (AAV.hu21), serotype hu12 (AAV.hu12), or serotype hu26 (AAV.hu26).

FIG. 1

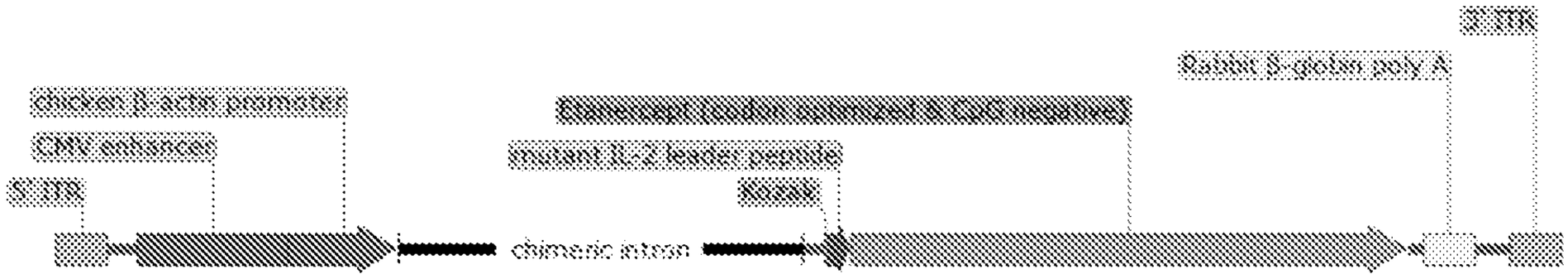
chicken β-actin promoter
CMV enhancer
5' ITR
chimeric intron
mutant IL-2 leader peptide
Kozak
Rabbit β-globin poly A
3' ITR

FIG. 2A ETANERCEPT TNFR2:Fc FUSION CONSTRUCT:

Leader:
MYRMQLLLLIALSLALVTNS (SEQ ID NO:62)
Etanercept TNFR2:Fc Fusion Protein (SEQ ID NO:10):

LPAQVAFTPY APEPGSTCRL REYYDQTAQM CCSKCSPGQH AKVFCTKTSD TVCDSCEDST YTQLWNWVPE
CLSCGSRCSS DQVETQACTR EQNRICTCRP GWYCALSKQE GCRLCAPLRK CRPGFGVARP GTETSDVVCK
PCAPGTFS**NT** **T**SSTDICRPH QICNVVAIPG **NAS**MDAVCTS TSPTRSMAPG AVHLPQPVST RSQHTQPTPE
PSTAPSTSFL LPMGPSPPAE GSTGD*EPKSC DKTHTCPPCP APELLGGPSV* FLFPPKPKDT LMISRTPEVT
CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQY**NST**Y RVVSVLTVLH QDWLNGKEYK CKVSNKALPA
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK

Legend:
Extracellular domain of the p75 TNFR is not highlighted
IgG1 Fc domain is highlighted in grey
O-glycosylation site underlined and highlighted
(S/T)XN or **NX(S/T)** = Nonconsensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO:145)

FIG. 2B EYS606 TNFR1:Fc FUSION CONSTRUCT:

Leader (SEQ ID NO: 62):
MYRMQLLLLIALSLALVTNS
EYS606 TNFR1:Fc Fusion Protein (SEQ ID NO:12):

MGLSTVPDLLLPLVLLELLVGIYPSGVIGLVPHLGDREKRDSVCPQGKYIHPQ**NNS**ICCTKCHKGTYLYNDCPGPGQ
DTDCRECESGSFTA**SEN**HLRHCLSCSKCRKEMGQVEISSCTVDRDTVCGCRKNQYRHY*W**SEN***LFQCF**NCS**LCL**NGT**V
HLSCQEKQNTVCTCHAGFFLRENECVSCSNCKKSLECTKLCLPQIENVKGTEDSGTTLVPRG§*DKTHTCPPCPAPEL*
*LGGPSV*FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY**NST**YRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM**TKN**QVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGS

Legend:
Extracellular domain of the p55 TNFR is shown in bold
IgG1 Fc domain is highlighted in grey
O-glycosylation site in highlighted and underlined
(S/T)XN or **NX(S/T)** = Consensus/Nonconsensus Asparaginal (N) glycosylation site
LVPRGS: Thrombin cleavage site (SEQ ID NO:8)
DKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO:21)

FIG. 3

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                          |         |         |         |         |         |
AAV1            MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
AAV2            MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLD 60
AAV3            MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKYLGPGNGLD 60
AAV3-3          MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKYLGPGNGLD 60
AAV3B           MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKYLGPGNGLD 60
AAV4            -MTDGYLPDWLEDNLSEGVREWWALQPGAPKPKANQQHQDNARGLVLPGYKYLGPGNGLD 59
AAV4-4          -MTDGYLPDWLEDNLSEGVREWWALQPGAPKPKANQQHQDNARGLVLPGYKYLGPGNGLD 59
AAV5            MSFVDHPPDWLEE-VGEGLREFLGLEAGPPKPKPNQQHQDQARGLVLPGYNYLGPGNGLD 59
AAV6            MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
AAV7            MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDNGRGLVLPGYKYLGPFNGLD 60
AAV8            MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
AAV9            MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGLD 60
AAV9e           MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGLD 60
rh.10           MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
rh.20           MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
rh.39           MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
rh.73           MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
rh.74v1         MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDNGRGLVLPGYKYLGPFNGLD 60
rh.74v2         MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDNGRGLVLPGYKYLGPFNGLD 60
hu.12           MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHQDDSRGLVLPGYKYLGPFNGLD 60
hu.21           MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLD 60
hu.26           MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLD 60
hu.37           MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
hu.51           MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLD 60
hu.53           MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLD 60
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FIG. 3 (Continued)

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FIG. 3 (Continued)

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FIG. 3 (Continued)

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                                  |         |         |         |         |         |
AAV1              QRLINNNWGFRPKRLNFKLFNIQVKEVTTNDGVTTIANNLTSTVQVFSDSEYQLPYVLGS 357
AAV2              QRLINNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
AAV3              QRLINNNWGFRPKKLSFKLFNIQVRGVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
AAV3-3            QRLINNNWGFRPKKLSFKLFNIQVRGVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
AAV3B             QRLINNNWGFRPKKLSFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
AAV4              QRLINNNWGMRPKAMRVKIFNIQVKEVTTSNGETTVANNLTSTVQIFADSSYELPYVMDA 347
AAV4-4            QRLINNNWGMRPKAMRVKIFNIQVKEVTTSNGETTVANNLTSTVQIFADSSYELPYVMDA 347
AAV5              QRLINNYWGFRPRSLRVKIFNIQVKEVTVQDSTTTIANNLTSTVQVFTDDDYQLPYVVGN 347
AAV6              QRLINNNWGFRPKRLNFKLFNIQVKEVTTNDGVTTIANNLTSTVQVFSDSEYQLPYVLGS 357
AAV7              QRLINNNWGFRPKKLRFKLFNIQVKEVTTNDGVTTIANNLTSTIQVFSDSEYQLPYVLGS 358
AAV8              QRLINNNWGFRPKRLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
AAV9              QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
AAV9e             QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
rh.10             QRLINNNWGFRPKRLNFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
rh.20             QRLINNNWGFRPKRLNFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
rh.39             QRLINNNWGFRPKRLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
rh.73             QRLINNNWGFRPKRLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
rh.74v1           QRLINNNWGFRPKRLNFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
rh.74v2           QRLINNNWGFRPKRLNFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
hu.12             QRLINNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 359
hu.21             QRLINNNWGFRPKRLSFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
hu.26             QRLINNNWGFRPKRLSFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
hu.37             QRLINNNWGFRPKRLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
hu.51             QRLINNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
hu.53             QRLINNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
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                                  |         |         |         |         |         |
AAV1              AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFTFSY 414
AAV2              AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFTFSY 413
AAV3              AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFSY 413
AAV3-3            AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFSY 413
AAV3B             AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFSY 413
AAV4              GQEGSLPPFPNDVFMVPQYGYCGLVTGNTSQQQTDRNAFYCLEYFPSQMLRTGNNFEITY 407
AAV4-4            GQEGSLPPFPNDVFMVPQYGYCGLVTGNTSQQQTDRNAFYCLEYFPSQMLRTGNNFEITY 407
AAV5              GTEGCLPAFPPQVFTLPQYGYATLNRDNT-ENPTERSSFFCLEYFPSKMLRTGNNFEFTY 406
AAV6              AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFTFSY 414
AAV7              AHQGCLPPFPADVFMIPQYGYLTLNNG---SQSVGRSSFYCLEYFPSQMLRTGNNFEFSY 415
AAV8              AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFTY 416
AAV9              AHEGCLPPFPADVFMIPQYGYLTLNDG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFSY 415
AAV9e             AHEGCLPPFPADVFMIPQYGYLTLNDG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFSY 415
rh.10             AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFEFSY 416
rh.20             AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFEFSY 416
rh.39             AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFEFSY 416
rh.73             AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFSFSY 416
rh.74v1           AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFEFSY 416
rh.74v2           AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFEFSY 416
hu.12             AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRPSFYCLEYFPSQMLRTGNNFTFSY 413
hu.21             AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFTFSY 413
hu.26             AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFTFSY 413
hu.37             AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFEFSY 416
hu.51             AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFTFSY 413
hu.53             AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFSY 413
                  . :*.** ** :** :*****  *  .   .: . *.:*:*******:******** ::*
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FIG. 3 (Continued)

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                 |          |          |          |          |          |
AAV1             TFEEVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQN-QSGSAQNKDLLFSRGSPAGMSV 473
AAV2             TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTN-TPSGTTTQSRLQFSQAGASDIRD 472
AAV3             TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQGTTSGTTNQSRLLFSQAGPQSMSL 473
AAV3-3           TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQGTTSGTTNQSRLLFSQAGPQSMSL 473
AAV3B            TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQGTTSGTTNQSRLLFSQAGPQSMSL 473
AAV4             SFEKVPFHSMYAHSQSLDRLMNPLIDQYLWGLQSTTTGTTLNAGTATTNFTKLRPTNFSN 467
AAV4-4           SFEKVPFHSMYAHSQSLDRLMNPLIDQYLWGLQSTTTGTTLNAGTATTNFTKLRPTNFSN 467
AAV5             NFEEVPFHSSFAPSQNLFKLANPLVDQYLYRFVSTNNTG-------GVQFNKNLAGRYAN 459
AAV6             TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQN-QSGSAQNKDLLFSRGSPAGMSV 473
AAV7             SFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLARTQSNPGGTAGNRELQFYQGGPSTMAE 475
AAV8             TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQT-TGGTANTQTLGFSQGGPNTMAN 475
AAV9             EFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGS--GQNQQTLKFSVAGPSNMAV 473
AAV9e            EFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGS--GQNQQTLKFSVAGPSNMAV 473
rh.10            QFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQS-TGGTAGTQQLLFSQAGPNNMSA 475
rh.20            QFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQS-TGGTAGTQQLLFSQAGPNNMSA 475
rh.39            TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQS-TGGTQGTQQLLFSQAGPANMSA 475
rh73             TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQS-TGGTAGTQQLLFSQAGPSNMSA 475
rh.74v1          NFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQS-TGGTAGTQQLLFSQAGPNNMSA 475
rh.74v2          NFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQS-TGGTAGTQQLLFSQAGPNNMSA 475
hu.12            TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQS-NSGTLQQSRLLFSQAGPTSMSL 472
hu.21            TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTN-TPSGTTTMSRLQFSQAGASDIRD 472
hu.26            TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTN-TPSGTTTMSRLQFSQAGASDIRD 472
hu.37            TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQS-TGGTQGTQQLLFSQAGPANMSA 475
hu.51            TFEDVPFHSGYAHSQSLDRLMNPLIDQYLYYLSTTN-TPSGTTTQSRLQFSQAGASDIRD 472
hu.53            TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQ-TASGTQ-QSRLLFSQAGPTSMSL 471
                  **.***** :* **.* :* ***:****: :  *              *

                 |          |          |          |          |          |
AAV1             QPKNWLPGPCYRQQRVSKTKTDNNNSNF-----TWTGASKYNLNGRESIINPGTAMASHK 528
AAV2             QSRNWLPGPCYRQQRVSKTSADNNNSEY-----SWTGATKYHLNGRDSLVNPGPAMASHK 527
AAV3             QARNWLPGPCYRQQRLSKTANDNNNSNF-----PWTAASKYHLNGRDSLVNPGPAMASHK 528
AAV3-3           QARNWLPGPCYRQQRLSKTANDNNNSNF-----PWTAASKYHLNGRDSLVNPGPAMASHK 528
AAV3B            QARNWLPGPCYRQQRLSKTANDNNNSNF-----PWTAASKYHLNGRDSLVNPGPAMASHK 528
AAV4             FKKNWLPGPSIKQQGFSKTANQNYKIPATGSDSLIKYETHSTLDGRWSALTPGPPMATAG 527
AAV4-4           FKKNWLPGPSIKQQGFSKTANQNYKIPATGSDSLIKYETHSTLDGRWSALTPGPPMATAG 527
AAV5             TYKNWFPGPMGRTQGWNLGSGVNRASVS-----AFATTNRMELEGASYQVPPQPNGMTNN 514
AAV6             QPKNWLPGPCYRQQRVSKTKTDNNNSNF-----TWTGASKYNLNGRESIINPGTAMASHK 528
AAV7             QAKNWLPGPCFRQQRVSKTLDQNNNSNF-----AWTGATKYHLNGRNSLVNPGVAMATHK 530
AAV8             QAKNWLPGPCYRQQRVSTTTGQNNNSNF-----AWTAGTKYHLNGRNSLANPGIAMATHK 530
AAV9             QGRNYIPGPSYRQQRVSTTVTQNNNSEF-----AWPGASSWALNGRNSLMNPGPAMASHK 528
AAV9e            QGRNYIPGPSYRQQRVSTTVTQNNNSEF-----AWPGASSWALNGRNSLMNPGPAMASHK 528
rh.10            QAKNWLPGPCYRQQRVSTTLSQNNNSNF-----AWTGATKYHLNGRDSLVNPGVAMATHK 530
rh.20            QAKNWLPGPCYRQQRVSTTLSQNNNSNF-----AWTGATKYHLNGRDSLVNPGVAMATHK 530
rh.39            QAKNWLPGPCYRQQRVSTTLSQNNNSNF-----AWTGATKYHLNGRDSLVNPGVAMATHK 530
rh.73            QARNWLPGPCYRQQRVSTTLSQNNNSNF-----AWTGATKYHLNGRDSLVNPGVAMATNK 530
rh.74v1          QAKNWLPGPCYRQQRVSTTLSQNNNSNF-----AWTGATKYHLNGRDSLVNPGVAMATHK 530
rh.74v2          QAKNWLPGPCYRQQRVSTTLSQNNNSNF-----AWTGATKYHLNGRDSLVNPGVAMATHK 530
hu.12            QAKNWLPGPCYRQQRLSKQANDNNNSNF-----PWTAATKYHLNGRDSLVNPGPAMASHK 527
hu.21            QSRNWLPGPCYRQQRVSKTAADNNNSDY-----SWTGATKYHLNGRDSLVNPGPAMASHK 527
hu.26            QSRNWLPGPCYRQQRVSKTAADNNNSDY-----SWTGATKYHLNGRDSLVNPGPAMASHK 527
hu.37            QAKNWLPGPCYRQQRVSTTLSQNNNSNF-----AWTGATKYHLNGRDSLVNPGVAMATHK 530
hu.51            QSRNWLPGPCYRQQRVSKTSADNNNSEY-----SWTGATKYHLNGRDSLVNPGPAMASHK 527
hu.53            QAKNWLPGPCYRQQRLSKQANDNNNSNF-----PWTGATKYYLNGRDSLVNPGPAMASHK 526
                   :*::***  : *  .     *               .   *:*      *     :
```

FIG. 3 (Continued)

