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FIGS. 1A-1B

FIG. 1A

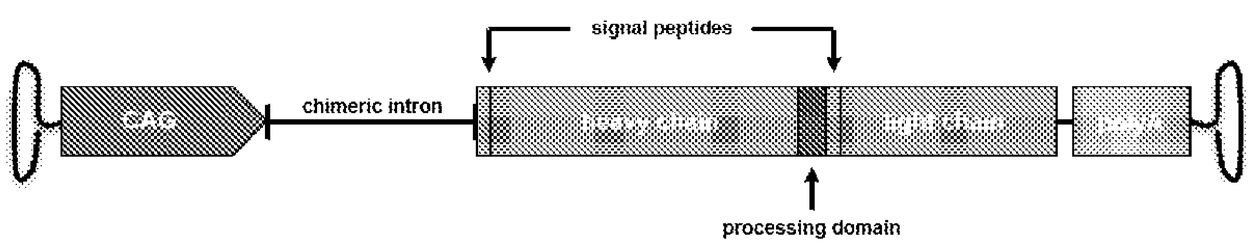
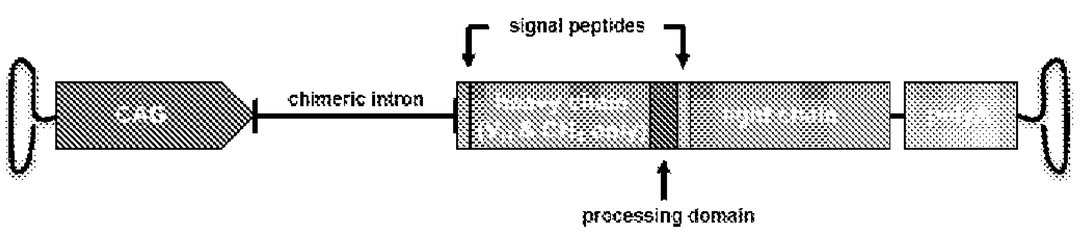


FIG. 1B



(57) Abstract: Compositions and methods are described for the delivery of a fully human post-translationally modified therapeutic monoclonal antibody, or an antigen binding fragment thereof, that binds to TNF-α, IL6 or IL6-R to a human subject for treatment of an ocular indication, particularly non-infectious uveitis. The nucleotide sequence encoding the antibody is delivered in a rAAV vector that targets ocular tissue cells for expression of the transgene.

[Continued on next page]

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VECTORIZED ANTI-TNF-α ANTIBODIES FOR OCULAR INDICATIONS

1. INTRODUCTION

[0001] Compositions and methods are described for the delivery of a fully human post-translationally modified (HuPTM) therapeutic monoclonal antibody ("mAb") that binds to tumor necrosis factor alpha (TNFα), interleukin-6 (IL6), or interleukin-6 receptor (IL6R) or the HuPTM antigen-binding fragment of a therapeutic mAb that binds to TNFα, IL6, or IL6R—e.g., a fully human-glycosylated (HuGly) Fab of the therapeutic mAb—to a human subject diagnosed with non-infectious uveitis (NIU).

2. BACKGROUND OF THE INVENTION

[0002] Therapeutic mAbs 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. When conventional immunosuppressive treatments and/or anti-TNF-α therapies fail, other biological agents are recommended. Some of the newest therapies have focused on blocking interleukin actions (e.g. anti-IL6 therapy) (Ming et al, Drug Des Devel Ther. 2018; 12: 2005–2016).

[0005] Adalimumab is an entirely humanized monoclonal antibody against TNF-α which is subcutaneously self-administered. It is the most used and studied biologic medication for the treatment of adulthood non-infectious uveitis since its approval in 2016 (Ming et al, Drug Des Devel Ther. 2018; 12: 2005–2016). Infliximab (Remicade®) is a chimeric monoclonal antibody used since 2001. It has 25% murine and 75% humanized domains. Its use is FDA-approved for RA, psoriatic arthritis, IBD, and AS, but not for non-infectious uveitis. It is only intravenously administered, usually in conjunction with methotrexate to prevent the generation of antibodies against the drug. Infliximab is associated with multitude of side effects on systemic administration such as congestive heart failure, reactivation of latent tuberculosis, and increased risk of infections, all of which can be minimized by administering the drug intravitreally. Golimumab (Simponi®) is a fully humanized monoclonal antibody, subcutaneously administered with a dose of 50 mg every 4 weeks. There is little evidence, but its efficacy has been described in patients with non-infectious uveitis refractory to adalimumab or infliximab, and thus golimumab is usually reserved as treatment for this subset of non-responders.

[0006] 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

[0007] Therapeutic antibodies delivered by gene therapy have several advantages over injected or infused therapeutic antibodies that dissipate over time resulting in peak and trough levels. Sustained expression of the transgene product antibody, as opposed to injecting an antibody repeatedly, allows for a more consistent level of antibody 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, antibodies 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 antibodies 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 antibodies. Accordingly, provided herein are compositions and methods for anti-TNFα, anti-IL6, or anti-IL6R gene therapy, particularly recombinant AAV gene therapy, designed to target the eye and generate a depot of transgenes for expression of anti-TNFα antibodies, particularly adalimumab, or an antigen binding fragment thereof, or anti-IL6 or anti-IL6R antibodies, that result in a therapeutic or prophylactic serum levels of the antibody within 20 days, 30 days, 40 days, 50 days, 60 days, or 90 days of administration of the rAAV composition.

[0008] Compositions and methods are described for the systemic delivery of an anti-TNFα, anti-IL6, or anti-IL6R HuPTM mAb or an anti-TNFα, anti-IL6, or anti-IL6R HuPTM antigen-binding fragment of a therapeutic mAb (for example, a fully human-glycosylated Fab (HuGlyFab) of a therapeutic mAb, to a patient (human subject) diagnosed with non-infectious uveitis or other condition indicated for treatment with the therapeutic anti-TNFα, anti-IL6, or anti-IL6R mAb. Such antigen-binding fragments of therapeutic mAbs include a Fab, $F(ab')_2$, or scFv (single-chain variable fragment) (collectively referred to herein as "antigen-binding fragment"). "HuPTM Fab" as used herein may include other antigen binding fragments of a mAb. In an alternative embodiment, full-length mAbs can be used. 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, anti-IL6, or anti-IL6R mAb or its antigen-binding fragment (or a hyperglycosylated derivative of either) diagnosed with a condition indicated for treatment with the therapeutic anti-TNFα, anti-IL6, or anti-IL6R mAb—

to create a permanent depot in the eye, or in alternative embodiments, liver and/or muscle, of the patient that continuously supplies the HuPTM mAb or antigen-binding fragment of the therapeutic mAb, *e.g.*, a human-glycosylated transgene product, or peptide to one or more ocular tissues where the mAb or antigen-binding fragment thereof or peptide exerts its therapeutic or prophylactic effect.

[0009] Provided are gene therapy vectors, particularly rAAV gene therapy vectors, which when administered to a human subject result in expression of an anti-TNFα, anti-IL6, or anti-IL6R antibody to achieve a maximum or steady state serum concentration, for example, 20, 30, 40, 50, 60 or 90 days after administration of the vector encoding the anti-TNFα, anti-IL6, or anti-IL6R antibody. In certain embodiments, the antibody binds to its target, for example, in an antibody binding assay (e.g. enzyme-linked immunosorbent assay (ELISA) binding assay or surface plasmon resonance (SPR)–based real-time kinetics assay), preferably in the picomolar or nanomolar range, and/or exhibits biological activity in an appropriate assay.

[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 retinal cells, for example AAV8 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, liver and/or muscle specific control elements, for example one or more elements of Tables 1 and 1a.

[0011] In certain embodiments, the HuPTM mAb or HuPTM antigen-binding fragment encoded by the transgene can include, but is not limited to, a full-length or an antigen-binding fragment of a therapeutic antibody that binds to TNFα, particularly adalimumab, infliximab or golimumab, or therapeutic antibodies that bind to IL6 or IL6R, including satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, erilimzumab, gerilizumab, or tocilizumab, see, for example **FIGS. 1A and 1B**.

[0012] Gene therapy constructs for the therapeutic antibodies are designed such that both the heavy and light chains are expressed. The coding sequences for the heavy and light chains can be engineered in a single construct in which the heavy and light chains are separated by a cleavable linker or IRES so that separate heavy and light chain polypeptides are expressed. In particular embodiments,

the linker is a Furin T2A linker (SEQ ID NOS:143 or 144). In certain embodiments, the coding sequences encode for a Fab or F(ab')$_2$ or an scFv. In certain embodiments the full length heavy and light chains of the antibody are expressed. In other embodiments, the constructs express an scFv in which the heavy and light chain variable domains are connected via a flexible, non-cleavable linker. In certain embodiments, the construct expresses, from the N-terminus, NH_2-V_L-linker-V_H-COOH or NH_2-V_H-linker-V_L-COOH.

[0013] In addition, antibodies expressed from transgenes in vivo are not likely to contain degradation products associated with antibodies 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 mAb or HuPTM Fab in ocular tissue cells 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 full-length HuPTM mAb or HuPTM Fab of a therapeutic mAb to a patient (human subject) diagnosed with a disease indication for that mAb, 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 HuPTMmAb or HuPTM Fab 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 full-length HuPTM mAb or HuPTM Fab 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 full-length HuPTM anti- anti-TNFα, anti-IL6, or anti-IL6R, mAb or HuPTM anti- anti-TNFα, anti-IL6, or anti-IL6R Fab 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 mAb.

[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] The inventors found that intravenous administration of an AAV8-based vector comprising an optimized expression cassette containing a liver-specific promoter and a codon optimized and CpG depleted transgene with a modified furin-T2A processing signal results in dose-dependent and sustained serum antibody concentrations in non-human primates. Accordingly, provided are compositions comprising rAAV vectors which comprise an optimized expression cassette containing a liver-specific promoter and a codon optimized and CpG depleted transgene with a modified furin-T2A processing signal that express a transgene, for example, heavy and light chains of an anti-TNFα (including adalimumab), anti-IL6, or anti-IL6R therapeutic antibody. Methods of administration and manufacture are also provided.

3.1 ILLUSTRATIVE EMBODIMENTS

Compositions of Matter

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 inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding a heavy chain and a light chain of a substantially full-length or full-length anti-TNFα mAb, anti-IL6 mAb, or anti-IL6R mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue 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 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).