```
                                                
```

FIG. 3 (Continued)

```
                                  |         |         |         |         |         |
AAV1              QILIKNTPVPANPPAEFSATKFASFITQYSTGQVSVEIEWELQKENSKRWNPEVQYTSNY 705
AAV2              QILIKNTPVPANPSTTFSAAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 704
AAV3              QIMIKNTPVPANPPTTFSPAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
AAV3-3            QIMIKNTPVPANPPTTFSPAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
AAV3B             QIMIKNTPVPANPPTTFSPAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
AAV4              QIFIKNTPVPANPATTFSSTPVNSFITQYSTGQVSVQIDWEIQKERSKRWNPEVQFTSNY 703
AAV4-4            QIFIKNTPVPANPATTFSSTPVNSFITQYSTGQVSVQIDWEIQKERSKRWNPEVQFTSNY 703
AAV5              MMLIKNTPVPGNI-TSFSDVPVSSFITQYSTGQVTVEMEWELKKENSKRWNPEIQYTNNY 693
AAV6              QILIKNTPVPANPPAEFSATKFASFITQYSTGQVSVEIEWELQKENSKRWNPEVQYTSNY 705
AAV7              QILIKNTPVPANPPEVFTPAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNF 706
AAV8              QILIKNTPVPADPPTTFNQSKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 707
AAV9              QILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
AAV9e             QILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
rh.10             QILIKNTPVPADPPTTFSQAKLASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 707
rh.20             QILIKNTPVPADPPTTFSQAKLASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 707
rh.39             QILIKNTPVPADPPTTFSQAKLASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 707
rh.73             QILIKNTPVPADPPTAFNQAKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 707
rh.74v1           QILIKNTPVPADPPTTFTKAKLASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 707
rh.74v2           QILIKNTPVPADPPTTFNQAKLASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 707
hu.12             QIMIKNTPVPANPPTNFSSAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 704
rh.21             QILIKNTPVPANPSTTFSAAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 704
hu.26             QILIKNTPVPANPSTTFSAAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 704
hu.37             QILIKNTPVPADPPTTFSQAKLASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 707
hu.51             QILIKNTPVPANPSTTFSAAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
hu.53             QIMIKNTPVPANPPTNFSSAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 704
                   ::*******.:    *.   . ***********:*:::**::**.*******:*:*.*:

                             |         |         |
AAV1              AKSANVDFTVDNNGLYTEPRPIGTRYLTRPL 736 (SEQ ID NO:22)
AAV2              NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 735 (SEQ ID NO:23)
AAV3              NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 736 (SEQ ID NO:24)
AAV3-3            NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 736 (SEQ ID NO:25)
AAV3B             NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 736 (SEQ ID NO:26)
AAV4              GQQNSLLWAPDAAGKYTEPRAIGTRYLTHHL 734 (SEQ ID NO:27)
AAV4-4            GQQNSLLWAPDAAGKYTEPRAIGTRYLTHHL 734 (SEQ ID NO:28)
AAV5              NDPQFVDFAPDSTGEYRTTRPIGTRYLTRPL 724 (SEQ ID NO:29)
AAV6              AKSANVDFTVDNNGLYTEPRPIGTRYLTRPL 736 (SEQ ID NO:30)
AAV7              EKQTGVDFAVDSQGVYSEPRPIGTRYLTRNL 737 (SEQ ID NO:31)
AAV8              YKSTSVDFAVNTEGVYSEPRPIGTRYLTRNL 738 (SEQ ID NO:32)
AAV9              YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL 736 (SEQ ID NO:33)
AAV9e             YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL 736 (SEQ ID NO:34)
rh.10             YKSTNVDFAVNTDGTYSEPRPIGTRYLTRNL 738 (SEQ ID NO:35)
rh.20             YKSTNVDFAVNTEGTYSEPRPIGTRYLTRNL 738 (SEQ ID NO:36)
rh.39             YKSTNVDFAVNTEGTYSEPRPIGTRYLTRNL 738 (SEQ ID NO:37)
rh.73             YKSTNVDFAVNTEGVYSEPRPIGTRYLTRNL 739 (SEQ ID NO:38)
rh.74v1           YKSTNVDFAVNTEGTYSEPRPIGTRYLTRNL 738 (SEQ ID NO:39)
rh.74v2           YKSTNVDFAVNTEGTYSEPRPIGTRYLTRNL 738 (SEQ ID NO:40)
hu.12             NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 735 (SEQ ID NO:41)
hu.21             NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 735 (SEQ ID NO:42)
hu.26             NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 735 (SEQ ID NO:43)
hu.37             YKSTNVDFAVNTEGTYSEPRPIGTRYLTRNL 738 (SEQ ID NO:44)
hu.51             NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 736 (SEQ ID NO:45)
hu.53             NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 737 (SEQ ID NO:46)
                   .   : :: :  * *   * *******: *
```

FIG. 4

```
IgG1    EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK     274
IgG2    E---RKCCVECPPCPAPPV-AGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQ     274
IgG4    E---SKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ     274
        *    :    ** **** . .*******************************:*****:

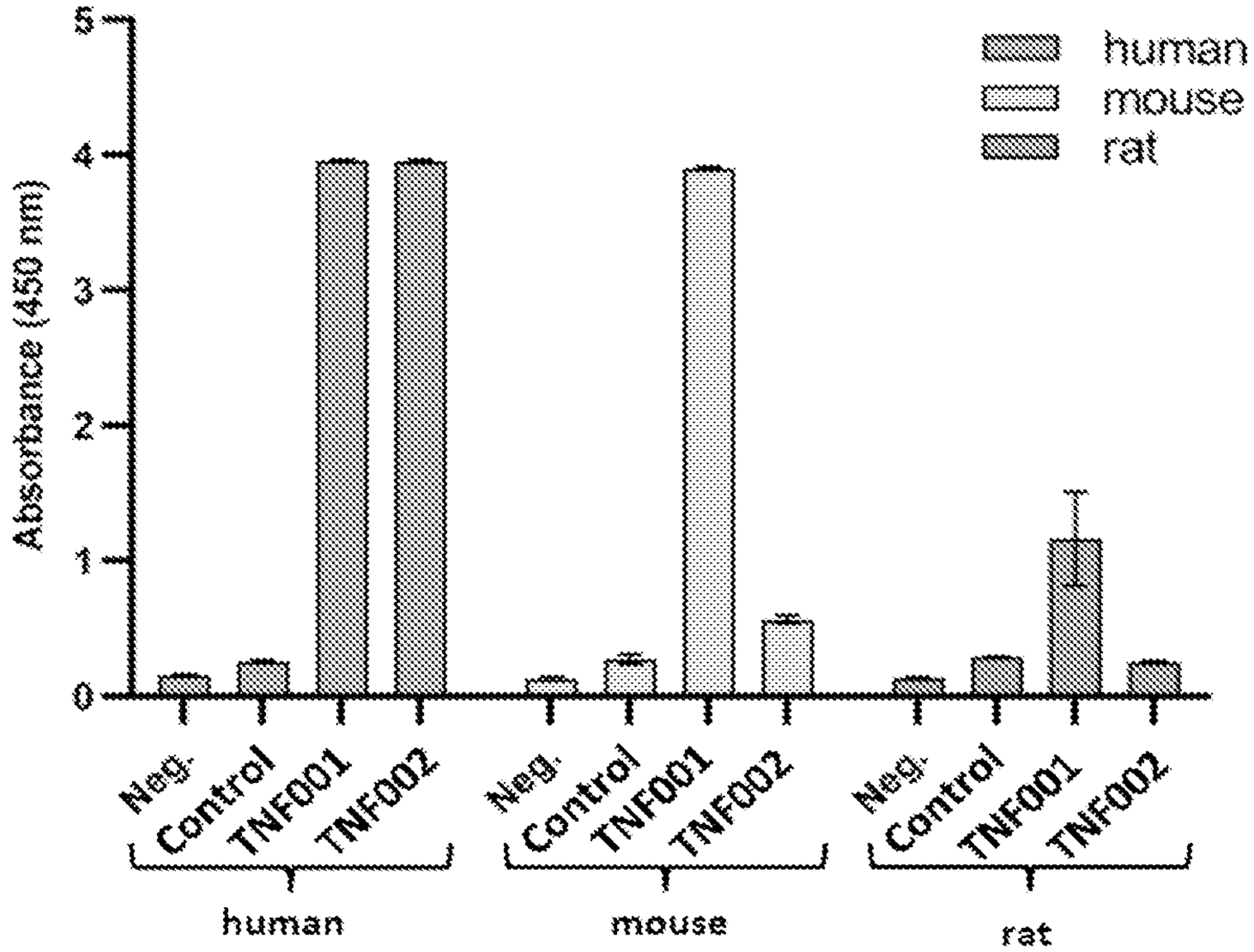
IgG1    FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK    334
IgG2    FNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEK    334
IgG4    FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK    334
        **********************.***.********.**************** **. ***

IgG1    TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT    394
IgG2    TISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTT    394
IgG4    TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT    394
        ****:****************::*:********************:****************

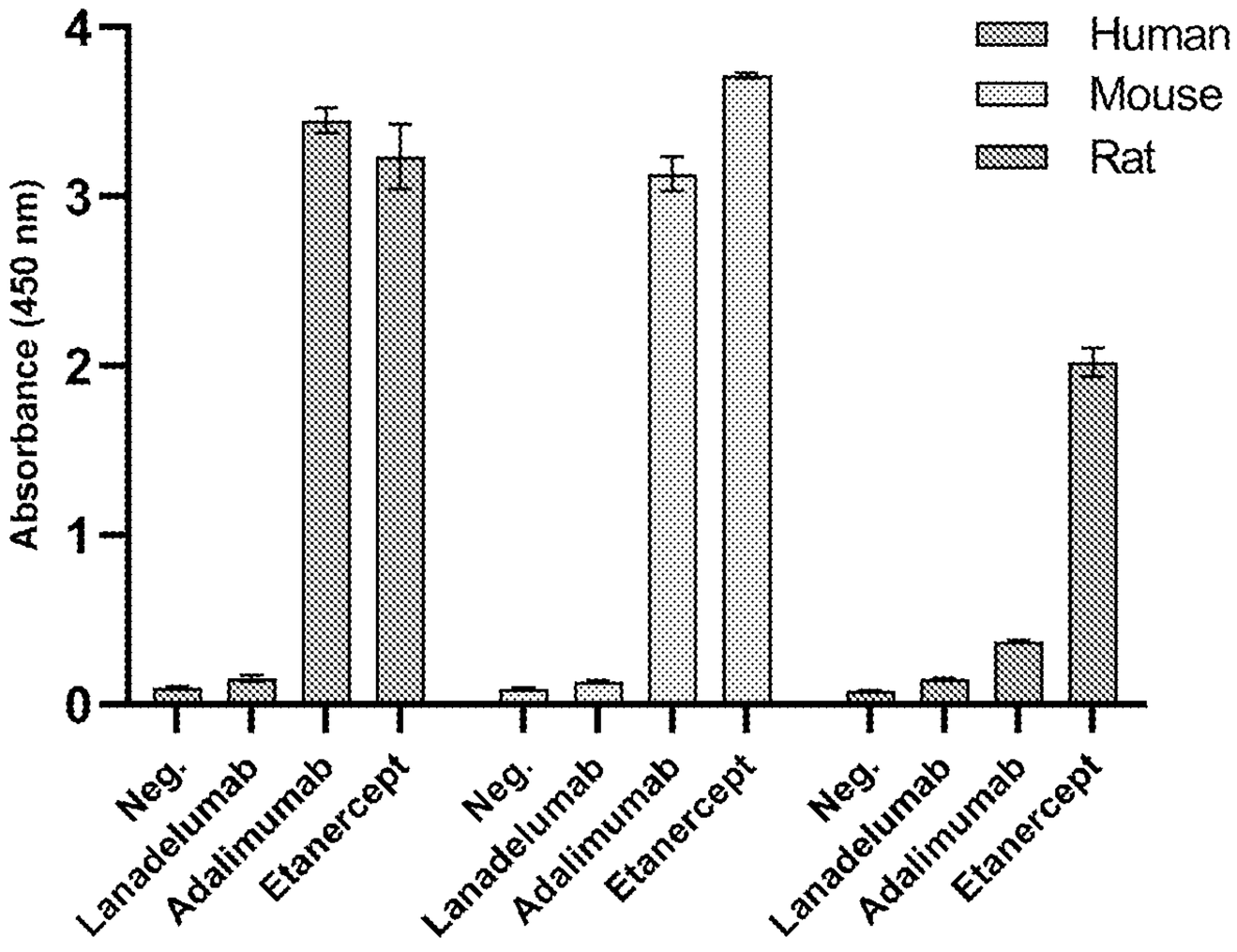
IgG1    PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK  447 (SEQ ID NO:47)
IgG2    PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK  447 (SEQ ID NO:48)
IgG4    PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK  447 (SEQ ID NO:49)
        **:***********:*********:***************************:**
```

FIG. 5A and B

A.



B.



SEQUENCE LISTING

<110> REGENXBIO INC

<120> VECTORIZED TNF-ALPHA ANTAGONISTS FOR OCULAR INDICATIONS

<130> 38013.0016P1

<150> 63/107,415
<151> 2020-10-29

<160> 161

<170> PatentIn version 3.5

<210> 1
<211> 211
<212> PRT
<213> Artificial Sequence

<220>
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<400> 1

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

Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
20 25 30

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

Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
50 55 60

Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
65 70 75 80

Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu
85 90 95

Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val
100 105 110

Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg

```
        115                 120                 125

Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
    130                 135                 140

Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
145                 150                 155                 160

Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
                165                 170                 175

Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
            180                 185                 190

Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser
        195                 200                 205

Gly Thr Thr Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu
    210     1               5                   10

Val Leu Leu Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly
    15                  20                  25

Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro
30                  35                  40                  45

Gln Gly Lys Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys
                50                  55                  60

Cys His Lys Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln
            65                  70                  75

Asp Thr Asp Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu
        80                  85                  90

Asn His Leu Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met
    95                  100                 105

Gly Gln Val Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys
110                 115                 120                 125
```

```
Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe
                130                 135                 140

Gln Cys Phe Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser
            145                 150                 155

Cys Gln Glu Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe
        160                 165                 170

Leu Arg Glu Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu
    175                 180                 185

Glu Cys Thr Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr
190                 195                 200                 205

Glu Asp Ser Gly Thr Thr
                210
```

<210> 2
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; Anti-TNFalpha Fc Fusion

<400> 2

```
Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser
1               5                   10                  15

Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys
            20                  25                  30

Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys Thr
        35                  40                  45

Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu
    50                  55                  60

Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser
65                  70                  75                  80
```

```
Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys
                85                  90                  95

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

Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala
        115                 120                 125

Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro
    130                 135                 140

Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His
145                 150                 155                 160

Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp Ala
                165                 170                 175

Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val
            180                 185                 190

His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr
        195                 200                 205

Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly
    210                 215                 220

Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp
225                 230                 235
```

<210> 3
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; Anti-TNFalpha Fc Fusion

<400> 3

```
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                   10                  15
```

```
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50                  55                  60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly Lys
```

225 230

<210> 4
<211> 207
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; Anti-TNFalpha Fc Fusion

<400> 4

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
1 5 10 15

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
20 25 30

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
35 40 45

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
50 55 60

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
65 70 75 80

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
85 90 95

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
100 105 110

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
115 120 125

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
130 135 140

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
145 150 155 160

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg

```
                165                 170                 175

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            180                 185                 190

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        195                 200                 205
```

<210> 5
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hing region

<400> 5

```
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                   10                  15

Pro Glu Leu Leu Gly Gly Pro Ser Val
            20                  25
```

<210> 6
<211> 183
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; EYS606: Fc

<400> 6

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60
```

```
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser
            180
```

<210> 7
<211> 163
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; EYS606: Fc

<400> 7

```
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
1               5                   10                  15


Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            20                  25                  30


Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        35                  40                  45
```

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
50 55 60

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
65 70 75 80

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
85 90 95

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
100 105 110

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
115 120 125

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
130 135 140

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
145 150 155 160

Asp Gly Ser

<210> 8
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; cleavage site

<400> 8

Leu Val Pro Arg Gly Ser
1 5

<210> 9
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 9

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val
20

<210> 10
<211> 467
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; Etanercept TNFR2:Fc fusion

<400> 10

Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser
1 5 10 15

Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys
20 25 30

Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys Thr
35 40 45

Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu
50 55 60

Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser
65 70 75 80

Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys
85 90 95

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

Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala
115 120 125

Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro

```
    130                 135                 140

Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His
145                 150                 155                 160

Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp Ala
                165                 170                 175

Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val
            180                 185                 190

His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr
        195                 200                 205

Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly
    210                 215                 220

Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp Glu Pro Lys Ser Cys
225                 230                 235                 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            340                 345                 350
```

```
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        355                 360                 365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    370                 375                 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385                 390                 395                 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                405                 410                 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        435                 440                 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    450                 455                 460

Pro Gly Lys
465
```

<210> 11
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; Etanercept plus leader sequence

<400> 11

```
Met Tyr Arg Met Gln Leu Leu Leu Leu Ile Ala Leu Ser Leu Ala Leu
1               5                   10                  15

Val Thr Asn Ser Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro
            20                  25                  30

Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala
        35                  40                  45
```

```
Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe
    50                  55                  60

Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr
65                  70                  75                  80

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

Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln
            100                 105                 110

Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys
        115                 120                 125

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

Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys
145                 150                 155                 160

Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile
                165                 170                 175

Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala
            180                 185                 190

Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala
        195                 200                 205

Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His
    210                 215                 220

Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu
225                 230                 235                 240

Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp Glu
                245                 250                 255

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
```

```
            260                 265                 270

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        275                 280                 285

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    290                 295                 300

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
305                 310                 315                 320

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
                325                 330                 335

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            340                 345                 350

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
        355                 360                 365

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    370                 375                 380

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
385                 390                 395                 400

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                405                 410                 415

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            420                 425                 430

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        435                 440                 445

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
    450                 455                 460

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
465                 470                 475                 480
```

Leu Ser Leu Ser Pro Gly Lys
485

<210> 12
<211> 400
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; EYS606

<400> 12

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

Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
20 25 30

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

Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
50 55 60

Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
65 70 75 80

Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu
85 90 95

Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val
100 105 110

Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
115 120 125

Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
130 135 140

Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
145 150 155 160

```
Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
                165                 170                 175

Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
            180                 185                 190

Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser
        195                 200                 205

Gly Thr Thr Leu Val Pro Arg Gly Ser Asp Lys Thr His Thr Cys Pro
    210                 215                 220

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
225                 230                 235                 240

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
                245                 250                 255

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
            260                 265                 270

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        275                 280                 285

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
    290                 295                 300

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305                 310                 315                 320

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
                325                 330                 335

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
            340                 345                 350

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
        355                 360                 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
```

370 375 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
385 390 395 400

<210> 13
<211> 1404
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; Etanercept

<400> 13
ctgcctgcac aggtggcttt taccccatat gctcctgagc ctggatccac ttgtaggctg 60

agggagtatt atgatcagac agcccagatg tgctgttcaa aatgttcccc tggacagcat 120

gctaaggtgt tttgtaccaa gacaagtgac actgtctgtg acagctgtga ggattctact 180

tacacccagc tgtggaattg ggtgccagaa tgtctgtcat gtgggagcag gtgttctagt 240

gaccaggtgg aaactcaggc ctgtacaaga gagcagaaca ggatttgtac atgtagacca 300

gggtggtact gtgccctgag caaacaggaa gggtgtaggc tctgtgctcc cctgaggaaa 360

tgtagacctg ggtttggggt ggccagacca ggaacagaaa cttctgatgt ggtctgtaag 420

ccctgtgcac caggaacctt ttcaaacact accagcagta cagacatctg cagaccccat 480

cagatctgta atgtggtggc cattcctggg aatgcaagta tggatgctgt ctgtacttcc 540

accagcccaa ctagatccat ggccccaggg gcagtccacc tgccccagcc tgtcagcact 600

agaagccagc atactcagcc cacacctgag ccttctacag caccctccac ctctttcctg 660

ctgcctatgg ggccatcacc tccagctgag ggcagtacag gggatgaacc taagtcatgt 720

gacaaaaccc atacctgtcc accctgccct gctcctgagc tgctgggggg acccagtgtc 780

ttcctgtttc ctcccaaacc taaagatact ctgatgatca gcagaacccc agaggtcaca 840

tgcgtggtag tggatgtctc ccatgaagac cctgaagtga agtttaattg gtatgtagat 900

ggggtggagg tccataatgc aaagaccaag cccagggaag aacagtataa cagtacttac 960

agggtggtgt ctgtgctgac agtactgcac caggactggc tgaatgggaa ggagtataag 1020

tgcaaagtca gcaataaggc actgcctgcc cctattgaaa agacaattag taaagctaag 1080

gggcagccca gggaaccaca ggtctacact ctgccccta gtagagagga aatgacaaag 1140

aatcaggtca gtctgacatg tctggtcaag ggattctatc caagtgatat tgcagtggag 1200

tgggaaagta atggccagcc agagaataac tacaagacta ccccccccagt gctggacagt 1260

gatggatctt tctttctgta ctccaaactg actgtggata aatcaagatg gcagcagggc 1320

aatgtctttt cctgttcagt catgcatgaa gccctgcata atcactacac tcagaagagc 1380

ctgtccctgt cccctggcaa atga 1404

<210> 14
<211> 1464
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; Etanercept plus leader sequence

<400> 14
atgtatagga tgcagctgct gctgctgatt gctctgagtc tggctctggt cacaaatagt 60

ctgcctgcac aggtggcttt taccccatat gctcctgagc ctggatccac ttgtaggctg 120

agggagtatt atgatcagac agcccagatg tgctgttcaa aatgttcccc tggacagcat 180

gctaaggtgt tttgtaccaa gacaagtgac actgtctgtg acagctgtga ggattctact 240

tacacccagc tgtggaattg ggtgccagaa tgtctgtcat gtgggagcag gtgttctagt 300

gaccaggtgg aaactcaggc ctgtacaaga gagcagaaca ggatttgtac atgtagacca 360

gggtggtact gtgccctgag caaacaggaa gggtgtaggc tctgtgctcc cctgaggaaa 420

tgtagacctg ggtttggggt ggccagacca ggaacagaaa cttctgatgt ggtctgtaag 480

ccctgtgcac caggaacctt ttcaaacact accagcagta cagacatctg cagaccccat 540

cagatctgta atgtggtggc cattcctggg aatgcaagta tggatgctgt ctgtacttcc 600

accagcccaa ctagatccat ggccccaggg gcagtccacc tgccccagcc tgtcagcact 660

agaagccagc atactcagcc cacacctgag ccttctacag caccctccac ctctttcctg 720

ctgcctatgg ggccatcacc tccagctgag ggcagtacag gggatgaacc taagtcatgt 780

gacaaaaccc atacctgtcc accctgccct gctcctgagc tgctgggggg acccagtgtc 840

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tgcgtggtag tggatgtctc ccatgaagac cctgaagtga agtttaattg gtatgtagat 960

ggggtggagg tccataatgc aaagaccaag cccagggaag aacagtataa cagtacttac 1020

agggtggtgt ctgtgctgac agtactgcac caggactggc tgaatgggaa ggagtataag 1080

tgcaaagtca gcaataaggc actgcctgcc cctattgaaa agacaattag taaagctaag 1140

gggcagccca gggaaccaca ggtctacact ctgccccta gtagagagga aatgacaaag 1200

aatcaggtca gtctgacatg tctggtcaag ggattctatc caagtgatat tgcagtggag 1260

tgggaaagta atggccagcc agagaataac tacaagacta ccccccccagt gctggacagt 1320

gatggatctt tctttctgta ctccaaactg actgtggata aatcaagatg gcagcagggc 1380

aatgtctttt cctgttcagt catgcatgaa gccctgcata atcactacac tcagaagagc 1440

ctgtccctgt cccctggcaa atga 1464

<210> 15
<211> 3784
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; pAAV.CAG.Etanercept (from 5'-ITR to 3-ITR)

<400> 15
ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgaccttt 60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtggccaa ctccatcact 120

aggggttcct tgtagttaat gattaacccg ccatgctact tatctaccag ggtaatgggg 180

atcctctaga actatagcta gtcgacattg attattgact agttattaat agtaatcaat 240

tacggggtca ttagttcata gcccatatat ggagttccgc gttacataac ttacggtaaa 300

tggcccgcct ggctgaccgc ccaacgaccc ccgcccattg acgtcaataa tgacgtatgt 360

tcccatagta acgccaatag ggactttcca ttgacgtcaa tgggtggagt atttacggta 420

aactgcccac ttggcagtac atcaagtgta tcatatgcca agtacgcccc ctattgacgt 480

caatgacggt aaatggcccg cctggcatta tgcccagtac atgaccttat gggactttcc 540

tacttggcag tacatctacg tattagtcat cgctattacc atggtcgagg tgagccccac 600

gttctgcttc actctcccca tctccccccc ctccccaccc ccaattttgt atttatttat 660

tttttaatta ttttgtgcag cgatgggggc gggggggggg ggggggcgcg cgccaggcgg 720

ggcggggcgg ggcgaggggc ggggcggggc gaggcggaga ggtgcggcgg cagccaatca 780

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cggcggcccc cggagcgccg gcggctgtcg aggcgcggcg agccgcagcc attgcctttt 1560

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cagctgtgag gattctactt acacccagct gtggaattgg gtgccagaat gtctgtcatg 2220

tgggagcagg tgttctagtg accaggtgga aactcaggcc tgtacaagag agcagaacag 2280

gatttgtaca tgtagaccag ggtggtactg tgccctgagc aaacaggaag ggtgtaggct 2340

ctgtgctccc ctgaggaaat gtagacctgg gtttggggtg gccagaccag gaacagaaac 2400

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agacatctgc agaccccatc agatctgtaa tgtggtggcc attcctggga atgcaagtat 2520

ggatgctgtc tgtacttcca ccagcccaac tagatccatg gccccagggg cagtccacct 2580

gccccagcct gtcagcacta gaagccagca tactcagccc acacctgagc cttctacagc 2640

accctccacc tctttcctgc tgcctatggg gccatcacct ccagctgagg gcagtacagg 2700

ggatgaacct aagtcatgtg acaaaaccca tacctgtcca ccctgccctg ctcctgagct 2760

gctgggggga cccagtgtct tcctgtttcc tcccaaacct aaagatactc tgatgatcag 2820

cagaacccca gaggtcacat gcgtggtagt ggatgtctcc catgaagacc ctgaagtgaa 2880

gtttaattgg tatgtagatg gggtggaggt ccataatgca aagaccaagc ccagggaaga 2940

acagtataac agtacttaca gggtggtgtc tgtgctgaca gtactgcacc aggactggct 3000

gaatgggaag gagtataagt gcaaagtcag caataaggca ctgcctgccc ctattgaaaa 3060

gacaattagt aaagctaagg ggcagcccag ggaaccacag gtctacactc tgcccctag 3120

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aagtgatatt gcagtggagt gggaaagtaa tggccagcca gagaataact acaagactac 3240

ccccccagtg ctggacagtg atggatcttt ctttctgtac tccaaactga ctgtggataa 3300

atcaagatgg cagcagggca atgtcttttc ctgttcagtc atgcatgaag ccctgcataa 3360

tcactacact cagaagagcc tgtccctgtc ccctggcaaa tgataactcg aggacggggt 3420

gaactacgcc tgaggatccg atctttttcc ctctgccaaa aattatgggg acatcatgaa 3480

gcccccttgag catctgactt ctggctaata aaggaaattt attttcattg caatagtgtg 3540

ttggaatttt ttgtgtctct cactcggaag caattcgttg atctgaattt cgaccaccca 3600

taatacccat taccctggta gataagtagc atggcgggtt aatcattaac tacaaggaac 3660

ccctagtgat ggagttggcc actccctctc tgcgcgctcg ctcgctcact gaggccgggc 3720

gaccaaaggt cgcccgacgc ccgggctttg cccgggcggc ctcagtgagc gagcgagcgc 3780

gcag 3784

<210> 16
<211> 3362
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; pAAV.CAG.Etanercept

<400> 16
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atatatggag ttccgcgtta cataacttac ggtaaatggc ccgcctggct gaccgcccaa 120

cgacccccgc ccattgacgt caataatgac gtatgttccc atagtaacgc caatagggac 180

tttccattga cgtcaatggg tggagtattt acggtaaact gcccacttgg cagtacatca 240

agtgtatcat atgccaagta cgccccctat tgacgtcaat gacggtaaat ggcccgcctg 300

gcattatgcc cagtacatga ccttatggga ctttcctact tggcagtaca tctacgtatt 360

agtcatcgct attaccatgg tcgaggtgag ccccacgttc tgcttcactc tccccatctc 420

ccccccctcc ccacccccaa ttttgtattt atttattttt taattatttt gtgcagcgat 480

gggggcgggg gggggggggg ggcgcgcgcc aggcggggcg gggcggggcg aggggcgggg 540

cggggcgagg cggagaggtg cggcggcagc caatcagagc ggcgcgctcc gaaagtttcc 600

ttttatggcg aggcggcggc ggcggcggcc ctataaaaag cgaagcgcgc ggcgggcggg 660

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cgcggggctc gccgtgccgg gcgggggggtg gcggcaggtg ggggtgccgg gcggggcggg 1260