3. The pharmaceutical composition of any of paragraphs 1 or 2, wherein the AAV capsid is AAV8, AAV3B, AAV2.7m8, or AAVrh73.

4. The pharmaceutical composition of paragraphs 1 to 3, 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.

5. The pharmaceutical composition of paragraphs 1 to 4, wherein the regulatory sequence includes a regulatory sequence from Table 1 or Table 1a.

6. The pharmaceutical composition of paragraph 5, wherein the regulatory sequence is a CAG promoter (SEQ ID NO: 74), human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:77 or 217), a mouse cone arresting (CAR) promoter (SEQ ID NOS:214-216), a human red opsin (RedO) promoter (SEQ ID NO:212), a CB promoter (SEQ ID NO: 273 or 274), or a Best1/GRK tandem promoter (SEQ ID NO: 275).

7. The pharmaceutical composition of any of paragraphs 1 to 6, wherein the transgene comprises a Furin/2A linker between the nucleotide sequences coding for the heavy and light chains of said mAb.

8. The pharmaceutical composition of paragraph 7, wherein said Furin 2A linker is a Furin/T2A linker having the amino acid sequence RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NOS:143 or 144).

9. The pharmaceutical composition of any of paragraphs 1 to 8, wherein the transgene encodes a signal sequence at the N-terminus of the heavy chain and the light chain of said antigen-binding fragment that directs secretion and post translational modification in said human ocular tissue cells.

10. The pharmaceutical composition of paragraph 9, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO:85) or a signal sequence from Table 2.

11. The pharmaceutical composition of any of paragraphs 1 to 10, wherein transgene has the structure: signal sequence– Heavy chain – Furin site – 2A site – signal sequence– Light chain – PolyA.

12. The pharmaceutical composition of any of paragraphs 1 to 11, wherein the anti-TNFα antibody is adalimumab, infliximab, or golimumab, or an antigen binding fragment thereof.

13. The pharmaceutical composition of any of paragraphs 1 to 12, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 1 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 64 and a light chain with an amino acid sequence of SEQ ID NO: 2; a heavy chain with an amino acid sequence of SEQ ID NO: 3 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 4; or a heavy

chain with an amino acid sequence of SEQ ID NO: 5 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 6.

14. The pharmaceutical composition of any of paragraphs 1 to 13 , wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 26 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 27 encoding the light chain; a nucleotide sequence of SEQ ID NO: 28 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 29 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 30 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 31 encoding the light chain.

15. The pharmaceutical composition of any of paragraphs 1 to 11, wherein the antiIL6 or anti-IL6R antibody is satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab, or an antigen binding fragment thereof.

16. The pharmaceutical composition of any of paragraphs 1 to 11 or 15, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 7 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 67 and a light chain with an amino acid sequence of SEQ ID NO: 8; a heavy chain with an amino acid sequence of SEQ ID NO: 9 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO:185 and a light chain with an amino acid sequence of SEQ ID NO: 10; a heavy chain with an amino acid sequence of SEQ ID NO: 11 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 68 and a light chain with an amino acid sequence of SEQ ID NO: 12; comprises a heavy chain with an amino acid sequence of SEQ ID NO: 13 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 69 and a light chain with an amino acid sequence of SEQ ID NO: 14; a heavy chain with an amino acid sequence of SEQ ID NO: 15 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 70 and a light chain with an amino acid sequence of SEQ ID NO: 16; a heavy chain with an amino acid sequence of SEQ ID NO: 17 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 71 and a light chain with an amino acid sequence of SEQ ID NO: 18; a heavy chain with an amino acid sequence of SEQ ID NO: 19 and a light chain with an amino acid sequence of SEQ ID NO: 20; or a heavy chain with an amino acid sequence of SEQ ID NO:

21 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 72 and a light chain with an amino acid sequence of SEQ ID NO: 22.

17. The pharmaceutical composition of any of paragraphs 1, 11 or 15-16, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 32 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 33 encoding the light chain; a nucleotide sequence of SEQ ID NO: 34 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 35 encoding the light chain; a nucleotide sequence of SEQ ID NO: 36 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 37 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 38 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 39 encoding the light chain; a nucleotide sequence of SEQ ID NO: 40 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 41 encoding the light chain; a nucleotide sequence of SEQ ID NO: 42 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 43 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 44 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 45 encoding the light chain; or a nucleotide sequence of SEQ ID NO:183 encoding the heavy chain and a nucleotide sequence of SEQ ID NO:184 encoding the light chain.

18. The pharmaceutical composition of paragraphs 1 to 17, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

19. The pharmaceutical composition of any of paragraphs 1 to 18, wherein the mAb or the antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

20. The pharmaceutical composition of any of paragraphs 1 to 19, wherein the artificial genome is self complementary.

21. The pharmaceutical composition of any of paragraphs 1 to 20 wherein the artificial genome is the construct EF1ac.Vh4i.Adalimumab.Fab scAAV, mU1a.Vh4i.Adalimumab.Fab scAAV, CAG.Adalimumab.IgG, CAG.Adalimumab.Fab, GRK1.Vh4i.Adalimumab.IgG, CB.VH4i.adalimumab.IgG, CBlong.VH4.adalimumab.IgG or Best1.GRK.VH4.adalimumab.IgG.

22. 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 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); and

b. an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding a heavy and a light chain of a substantially full-length or full-length anti-TNFα mAb anti-IL6 antibody or anti-IL6R antibody, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

c. wherein the transgene encodes a signal sequence at the N-terminus of the heavy chain and the light chain of said mAb that directs secretion and post translational modification of said mAb in ocular tissue cells.

23. The composition of paragraph 22, 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.

24. The composition of paragraphs 22 or 23, wherein the AAV capsid is AAV2.7m8, AAV8, AAV3B, or AAVrh73.

25. The composition of paragraphs 22 to 24, wherein the anti-TNFα antibody is adalimumab, infliximab, or golimumab, or an antigen binding fragment thereof.

26. The pharmaceutical composition of any of paragraphs 22 to 25, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 1 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 64 and a light chain with an amino acid sequence of SEQ ID NO: 2; a heavy chain with an amino acid sequence of SEQ ID NO: 3 and optionally an Fc polypeptide with an amino acid sequence of

SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 4; or a heavy chain with an amino acid sequence of SEQ ID NO: 5 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 6.

27. The pharmaceutical composition of paragraph 22 to 26, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 26 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 27 encoding the light chain; a nucleotide sequence of SEQ ID NO: 28 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 29 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 30 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 31 encoding the light chain.

28. The pharmaceutical composition of any of paragraphs 22 to 27, wherein the antiIL6 or anti-IL6R antibody is satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab, or an antigen binding fragment thereof.

29. The pharmaceutical composition of any of paragraphs 22 to 24 or 27, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 7 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 67 and a light chain with an amino acid sequence of SEQ ID NO: 8; a heavy chain with an amino acid sequence of SEQ ID NO: 9 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO:185 and a light chain with an amino acid sequence of SEQ ID NO: 10; a heavy chain with an amino acid sequence of SEQ ID NO: 11 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 68 and a light chain with an amino acid sequence of SEQ ID NO: 12; comprises a heavy chain with an amino acid sequence of SEQ ID NO: 13 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 69 and a light chain with an amino acid sequence of SEQ ID NO: 14; a heavy chain with an amino acid sequence of SEQ ID NO: 15 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 70 and a light chain with an amino acid sequence of SEQ ID NO: 16; a heavy chain with an amino acid sequence of SEQ ID NO: 17 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 71 and a light chain with an amino acid sequence of SEQ ID NO: 18; a heavy chain with an amino acid sequence of SEQ ID NO: 19 and a light chain with an amino

acid sequence of SEQ ID NO: 20; or a heavy chain with an amino acid sequence of SEQ ID NO: 21 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 72 and a light chain with an amino acid sequence of SEQ ID NO: 22.

30. The pharmaceutical composition of any of paragraphs 22-24 or 28-29, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 32 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 33 encoding the light chain; a nucleotide sequence of SEQ ID NO: 34 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 35 encoding the light chain; a nucleotide sequence of SEQ ID NO: 36 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 37 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 38 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 39 encoding the light chain; a nucleotide sequence of SEQ ID NO: 40 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 41 encoding the light chain; a nucleotide sequence of SEQ ID NO: 42 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 43 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 44 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 45 encoding the light chain; or a nucleotide sequence of SEQ ID NO:183 encoding the heavy chain and a nucleotide sequence of SEQ ID NO:184 encoding the light chain.

31. The composition of any of paragraphs 22 to 30, wherein the transgene comprises a Furin/2A linker between the nucleotide sequences coding for the heavy and light chains of said mAb.

32. The composition of any of paragraphs 22 to 31, wherein the nucleic acid encoding a Furin 2A linker is incorporated into the expression cassette in between the nucleotide sequences encoding the heavy and light chain sequences, resulting in a construct with the structure: Signal sequence – Heavy chain – Furin site – 2A site – Signal sequence – Light chain – PolyA.

33. The composition of paragraphs 22 to 32, wherein said Furin 2A linker is a Furin/T2A linker having the amino acid sequence RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NOS:143 or 144).

34. The composition of any of paragraphs 22 to 33, wherein said signal sequence is MYRMQLLLLLIALSLALVTNS (SEQ ID NO:85) or a signal sequence from Table 2.

35. The composition of any of paragraphs 22 to 34, wherein the artificial genome is self complementary.

36. The composition of any of paragraphs 22 to 27 or 31 to 35, wherein the artificial genome is the construct EF1ac.Vh4i.Adalimumab.Fab scAAV, mU1a.Vh4i.Adalimumab.Fab scAAV, CAG.Adalimumab.IgG, CAG.Adalimumab.Fab, GRK1.Vh4i.Adalimumab.IgG, CB.VH4i.adalimumab.IgG, CBlong.VH4i.adalimumab.IgG. or Best1/GRK1.VH4i.adalimumab.IgG.

Method of Treatment

37. 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 mAb, anti-IL6 mAb, or anti-IL6R mAb, or antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in ocular tissue cells.

38. 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 mAb, anti-IL6 mAb, or anti-IL6R mAb, or antigen-binding fragment thereof, 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 mAb, anti-IL6 mAb, or anti-IL6R mAb or antigen-binding fragment thereof.

39. The method of paragraphs 37 or 38 wherein the anti-TNFα mAb is adalimumab, infliximab or golimumab.

40. The method of paragraphs 37 to 39, wherein the full-length anti-TNFα mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 1 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 64 and a light chain with an amino acid sequence of SEQ ID NO: 2; or a heavy chain with an amino acid sequence

of SEQ ID NO: 3 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 4; a heavy chain with an amino acid sequence of SEQ ID NO: 5 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 6.