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gggacttcct ttgtcccaaa tctgtgcgga gccgaaatct gggaggcgcc gccgcacccc 1440

ctctagcggg cgcggggcga agcggtgcgg cgccggcagg aaggaaatgg gcggggaggg 1500

ccttcgtgcg tcgccgcgcc gccgtcccct tctccctctc cagcctcggg gctgtccgcg 1560

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gggggacggc tgccttcggg ggggacgggg cagggcgggg ttcggcttct ggcgtgtgac     1620

cggcggctct agagcctctg ctaaccatgt tcatgccttc ttctttttcc tacagctcct     1680

gggcaacgtg ctggttattg tgctgtctca tcattttggc aaagaattcg ccaccatgta     1740

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gtattatgat cagacagccc agatgtgctg ttcaaaatgt tcccctggac agcatgctaa     1920

ggtgttttgt accaagacaa gtgacactgt ctgtgacagc tgtgaggatt ctacttacac     1980

ccagctgtgg aattgggtgc cagaatgtct gtcatgtggg agcaggtgtt ctagtgacca     2040

ggtggaaact caggcctgta caagagagca gaacaggatt tgtacatgta gaccagggtg     2100

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tgcaccagga acctttttcaa acactaccag cagtacagac atctgcagac cccatcagat     2280

ctgtaatgtg gtggccattc ctgggaatgc aagtatggat gctgtctgta cttccaccag     2340

cccaactaga tccatggccc caggggcagt ccacctgccc cagcctgtca gcactagaag     2400

ccagcatact cagcccacac ctgagccttc tacagcaccc tccacctctt tcctgctgcc     2460

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ggtagtggat gtctcccatg aagaccctga agtgaagttt aattggtatg tagatggggt     2700

ggaggtccat aatgcaaaga ccaagcccag ggaagaacag tataacagta cttacagggt     2760

ggtgtctgtg ctgacagtac tgcaccagga ctggctgaat gggaaggagt ataagtgcaa     2820

agtcagcaat aaggcactgc ctgcccctat tgaaaagaca attagtaaag ctaaggggca     2880

gcccagggaa ccacaggtct acactctgcc ccctagtaga gaggaaatga caaagaatca     2940

ggtcagtctg acatgtctgg tcaagggatt ctatccaagt gatattgcag tggagtggga     3000

aagtaatggc cagccagaga ataactacaa gactaccccc ccagtgctgg acagtgatgg     3060

atctttcttt ctgtactcca aactgactgt ggataaatca agatggcagc agggcaatgt     3120

cttttcctgt tcagtcatgc atgaagccct gcataatcac tacactcaga agagcctgtc     3180
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cctgtcccct ggcaaatgat aactcgagga cggggtgaac tacgcctgag gatccgatct 3240

ttttccctct gccaaaaatt atggggacat catgaagccc cttgagcatc tgacttctgg 3300

ctaataaagg aaatttattt tcattgcaat agtgtgttgg aatttttgt gtctctcact 3360

cg 3362

<210> 17
<211> 2259
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; pAAV.sc.mU1a.Vh4i. Etanercept (5'-ITR to 3'-ITR)

<400> 17
ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgaccttt 60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtggaatt cacgcgtatg 120

gaggcggtac tatgtagatg agaattcagg agcaaactgg gaaaagcaac tgcttccaaa 180

tatttgtgat ttttacagtg tagttttgga aaaactctta gcctaccaat tcttctaagt 240

gttttaaaat gtgggagcca gtacacatga agttatagag tgttttaatg aggcttaaat 300

atttaccgta actatgaaat gctacgcata tcatgctgtt caggctccgt ggccacgcaa 360

ctcatactca ggtgagtatc tcagggatcc agacatgggg atatgggagg tgcctctgat 420

cccagggctc actgtgggtc tctctgttca caggttaccg gtgccaccat gtataggatg 480

cagctgctgc tgctgattgc tctgagtctg gctctggtca caaatagtct gcctgcacag 540

gtggctttta ccccatatgc tcctgagcct ggatccactt gtaggctgag ggagtattat 600

gatcagacag cccagatgtg ctgttcaaaa tgttcccctg gacagcatgc taaggtgttt 660

tgtaccaaga caagtgacac tgtctgtgac agctgtgagg attctactta cacccagctg 720

tggaattggg tgccagaatg tctgtcatgt gggagcaggt gttctagtga ccaggtggaa 780

actcaggcct gtacaagaga gcagaacagg atttgtacat gtagaccagg gtggtactgt 840

gccctgagca aacaggaagg gtgtaggctc tgtgctcccc tgaggaaatg tagacctggg 900

tttggggtgg ccagaccagg aacagaaact tctgatgtgg tctgtaagcc ctgtgcacca 960

ggaacctttt caaacactac cagcagtaca gacatctgca gaccccatca gatctgtaat 1020

gtggtggcca ttcctgggaa tgcaagtatg gatgctgtct gtacttccac cagcccaact 1080

agatccatgg ccccaggggc agtccacctg ccccagcctg tcagcactag aagccagcat 1140

actcagccca cacctgagcc ttctacagca ccctccacct ctttcctgct gcctatgggg 1200

ccatcacctc cagctgaggg cagtacaggg gatgaaccta agtcatgtga caaaacccat 1260

acctgtccac cctgccctgc tcctgagctg ctgggggggac ccagtgtctt cctgtttcct 1320

cccaaaccta aagatactct gatgatcagc agaaccccag aggtcacatg cgtggtagtg 1380

gatgtctccc atgaagaccc tgaagtgaag tttaattggt atgtagatgg ggtggaggtc 1440

cataatgcaa agaccaagcc cagggaagaa cagtataaca gtacttacag ggtggtgtct 1500

gtgctgacag tactgcacca ggactggctg aatgggaagg agtataagtg caaagtcagc 1560

aataaggcac tgcctgcccc tattgaaaag acaattagta aagctaaggg gcagcccagg 1620

gaaccacagg tctacactct gccccctagt agagaggaaa tgacaaagaa tcaggtcagt 1680

ctgacatgtc tggtcaaggg attctatcca agtgatattg cagtggagtg ggaaagtaat 1740

ggccagccag agaataacta caagactacc cccccagtgc tggacagtga tggatctttc 1800

tttctgtact ccaaactgac tgtggataaa tcaagatggc agcagggcaa tgtcttttcc 1860

tgttcagtca tgcatgaagc cctgcataat cactacactc agaagagcct gtccctgtcc 1920

cctggcaaat gataaaagct tgatcttttt ccctctgcca aaaattatgg ggacatcatg 1980

aagccccttg agcatctgac ttctggctaa taaaggaaat ttattttcat tgcaatagtg 2040

tgttggaatt ttttgtgtct ctcactcggc tagcgaagca attctagcag gcatgctggg 2100

gagagatcga tctgaggaac ccctagtgat ggagttggcc actccctctc tgcgcgctcg 2160

ctcgctcact gaggccgccc gggcaaagcc cgggcgtcgg gcgacctttg gtcgcccggc 2220

ctcagtgagc gagcgagcgc gcagagaggg agtggccaa 2259

<210> 18
<211> 1951
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; pAAV.sc.mU1a.Vh4i. Etanercept (promoter to polyA)

<400> 18
atggaggcgg tactatgtag atgagaattc aggagcaaac tgggaaaagc aactgcttcc 60

aaatatttgt gatttttaca gtgtagtttt ggaaaaactc ttagcctacc aattcttcta 120

agtgttttaa aatgtgggag ccagtacaca tgaagttata gagtgtttta atgaggctta 180

aatatttacc gtaactatga aatgctacgc atatcatgct gttcaggctc cgtggccacg 240

caactcatac tcaggtgagt atctcaggga tccagacatg gggatatggg aggtgcctct 300

gatcccaggg ctcactgtgg gtctctctgt tcacaggtta ccggtgccac catgtatagg 360

atgcagctgc tgctgctgat tgctctgagt ctggctctgg tcacaaatag tctgcctgca 420

caggtggctt ttaccccata tgctcctgag cctggatcca cttgtaggct gagggagtat 480

tatgatcaga cagcccagat gtgctgttca aaatgttccc ctggacagca tgctaaggtg 540

ttttgtacca agacaagtga cactgtctgt gacagctgtg aggattctac ttacacccag 600

ctgtggaatt gggtgccaga atgtctgtca tgtgggagca ggtgttctag tgaccaggtg 660

gaaactcagg cctgtacaag agagcagaac aggatttgta catgtagacc agggtggtac 720

tgtgccctga gcaaacagga agggtgtagg ctctgtgctc ccctgaggaa atgtagacct 780

gggtttgggg tggccagacc aggaacagaa acttctgatg tggtctgtaa gccctgtgca 840

ccaggaacct tttcaaacac taccagcagt acagacatct gcagacccca tcagatctgt 900

aatgtggtgg ccattcctgg gaatgcaagt atggatgctg tctgtacttc caccagccca 960

actagatcca tggccccagg ggcagtccac ctgccccagc ctgtcagcac tagaagccag 1020

catactcagc ccacacctga gccttctaca gcaccctcca cctctttcct gctgcctatg 1080

gggccatcac ctccagctga gggcagtaca ggggatgaac ctaagtcatg tgacaaaacc 1140

catacctgtc caccctgccc tgctcctgag ctgctggggg gacccagtgt cttcctgttt 1200

cctcccaaac ctaaagatac tctgatgatc agcagaaccc cagaggtcac atgcgtggta 1260

gtggatgtct cccatgaaga ccctgaagtg aagtttaatt ggtatgtaga tggggtggag 1320

gtccataatg caaagaccaa gcccagggaa gaacagtata acagtactta cagggtggtg 1380

tctgtgctga cagtactgca ccaggactgg ctgaatggga aggagtataa gtgcaaagtc 1440

agcaataagg cactgcctgc ccctattgaa aagacaatta gtaaagctaa ggggcagccc 1500

agggaaccac aggtctacac tctgccccct agtagagagg aaatgacaaa gaatcaggtc 1560

agtctgacat gtctggtcaa gggattctat ccaagtgata ttgcagtgga gtgggaaagt 1620

aatggccagc cagagaataa ctacaagact acccccccag tgctggacag tgatggatct 1680

ttctttctgt actccaaact gactgtggat aaatcaagat ggcagcaggg caatgtcttt 1740

tcctgttcag tcatgcatga agccctgcat aatcactaca ctcagaagag cctgtccctg 1800

tcccctggca aatgataaaa gcttgatctt tttccctctg ccaaaaatta tggggacatc 1860

atgaagcccc ttgagcatct gacttctggc taataaagga aatttatttt cattgcaata 1920

gtgtgttgga atttttttgtg tctctcactc g 1951

<210> 19
<211> 467
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody construct

<400> 19

Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser
1 5 10 15

Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys
20 25 30

Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys Thr
35 40 45

Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu
50 55 60

Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser
65 70 75 80

Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys
85 90 95

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

Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala
115 120 125

Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro

```
    130                 135                 140

Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His
145                 150                 155                 160

Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp Ala
                165                 170                 175

Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val
            180                 185                 190

His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr
        195                 200                 205

Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly
    210                 215                 220

Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp Glu Pro Lys Ser Cys
225                 230                 235                 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            340                 345                 350
```

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        355   360   365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    370   375   380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385   390   395   400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                405   410   415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            420   425   430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        435   440   445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    450   455   460

Pro Gly Lys
465

<210> 20
<211> 400
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody construct

<400> 20

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

Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
            20   25   30

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

```
Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
    50                  55                  60

Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
65                  70                  75                  80

Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu
                85                  90                  95

Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val
            100                 105                 110

Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
        115                 120                 125

Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
    130                 135                 140

Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
145                 150                 155                 160

Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
                165                 170                 175

Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
            180                 185                 190

Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser
        195                 200                 205

Gly Thr Thr Leu Val Pro Arg Gly Ser Asp Lys Thr His Thr Cys Pro
    210                 215                 220

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
225                 230                 235                 240

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
                245                 250                 255

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
```

260 265 270

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
275 280 285

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
290 295 300

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305 310 315 320

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
325 330 335

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
340 345 350

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
355 360 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
370 375 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
385 390 395 400

<210> 21
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 21

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly

<210> 22

<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 22

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

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 Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
145 150 155 160

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

Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro

```
            180                 185                 190

Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

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

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu 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 Ala Ser Thr Gly Ala Ser Asn Asp Asn His
            260                 265                 270

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

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

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

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

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

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

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

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

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

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

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

Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser
    450                 455                 460

Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro
465                 470                 475                 480

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

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

Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys
        515                 520                 525

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

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

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

Phe Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala
            580                 585                 590

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

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
```

610 615 620

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

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

Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr
660 665 670

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

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

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

Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
725 730 735

<210> 23
<211> 735
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 23

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 Asn Leu
725 730 735

<210> 24
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 24

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

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

Lys Ala Asn Gln Gln His Gln Asp Asn Arg Arg Gly Leu Val Leu Pro
35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Gly 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

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys 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 Ile Leu Glu Pro
115 120 125

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

```
Ala Val Asp Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Val Gly
145                 150                 155                 160

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

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

Ala Ala Pro Thr Ser Leu Gly Ser Asn Thr Met Ala Ser Gly Gly 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 Gln Trp Leu 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 Lys Leu Ser Phe Lys Leu Phe Asn Ile Gln Val
305                 310                 315                 320

Arg Gly 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 Gln 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 Asn Arg Thr
        435                 440                 445

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

Gln Ala Gly Pro Gln Ser Met Ser Leu Gln Ala Arg Asn Trp Leu Pro
465                 470                 475                 480

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

Asn Asn Ser Asn Phe Pro Trp Thr Ala Ala Ser Lys Tyr His Leu Asn
            500                 505                 510

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

Asp Asp Glu Glu Lys Phe Phe Pro Met His Gly Asn Leu Ile Phe Gly
    530                 535                 540

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

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

```
Tyr Gly Thr Val Ala Asn Asn Leu Gln Ser Ser Asn Thr Ala Pro Thr
            580                 585                 590

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

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

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

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

Asn Pro Pro Thr Thr Phe Ser Pro Ala Lys Phe Ala Ser Phe Ile Thr
            660                 665                 670

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

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

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

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735
```

<210> 25
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 25

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

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

Lys Ala Asn Gln Gln His Gln Asp Asn Arg Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly 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

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys 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 Ile Leu Glu Pro
        115                 120                 125

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

Ala Val Asp Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Val Gly
145                 150                 155                 160

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

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

Ala Ala Pro Thr Ser Leu Gly Ser Asn Thr Met Ala Ser Gly Gly 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 Gln Trp Leu 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 Lys Leu Ser Phe Lys Leu Phe Asn Ile Gln Val
305                 310                 315                 320

Arg Gly 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 Gln 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 Asn Arg Thr
        435                 440                 445
```

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

Gln Ala Gly Pro Gln Ser Met Ser Leu Gln Ala Arg Asn Trp Leu Pro
465                 470                 475                 480

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

Asn Asn Ser Asn Phe Pro Trp Thr Ala Ala Ser Lys Tyr His Leu Asn
            500                 505                 510