41. The method of paragraphs 37 to 40, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 26 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 27 encoding the light chain; a nucleotide sequence of SEQ ID NO: 28 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 29 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 30 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 31 encoding the light chain.

42. The method of any of paragraphs 37 to 38, wherein the antiIL6 or anti-IL6R antibody is satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab, or an antigen binding fragment thereof.

43. The method of any of paragraphs 37 to 38 or 42, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 7 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 67 and a light chain with an amino acid sequence of SEQ ID NO: 8; a heavy chain with an amino acid sequence of SEQ ID NO: 9 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO:185 and a light chain with an amino acid sequence of SEQ ID NO: 10; a heavy chain with an amino acid sequence of SEQ ID NO: 11 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 68 and a light chain with an amino acid sequence of SEQ ID NO: 12; comprises a heavy chain with an amino acid sequence of SEQ ID NO: 13 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 69 and a light chain with an amino acid sequence of SEQ ID NO: 14; a heavy chain with an amino acid sequence of SEQ ID NO: 15 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 70 and a light chain with an amino acid sequence of SEQ ID NO: 16; a heavy chain with an amino acid sequence of SEQ ID NO: 17 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 71 and a light chain with an amino acid sequence of SEQ ID NO: 18; a heavy chain with an amino acid sequence of SEQ ID NO: 19 and a light chain with an amino acid sequence of SEQ ID NO: 20;

or a heavy chain with an amino acid sequence of SEQ ID NO: 21 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 72 and a light chain with an amino acid sequence of SEQ ID NO: 22.

44. The method of any of paragraphs 37 to 38 or 42 to 43, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 32 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 33 encoding the light chain; a nucleotide sequence of SEQ ID NO: 34 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 35 encoding the light chain; a nucleotide sequence of SEQ ID NO: 36 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 37 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 38 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 39 encoding the light chain; a nucleotide sequence of SEQ ID NO: 40 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 41 encoding the light chain; a nucleotide sequence of SEQ ID NO: 42 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 43 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 44 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 45 encoding the light chain; or a nucleotide sequence of SEQ ID NO:183 encoding the heavy chain and a nucleotide sequence of SEQ ID NO:184 encoding the light chain.

45. The method of paragraphs 37 to 44, 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.

46. The method of any of paragraphs 37 to 44 wherein the viral capsid is at least 95% identical to the amino acid sequence of an 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);

47. The method of any of paragraphs 37 to 46, wherein the AAV capsid is AAV2.7m8, AAV8, AAV3B, or AAVrh73.

48. The method of any of paragraphs 37 to 46, wherein the regulatory sequence includes a regulatory sequence from Table 1.

49. The method of paragraph 48, wherein the regulator sequence is a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:77 or 217), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 214-216), or a human red opsin (RedO) promoter (SEQ ID NO: 212).

50. The method of any of paragraphs 37 to 49, wherein the transgene comprises a Furin/2A linker between the nucleotide sequences coding for the heavy and light chains of said mAb.

51. The method of paragraph 50, wherein said Furin 2A linker is a Furin/T2A linker having the amino acid sequence RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NOS:143 or 144).

52. The method of any of paragraphs 37 to 51, wherein the transgene encodes a signal sequence at the N-terminus of the heavy chain and the light chain of said antigen-binding fragment that directs secretion and post translational modification in said human ocular tissue cells.

53. The method of paragraph 52, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO:85) or a signal sequence from Table 2.

54. The method of any of paragraphs 37 to 53, wherein transgene has the structure: Signal sequence– Heavy chain – Furin site – 2A site – Signal sequence– Light chain – PolyA.

55. The method of any of paragraphs 37 to 54, wherein the mAb is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

56. The method of any of paragraphs 37 to 55 wherein the mAb contains an alpha 2,6-sialylated glycan.

57. The method of any of paragraphs 37 to 56 wherein the mAb is glycosylated but does not contain detectable NeuGc and/or α-Gal.

58. The method of any of paragraphs 37 to 57 wherein the mAb contains a tyrosine sulfation.

59. The method of any of paragraphs 37 to 58 in which production of said HuPTM form of said mAb or antigen-binding fragment thereof is confirmed by transducing human ocular tissue cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

60. The method of paragraphs 37 or 59, wherein the therapeutically effective amount is determined to be sufficient to maintain a concentration of at least 10 ng/ml in aqueous humor, vitreous humor, RPE, retina, and/or anterior segment/chamber.

61. The method of paragraphs 37 or 60, 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.

62. The method of any of paragraphs 37 to 61, wherein the rAAV is self complementary.

63. The method of any of paragraphs 37 to 62 wherein the transgene within the construct EF1ac.Vh4i.Adalimumab.Fab scAAV, mU1a.Vh4i.Adalimumab.Fab scAAV, CAG.Adalimumab.IgG, CAG.Adalimumab.Fab, GRK1.Vh4i.Adalimumab.IgG, CB.VH4i.adalimumab.IgG, CBlong.VH4i.adalimumab.IgG or Best1/GRK1.VH4i.adalimumab.IgG.

Method of Manufacture

64. 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 comprising a transgene encoding a substantially full-length or full-length anti-TNFα mAb, anti-IL6, or anti-IL6R or antigen-binding fragment thereof, 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 cell 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.

65. The method of paragraph 64, wherein the transgene encodes a substantially full-length or full-length mAb or antigen binding fragment that comprises the heavy and light chain variable domains of adalimumab, infliximab, golimumab, satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab wherein the AAV capsid protein is an AAV2.7m8, AAV8, AAV3B, or AAVrh73, capsid protein.

66. The method of paragraphs 64 or 65, 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.

67. A host cell containing:

a. an artificial genome comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises comprising a transgene encoding a substantially full-length or full-length anti-TNFα mAb, anti-IL6 mAb or anti-IL6R mAb, or antigen-binding fragment thereof, 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 cell tropism;

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

68. The host cell of paragraph 67, wherein the transgene encodes a substantially full-length or full-length mAb or antigen binding fragment that comprises the heavy and light chain variable

domains of adalimumab, infliximab, golimumab, satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab.

69. The host cell of paragraphs 67 or 68, wherein the AAV capsid protein is an AAV2.7m8, AAV8, AAV3B, or AAVrh73 capsid protein.

70. The host cell of paragraphs 67 to 69, 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.

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0019] **FIGS. 1A-1B**. Schematics of rAAV vector genome constructs containing an expression cassette encoding the heavy and light chains of a therapeutic mAb separated by a Furin-2A linker, operably linked to a CAG promoter, controlled by expression elements, flanked by the AAV ITRs. The transgene can comprise nucleotide sequences encoding the full-length heavy and light chains with Fc regions **(A)** or the heavy and light chains of the Fab portion (**B**).

[0020] **FIGS. 2A-2C.** The amino acid sequence of a transgene construct for the Fab region of adalimumab **(A)**, infliximab **(B)**, and golimumab **(C)**, therapeutic antibodies to tumor necrosis factor (TNFα). Glycosylation sites are boldface. Glutamine glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (italics) are as indicated in the legend. Complementarity-determining regions (CDR) are underscored. The hinge region is highlighted in grey.

[0021] **FIGS. 3A-3H.** The amino acid sequence of a transgene construct for the Fab region of satralizumab **(A)**, sarilumab **(B)**, siltuximab **(C)**, Clazakizumab **(D)**, Sirukumab **(E)**, olokizumab **(F)**, gerilizumab **(G)**, or tocilizumab **(H)**. Glycosylation sites are boldface. Glutamine glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (italics) are as indicated in the legend. Complementarity-determining regions (CDR) are underscored. The hinge region is highlighted in grey.

[0022] **FIG. 4**. 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. 4**.

[0023] **FIG. 5** Glycans that can be attached to HuGlyFab regions of full length mAbs or the antigen-binding domains. (Adapted from Bondt et al., 2014, Mol & Cell Proteomics 13.1: 3029-3039).

[0024] **FIG. 6**. Clustal Multiple Sequence Alignment of constant heavy chain regions (CH2 and CH3) of IgG1 (SEQ ID NO: 61), IgG2 (SEQ ID NO: 62), and IgG4 (SEQ ID NO: 63). 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.

[0025] **FIG. 7.** Expression levels of vectorized adalimumab (AAV8.CAG.adalimumab.IgG) in ocular tissues (retina, retinal pigment epithelial (RPE), and anterior segment) at three different doses (1e7, 1e8, and 1e9 vg/eye). PBS is used a vehicle control and AAV.GFP as control vector. Adalimumab expression levels (ng) are depicted relative to the total amount of protein (g).

[0026] **FIGs 8. .** Expression levels of vectorized adalimumab (AAV8.CAG.adalimumab.IgG) in ocular tissues (retina, retinal pigment epithelial (RPE), and anterior segment) at three different doses (1e7, 1e8, and 1e9 vg/eye). PBS is used a vehicle control and AAV.GFP as control vector. Adalimumab expression levels (ng) are depicted as concentration per ml.

[0027] **FIGS. 9A and 9B** show the alignment of different antibody sequences. A) heavy chain sequences of antibodies. Top to bottom: amino acids 1-229 of SEQ ID NO:23, amino acids 1-228 of SEQ ID NO:3, amino acids 1-237 of SEQ ID NO:5, amino acids 1-224 of SEQ ID NO:7, amino acids 1-224 of SEQ ID NO:9, amino acids 1-227 of SEQ ID NO:11, amino acids 1-228 of SEQ ID NO:13, amino acids 1-227 of SEQ ID NO:15, amino acids 1-224 of SEQ ID NO:17, amino acids 1-230 of SEQ ID NO:19, amino acids 1-228 of SEQ ID NO:21. B) Light chain sequences of antibodies. Top to bottom: amino acids 1-229 of SEQ ID NO:24, amino acids 1-228 of SEQ ID NO:4, amino acids 1-237 of SEQ ID NO:6, amino acids 1-224 of SEQ ID NO:8, amino acids 1-224 of SEQ ID NO:10, amino acids 1-227 of SEQ ID NO:12, amino acids 1-228 of SEQ ID NO:14, amino acids 1-227 of SEQ ID NO:16, amino acids 1-224 of SEQ ID NO:18, amino acids 1-230 of SEQ ID NO:20, amino acids 1-228 of SEQ ID NO:22.