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

Asp Asp Glu Glu Lys Phe Phe Pro Met His Gly Asn Leu Ile Phe Gly
    530                 535                 540

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

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

Tyr Gly Thr Val Ala Asn Asn Leu Gln Ser Ser Asn Thr Ala Pro Thr
            580                 585                 590

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

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

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

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

Asn Pro Pro Thr Thr Phe Ser Pro Ala Lys Phe Ala Ser Phe Ile Thr
```

660 665 670

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

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

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

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
725 730 735

<210> 26
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 26

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

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

Lys Ala Asn Gln Gln His Gln Asp Asn Arg Arg Gly Leu Val Leu Pro
35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Gly 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

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys 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 Ile Leu Glu Pro
        115                 120                 125

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

Pro Val Asp Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Val Gly
145                 150                 155                 160

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

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

Ala Ala Pro Thr Ser Leu Gly Ser Asn Thr Met Ala Ser Gly Gly 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 Gln Trp Leu 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 Lys Leu Ser 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 Gln 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 Asn Arg Thr
        435                 440                 445

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

Gln Ala Gly Pro Gln Ser Met Ser Leu Gln Ala Arg Asn Trp Leu Pro
465                 470                 475                 480

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

Asn Asn Ser Asn Phe Pro Trp Thr Ala Ala Ser Lys Tyr His Leu Asn
            500                 505                 510

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

Asp Asp Glu Glu Lys Phe Phe Pro Met His Gly Asn Leu Ile Phe Gly
```

530 535 540

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

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

Tyr Gly Thr Val Ala Asn Asn Leu Gln Ser Ser Asn Thr Ala Pro Thr
580 585 590

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

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

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

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

Asn Pro Pro Thr Thr Phe Ser Pro Ala Lys Phe Ala Ser Phe Ile Thr
660 665 670

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

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

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

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
725 730 735

<210> 27
<211> 734
<212> PRT

<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 27

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

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

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


Glu Pro Arg Ala Ile Gly Thr Arg Tyr Leu Thr His His Leu
                725                 730


<210>  28
<211>  734
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic construct; AAV vector

<400>  28

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


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

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

Glu Pro Arg Ala Ile Gly Thr Arg Tyr Leu Thr His His Leu
725 730

<210> 29
<211> 724
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 29

Met Ser Phe Val Asp His Pro Pro Asp Trp Leu Glu Glu Val Gly Glu
1 5 10 15

Gly Leu Arg Glu Phe Leu Gly Leu Glu Ala Gly Pro Pro Lys Pro Lys
20 25 30

Pro Asn Gln Gln His Gln Asp Gln Ala Arg Gly Leu Val Leu Pro Gly
35 40 45

Tyr Asn Tyr Leu Gly Pro Gly Asn Gly Leu Asp Arg Gly Glu Pro Val
50 55 60

Asn Arg Ala Asp Glu Val Ala Arg Glu His Asp Ile Ser Tyr Asn Glu
65 70 75 80

Gln Leu Glu Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala Asp
85 90 95

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

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

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

Asp Asp His Phe Pro Lys Arg Lys Lys Ala Arg Thr Glu Glu Asp Ser

```
145                 150                 155                 160

Lys Pro Ser Thr Ser Ser Asp Ala Glu Ala Gly Pro Ser Gly Ser Gln
                165                 170                 175

Gln Leu Gln Ile Pro Ala Gln Pro Ala Ser Ser Leu Gly Ala Asp Thr
            180                 185                 190

Met Ser Ala Gly Gly Gly Gly Pro Leu Gly Asp Asn Asn Gln Gly Ala
        195                 200                 205

Asp Gly Val Gly Asn Ala Ser Gly Asp Trp His Cys Asp Ser Thr Trp
    210                 215                 220

Met Gly Asp Arg Val Val Thr Lys Ser Thr Arg Thr Trp Val Leu Pro
225                 230                 235                 240

Ser Tyr Asn Asn His Gln Tyr Arg Glu Ile Lys Ser Gly Ser Val Asp
                245                 250                 255

Gly Ser Asn Ala Asn Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr
            260                 265                 270

Phe Asp Phe Asn Arg Phe His Ser His Trp Ser Pro Arg Asp Trp Gln
        275                 280                 285

Arg Leu Ile Asn Asn Tyr Trp Gly Phe Arg Pro Arg Ser Leu Arg Val
    290                 295                 300

Lys Ile Phe Asn Ile Gln Val Lys Glu Val Thr Val Gln Asp Ser Thr
305                 310                 315                 320

Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp
                325                 330                 335

Asp Asp Tyr Gln Leu Pro Tyr Val Val Gly Asn Gly Thr Glu Gly Cys
            340                 345                 350

Leu Pro Ala Phe Pro Pro Gln Val Phe Thr Leu Pro Gln Tyr Gly Tyr
        355                 360                 365
```

```
Ala Thr Leu Asn Arg Asp Asn Thr Glu Asn Pro Thr Glu Arg Ser Ser
    370                 375                 380

Phe Phe Cys Leu Glu Tyr Phe Pro Ser Lys Met Leu Arg Thr Gly Asn
385                 390                 395                 400

Asn Phe Glu Phe Thr Tyr Asn Phe Glu Glu Val Pro Phe His Ser Ser
                405                 410                 415

Phe Ala Pro Ser Gln Asn Leu Phe Lys Leu Ala Asn Pro Leu Val Asp
            420                 425                 430

Gln Tyr Leu Tyr Arg Phe Val Ser Thr Asn Asn Thr Gly Gly Val Gln
        435                 440                 445

Phe Asn Lys Asn Leu Ala Gly Arg Tyr Ala Asn Thr Tyr Lys Asn Trp
    450                 455                 460

Phe Pro Gly Pro Met Gly Arg Thr Gln Gly Trp Asn Leu Gly Ser Gly
465                 470                 475                 480

Val Asn Arg Ala Ser Val Ser Ala Phe Ala Thr Thr Asn Arg Met Glu
                485                 490                 495

Leu Glu Gly Ala Ser Tyr Gln Val Pro Pro Gln Pro Asn Gly Met Thr
            500                 505                 510

Asn Asn Leu Gln Gly Ser Asn Thr Tyr Ala Leu Glu Asn Thr Met Ile
        515                 520                 525

Phe Asn Ser Gln Pro Ala Asn Pro Gly Thr Thr Ala Thr Tyr Leu Glu
    530                 535                 540

Gly Asn Met Leu Ile Thr Ser Glu Ser Glu Thr Gln Pro Val Asn Arg
545                 550                 555                 560

Val Ala Tyr Asn Val Gly Gly Gln Met Ala Thr Asn Asn Gln Ser Ser
                565                 570                 575

Thr Thr Ala Pro Ala Thr Gly Thr Tyr Asn Leu Gln Glu Ile Val Pro
```

580 585 590

Gly Ser Val Trp Met Glu Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp
595 600 605

Ala Lys Ile Pro Glu Thr Gly Ala His Phe His Pro Ser Pro Ala Met
610 615 620

Gly Gly Phe Gly Leu Lys His Pro Pro Pro Met Met Leu Ile Lys Asn
625 630 635 640

Thr Pro Val Pro Gly Asn Ile Thr Ser Phe Ser Asp Val Pro Val Ser
645 650 655

Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Thr Val Glu Met Glu
660 665 670

Trp Glu Leu Lys Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln
675 680 685

Tyr Thr Asn Asn Tyr Asn Asp Pro Gln Phe Val Asp Phe Ala Pro Asp
690 695 700

Ser Thr Gly Glu Tyr Arg Thr Thr Arg Pro Ile Gly Thr Arg Tyr Leu
705 710 715 720

Thr Arg Pro Leu

<210> 30
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 30

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

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

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

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
145                 150                 155                 160

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

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

Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

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

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu 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 Ala Ser Thr Gly Ala Ser Asn Asp Asn His
            260                 265                 270

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

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

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

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

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

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

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

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

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

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

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

Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser
```

```
    450                 455                 460

Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro
465                 470                 475                 480

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

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

Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys
        515                 520                 525

Asp Asp Lys Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly
    530                 535                 540

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

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

Phe Gly Thr Val Ala Val Asn Leu Gln Ser Ser Ser Thr Asp Pro Ala
            580                 585                 590

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

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

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

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

Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr
            660                 665                 670
```

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


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


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


Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
                725                 730                 735


<210>  31
<211>  737
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic construct; AAV vector

<400>  31

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


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 Asn 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 Ala 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 Arg 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 Ala Pro Ser Ser Val Gly Ser Gly Thr Val 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 Glu Thr Ala Gly Ser Thr Asn Asp Asn
            260                 265                 270

Thr 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 Lys Leu Arg 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 Ile 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 Ser 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 Glu Phe Ser Tyr Ser
                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 Ala
        435                 440                 445

Arg Thr Gln Ser Asn Pro Gly Gly Thr Ala Gly Asn Arg Glu Leu Gln
    450                 455                 460

Phe Tyr Gln Gly Gly Pro Ser Thr Met Ala Glu Gln Ala Lys Asn Trp
465                 470                 475                 480

Leu Pro Gly Pro Cys Phe Arg Gln Gln Arg Val Ser Lys Thr Leu Asp
                485                 490                 495

Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His
            500                 505                 510

Leu Asn Gly Arg Asn Ser Leu Val Asn Pro Gly Val Ala Met Ala Thr
        515                 520                 525

His Lys Asp Asp Glu Asp Arg Phe Phe Pro Ser Ser Gly Val Leu Ile
    530                 535                 540
```

```
Phe Gly Lys Thr Gly Ala Thr Asn Lys Thr Thr Leu Glu Asn Val Leu
545                 550                 555                 560

Met Thr Asn Glu Glu Glu Ile Arg Pro Thr Asn Pro Val Ala Thr Glu
                565                 570                 575

Glu Tyr Gly Ile Val Ser Ser Asn Leu Gln Ala Ala Asn Thr Ala Ala
            580                 585                 590

Gln Thr Gln Val Val Asn Asn 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 Glu Val Phe Thr Pro 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 Phe Glu Lys Gln Thr Gly Val Asp Phe Ala Val Asp Ser Gln Gly
705                 710                 715                 720

Val Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn
                725                 730                 735

Leu
```

<210> 32

<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 32

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

Glu Gly Ile Arg Glu Trp Trp Ala 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 Gln 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 Arg 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 Ala Pro Ser Gly Val Gly Pro Asn Thr Met Ala Ala Gly Gly
        195                 200                 205

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

Ser 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 Asn Gly Thr Ser Gly Gly Ala Thr Asn Asp
            260                 265                 270

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

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

Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Ser Phe Lys Leu Phe Asn
305                 310                 315                 320

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

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

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

Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn
    370                 375                 380

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

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

Thr Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser
            420                 425                 430

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

Ser Arg Thr Gln Thr Thr Gly Gly Thr Ala Asn Thr Gln Thr Leu Gly
    450                 455                 460

Phe Ser Gln Gly Gly Pro Asn Thr Met Ala Asn Gln Ala Lys Asn Trp
465                 470                 475                 480

Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Thr Gly
                485                 490                 495

Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Ala Gly Thr Lys Tyr His
            500                 505                 510

Leu Asn Gly Arg Asn Ser Leu Ala Asn Pro Gly Ile Ala Met Ala Thr
        515                 520                 525

His Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Asn Gly Ile Leu Ile
    530                 535                 540

Phe Gly Lys Gln Asn Ala Ala Arg Asp Asn Ala Asp Tyr Ser Asp Val
545                 550                 555                 560

Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr
                565                 570                 575

Glu Glu Tyr Gly Ile Val Ala Asp Asn Leu Gln Gln Gln Asn Thr Ala
            580                 585                 590

Pro Gln Ile Gly Thr Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val
        595                 600                 605

Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile
```

610 615 620

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

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

Pro Ala Asp Pro Pro Thr Thr Phe Asn Gln Ser Lys Leu Asn Ser Phe
660 665 670

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

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

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

Gly Val Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg
725 730 735

Asn Leu

<210> 33
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 33

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

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

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro

```
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly 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 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 Leu Leu Glu Pro
        115                 120                 125

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

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

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

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

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

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

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu 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 Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala 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 Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu 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 Asp
    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 Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn 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 Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
```

```
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

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

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

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

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

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

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

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

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

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

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

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
725 730 735

<210> 34
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 34

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

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

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Gly 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 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 Leu Leu Glu Pro
115 120 125

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

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

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

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

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

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

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu 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 Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala 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 Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
```

```
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu 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 Asp
    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 Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn 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 Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

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

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560
```

```
Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Asp Gly Ala Gln Ala Gln
            580                 585                 590

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

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

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

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

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

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

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

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

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735
```

<210> 35
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 35

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

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 Ile 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 Ser
```

```
    210                 215                 220

Ser 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 Asn Gly Thr Ser Gly Gly Ser Thr Asn Asp
            260                 265                 270

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

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

Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn
305                 310                 315                 320

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

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

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

Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn
    370                 375                 380

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

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

Gln Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser
            420                 425                 430
```

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

Ser Arg Thr Gln Ser Thr Gly Gly Thr Ala Gly Thr Gln Gln Leu Leu
    450                 455                 460

Phe Ser Gln Ala Gly Pro Asn Asn Met Ser Ala Gln Ala Lys Asn Trp
465                 470                 475                 480

Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Leu Ser
                485                 490                 495

Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His
            500                 505                 510

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

His Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Ser Gly Val Leu Met
    530                 535                 540

Phe Gly Lys Gln Gly Ala Gly Lys Asp Asn Val Asp Tyr Ser Ser Val
545                 550                 555                 560

Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr
                565                 570                 575

Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln Gln Gln Asn Ala Ala
            580                 585                 590

Pro Ile Val Gly Ala Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val
        595                 600                 605

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

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

Gly Leu Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val
```

645 650 655

Pro Ala Asp Pro Pro Thr Thr Phe Ser Gln Ala Lys Leu Ala Ser Phe
660 665 670

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

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

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

Gly Thr Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg
725 730 735

Asn Leu

<210> 36
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 36

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

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 Thr 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 Ile 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 Ser
    210                 215                 220

Ser 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 Asn Gly Thr Ser Gly Gly Ser Thr Asn Asp
            260                 265                 270

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

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

Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn
305                 310                 315                 320

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

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

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

Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn
    370                 375                 380

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

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

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

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

Ser Arg Thr Gln Ser Thr Gly Gly Thr Ala Gly Thr Gln Gln Leu Leu
    450                 455                 460

Phe Ser Gln Ala Gly Pro Asn Asn Met Ser Ala Gln Ala Lys Asn Trp
465                 470                 475                 480

Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Leu Ser
                485                 490                 495

Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His
```

```
            500                 505                 510

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

His Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Ser Gly Val Leu Met
    530                 535                 540

Phe Gly Lys Gln Gly Ala Gly Lys Asp Asn Val Asp Tyr Ser Ser Val
545                 550                 555                 560

Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr
                565                 570                 575

Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln Gln Gln Asn Ala Ala
            580                 585                 590

Pro Ile Val Gly Ala Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val
        595                 600                 605

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

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

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

Pro Ala Asp Pro Pro Thr Thr Phe Ser Gln Ala Lys Leu Ala Ser Phe
            660                 665                 670

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

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

Ser Asn Tyr Tyr Lys Ser Thr Asn Val Asp Phe Ala Val Asn Thr Glu
705                 710                 715                 720
```

Gly Thr Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg
725 730 735

Asn Leu

<210> 37
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 37

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

Glu Gly Ile Arg Glu Trp Trp Ala 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 Ala 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 Ile 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 Ser
    210                 215                 220

Ser 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 Asn Gly Thr Ser Gly Gly Ser Thr Asn Asp
            260                 265                 270

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

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

Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Ser Phe Lys Leu Phe Asn
305                 310                 315                 320

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

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

Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe
```

```
        355                 360                 365

Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn
    370                 375                 380

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

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

Thr Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser
            420                 425                 430

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

Ser Arg Thr Gln Ser Thr Gly Gly Thr Gln Gly Thr Gln Gln Leu Leu
    450                 455                 460

Phe Ser Gln Ala Gly Pro Ala Asn Met Ser Ala Gln Ala Lys Asn Trp
465                 470                 475                 480

Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Leu Ser
                485                 490                 495

Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His
            500                 505                 510

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

His Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Ser Gly Val Leu Met
    530                 535                 540

Phe Gly Lys Gln Gly Ala Gly Arg Asp Asn Val Asp Tyr Ser Ser Val
545                 550                 555                 560

Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr
                565                 570                 575
```

```
Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln Gln Thr Asn Thr Gly
            580                 585                 590

Pro Ile Val Gly Asn Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val
        595                 600                 605

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

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

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

Pro Ala Asp Pro Pro Thr Thr Phe Ser Gln Ala Lys Leu Ala Ser Phe
            660                 665                 670

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

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

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

Gly Thr Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg
                725                 730                 735

Asn Leu
```

<210> 38
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 38

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

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 Arg 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 Ala Pro Ser Ser Val 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 Ser
```

```
    210                 215                 220

Ser 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 Asn Gly Thr Ser Gly Gly Ser Thr Asn Asp
            260                 265                 270

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

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

Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Ser Phe Lys Leu Phe Asn
305                 310                 315                 320

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

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

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

Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn
    370                 375                 380

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

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

Thr Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser
            420                 425                 430
```

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

Ser Arg Thr Gln Ser Thr Gly Gly Thr Ala Gly Thr Gln Gln Leu Leu
    450                 455                 460

Phe Ser Gln Ala Gly Pro Ser Asn Met Ser Ala Gln Ala Arg Asn Trp
465                 470                 475                 480

Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Leu Ser
                485                 490                 495

Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His
            500                 505                 510

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

Asn Lys Asp Asp Glu Asp Arg Phe Phe Pro Ser Ser Gly Ile Leu Met
    530                 535                 540

Phe Gly Lys Gln Gly Ala Gly Lys Asp Asn Val Asp Tyr Ser Asn Val
545                 550                 555                 560

Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr
                565                 570                 575

Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln Arg Gln Asn Thr Ala
            580                 585                 590

Pro Ile Val Gly Ala Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val
        595                 600                 605

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

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

Gly Leu Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val
```

645 650 655

Pro Ala Asp Pro Pro Thr Ala Phe Asn Gln Ala Lys Leu Asn Ser Phe
660 665 670

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

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

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

Gly Val Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg
725 730 735

Asn Leu

<210> 39
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 39

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

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 Asn 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 Gln 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 Ser Pro Val 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 Ile 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 Ser
    210                 215                 220

Ser 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 Asn Gly Thr Ser Gly Gly Ser Thr Asn Asp
            260                 265                 270

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

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

Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn
305                 310                 315                 320

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

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

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

Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn
    370                 375                 380

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

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

Asn Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser
            420                 425                 430

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

Ser Arg Thr Gln Ser Thr Gly Gly Thr Ala Gly Thr Gln Gln Leu Leu
    450                 455                 460

Phe Ser Gln Ala Gly Pro Asn Asn Met Ser Ala Gln Ala Lys Asn Trp
465                 470                 475                 480

Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Leu Ser
                485                 490                 495

Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His
```

```
            500                 505                 510

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

His Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Ser Gly Val Leu Met
    530                 535                 540

Phe Gly Lys Gln Gly Ala Gly Lys Asp Asn Val Asp Tyr Ser Ser Val
545                 550                 555                 560

Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr
                565                 570                 575

Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln Gln Gln Asn Ala Ala
            580                 585                 590

Pro Ile Val Gly Ala Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val
        595                 600                 605

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

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

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

Pro Ala Asp Pro Pro Thr Thr Phe Thr Lys Ala Lys Leu Ala Ser Phe
            660                 665                 670

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

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

Ser Asn Tyr Tyr Lys Ser Thr Asn Val Asp Phe Ala Val Asn Thr Glu
705                 710                 715                 720
```

Gly Thr Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg
725 730 735

Asn Leu

<210> 40
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 40

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

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 Asn 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 Gln 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 Ser Pro Val 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 Ile 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 Ser
    210                 215                 220

Ser 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 Asn Gly Thr Ser Gly Gly Ser Thr Asn Asp
            260                 265                 270

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

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

Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn
305                 310                 315                 320

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

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

Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe
```

```
        355                 360                 365

Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn
    370                 375                 380

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

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

Asn Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser
            420                 425                 430

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

Ser Arg Thr Gln Ser Thr Gly Gly Thr Ala Gly Thr Gln Gln Leu Leu
    450                 455                 460

Phe Ser Gln Ala Gly Pro Asn Asn Met Ser Ala Gln Ala Lys Asn Trp
465                 470                 475                 480

Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Leu Ser
                485                 490                 495

Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His
            500                 505                 510

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

His Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Ser Gly Val Leu Met
    530                 535                 540

Phe Gly Lys Gln Gly Ala Gly Lys Asp Asn Val Asp Tyr Ser Ser Val
545                 550                 555                 560

Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr
                565                 570                 575
```

```
Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln Gln Gln Asn Ala Ala
            580                 585                 590

Pro Ile Val Gly Ala Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val
        595                 600                 605

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

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

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

Pro Ala Asp Pro Pro Thr Thr Phe Asn Gln Ala Lys Leu Ala Ser Phe
            660                 665                 670

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

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

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

Gly Thr Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg
                725                 730                 735

Asn Leu
```

<210> 41
<211> 735
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 41

```
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 Gln 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 His 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 Thr Ser Leu Gly Ser Thr 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 Gln Trp Leu 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 Pro 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 Asn Arg Thr
        435                 440                 445

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

Ala Gly Pro Thr Ser Met Ser Leu Gln Ala Lys Asn Trp Leu Pro Gly
465                 470                 475                 480

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

Asn Ser Asn Phe Pro Trp Thr Ala 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 Met His Gly Thr Leu Ile Phe Gly Lys
    530                 535                 540

Gln Gly Thr Asn Ala Asn Asp Ala Asp Leu Glu His 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 Asn Val Ser Asn Asn Leu Gln Asn Ser Asn Thr Gly Pro Thr Thr
            580                 585                 590

Glu Asn Val Asn His Gln Gly Ala 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 Met Ile Lys Asn Thr Pro Val Pro Ala Asn
```

```
                645                 650                 655

Pro Pro Thr Asn Phe Ser Ser 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 Asn Leu
                725                 730                 735
```

<210> 42
<211> 735
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 42

```
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 Ile 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 Ala 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 Arg Pro Leu Gly Gln Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Leu Gly Thr Asn Thr Met Ala Ser 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 Ser 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 Met 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 Ala Ala Asp Asn Asn
                485                 490                 495

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

Gln Asp Ser Gly 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 Ser Gly Asn Thr Gln Ala Ala Thr
            580                 585                 590

Ser 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 Asn Leu
                725                 730                 735
```

<210> 43
<211> 735
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 43

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 Ile 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 Ala 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 Ser 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 Ser 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 Met 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 Ala Ala Asp Asn Asn
485 490 495

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

Gln Asp Ser Gly 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 Ser Gly Asn Thr Gln Ala Ala Thr
580 585 590

Ser 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 Asn Leu
                725                 730                 735
```

<210> 44
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 44

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

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 Ala 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 Ile 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 Ser
    210                 215                 220

Ser 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 Asn Gly Thr Ser Gly Gly Ser Thr Asn Asp
```

```
            260                 265                 270

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

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

Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Ser Phe Lys Leu Phe Asn
305                 310                 315                 320

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

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

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

Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn
    370                 375                 380

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

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

Thr Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser
            420                 425                 430

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

Ser Arg Thr Gln Ser Thr Gly Gly Thr Gln Gly Thr Gln Gln Leu Leu
    450                 455                 460

Phe Ser Gln Ala Gly Pro Ala Asn Met Ser Ala Gln Ala Lys Asn Trp
465                 470                 475                 480
```

```
Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Leu Ser
                485                 490                 495

Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His
            500                 505                 510

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

His Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Ser Gly Val Leu Met
    530                 535                 540

Phe Gly Lys Gln Gly Ala Gly Arg Asp Asn Val Asp Tyr Ser Ser Val
545                 550                 555                 560

Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr
                565                 570                 575

Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln Gln Thr Asn Thr Gly
            580                 585                 590

Pro Ile Val Gly Asn Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val
        595                 600                 605

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

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

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

Pro Ala Asp Pro Pro Thr Thr Phe Ser Gln Ala Lys Leu Ala Ser Phe
            660                 665                 670

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

Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr
```

690 695 700

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

Gly Thr Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg
725 730 735

Asn Leu

<210> 45
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 45

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 Gly 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 Gly 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 Thr 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

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

Asn Pro Ser Thr Thr Phe Ser Ala Ala Lys Phe Ala Ser Phe Ile Thr
660 665 670

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

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

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

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
725 730 735

<210> 46
<211> 734
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV vector

<400> 46

```
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 Ala 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 Arg Gln Pro Pro
            180                 185                 190

Ala Ala Pro Thr Ser Leu Gly Ser Thr 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 Gln Trp Leu 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 Gln 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 Asn Arg Thr
        435                 440                 445

Gln Thr Ala Ser Gly Thr Gln Gln Ser Arg Leu Leu Phe Ser Gln Ala
    450                 455                 460

Gly Pro Thr Ser Met Ser Leu Gln Ala Lys Asn Trp Leu Pro Gly Pro
465                 470                 475                 480

Cys Tyr Arg Gln Gln Arg Leu Ser Lys Gln Ala Asn Asp Asn Asn Asn
                485                 490                 495

Ser Asn Phe Pro Trp Thr Gly Ala Thr Lys Tyr Tyr Leu Asn Gly Arg
            500                 505                 510

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

Glu Glu Lys Phe Phe Pro Met His Gly Thr Leu Ile Phe Gly Lys Glu
    530                 535                 540

Gly Thr Asn Ala Thr Asn Ala Glu Leu Glu Asn Val Met Ile Thr Asp
545                 550                 555                 560

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

Tyr Val Ser Asn Asn Leu Gln Asn Ser Asn Thr Ala Ala Ser Thr Glu
            580                 585                 590

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

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

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

Pro Pro Pro Gln Ile Met Ile Lys Asn Thr Pro Val Pro Ala Asn Pro
645 650 655

Pro Thr Asn Phe Ser Ser Ala Lys Phe Ala Ser Phe Ile Thr Gln Tyr
660 665 670

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

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

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

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

<210> 47
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; IgG1

<400> 47

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

```
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125

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

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly Lys
225                 230
```

<210> 48
<211> 228
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; IgG2

<400> 48

```
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
1               5                   10                  15
```

```
Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            20                  25                  30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        35                  40                  45

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
    50                  55                  60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
65                  70                  75                  80

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
                85                  90                  95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
            100                 105                 110

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
        115                 120                 125

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
    130                 135                 140

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ser Val
145                 150                 155                 160

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                165                 170                 175

Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            180                 185                 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        195                 200                 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    210                 215                 220

Ser Pro Gly Lys
```

225

<210> 49
<211> 229
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; Igg4

<400> 49

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

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

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145 150 155 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr

165 170 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
180 185 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
195 200 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
210 215 220

Leu Ser Leu Gly Lys
225

<210> 50
<211> 1725
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 50
gacattgatt attgactagt tattaatagt aatcaattac ggggtcatta gttcatagcc 60

catatatgga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 120

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaatagggа 180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240

aagtgtatca tatgccaagt acgccccctа ttgacgtcaa tgacggtaaa tggcccgcct 300

ggcattatgc ccagtacatg accttatggg actttcctac ttggcagtac atctacgtat 360

tagtcatcgc tattaccatg gtcgaggtga gccccacgtt ctgcttcact ctccccatct 420

ccccccccтc cccaccccca attttgtatt tatttatttt ttaattattt tgtgcagcga 480

tgggggcggg gggggggggg gggcgcgcgc caggcggggc ggggcggggc gaggggcggg 540

gcggggcgag gcggagaggt gcggcggcag ccaatcagag cggcgcgctc cgaaagtttc 600

cttttatggc gaggcggcgg cggcggcggc cctataaaaa gcgaagcgcg cggcgggcgg 660

gagtcgctgc gcgctgcctt cgccccgtgc cccgctccgc cgccgcctcg cgccgcccgc 720

cccggctctg actgaccgcg ttactcccac aggtgagcgg gcgggacggc ccttctcctc 780

cgggctgtaa ttagcgcttg gtttaatgac ggcttgtttc ttttctgtgg ctgcgtgaaa 840

gccttgaggg gctccgggag ggccctttgt gcgggggggag cggctcgggg ggtgcgtgcg 900

tgtgtgtgtg cgtggggagc gccgcgtgcg gctccgcgct gcccggcggc tgtgagcgct 960

gcgggcgcgg cgcggggctt tgtgcgctcc gcagtgtgcg cgaggggagc gcggccgggg 1020

gcggtgcccc gcggtgcggg gggggctgcg aggggaacaa aggctgcgtg cggggtgtgt 1080

gcgtgggggg gtgagcaggg ggtgtgggcg cgtcggtcgg gctgcaaccc cccctgcacc 1140

cccctccccg agttgctgag cacggcccgg cttcgggtgc ggggctccgt acggggcgtg 1200

gcgcggggct cgccgtgccg ggcgggggggt ggcggcaggt gggggtgccg ggcggggcgg 1260

ggccgcctcg ggccggggag ggctcggggg aggggcgcgg cggcccccgg agcgccggcg 1320

gctgtcgagg cgcggcgagc cgcagccatt gccttttatg gtaatcgtgc gagagggcgc 1380

agggacttcc tttgtcccaa atctgtgcgg agccgaaatc tgggaggcgc cgccgcaccc 1440

cctctagcgg gcgcggggcg aagcggtgcg gcgccggcag gaaggaaatg ggcggggagg 1500

gccttcgtgc gtcgccgcgc cgccgtcccc ttctccctct ccagcctcgg ggctgtccgc 1560

ggggggacgg ctgccttcgg gggggacggg gcagggcggg gttcggcttc tggcgtgtga 1620

ccggcggctc tagagcctct gctaaccatg ttcatgcctt cttcttttttc ctacagctcc 1680

tgggcaacgt gctggttatt gtgctgtctc atcattttgg caaag 1725

<210> 51
<211> 1676
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 51
gacattgatt attgactagt tattaatagt aatcaattac ggggtcatta gttcatagcc 60