[0028] **FIGS 10A and 10B** show binding to various concentrations of mouse or human TNFα compared in a competitive ELISA assay for both vector-expressed adalimumab extracted from mouse eye (following subretinal) administration) (**10A**) and commercial adalimumab (**10B)**.

[0029] **FIGs. 11A and B** show results of dose response studies. **A** depicts results of an ADCC dose response study with CHO/DG44-tm TNFα cells used as the target cells with E/T ratio at 25:1. **B.** CHO/DG44-tm TNFα cells were used as the target cells with 5% normal human serum complement (NHSC) in CDC dose-response study. Dose-responses and best-fit values of positive control (Adalimumab), samples (AAV-Adalimumab) and negative control (Human IgG1) are shown in **A** and **B**.

[0030] **FIG. 12** depicts total scores over time for 3 (rat) groups administered with varying doses of hTNFα (50ng, 100 ng and 170 ng) and a control (vehicle) group and naïve group.

[0031] **FIG. 13** shows levels of adalimumab (as measured by ELISA with wells coated with recombinant human TNF) in eyes of Lewis Rats 21 days after subretinal injection with AAV8.CAG.Adalimumab at 1.0E+9 GC/eye and 3.0E+8 GC/eye have 86.0 ng/eye and 17.1 ng/eye of adalimumab/eye, respectively.

[0032] **FIG. 14** depicts adalimumab levels in ocular tissues RPE, Retina and Anterior Segment, from mice following subretinal administration of AAV8.CAG.adalumumab or AAV8.GRK1.adalimumab at doses of 1.0E08 or 1.0E09 and vehicle control 4 to 5 weeks after administration.

5. DETAILED DESCRIPTION OF THE INVENTION

[0033] Compositions and methods are described for the systemic delivery of a fully human post-translationally modified (HuPTM) therapeutic monoclonal antibody (mAb) or a HuPTM antigen-binding fragment of a therapeutic anti-TNFα, anti-IL6, or anti-IL6R mAb (for example, a fully human-glycosylated Fab (HuGlyFab) of a therapeutic mAb) to a patient (human subject) diagnosed with non-infectious uveitis or other indication indicated for treatment with the therapeutic mAb. Delivery may be advantageously accomplished via gene therapy—*e.g.*, by administering a viral vector or other DNA expression construct encoding a therapeutic mAb or its antigen-binding fragment (or a

hyperglycosylated derivative of either) to a patient (human subject) diagnosed with a condition indicated for treatment with the therapeutic mAb—to create a permanent depot in a tissue or organ of the patient, particularly the eye that continuously supplies the HuPTM mAb or antigen-binding fragment of the therapeutic mAb, *e.g.*, a human-glycosylated transgene product, into ocular tissues of the subject to where the mAb or antigen-binding fragment there of exerts its therapeutic effect.

[0034] In certain embodiments, the HuPTM mAb or HuPTM antigen-binding fragment encoded by the transgene, but it not limited to, is a full-length or an antigen-binding fragment of a HuPTM mAb or HuPTM that binds TNFα, particularly adalimumab (see **FIG. 2A** for the heavy and light chain sequences of the Fab portion of adalimumab), IL6, or IL6R.

[0035] The compositions and methods provided herein systemically deliver anti-TNFα, particularly, adalimumab, anti-IL6, or anti-IL6R antibodies, 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, anti-IL6, or anti-IL6R antibody. Identified herein are viral vectors for delivery of transgenes encoding the therapeutic anti-TNFα, anti-IL6 or anti-IL6R antibodies 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 heavy and light chains of the anti-TNFα, anti-IL6, or anti-IL6R antibody 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, the anti-TNFα, anti-IL6, or anti-IL6R antibody 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-TNFα, anti-IL6, or anti-IL6R antibody is determined (in human trials, animal models, 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.

[0036] The HuPTM mAb or HuPTM antigen-binding fragment encoded by the transgene can include, but is not limited to, a full-length or an antigen-binding fragment of a therapeutic antibody that binds to TNFα, including but not limited to, adalimumab, infliximab or golimumab, or to IL6, or IL6R, including but not limited to satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab. The amino acid sequences of the heavy and light chain of antigen binding fragments of the foregoing are provided in **Table** 7, *infra*. Heavy chain variable domain having an amino acid sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, or 23 (encoded by nucleotide sequence SEQ ID NO: 26, 28, 30, 32, 34, 36, 38, 40, 42, or 44, respectively) and light chain variable domain having an amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, or 22 (encoded by nucleotide sequence SEQ ID NO: 27, 29, 31, 33, 35, 37, 39, 41, 43, or 45, respectively). The HuPTM mAb or HuPTM antigen-binding fragment encoded by the transgene can include, but is not limited to, a full-length or an antigen-binding fragment of a therapeutic antibody or antigen-binding fragments engineered to contain additional glycosylation sites on the Fab domain (*e.g.*, see Courtois et al., 2016, mAbs 8: 99-112 which is incorporated by reference herein in its entirety for its description of derivatives of antibodies that are hyperglycosylated on the Fab domain of the full-length antibody).

[0037] 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 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. The AAV types for use here in preferentially target the eye, *i.e.*, have a tropism for retinal cells. Such rAAVs include but are not limited to AAV based vectors comprising capsid components from one or more of AAV1, AAV2, 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 AA2.7m8, AAV3B, AAV8, AAV9, AAVrh10, AAV10, or AAVrh73 serotypes.

[0038] 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.

[0039] Gene therapy constructs are designed such that both the heavy and light chains are expressed. In certain embodiments, the full length heavy and light chains of the antibody are expressed. In certain embodiments, the coding sequences encode for a Fab or $F(ab')_2$ or an scFv. The heavy and light chains should be expressed at about equal amounts, in other words, the heavy and light chains are expressed at approximately a 1:1 ratio of heavy chains to light chains. The coding sequences for the heavy and light chains can be engineered in a single construct in which the heavy and light chains are separated by a cleavable linker or IRES so that separate heavy and light chain polypeptides are expressed. In specific embodiments, the linker separating the heavy and light chains is a Furin-2A linker, for example a Furin-F2A linker RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NOS:143 or 144) or a Furin-T2A linker RKRR(GSG)EGRGSLLTCGDVEENPGP (SEQ ID NOS:141 or 142). In certain embodiments, the construct expresses, from the N-terminus to C-terminus, NH2-VL-linker-VH-COOH or NH2-VH-linker-VL-COOH. In other embodiments, the construct expresses, from the N-terminus to C-terminus, NH2-signal or localization sequence-VL-linker-VH-COOH or NH2- signal or localization sequence-VH-linker-VL-COOH. In other embodiments, the constructs express a scFv in which the heavy and light chain variable domains are connected via a flexible, non-cleavable linker.

[0040] 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. Codon optimized sequences of the adalimumab heavy and light chains are provided in **Table 8** (SEQ ID NOs: 46 to 60). Each heavy and light chain requires a signal sequence to ensure proper post-translation processing and secretion (unless expressed as a scFv, in which only the N-terminal chain requires a signal sequence sequence). Useful signal sequences for the expression of the heavy and light chains of the therapeutic antibodies in human cells are disclosed herein. Exemplary recombinant expression constructs are shown in **FIGS. 1A and 1B**.

[0041] The production of HuPTM mAb or HuPTM Fab (including an HuPTM scFv) 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 full-length HuPTM mAb or HuPTM Fab or other antigen binding fragment, such as an scFv, of a therapeutic mAb to a patient (human subject) diagnosed with a disease indication for that mAb, 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 mAb or HuPTM Fab or HuPTM scFv should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced human cells.

[0042] 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.

[0043] As an alternative, or an additional treatment to gene therapy, the full-length HuPTM mAb or HuPTM Fab or other antigen binding fragment thereof 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 mAb, HuPTM Fab or HuPTM scFv product, *e.g.*, HuPTM Fab glycoprotein). 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.

[0044] 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.

[0045] Combination therapies involving delivery of the full-length HuPTM mAb or HuPTM Fab or antigen binding fragment thereof 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 mAb.

[0046] 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.

5.1 CONSTRUCTS

[0047] Viral vectors or other DNA expression constructs encoding an anti-TNFα, anti-IL6, or anti-IL6 HuPTM mAb or antigen-binding fragment thereof, particularly a HuGlyFab, or a hyperglycosylated derivative of a HuPTM mAb antigen-binding fragment 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 ocular tissue cells or a vector that has a tropism for ocular tissue cells.

[0048] In some aspects, the disclosure provides for a nucleic acid for use, wherein the nucleic acid comprises a nucleotide sequence that encodes a HuPTM mAb or HuGlyFab or other antigen-binding fragment thereof, as a transgene described herein, operatively linked to an ubiquitous promoter, a ocular tissue-specific promoter, or an inducible promoter, wherein the promoter is selected

for expression in tissue targeted for expression of the transgene. Promoters may, for example, be a CB7/CAG promoter (SEQ ID NO: 73) and associated upstream regulatory sequences, cytomegalovirus (CMV) promoter, EF-1 alpha promoter (SEQ ID NO: 76), mU1a (SEQ ID NO: 75), UB6 promoter, chicken beta-actin (CBA) promoter, and ocular-tissue specific promoters, such as human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:77 or 217), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 214-216), or a human red opsin (RedO) promoter (SEQ ID NO: 212). See Tables 1 and 1a for a list of useful promoters.

[0049] 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 the heavy and light chains of the HuPTMmAb or HuGlyFab or other antigen-binding fragment), untranslated regions, and termination sequences. In certain embodiments, viral vectors provided herein comprise a promoter operably linked to the gene of interest.

[0050] 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).

[0051] 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 the heavy and light chains of a mAb or Fab, separated by a self-cleaving furin (F)/(F/T)2A linker (SEQ ID NOS:141-144), ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is shown in **FIGS. 1A and 1B**.

[0052] In a specific embodiment, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) GRK1 promoter (SEQ ID NO:77), b) optionally, a VH4 intron (SEQ ID NO:80) or other intron and c) a rabbit β-globin polyA signal (SEQ ID NO:78); and (3) nucleic acid sequences coding for a full-length

antibody comprising the heavy and light chain sequences using sequences that encode the Fab portion of the heavy chain, including the hinge region sequence, plus the Fc polypeptide of the heavy chain for the appropriate isotype and the light chain, wherein heavy and light chain nucleotide sequences are separated by a self-cleaving furin (F)/(F/T)2A linker (SEQ ID NOS:141-144), ensuring expression of equal amounts of the heavy and the light chain polypeptides.