catatatgga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 120

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaataggga 180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240

aagtgtatca tatgccaagt acgcccccta ttgacgtcaa tgacggtaaa tggcccgcct 300

ggcattatgc ccagtacatg accttatggg actttcctac ttggcagtac atctacgtat 360

tagtcatcgc tattaccatg gtcgaggtga gccccacgtt ctgcttcact ctccccatct 420

ccccccccctc cccaccccca attttgtatt tatttatttt ttaattattt tgtgcagcga 480

tgggggcggg gggggggggg gggcgcgcgc caggcggggc ggggcggggc gaggggcggg 540

gcggggcgag gcggagaggt gcggcggcag ccaatcagag cggcgcgctc cgaaagtttc 600

cttttatggc gaggcggcgg cggcggcggc cctataaaaa gcgaagcgcg cggcgggcgg 660

gagtcgctgc gcgctgcctt cgccccgtgc cccgctccgc cgccgcctcg cgccgcccgc 720

cccggctctg actgaccgcg ttactcccac aggtgagcgg gcgggacggc ccttctcctc 780

cgggctgtaa ttagcgcttg gtttaatgac ggcttgtttc ttttctgtgg ctgcgtgaaa 840

gccttgaggg gctccgggag ggccctttgt gcgggggggag cggctcgggg ggtgcgtgcg 900

tgtgtgtgtg cgtggggagc gccgcgtgcg gctccgcgct gcccggcggc tgtgagcgct 960

gcgggcgcgg cgcggggctt tgtgcgctcc gcagtgtgcg cgaggggagc gcggccgggg 1020

gcggtgcccc gcggtgcggg gggggctgcg aggggaacaa aggctgcgtg cggggtgtgt 1080

gcgtgggggg gtgagcaggg ggtgtgggcg cgtcggtcgg gctgcaaccc cccctgcacc 1140

cccctccccg agttgctgag cacggcccgg cttcgggtgc ggggctccgt acggggcgtg 1200

gcgcggggct cgccgtgccg ggcgggggggt ggcggcaggt gggggtgccg ggcggggcgg 1260

ggccgcctcg ggccggggag ggctcggggg aggggcgcgg cggcccccgg agcgccggcg 1320

gctgtcgagg cgcggcgagc cgcagccatt gccttttatg gtaatcgtgc gagagggcgc 1380

agggacttcc tttgtcccaa atctgtgcgg agccgaaatc tgggaggcgc cgccgcaccc 1440

cctctagcgg gcgcggggcg aagcggtgcg gcgccggcag gaaggaaatg ggcggggagg 1500

gccttcgtgc gtcgccgcgc cgccgtcccc ttctccctct ccagcctcgg ggctgtccgc 1560

ggggggacgg ctgccttcgg gggggacggg gcagggcggg gttcggcttc tggcgtgtga 1620

ccggcggctc tagagcctct gctaaccatg ttcatgcctt cttcttttтc ctacag 1676

<210> 52
<211> 251
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 52

atggaggcgg tactatgtag atgagaattc aggagcaaac tgggaaaagc aactgcttcc 60

aaatatttgt gatttttaca gtgtagtttt ggaaaaactc ttagcctacc aattcttcta 120

agtgttttaa aatgtgggag ccagtacaca tgaagttata gagtgtttta atgaggctta 180

aatatttacc gtaactatga aatgctacgc atatcatgct gttcaggctc cgtggccacg 240

caactcatac t 251

<210> 53
<211> 212
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 53
gggcagagcg cacatcgccc acagtccccg agaagttggg gggaggggtc ggcaattgaa 60

cgggtgccta gagaaggtgg cgcggggtaa actgggaaag tgatgtcgtg tactggctcc 120

gccttttcc cgagggtggg ggagaaccgt atataagtgc agtagtcgcc gtgaacgttc 180

tttttcgcaa cgggtttgcc gccagaacac ag 212

<210> 54
<211> 295
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 54
gggccccaga agcctggtgg ttgtttgtcc ttctcagggg aaaagtgagg cggccccttg 60

gaggaagggg ccgggcagaa tgatctaatc ggattccaag cagctcaggg gattgtcttt 120

ttctagcacc ttcttgccac tcctaagcgt cctccgtgac cccggctggg atttagcctg 180

gtgctgtgtc agccccgggc tcccaggggc ttcccagtgg tccccaggaa ccctcgacag 240

ggccagggcg tctctctcgt ccagcaaggg cagggacggg ccacaggcca agggc 295

<210> 55
<211> 127
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 55
gatctttttc cctctgccaa aaattatggg gacatcatga agccccttga gcatctgact 60

tctggctaat aaaggaaatt tattttcatt gcaatagtgt gttggaattt tttgtgtctc 120

tcactcg 127

<210> 56
<211> 133
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 56
gtaagtatca aggttacaag acaggtttaa ggagaccaat agaaactggg cttgtcgaga 60

cagagaagac tcttgcgttt ctgataggca cctattggtc ttactgacat ccactttgcc 120

tttctctcca cag 133

<210> 57
<211> 82
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 57
gtgagtatct cagggatcca gacatgggga tatgggaggt gcctctgatc ccagggctca 60

ctgtgggtct ctctgttcac ag 82

<210> 58
<211> 130
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 58
ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgaccttt 60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtggccaa ctccatcact 120

aggggttcct 130

<210> 59
<211> 106
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 59
ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgaccttt 60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtgg 106

<210> 60
<211> 143
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 60
gaacccctag tgatggagtt ggccactccc tctctgcgcg ctcgctcgct cactgaggcc 60

gcccgggcaa agcccgggcg tcgggcgacc tttggtcgcc cggcctcagt gagcgagcga 120

gcgcgcagag agggagtggc caa 143

<210> 61
<211> 110
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 61
ttggccactc cctctctgcg cgctcgctcg ctcactgagg ccgggcgacc aaaggtcgcc 60

cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc gagcgcgcag 110

<210> 62
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 62

Met Tyr Arg Met Gln Leu Leu Leu Leu Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser
20

<210> 63
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 63
atgtatagga tgcaactgct cctcctgatt gctctgagcc tggctcttgt gaccaactct 60

<210> 64
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 64

Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu
1 5 10 15

Tyr Leu His His Ala Lys Trp Ser Gln Ala
20 25

<210> 65
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 65

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

Leu Gly Gly Leu Ala Leu Leu Ala Ala Gly Val Asp Ala
20 25

<210> 66
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 66

Met Ala Pro Leu Arg Pro Leu Leu Ile Leu Ala Leu Leu Ala Trp Val
1 5 10 15

Ala Leu Ala

<210> 67
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 67

Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1 5 10 15

Val Ala

<210> 68
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 68

Met Arg Leu Leu Ala Phe Leu Ser Leu Leu Ala Leu Val Leu Gln Glu
1 5 10 15

Thr Gly Thr

<210> 69
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 69

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser

<210> 70
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 70

Met Ala Phe Leu Trp Leu Leu Ser Cys Trp Ala Leu Leu Gly Thr Thr
1 5 10 15

Phe Gly

<210> 71
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 71

Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ile Leu Ala Leu
1 5 10 15

Val Thr Asn Ser
            20

<210> 72
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 72

Met Asn Leu Leu Leu Ile Leu Thr Phe Val Ala Ala Ala Val Ala
1   5   10   15

<210> 73
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 73

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1   5   10   15

Tyr Ser

<210> 74
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 74

Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys
1   5   10   15

Cys Leu Val Pro Val Ser Leu Ala
            20

<210> 75
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 75

Met Lys Ala Ala Val Leu Thr Leu Ala Val Leu Phe Leu Thr Gly Ser
1 5 10 15

Gln Ala

<210> 76
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 76

Met Lys Leu Leu Ala Ala Thr Val Leu Leu Leu Thr Ile Cys Ser Leu
1 5 10 15

Glu Gly

<210> 77
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 77

Met Asp Pro Pro Arg Pro Ala Leu Leu Ala Leu Leu Ala Leu Pro Ala
1 5 10 15

Leu Leu Leu Leu Leu Leu Ala Gly Ala Arg Ala
20 25

<210> 78
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 78

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys
20 25

<210> 79
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 79

Met Gly Pro Leu Met Val Leu Phe Cys Leu Leu Phe Leu Tyr Pro Gly
1 5 10 15

Leu Ala Asp Ser
20

<210> 80
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 80

Met Trp Leu Leu Val Ser Val Ile Leu Ile Ser Arg Ile Ser Ser Val
1 5 10 15

Gly Gly

<210> 81
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 81

Met Leu Leu Leu Phe Ser Val Ile Leu Ile Ser Trp Val Ser Thr Val
1   5   10   15

Gly Gly

<210> 82
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 82

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

Ala Trp Thr

<210> 83
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 83

Met Lys Arg Met Val Ser Trp Ser Phe His Lys Leu Lys Thr Met Lys
1   5   10   15

His Leu Leu Leu Leu Leu Leu Cys Val Phe Leu Val Lys Ser
            20   25   30

<210> 84
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 84

Met Ser Trp Ser Leu His Pro Arg Asn Leu Ile Leu Tyr Phe Tyr Ala
1 5 10 15

Leu Leu Phe Leu Ser Ser Thr Cys Val Ala
20 25

<210> 85
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 85

Met Lys Ser Leu Val Leu Leu Leu Cys Leu Ala Gln Leu Trp Gly Cys
1 5 10 15

His Ser

<210> 86
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 86

Met Ala Arg Val Leu Gly Ala Pro Val Ala Leu Gly Leu Trp Ser Leu
1 5 10 15

Cys Trp Ser Leu Ala Ile Ala
20

<210> 87
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 87

Met Lys Leu Ile Thr Ile Leu Phe Leu Cys Ser Arg Leu Leu Leu Ser
1 5 10 15

Leu Thr

<210> 88
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 88

Met Ser Leu Phe Pro Ser Leu Pro Leu Leu Leu Leu Ser Met Val Ala
1 5 10 15

Ala Ser Tyr Ser
20

<210> 89
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 89

Met Glu His Lys Glu Val Val Leu Leu Leu Leu Leu Phe Leu Lys Ser
1 5 10 15

Gly Gln Gly

<210> 90
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 90

Met Ala His Val Arg Gly Leu Gln Leu Pro Gly Cys Leu Ala Leu Ala
1 5 10 15

Ala Leu Cys Ser Leu Val His Ser
20

<210> 91
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 91

Met Ile Ser Arg Met Glu Lys Met Thr Met Met Met Lys Ile Leu Ile
1 5 10 15

Met Phe Ala Leu Gly Met Asn Tyr Trp Ser Cys Ser Gly
20 25

<210> 92
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 92

Met Tyr Ser Asn Val Ile Gly Thr Val Thr Ser Gly Lys Arg Lys Val
1 5 10 15

Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys
20 25 30

<210> 93
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 93

Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu
1 5 10 15

Cys Leu Ala

<210> 94
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 94

Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu
1 5 10 15

Ala

<210> 95
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 95

Met Phe Ser Phe Val Asp Leu Arg Leu Leu Leu Leu Leu Ala Ala Thr
1 5 10 15

Ala Leu Leu Thr His Gly
20

<210> 96
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 96

Met Lys Leu Val Phe Leu Val Leu Leu Phe Leu Gly Ala Leu Gly Leu
1   5   10   15

Cys Leu Ala

<210> 97
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 97

Met Gly Pro Thr Ser Gly Pro Ser Leu Leu Leu Leu Leu Leu Thr His
1   5   10   15

Leu Pro Leu Ala Leu Gly
            20

<210> 98
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 98

Met Ser Leu Ser Ala Phe Thr Leu Phe Leu Ala Leu Ile Gly Gly Thr
1   5   10   15

Ser Gly

<210> 99
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 99

Met Ala Pro His Arg Pro Ala Pro Ala Leu Leu Cys Ala Leu Ser Leu
1 5 10 15

Ala Leu Cys Ala Leu Ser Leu Pro Val Arg Ala
20 25

<210> 100
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 100

Met Trp Ala Thr Leu Pro Leu Leu Cys Ala Gly Ala Trp Leu Leu Gly
1 5 10 15

Val Pro Val Cys Gly Ala
20

<210> 101
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 101

Met Gln Ala Leu Val Leu Leu Leu Cys Ile Gly Ala Leu Leu Gly His
1 5 10 15

Ser Ser Cys

<210> 102
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 102

Met Gln Met Ser Pro Ala Leu Thr Cys Leu Val Leu Gly Leu Ala Leu
1 5 10 15

Val Phe Gly Glu Gly Ser Ala
20

<210> 103
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 103

Met Gln Pro Ser Ser Leu Leu Pro Leu Ala Leu Cys Leu Leu Ala Ala
1 5 10 15

Pro Ala Ser Ala
20

<210> 104
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 104

Met Ala Pro Phe Glu Pro Leu Ala Ser Gly Ile Leu Leu Leu Leu Trp
1 5 10 15

Leu Ile Ala Pro Ser Arg Ala
20

<210> 105
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 105

Met Leu Arg Gly Pro Gly Pro Gly Leu Leu Leu Leu Ala Val Gln Cys
1   5   10   15

Leu Gly Thr Ala Val Pro Ser Thr Gly Ala Ser Lys Ser Lys Arg
            20   25   30

<210> 106
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 106

Met Trp Cys Ile Val Leu Phe Ser Leu Leu Ala Trp Val Tyr Ala
1   5   10   15

<210> 107
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 107

Met Asn Pro Thr Leu Ile Leu Ala Ala Phe Cys Leu Gly Ile Ala Ser
1   5   10   15

Ala

<210> 108
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 108

Met Trp Gln Leu Trp Ala Ser Leu Cys Cys Leu Leu Val Leu Ala Asn
1 5 10 15

Ala

<210> 109
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 109

Met Leu Leu Ile Leu Leu Ser Val Ala Leu Leu Ala Phe Ser Ser Ala
1 5 10 15

<210> 110
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 110

Met Trp Lys Arg Trp Leu Ala Leu Ala Leu Ala Leu Val Ala Val Ala
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Trp Val Arg Ala
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<210> 111
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<220>
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<400> 111
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cacactcgcc aaccccgagc gcatagttca aaaccggagc ttcagctact taagaagata 180

ggtacataaa accgaccaaa gaaactgacg cctcacttat ccctcccctc accagaggtc 240

cggcgcctgt cgattcagga gagcctaccc taggcccgaa ccctgcgtcc tgcgacggag 300

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ggcaccgcca taactgccgc ccccgcaaca gacgacaaac cgagttctcc agtcagtgac 480

aaacttcacg tcagggtccc cagatggtgc cccagcccat ctcacccgaa taagagcttt 540

cccgcattag cgaaggcctc aagaccttgg gttcttgccg cccaccatgc cccccacctt 600

gtttcaacga cctcacagcc cgcctcacaa gcgtcttcca ttcaagactc gggaacagcc 660

gccattttgc tgcgctcccc ccaaccccca gttcagggca accttgctcg cggacccaga 720

ctacagccct tggcggtctc tccacacgct tccgtcccac cgagcggccc ggcggccacg 780

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agcagcgggc cgctgtcctg agcgtccggg cggaaggatc aggacgctcg ctgcgccctt 1140