5.1.1 mRNA Vectors

[0053] 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, HuPTMmAb or HuGlyFab or other antigen binding fragment thereof). 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 HuPTMmAb, HuPTM Fab, or HuPTM scFv.

5.1.2 Viral vectors

[0054] Viral vectors include adenovirus, adeno-associated virus (AAV, *e.g.*, AAV2.7m8, AAV8, AAV9, AAVrh10, AAV10), 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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. In certain embodiments, AAV based vectors provided herein comprise capsid components from one or more of AAV1, AAV2, 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 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:196), AAV3B capsid protein (SEQ ID NO:190), or AAVrh73 capsid protein (SEQ ID NO:202), 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:196), AAV3B capsid protein (SEQ ID NO:190), or AAVrh73 capsid protein (SEQ ID NO:202), while retaining the biological function of the native capsid. In certain embodiments, the encoded AAV capsid has the sequence of SEQ ID NO:196 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. 4** 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. 4**. Amino acid sequence for AAV8, AAV3B, or AAVrh73 capsids are provided in **FIG. 4**.

[0061] The amino acid sequence of hu37 capsid can be found in international application PCT WO 2005/033321 (SEQ ID NO: 88 thereof) and the amino acid sequence for the rh8 capsid can be found in international application PCT WO 03/042397 (SEQ ID NO:97). The amino acid sequence for the rh64R1 sequence is found in WO2006/110689 (a R697W substitution of the Rh.64 sequence, which is SEQ ID NO: 43 of WO 2006/110689).

[0062] 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, AAVS3, AAV.rh8, AAV.rh10, AAV.rh20, AAV.rh39, AAV.rh46, AAV.rh73, 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, AAVS3, AAV.rh8, AAV.rh10, AAV.rh20, AAV.rh39, AAV.rh46, AAV.rh73, 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, AAVS3, AAV.rh8, AAV.rh10, AAV.rh20, AAV.rh39, AAV.rh46, AAV.rh73, 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.

[0063] In particular embodiments, the recombinant AAV for us in compositions and methods herein is AAVS3 (including variants thereof) (see e.g., US Patent Application No. 20200079821, which is incorporated herein by reference in its entirety). In particular embodiments, rAAV particles comprise the capsids of AAV-LK03 or AAV3B, as described in Puzzo et al., 2017, Sci. Transl. Med. 29(9): 418, which is incorporated by reference in its entirety. In particular embodiments, the AAV for use in compositions and methods herein is any AAV disclosed in US 10,301,648, such as AAV.rh46 or AAV.rh73. In some 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 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.

[0064] 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 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.

[0065] 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).

[0066] 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).

[0067] AAV8-based, AAV3B-based, and AAVrh73-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. 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.*, AAV8, AAV3B, AAVrh73, or AAVrh10)-based viral vectors encoding a transgene (*e.g.*, an HuPTM Fab). The amino acid sequences of AAV capsids, including AAV8, AAV3B, AAVrh73 and AAVrh10 are provided in **FIG. 4**.

[0068] 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).

[0069] 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 HuPTMmAb or HuGlyFab or antigen-binding fragment. 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.

[0070] 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 mAb antigen binding fragment. 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 antigen-binding fragment gene.

[0071] 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.

[0072] In a specific embodiment, a vector for use in the methods described herein is one that encodes an HuPTM mAb, such that, upon introduction of the vector into a relevant cell, a glycosylated and/or tyrosine sulfated variant of the HuPTM mAb is expressed by the cell.

5.1.3 Promoters and Modifiers of Gene Expression

[0073] 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.

[0074] 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 the eye. In certain embodiments, the promoter is a constitutive promoter.

[0075] 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: 74) or CB7 promoter (SEQ ID NO: 73)

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:78). 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.

[0076] 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:77 or 217), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 214-216), or a human red opsin (RedO) promoter (SEQ ID NO: 212).

[0077] 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.

[0078] 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 (SEQ ID NO:227) 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.

[0079] 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: 73	gacattgattattgactagttattaatagtaatcaattacggggtcattagt tcatagcccatatatggagttccgcgttacataacttacggtaaatggcccg cctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatg ttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagta tttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagt acgcccctattgacgtcaatgacggtaaatggcccgcctggcattatgccc agtacatgaccttatgggactttcctacttggcagtacatctacgtattagt catcgctattaccatggtcgaggtgagccccacgttctgcttcactctcccc atctccccccccctccccaccccaattttgtatttatttatttttttaattat tttgtgcagcgatgggggcgggggggggggggggcgcgcgccaggcggggc ggggcggggcgaggggcggggcggggcgaggcggagaggtgcggcggcagcc aatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggc

Name/ SEQ ID NO.	Sequence
	ggcggccctataaaaagcgaagcgcgcggcgggcgggagtcgctgcgcgctg ccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgccccggctc tgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctc cgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggct gcgtgaaagccttgaggggctccgggagggcccttgtgcgggggggagcggc tcgggggggtgcgtgcgtgtgtgtgtgcgtggggagcgccgcgtgcggctccg cgctgcccggcggctgtgagcgctgcgggcgcggcgcggggctttgtgcgct ccgcagtgtgcgcgaggggagcgcggccgggggcggtgccccgcggtgcggg gggggctgcgaggggaacaaaggctgcgtgcggggtgtgtgcgtgggggggt gagcaggggggtgtgggcgcgtcggtcgggctgcaaccccccctgcacccccc tccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacgggg cgtggcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgc cgggcggggcggggccgcctcgggccggggagggctcgggggaggggcgcgg cggcccccggagcgccggcggctgtcgaggcgcggcgagccgcagccattgc cttttatggtaatcgtgcgagagggcgcagggacttcctttgtcccaaatct gtgcggagccgaaatctgggaggcgccgccgcacccccctctagcgggcgcgg ggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagggccttcgt gcgtcgccgcgccgccgtcccccttctccctctccagcctcggggctgtccgc ggggggacggctgccttcgggggggacggggcagggcggggttcggcttctg gcgtgtgaccggcggctctagagcctctgctaaccatgttcatgccttcttc tttttcctacagctcctgggcaacgtgctggttattgtgctgtctcatcatt ttggcaaag
CAG (CMV-Chicken B-Actin Promoter-chimeric intron) SEQ ID NO: 74	gacattgattattgactagttattaatagtaatcaattacggggtcattagt tcatagcccatatatggagttccgcgttacataacttacggtaaatggcccg cctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatg ttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagta tttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagt acgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgccc agtacatgaccttatgggactttcctacttggcagtacatctacgtattagt catcgctattaccatggtcgaggtgagccccacgttctgcttcactctcccc atctccccccccctccccaccccaattttgtatttatttatttttttaattat tttgtgcagcgatgggggcgggggggggggggggcgcgcgccaggcggggc ggggcggggcgaggggcggggcggggcgaggcggagaggtgcggcggcagcc aatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggc ggcggccctataaaaagcgaagcgcgcggcgggcgggagtcgctgcgcgctg ccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgccccggctc tgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctc cgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggct gcgtgaaagccttgaggggctccgggagggcccttgtgcgggggggagcggc tcgggggggtgcgtgcgtgtgtgtgtgcgtggggagcgccgcgtgcggctccg cgctgcccggcggctgtgagcgctgcgggcgcggcgcggggctttgtgcgct ccgcagtgtgcgcgaggggagcgcggccgggggcggtgccccgcggtgcggg gggggctgcgaggggaacaaaggctgcgtgcggggtgtgtgcgtgggggggt

Name/ SEQ ID NO.	Sequence
	gagcaggggtgtgggcgcgtcggtcgggctgcaaccccccctgcaccccc tccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacgggg cgtggcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgc cgggcggggcggggccgcctcgggccggggagggctcgggggagggggcgcgg cggcccccggagcgccggcggctgtcgaggcgcggcgagccgcagccattgc cttttatggtaatcgtgcgagagggcgcagggacttcctttgtcccaaatct gtgcggagccgaaatctgggaggcgccgccgcacccccctctagcgggcgcgg ggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagggccttcgt gcgtcgccgcgccgccgtccccttctccctctccagcctcggggctgtccgc ggggggacggctgccttcgggggggacggggcagggcggggttcggcttctg gcgtgtgaccggcggctctagagcctctgctaaccatgttcatgccttcttc ttttcctacag

mU1a SEQ ID NO: 75	atggaggcggtactatgtagatgagaattcaggagcaaactgggaaaagcaactgcttccaaa tatttgtgatttttacagtgtagttttggaaaaactcttagcctaccaattcttctaagtgtt ttaaaatgtgggagccagtacacatgaagttatagagtgttttaatgaggcttaaatatttac cgtaactatgaaatgctacgcatatcatgctgttcaggctccgtggccacgcaactcatact
EF-1α (core) SEQ ID NO: 76	gggcagagcgcacatcgcccacagtccccgagaagttgggggggagggtcggcaattgaacgg gtgcctagagaaggtggcgcggggtaaactgggaaagtgatgtcgtgtactggctccgccttt ttcccgagggtgggggagaaccgtatataagtgcagtagtcgccgtgaacgttctttttcgca acgggtttgccgccagaacacag
Human UbC SEQ ID NO:211	Gtctaacaaaaaagccaaaaacggccagaatttagcggacaatttactagtc taacactgaa Aattacatattgacccaaatgattacatttcaaaaggtgcctaaaaaacttc acaaaacacactCgccaaccccgagcgcatagttcaaaaccggagcttcagc tacttaagaagataggtacataaAaccgaccaaagaaactgacgcctcactt atccctcccctcaccagaggtccggcgcctgtcgaTtcaggagagcctaccc taggcccgaaccctgcgtcctgcgacggagaaaagcctaccgcacaCctacc ggcaggtggccccaccctgcattataagccaacagaacgggtgacgtcacga cacgaCgagggcgcgcgctcccaaaggtacgggtgcactgcccaacggcacc gccataactgccgcccCcgcaacagacgacaaaccgagttctccagtcagtg acaaacttcacgtcagggtccccagatgGtgccccagcccatctcacccgaa taagagctttcccgcattagcgaaggcctcaagaccttgggTtcttgccgcc caccatgcccccccaccttgtttcaacgacctcacagcccgcctcacaagcgt cttcCattcaagactcgggaacagccgccattttgctgcgctcccccccaacc cccagttcagggcaaccTtgctcgcggacccagactacagcccttggcggtc tctccacacgcttccgtcccaccgagcggccCggcggccacgaaagccccgg ccagcccagcagcccgctactcaccaagtgacgatcacagcgaTccacaaac aagaaccgcgacccaaatcccggctgcgacggaactagctgtgccacacccg gcgCgtccttatataatcatcggcgttcaccgccccacggagatccctccgc agaatcgccgagaagggActacttttcctcgcctgttccgctctctggaaag aaaaccagtgccctagagtcacccaagtcccgtCctaaaatgtccttctgct gatactggggttctaaggccgagtcttatgagcagcgggccgctgtcctGag cgtccgggcggaaggatcaggacgctcgctgcgcccttcgtctgacgtggca gcgctcgccgtgaggaggggggcgcccgcgggaggcgccaaaacccggcgcg gaggcc
CB Promoter SEQ ID NO: 273	gacgacattgattattgactagttattaatagtaatcaattacggggtcatt agttcatagcccatatatggagttccgcgttacataacttacggtaaatggc ccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgt atgttcccatagtaacgccaatagggactttccattgacgtcaatgggtgga gtatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgcca agtacgcccccctattgacgtcaatgacggtaaatggcccgcctggcattatg cccagtacatgaccttatgggactttcctacttggcagtacatctacgtatt agtcatcgctattaccatggtcgaggtgagccccacgttctgcttcactctc cccatctccccccccctccccacccccaattttgtatttatttatttttttaat tattttgtgcagcgatgggggcgggggggggggggggcgcgcgccaggcgg ggcggggcggggcgaggggcggggcggggcgaggcggagaggtgcggcggca gccaatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggc ggcggcggccctataaaaagcgaagcgcgcggcgggcgg

CB Long Promoter SEQ ID NO: 274	gacgacattgattattgactagttattaatagtaatcaattacggggtcatt agttcatagcccatatatggagttccgcgttacataacttacggtaaatggc ccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgt atgttcccatagtaacgccaatagggactttccattgacgtcaatgggtgga gtatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgcca agtacgcccccctattgacgtcaatgacggtaaatggcccgcctggcattatg cccagtacatgaccttatgggactttcctacttggcagtacatctacgtatt agtcatcgctattaccatggtcgaggtgagccccacgttctgcttcactctc cccatctccccccccctccccacccccaattttgtatttatttatttttttaat tattttgtgcagcgatgggggcgggggggggggggggcgcgcgccaggcgg ggcggggcggggcgaggggcggggcggggcgaggcggagaggtgcggcggca gccaatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggc ggcggcggccctataaaaagcgaagcgcgcggcgggcgggagtcgctgcgcg ctgccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgccccgg ctctgactgaccgcgttactcccacaggtgagcg

Human red opsin (RedO) (photoreceptor-specific) SEQ ID NO: 212	ggaggctgaggggtggggaaagggcatgggtgtttcatgaggacagagcttc cgtttcat gcaatgaaaagagtttggagacggatggtggtgactggactatacacttaca cacggtag cgatggtacactttgtattatgtatattttaccacgatcttttaaagtgtc aaaggcaa atggccaaatggttccttgtcctatagctgtagcagccatcggctgttagtg acaaagcc cctgagtcaagatgacagcagcccccataactcctaatcggctctcccgcgt ggagtcat ttaggagtagtcgcattagagacaagtccaacatctaatcttccaccctggc cagggccc cagctggcagcgagggtgggagactccgggcagagcagagggcgctgacatt ggggcccg gcctggcttgggtccctctggcctttccccaggggccctctttccttggggc tttcttgg gccgccactgctcccgctcctctcccccccatcccacccccctcacccccctcgt tcttcata tccttctctagtgctccctccactttcatccacccttctgcaagagtgtggg accacaaa tgagttttcacctggcctggggacacacgtgcccccacaggtgctgagtgac tttctagg acagtaatctgctttaggctaaaatgggacttgatcttctgttagccctaat catcaatt agcagagccggtgaaggtgcagaacctaccgcctttccaggcctcctcccac ctctgcca cctccactctccttcctgggatgtgggggctggcacacgtgtggcccagggc attggtgg gattgcactgagctgggtcattagcgtaatcctggacaagggcagacagggc gagcggag ggccagctccggggctcaggcaaggctgggggcttcccccagacaccccact cctcctct gctggacccccacttcatagggcacttcgtgttctcaaagggcttccaaata gcatggtg gccttggatgcccagggaagcctcagagttgcttatctccctctagacagaa ggggaatc tcggtcaagagggagaggtcgccctgttcaaggccacccagccagctcatgg cggtaatg ggacaaggctggccagccatcccaccctcagaagggacccggtggggcaggt gatctcag aggaggctcacttctgggtctcacattcttggatccggttccaggcctcggc cctaaata gtctccctgggctttcaagagaaccacatgagaaaggaggattcgggctctg agcagttt

	caccacccaccccccagtctgcaaatcctgacccgtgggtccacctgcccca aaggcgga cgcaggacagtagaagggaacagagaacacataaacacagagagggccacag cggctccc acagtcaccgccaccttcctggcggggatgggtggggcgtctgagtttggtt cccagcaa atccctctgagccgcccttgcgggctcgcctcaggagcaggggagcaagagg tgggagga ggaggtctaagtcccaggcccaattaagagatcaggtagtgtagggtttggg agctttta aggtgaagaggcccgggctgatcccacaggccagtataaagcgccgtgaccc tcaggtga tgcgccagggccggctgccgtcggggacagggctttccatagcc
Human rhodopsin (Rho) (photoreceptor-specific) SEQ ID NO:213	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:214	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:215	TTTTTTTTTTACCTTTTTGGTTCCTTTGGCCTTTTGGCTTTTGGCTTCCAGG GCTTCTGGATCCCCCCCAACCCCTCCCATACACATACACATGTGCACTCGTG CACTCAACCCAGCACAGGATA ATGTTCATTCTTGACCTTTCCACATACATCTGGCTATGTTCTCTCTCTTATC TACAATAAATCTCCTCCACTATACTTAGGAGCAGTTATGTTCTTCTTCTTTC TTTCTTTTTTTTTTTTTTTTTCATTCAGTAACATCATCAGAATCCCCTAGCTC TGGCCTACCTCCTCAGTAACAATCAGC**TGATCCCTGGCCACTAATCTGTACT** **CACTAATCTGTTTTCCAAACTCTTGGCCCCTGAGCTAATTATAGCAGTGCTT** **CATGCCACCCACCCCAACCCTATCCTTGTTCTCTGACTCCCACTAATCTACA** **CATTCAGAGGATTGTGGATATAAGAGGCTGGGAGGCCAGCTTAGCAACCAGA** **GCTCGAGGCTGATGCGAGCTTCATCTCTTCCCTC**
Mouse cone arrestin promoter (CAR) *(photoreceptor-specific)* SEQ ID NO:216	**TGATCCCTGGCCACTAATCTGTACTCACTAATCTGTTTTCCAAACTCTTGGC** **CCCTGAGCTAATTATAGCAGTGCTTCATGCCACCCACCCCAACCCTATCCTT** **GTTCTCTGACTCCCACTAATCTACACATTCAGAGGATTGTGGATATAAGAGG** **CTGGGAGGCCAGCTTAGCAACCAGAGCTCGAGGCTGATGCGAGCTTCATCTC** **TTCCCTC**
Human rhodopsin kinase (RK) or GRK1 *(photoreceptor-specific)* SEQ ID NO:217	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:218	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:219	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:220	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:221	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)
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Best/GRK1 Tandem Promoter SEQ ID NO: 275	GTCGACAAATTCTGTCATTTTACTAGGGTGATGAAATTCCCAAGCAACACCATCCTTTTCAGA TAAGGGCACTGAGGCTGAGAGAGGAGCTGAAACCTACCCGGGGTCACCACACACAGGTGGCAA GGCTGGGACCAGAAACCAGGACTGTTGACTGCAGCCCGGTATTCATTCTTTCCATAGCCCACA GGGCTGTCAAAGACCCCAGGGCCTAGTCAGAGGCTCCTCCTTCCTGGAGAGTTCCTGGCACAG AAGTTGAAGCTCAGCACAGCCCCCTAACCCCCAACTCTCTCTGCAAGGCCTCAGGGGTCAGAA CACTGGTGGAGCAGATCCTTTAGCCTCTGGATTTTAGGGCCATGGTAGAGGGGGTGTTGCCCT AAATTCCAGCCCTGGTCTCAGCCCAACACCCTCCAAGAAGAAATTAGAGGGGCCATGGCCAGG CTGTGCTAGCCGTTGCTTCTGAGCAGATTACAAGAAGGGACTAAGACAAGGACTCCTTTGTGG AGGTCCTGGCTTAGGGAGTCAAGTGACGGCGGCTCAGCACTCACGTGGGCAGTGCCAGCCTCT AAGAGTGGGCAGGGGCACTGGCCACAGAGTCCCAGGGAGTCCCACCAGCCTAGTCGCCAGAtC TAGAGGGCCCCAGAAGCCTGGTGGTTGTTTGTCCTTCTCAGGGGAAAAGTGAGGCGGCCCCTT GGAGGAAGGGGCCGGGCAGAAGATCTAATCGGATTCCAAGCAGCTCAGGGGATTGTCTTTTTC TAGCACCTTCTTGCCACTCCTAAGCGTCCTCCGTGACCCCGGCTGGGATTTAGCCTGGTGCTG TGTCAGCCCCGGGCTCCCAGGGGCTTCCCAGTGGTCCCCAGGAACCCTCGACAGGGCCAGGGC GTCTCTCTCGTCCAGCAAGGGCAGGGACGGGCCACAGGCCAAGGGCCTTAAGC
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Table 1a. Other regulatory sequences

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LMTP20 SEQ ID NO:239	aggctcagaggcacacaggagtttctgggctcaccctgccccccttccaaccc ctcagttcccatcctccagcagctgtttgtgtgctgcctctgaagtccacac tgaacaaacttcagcctactcatgtccctaaaatgggcaaacattgcaagca gcaaacagcaaacacacagccctccctgcctgctgaccttggagctggggca gaggtcagagacctctctgggcccatgccacctccaacatccactcgacccc ttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagt gtgagagggcccttcagattaaaaataactgaggtaagggcctgggtagggg aggtggtgtgagacgctcctgtctctcctctatctgcccatcggcccttttgg ggaggaggaatgtgcccaaggactaaaaaaaggccatggagccagaggggcg agggcaacagacctttcatgggcaaaccttggggccctgctgaagctttggc ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccg agatgcctggttataattaacccagacatgtggctgccccccccccccccaa cacctgctgcctctaaaaataaccctgtccctggtggatcccctgcatgcga agatcttcgaacaaggctgtgggggactgagggcaggctgtaacaggcttgg gggccagggcttatacgtgcctgggactcccaaagtattactgttccatgtt cccggcgaagggccagctgtcccccgccagctagactcagcacttagtttag gaaccagtgagcaagtcagcccttggggcagcccatacaaggccatggggct gggcaagctgcacgcctgggtccggggtgggcacggtgcccgggcaacgagc