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ggcgcggagg cc 1212

<210> 112
<211> 1724
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 112

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atggccaaat ggttccttgt cctatagctg tagcagccat cggctgttag tgacaaagcc 240

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agcagagccg gtgaaggtgc agaacctacc gcctttccag gcctcctccc acctctgcca 780

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ggaggtctaa gtcccaggcc caattaagag atcaggtagt gtagggtttg ggagctttta 1620

aggtgaagag gcccgggctg atcccacagg ccagtataaa gcgccgtgac cctcaggtga 1680

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<210> 113
<211> 806
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 113
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gacggaatct gcttcttccc acatttgagt cctcctcagc ccctgagctc ctctgggcag 180

ggctgtttct ttccatcttt gtattcccag gggcctgcaa ataaatgttt aatgaacgaa 240

caagagagtg aattccaatt ccatgcaaca aggattgggc tcctgggccc taggctatgt 300

gtctggcacc agaaacggaa gctgcaggtt gcagcccctg ccctcatgga gctcctcctg 360

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ggggctgtgt gacgagatga gagactggga gaataaacca gaaagtctct agctgtccag 480

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gtctgggggg gtcagaaccc agagtc 806

<210> 114
<211> 1003
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 114
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ccttgtgtac tctttggtgg tggttactct gggggtacta ggttagttcg tattgttgtt 180

cctcctaggg gactgcaaac cccttcagct ccttgggtcc tttctctagt tccttctttg 240

gggaccctgt gctcagttca atggatggcc aatttccttc ttaaatgccc ctagcagtaa 300

ctgttaggtc tcaatcccaa gacaaatgtc tgaggtgcct atttaacaga tcaaagcgga 360

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cagcccatga gcttcgggct gtacttcccc aacgggttct cccattttgg gtacatggcc 480

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atccccccca acccctccca tacacataca catgtgcact cgtgcactca acccagcaca 600

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aataaatctc ctccactata cttaggagca gttatgttct tcttctttct ttctttttt 720

ttttttttc attcagtaac atcatcagaa tcccctagct ctggcctacc tcctcagtaa 780

caatcagctg atccctggcc actaatctgt actcactaat ctgttttcca aactcttggc 840

ccctgagcta attatagcag tgcttcatgc cacccacccc aaccctatcc ttgttctctg 900

actcccacta atctacacat tcagaggatt gtggatataa gaggctggga ggccagctta 960

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<210> 115
<211> 523
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 115
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ggataatgtt cattcttgac ctttccacat acatctggct atgttctctc tcttatctac 180

aataaatctc ctccactata cttaggagca gttatgttct tcttctttct ttctttttt 240

ttttttttc attcagtaac atcatcagaa tcccctagct ctggcctacc tcctcagtaa 300

caatcagctg atccctggcc actaatctgt actcactaat ctgttttcca aactcttggc 360

ccctgagcta attatagcag tgcttcatgc cacccacccc aaccctatcc ttgttctctg 420

actcccacta atctacacat tcagaggatt gtggatataa gaggctggga ggccagctta 480

gcaaccagag ctcgaggctg atgcgagctt catctcttcc ctc 523

<210> 116
<211> 215
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 116
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taattatagc agtgcttcat gccacccacc ccaaccctat ccttgttctc tgactcccac 120

taatctacac attcagagga ttgtggatat aagaggctgg gaggccagct tagcaaccag 180

agctcgaggc tgatgcgagc ttcatctctt ccctc 215

<210> 117
<211> 198
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 117
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gaggaagggg ccgggcagaa tgatctaatc ggattccaag cagctcaggg gattgtcttt 120

ttctagcacc ttcttgccac tcctaagcgt cctccgtgac cccggctggg atttagcctg 180

gtgctgtgtc agccccgg 198

<210> 118
<211> 142
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 118
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<210> 119
<211> 109
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 119
gtcaagtgac ggcggctcag cactcacgtg ggcagtgcca gcctctaaga gtgggcaggg 60

gcactggcca cagagtccca gggagtccca ccagcctagt cgccagacc 109

<210> 120
<211> 93
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 120
ctcagcactc acgtgggcag tgccagcctc taagagtggg caggggcact ggccacagag 60

tcccagggag tcccaccagc ctagtcgcca gac 93

<210> 121
<211> 1080
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 121
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gctctgctct cttcattgaa caatacaaga ggagtgtgta ggtagacacc caccacttcc 120

aacagcttag gagagccctt gagtatggat tgatgtatta aaatttattg aatcacatgc 180

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<210> 122
<211> 969
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory sequence

<400> 122
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gccctccctg cctgctgacc ttggagctgg ggcagaggtc agagacctct ctgggcccat 480

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<211> 1050
<212> DNA
<213> Artificial Sequence

<220>
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<400> 123
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cttgctacca gtggaacagc cactaaggat tctgcagtga gagcagaggg ccagctaagt 720

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<210> 124
<211> 1089
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory sequence

<400> 124
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aataatctca ggagcacaaa cattccagat ccggcgcgcc agggctggaa gctacctttg 240

acatcatttc ctctgcgaat gcatgtataa tttctacaga acctattaga aaggatcacc 300

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<220>
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<220>
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<212> DNA
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<220>
<223> synthetic construct; regulatory sequence

<400> 133
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<220>
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<400> 134
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<220>
<223> synthetic construct; regulatory sequence

<400> 137
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<223> synthetic construct; regulatory sequence

<400> 138
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gtctagaagg ctcagaggca cacaggagtt tctgggctca 360

ccctgccccc ttccaacccc tcagttccca tcctccagca gctgtttgtg tgctgcctct 420

gaagtccaca ctgaacaaac ttcagcctac tcatgtccct aaaatgggca aacattgcaa 480

gcagcaaaca gcaaacacac agccctccct gcctgctgac cttggagctg gggcagaggt 540

cagagacctc tctg 554

<210> 139
<211> 393
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory sequence

<400> 139
gatcttgcta ccagtggaac agccactaag gattctgcag tgagagcaga gggccagcta 60

agtggtactc tcccagagac tgtctgactc acgccacccc ctccaccttg gacacaggac 120

gctgtggttt ctgagccagg tacaatgact cctttcggta agtgcagtgg aagctgtaca 180

ctgcccaggc aaagcgtccg ggcagcgtag gcgggcgact cagatcccag ccagtggact 240

tagcccctgt ttgctcctcc gataactggg gtgaccttgg ttaatattca ccagcagcct 300

cccccgttgc ccctctggat ccactgctta aatacggacg aggacagggc cctgtctcct 360

cagcttcagg caccaccact gacctgggac agt 393

<210> 140
<211> 393
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory sequence

<400> 140
gatcttgcta ccagtggaac agccactaag gattctgcag tgagagcaga gggccagcta 60

agtggtactc tcccagagac tgtctgactc acgccacccc ctccaccttg gacacaggac 120

gctgtggttt ctgagccagg tacagtgact cctttcggta agtgcagtgg aagctgtaca 180

ctgcccaggc aaagcgtccg ggcagcgtag gcgggcgact cagatcccag ccagtggact 240

tagcccctgt ttgctcctcc gataactggg gtgaccttgg ttaatattca ccagcagcct 300

cccccgttgc ccctctggat ccactgctta aatacggacg aggacagggc cctgtctcct 360

cagcttcagg caccaccact gacctgggac agt 393

<210> 141
<211> 144
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory sequence

<400> 141
ccactacggg tttaggctgc ccatgtaagg aggcaaggcc tggggacacc cgagatgcct 60

ggttataatt aacccagaca tgtggctgcc ccccccccc ccaacacctg ctgcctctaa 120

aaataaccct gtccctggtg gatc 144

<210> 142
<211> 288
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory sequence

<400> 142
ccactacggg tttaggctgc ccatgtaagg aggcaaggcc tggggacacc cgagatgcct 60

ggttataatt aacccagaca tgtggctgcc ccccccccc ccaacacctg ctgcctctaa 120

aaataaccct gtccctggtg gatcccacta cgggtttagg ctgcccatgt aaggaggcaa 180

ggcctgggga cacccgagat gcctggttat aattaaccca gacatgtggc tgccccccc 240

ccccccaaca cctgctgcct ctaaaaataa ccctgtccct ggtggatc 288

<210> 143
<211> 432
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory sequence

<400> 143
ccactacggg tttaggctgc ccatgtaagg aggcaaggcc tggggacacc cgagatgcct 60

ggttataatt aacccagaca tgtggctgcc ccccccccc ccaacacctg ctgcctctaa 120

aaataaccct gtccctggtg gatcccacta cgggtttagg ctgcccatgt aaggaggcaa 180

ggcctgggga cacccgagat gcctggttat aattaaccca gacatgtggc tgccccccc 240

ccccccaaca cctgctgcct ctaaaaataa ccctgtccct ggtggatccc actacgggtt 300

taggctgccc atgtaaggag gcaaggcctg gggacacccg agatgcctgg ttataattaa 360

cccagacatg tggctgcccc ccccccccc aacacctgct gcctctaaaa ataaccctgt 420

ccctggtgga tc 432

<210> 144
<211> 199
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory sequence

<400> 144
cccttcagat taaaaataac tgaggtaagg gcctgggtag gggaggtggt gtgagacgct 60

cctgtctctc ctctatctgc ccatcggccc tttggggagg aggaatgtgc ccaaggacta 120

aaaaaaggcc atggagccag aggggcgagg gcaacagacc tttcatgggc aaaccttggg 180

gccctgctga agctttggc 199

<210> 145
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 145

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly
20

<210> 146
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 146

Glu Pro Lys Ser Cys Asp Lys Thr His Leu
1 5 10

<210> 147
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 147

Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10

<210> 148
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 148

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1   5   10   15

<210> 149
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 149

Glu Pro Lys Ser Cys Asp Lys Thr His Leu Cys Pro Pro Cys Pro Ala
1   5   10   15

<210> 150
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 150

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1   5   10   15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
            20   25

<210> 151
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 151

Glu Pro Lys Ser Cys Asp Lys Thr His Leu Cys Pro Pro Cys Pro Ala
1   5   10   15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
            20   25

<210> 152
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 152

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1   5   10   15

Gly Pro Ser Val Phe Leu
            20

<210> 153
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 153

Cys Cys Pro Cys Pro Ala
1   5

<210> 154
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 154

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1   5   10

<210> 155
<211> 11
<212> PRT

<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 155

Asp Lys Thr His Leu Cys Pro Pro Cys Pro Ala
1 5 10

<210> 156
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 156

Asp Lys Thr His Leu Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu
20

<210> 157
<211> 97
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 157
gtaagtttag tctttttgtc ttttatttca ggtcccggat ccggtggtgg tgcaaatcaa 60

agaactgctc ctcagtggat gttgccttta cttctag 97

<210> 158
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; cleavage

<400> 158

Leu Ser Pro Arg Gly Ser

1 5

<210> 159
<211> 663
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 159
gacgacattg attattgact agttattaat agtaatcaat tacggggtca ttagttcata 60

gcccatatat ggagttccgc gttacataac ttacggtaaa tggcccgcct ggctgaccgc 120

ccaacgaccc ccgcccattg acgtcaataa tgacgtatgt tcccatagta acgccaatag 180

ggactttcca ttgacgtcaa tgggtggagt atttacggta aactgcccac ttggcagtac 240

atcaagtgta tcatatgcca agtacgcccc ctattgacgt caatgacggt aaatggcccg 300

cctggcatta tgcccagtac atgaccttat gggactttcc tacttggcag tacatctacg 360

tattagtcat cgctattacc atggtcgagg tgagccccac gttctgcttc actctcccca 420

tctccccccc ctccccaccc ccaattttgt atttatttat tttttaatta ttttgtgcag 480

cgatgggggc gggggggggg gggggcgcgc cgccaggcgg ggcggggcgg ggcgaggggc 540

ggggcggggc gaggcggaga ggtgcggcgg cagccaatca gagcggcgcg ctccgaaagt 600

ttccttttat ggcgaggcgg cggcggcggc ggccctataa aaagcgaagc gcgcggcggg 660

cgg 663

<210> 160
<211> 762
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 160
gacgacattg attattgact agttattaat agtaatcaat tacggggtca ttagttcata 60

gcccatatat ggagttccgc gttacataac ttacggtaaa tggcccgcct ggctgaccgc 120

ccaacgaccc ccgcccattg acgtcaataa tgacgtatgt tcccatagta acgccaatag 180

ggactttcca ttgacgtcaa tgggtggagt atttacggta aactgcccac ttggcagtac 240

atcaagtgta tcatatgcca agtacgcccc ctattgacgt caatgacggt aaatggcccg 300

cctggcatta tgcccagtac atgaccttat gggactttcc tacttggcag tacatctacg 360

tattagtcat cgctattacc atggtcgagg tgagccccac gttctgcttc actctcccca 420

tctccccccc ctccccaccc ccaattttgt atttatttat tttttaatta ttttgtgcag 480

cgatgggggc gggggggggg gggggcgcgc cgccaggcgg ggcggggcgg ggcgaggggc 540

ggggcggggc gaggcggaga ggtgcggcgg cagccaatca gagcggcgcg ctccgaaagt 600

ttccttttat ggcgaggcgg cggcggcggc ggccctataa aaagcgaagc gcgcggcggg 660

cgggagtcgc tgcgcgctgc cttcgccccg tgccccgctc cgccgccgcc tcgcgccgcc 720

cgccccggct ctgactgacc gcgttactcc cacaggtgag cg 762

<210> 161
<211> 935
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 161
gtcgacaaat tctgtcattt tactagggtg atgaaattcc caagcaacac catccttttc 60

agataagggc actgaggctg agagaggagc tgaaacctac ccggggtcac cacacacagg 120

tggcaaggct gggaccagaa accaggactg ttgactgcag cccggtattc attctttcca 180

tagcccacag ggctgtcaaa gaccccaggg cctagtcaga ggctcctcct tcctggagag 240

ttcctggcac agaagttgaa gctcagcaca gccccctaac ccccaactct ctctgcaagg 300

cctcaggggt cagaacactg gtggagcaga tcctttagcc tctggatttt agggccatgg 360

tagagggggt gttgccctaa attccagccc tggtctcagc ccaacaccct ccaagaagaa 420

attagagggg ccatggccag gctgtgctag ccgttgcttc tgagcagatt acaagaaggg 480

actaagacaa ggactccttt gtggaggtcc tggcttaggg agtcaagtga cggcggctca 540

gcactcacgt gggcagtgcc agcctctaag agtgggcagg ggcactggcc acagagtccc 600

agggagtccc accagcctag tcgccagatc tagagggccc cagaagcctg gtggttgttt 660

gtccttctca ggggaaaagt gaggcggccc cttggaggaa ggggccgggc agaagatcta 720

atcggattcc aagcagctca ggggattgtc tttttctagc accttcttgc cactcctaag 780

cgtcctccgt gaccccggct gggatttagc ctggtgctgt gtcagccccg ggctcccagg 840

ggcttcccag tggtccccag gaaccctcga cagggccagg gcgtctctct cgtccagcaa 900

gggcagggac gggccacagg ccaagggcct taagc 935