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ApoE.hAAT SEQ ID NO:240	aggctcagaggcacacaggagtttctgggctcaccctgcccccttccaaccc ctcagttcccatcctccagcagctgtttgtgtgctgcctctgaagtccacac tgaacaaacttcagcctactcatgtccctaaaatgggcaaacattgcaagca gcaaacagcaaacacacagccctccctgcctgctgaccttggagctggggca gaggtcagagacctctctgggcccatgccacctccaacatccactcgacccc ttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagt gtgagaggggtacccggggatcttgctaccagtggaacagccactaaggatt ctgcagtgagagcagagggccagctaagtggtactctcccagagactgtctg actcacgccacccccctccaccttggacacaggacgctgtggtttctgagcca ggtacaatgactcctttcggtaagtgcagtggaagctgtacactgcccaggc aaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggactta gcccctgtttgctcctccgataactggggtgaccttggttaatattcaccag cagcctcccccgttgcccctctggatccactgcttaaatacggacgaggaca gggccctgtctcctcagcttcaggcaccaccactgacctgggacagt
Alpha-Mic/Bik Enhancer (Mic/BikE) SEQ ID NO:241	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcattt actctctctgtttgctctggttaataatctcaggagcacaaacattcc
Tandem (2) alpha-Mic/Bik Enhancers (2 Mic/BikE) SEQ ID NO:242	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcattt actctctctgtttgctctggttaataatctcaggagcacaaacattccaggt taatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactc tctctgtttgctctggttaataatctcaggagcacaaacattcc
ApoE Hepatic Control Region containing ApoE Enhancer SEQ ID NO:243	aggctcagaggcacacaggagtttctgggctcaccctgcccccttccaaccc ctcagttcccatcctccagcagctgtttgtgtgctgcctctgaagtccacac tgaacaaacttcagcctactcatgtccctaaaatgggcaaacattgcaagca gcaaacagcaaacacacagccctccctgcctgctgaccttggagctggggca gaggtcagagacctctctgggcccatgccacctccaacatccactcgacccc ttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagt gtgagaggg

Tandem (2) ApoE Enhancers SEQ ID NO:244	aggctcagaggcacacaggagtttctgggctcaccctgccccccttccaaccc ctcagttcccatcctccagcagctgtttgtgtgctgcctctgaagtccacac tgaacaaacttcagcctactcatgtccctaaaatgggcaaacattgcaagca gcaaacagcaaacacacagccctccctgcctgctgaccttggagctggggca gaggtcagagacctctctgggcccatgccacctccaacatccactcgacccc ttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagt gtgagagggtctagaaggctcagaggcacacaggagtttctgggctcaccct gccccccttccaaccccctcagttcccatcctccagcagctgtttgtgtgctgc ctctgaagtccacactgaacaaacttcagcctactcatgtccctaaaatggg caaacattgcaagcagcaaacagcaaacacacagccctccctgcctgctgac cttggagctggggcagaggtcagagacctctctg
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hAAT(ΔATG) Promoter SEQ ID NO:246	gatcttgctaccagtggaacagccactaaggattctgcagtgagagcagagg gccagctaagtggtactctcccagagactgtctgactcacgccacccccctcc accttggacacaggacgctgtggtttctgagccaggtacagtgactcctttc ggtaagtgcagtggaagctgtacactgcccaggcaaagcgtccgggcagcgt aggcgggcgactcagatcccagccagtggacttagcccctgtttgctcctcc gataactggggtgaccttggttaatattcaccagcagcctcccccgttgccc ctctggatccactgcttaaatacggacgaggacagggccctgtctcctcagc ttcaggcaccaccactgacctgggacagt
Mck Enhancer (MckE) SEQ ID NO:247	ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccg agatgcctggttataattaacccagacatgtggctgccccccccccccccccaa cacctgctgcctctaaaaataaccctgtccctggtggatc
Tandem (2) Mck Enhancers (2 MckE) SEQ ID NO:248	ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccg agatgcctggttataattaacccagacatgtggctgccccccccccccccccaa cacctgctgcctctaaaaataaccctgtccctggtggatcccactacgggtt taggctgcccatgtaaggaggcaaggcctggggacacccgagatgcctggtt ataattaacccagacatgtggctgccccccccccccccccaacacctgctgcct ctaaaaataaccctgtccctggtggatc
Tandem Mck (3) Enhancers (3 MckE) SEQ ID NO:249	ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccg agatgcctggttataattaacccagacatgtggctgccccccccccccccccaa cacctgctgcctctaaaaataaccctgtccctggtggatcccactacgggtt taggctgcccatgtaaggaggcaaggcctggggacacccgagatgcctggtt ataattaacccagacatgtggctgccccccccccccccccaacacctgctgcct ctaaaaataaccctgtccctggtggatcccactacgggtttaggctgcccat gtaaggaggcaaggcctggggacacccgagatgcctggttataattaaccca

	gacatgtggctgccccccccccccccaacacctgctgcctctaaaaataacc ctgtccctggtggatc
Myosin heavy chain enhancer (MhcE) SEQ ID NO:250	cccttcagattaaaaataactgaggtaagggcctgggtaggggaggtggtgt gagacgctcctgtctctcctctatctgcccatcggcccttggggaggagga atgtgcccaaggactaaaaaaaggccatggagccagaggggcgagggcaaca gacctttcatgggcaaaccttggggccctgctgaagctttggc

[0080] 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:80), SV40 intron (SEQ ID NO:272), or a chimeric intron (β-globin/Ig Intron) (SEQ ID NO:79). The viral vectors may also include a Kozak sequence to promote translation of the transgene product, for example GCCACC.

[0081] 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:78), 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.

5.1.4 Signal Peptides

[0082] 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 peptides. Signal peptides (also referred to as "signal sequences") 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.

[0083] 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:85) which can be encoded by a nucleotide sequence of SEQ ID NO: 90 (see **Table 2**, **FIGS 2A-2C** and **3A-3H**). Alternatively, signal sequences that are appropriate for expression, and may cause selective expression or directed expression of the HuPTM mAb or Fab or scFv in the eye/CNS, muscle, or liver are provided in Tables 2, 3, and 4, respectively, below.

Table 2. Signal peptides for expression in eye/CNS

Signal Peptide Origin	SEQ ID NO:	Sequence
Mutant interleukin 2 signal peptide	85	MYRMQLLLLIALSLALVTNS
Mutant interleukin 2 signal peptide coding sequence	86	atgtataggatgcaactgctcctcctgattgctctgagcctggctcttgtgaccaactct
VEGF-A signal peptide	87	MNFLLSWVHWSLALLLYLHHAKWSQA
Fibulin-1 signal peptide	88	MERAAPSRRVPLPLLLLGGLALLAAGVDA
Vitronectin signal peptide	89	MAPLRPLLILALLAWVALA
Complement Factor H signal peptide	90	MRLLAKIICLMLWAICVA
Opticin signal peptide	91	MRLLAFLSLLALVLQETGT
Albumin signal peptide	92	MKWVTFISLLFLFSSAYS
Chymotrypsinogen signal peptide	93	MAFLWLLSCWALLGTTFG
Interleukin-2 signal peptide	94	MYRMQLLSCIALILALVTNS
Trypsinogen-2 signal peptide	95	MNLLLILTFVAAAVA

Table 3. Signal peptides for expression in liver cells.

Signal Peptide Origin	SEQ ID NO:	Sequence
Human Serum albumin	96	MKWVTFISLLFLFSSAYS
Human α-1 Antitrypsin (SERPINA1)	97	MPSSVSWGILLLAGLCCLVPVSLA
Human Apolipoprotein A-1	98	MKAAVLTLAVLFLTGSQA
Human Apolipoprotein A-2	99	MKLLAATVLLLTICSLEG
Human Apolipoprotein B-100	100	MDPPRPALLALLALPALLLLLLAGARA
Human Coagulation Factor IX	101	MQRVNMIMAESPGLITICLLGYLLSAEC

Signal Peptide Origin	SEQ ID NO:	Sequence
Human Complement C2	102	MGPLMVLFCLLFLYPGLADS
Human Complement Factor H-related Protein 2 (CFHR2)	103	MWLLVSVILISRISSVGG
Human Complement Factor H-related Protein 5 (CFHR5)	104	MLLLFSVILISWVSTVGG
Human Fibrinogen α-chain (FGA)	105	MFSMRIVCLVLSVVGTAWT
Human Fibrinogen β-chain (FGB)	106	MKRMVSWSFHKLKTMKHLLLLLLCVFLVKS
Human Fibrinogen γ-chain (FGG)	107	MSWSLHPRNLILYFYALLFLSSTCVA
Human α-2-HS-Glycoprotein (AHSG)	108	MKSLVLLLCLAQLWGCHS
Human Hemopexin (HPX)	109	MARVLGAPVALGLWSLCWSLAIA
Human Kininogen-1	110	MKLITILFLCSRLLLSLT
Human Mannose-binding protein C (MBL2)	111	MSLFPSLPLLLLSMVAASYS
Human Plasminogen (PLMN)	112	MEHKEVVLLLLFLKSGQG
Human Prothrombin (Coagulation Factor II)	113	MAHVRGLQLPGCLALAALCSLVHS
Human Secreted Phosphoprotein 24	114	MISRMEKMTMMMKILIMFALGMNYWSCSG
Human Anti-thrombin-III (SERPINC1)	115	MYSNVIGTVTSGKRKVYLLSLLLIGFWDCVTC
Human Serotransferrin (TF)	116	MRLAVGALLVCAVLGLCLA

Table 4. Signal peptides for expression in muscle cells.

Signal Peptide Origin	**SEQ ID NO:**	**Sequence**
Human SPARC	117	MRAWIFFLLCLAGRALA
Human Collagen alpha-1(I) chain	118	MFSFVDLRLLLLLAATALLTHG
Human Lactotransferrin	119	MKLVFLVLLFLGALGLCLA
Human Complement C3	120	MGPTSGPSLLLLLLTHLPLALG
Human Lumican	121	MSLSAFTLFLALIGGTSG
Human Gelsolin isoform 1	122	MAPHRPAPALLCALSLALCALSLPVRA
Human Pro-cathepsin H	123	MWATLPLLCAGAWLLGVPVCGA
Human SERPINF1	124	MQALVLLLCIGALLGHSSC
Human SERPINE1	125	MQMSPALTCLVLGLALVFGEGSA
Human Cathepsin D	126	MQPSSLLPLALCLLAAPASA
Human TIMP1	127	MAPFEPLASGILLLLWLIAPSRA
Human Fibronectin	226	MLRGPGPGLLLLAVQCLGTAVPSTGASKSKR
Human Complement C1s subcomponent	178	MWCIVLFSLLAWVYA
Human Cathepsin L1	179	MNPTLILAAFCLGIASA
Human Cathepsin B	180	MWQLWASLCCLLVLANA
Human Salivary acidic proline-rich phosphoprotein ½	181	MLLILLSVALLAFSSA
Human Follistatin-related protein 1	182	MWKRWLALALALVAVAWVRA

5.1.5 Polycistronic Messages – IRES and 2A linkers and scFv Constructs

[0084] *Internal ribosome entry sites*. A single construct can be engineered to encode both the heavy and light chains separated by a cleavable linker or IRES so that separate heavy and light chain polypeptides are expressed by the transduced cells. In certain embodiments, the viral vectors provided herein provide polycistronic (*e.g.*, bicistronic) messages. For example, the viral construct can encode the heavy and light chains separated by an internal ribosome entry site (IRES) elements (for examples of the use of IRES elements to create bicistronic vectors *see, e.g.*, Gurtu et al., 1996, Biochem. Biophys. Res. Comm. 229(1):295-8, which is herein incorporated by reference in its entirety). IRES elements bypass the ribosome scanning model and begin translation at internal sites. The use of IRES in AAV is described, for example, in Furling et al., 2001, Gene Ther 8(11): 854-73, which is herein

incorporated by reference in its entirety. In certain embodiments, the bicistronic message is contained within a viral vector with a restraint on the size of the polynucleotide(s) therein. In certain embodiments, the bicistronic message is contained within an AAV virus-based vector (*e.g.*, an AAV8-based, AAV3B-based or AAVrh73-based vector).

[0085] *Furin-2A linkers*. In other embodiments, the viral vectors provided herein encode the heavy and light chains separated by a cleavable linker such as the self-cleaving 2A and 2A-like peptides, with or without upstream furin cleavage sites, e.g. Furin/2A linkers, such as furin/F2A (F/F2A) or furin/T2A (F/T2A) linkers (Fang et al., 2005, Nature Biotechnology 23: 584-590, Fang, 2007, Mol Ther 15: 1153-9, and Chang, J. et al, MAbs 2015, 7(2):403-412, each of which is incorporated by reference herein in its entirety). For example, a furin/2A linker may be incorporated into an expression cassette to separate the heavy and light chain coding sequences, resulting in a construct with the structure:

Signal sequence– Heavy chain – Furin site – 2A site – Signal Sequence – Light chain – PolyA.

A 2A site or 2A-like site, such as an F2A site comprising the amino acid sequence RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP(SEQ ID NOS:143 or 144) or a T2A site comprising the amino acid sequence RKRR(GSG)EGRGSLLTCGDVEENPGP (SEQ ID NOS:141 or 142), is self-processing, resulting in "cleavage" between the final G and P amino acid residues. Several linkers, with or without an upstream flexible Gly-Ser-Gly (GSG) linker sequence (SEQ ID NO:128), that could be used include but are not limited to:

T2A: (GSG)EGRGSLLTCGDVEENP**GP** (SEQ ID NOS:133 or 134);

P2A: (GSG)ATNFSLLKQAGDVEENP**GP** (SEQ ID NOS:135 or 136);

E2A: (GSG)QCTNYALLKLAGDVESNP**GP** (SEQ ID NOS:137 or 138);

F2A: (GSG)APVKQTLNFDLLKLAGDVESNP**GP** (SEQ ID NOS:139 or 140)

(see also, e.g., Szymczak, et al., 2004, Nature Biotechnol 22(5):589-594, and Donnelly, et al., 2001, J Gen Virol, 82:1013-1025, each of which is incorporated herein by reference). Exemplary amino acid and nucleotide sequences encoding different parts of the flexible linker are described in **Table 4**.

Table 4. Linker Sequences

ID	**SEQ ID NO:**	**Sequence**
GSG linker	128	GSG

ID	SEQ ID NO:	Sequence
Furin linker	129	RKRR
Furin linker	130	RRRR
Furin linker	131	RRKR
Furin linker	132	RKKR
T2A	133	EGRGSLLTCGDVEENP**GP**
T2A	134	GSGEGRGSLLTCGDVEENP**GP**
P2A	135	ATNFSLLKQAGDVEENP**GP**
P2A	136	GSGATNFSLLKQAGDVEENP**GP**
E2A	137	QCTNYALLKLAGDVESNP**GP**
E2A	138	GSGQCTNYALLKLAGDVESNP**GP**
F2A	139	APVKQTLNFDLLKLAGDVESNP**GP**
F2A	140	GSGAPVKQTLNFDLLKLAGDVESNP**GP**
Furin-T2A	141	RKRREGRGSLLTCGDVEENPGP
Furin-GSG-T2A	142	RKRRGSGEGRGSLLTCGDVEENPGP
Furin-F2A	143	RKRRAPVKQTLNFDLLKLAGDVESNPGP
Furin-GSG-F2A	144	RKRRGSGAPVKQTLNFDLLKLAGDVESNPGP
Furin-GSG-T2A	145	agaaagagaagaggctctggagaaggcagaggctccc tgctgacatgtggggatgttgaagagaatcctgggcc t
Furin	146	agaaagagaaga
Furin-GSG linker	147	agaaagagaagaggctctgga
GSG linker	148	ggctctgga
T2A	149	gaaggcagaggctccctgctgacatgtggggatgttg aagagaatcctgggcct

[0086] In certain embodiments an additional proteolytic cleavage site, e.g. a furin cleavage site, is incorporated into the expression construct adjacent to the self-processing cleavage site (e.g. 2A or 2A like sequence), thereby providing a means to remove additional amino acids that remain following cleavage by the self processing cleavage sequence. Without being bound to any one theory, a peptide bond is skipped when the ribosome encounters the 2A sequence in the open reading frame, resulting in the termination of translation, or continued translation of the downstream sequence (the light chain). This self-processing sequence results in a string of additional amino acids at the end of the C-terminus of the heavy chain. However, such additional amino acids can then be cleaved by host cell Furin at the furin cleavage site(s), e.g. located immediately prior to the 2A site and after the heavy chain sequence, and further cleaved by carboxypeptidases. The resultant heavy chain may have one, two, three, or more additional amino acids included at the C-terminus, or it may not have such additional amino acids, depending on the sequence of the Furin linker used and the carboxypeptidase

that cleaves the linker in vivo (*See, e.g.*, Fang et al., 17 April 2005, Nature Biotechnol. Advance Online Publication; Fang et al., 2007, Molecular Therapy 15(6):1153-1159; Luke, 2012, Innovations in Biotechnology, Ch. 8, 161-186). Furin linkers that may be used comprise a series of four basic amino acids, for example, RKRR (SEQ ID NO:129), RRRR (SEQ ID NO:130), RRKR (SEQ ID NO:131), or RKKR (SEQ ID NO:132). Once this linker is cleaved by a carboxypeptidase, additional amino acids may remain, such that an additional zero, one, two, three or four amino acids may remain on the C-terminus of the heavy chain, for example, R, RR, RK, RKR, RRR, RRK, RKK, RKRR (SEQ ID NO:129), RRRR (SEQ ID NO:130), RRKR (SEQ ID NO:131), or RKKR (SEQ ID NO:132). In certain embodiments, once the linker is cleaved by a carboxypeptidase, no additional amino acids remain. In certain embodiments, 0.5% to 1%, 1% to 2%, 5%, 10%, 15%, or 20% of the antibody, *e.g.*, antigen-binding fragment, population produced by the constructs for use in the methods described herein has one, two, three, or four amino acids remaining on the C-terminus of the heavy chain after cleavage. In certain embodiments, the furin linker has the sequence R-X-K/R-R, such that the additional amino acids on the C-terminus of the heavy chain are R, RX, RXK, RXR, RXKR (SEQ ID NO:251), or RXRR (SEQ ID NO:252), where X is any amino acid, for example, alanine (A). In certain embodiments, no additional amino acids may remain on the C-terminus of the heavy chain.

[0087] *Flexible peptide linker*. In some embodiments, a single construct can be engineered to encode both the heavy and light chains (e.g. the heavy and light chain variable domains) separated by a flexible peptide linker such as those encoding a scFv. A flexible peptide linker can be composed of flexible residues like glycine and serine so that the adjacent heavy chain and light chain domains are free to move relative to one another. The construct may be arranged such that the heavy chain variable domain is at the N-terminus of the scFv, followed by the linker and then the light chain variable domain. Alternatively, the construct may be arranged such that the light chain variable domain is at the N-terminus of the scFv, followed by the linker and then the heavy chain variable domain. That is, the components may be arranged as NH_2-V_L-linker-V_H-COOH or NH_2-V_H-linker-V_L-COOH.

[0088] In certain embodiments, an expression cassette described herein is contained within a viral vector with a restraint on the size of the polynucleotide(s) therein. In certain embodiments, the expression cassette is contained within an AAV virus-based vector. Due to the size restraints of certain vectors, the vector may or may not accommodate the coding sequences for the full heavy and light

chains of the therapeutic antibody but may accommodate the coding sequences of the heavy and light chains of antigen binding fragments, such as the heavy and light chains of a Fab or F(ab')$_2$ fragment or an scFv. In particular, the AAV vectors described herein may accommodate a transgene of approximately 4.7 kilobases. Substitution of smaller expression elements would permit the expression of larger protein products, such as full-length therapeutic antibodies.

5.1.6 Untranslated regions

[0089] 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.

5.1.7 Inverted terminal repeats

[0090] 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:81 (5'-ITR) or 82 (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:81 (5'-ITR) or 83 (3'-ITR) or modified for scAAV, SEQ ID NO:82 (m 5'ITR) or SEQ ID NO:84 (m 3' ITR).

5.1.8 Transgenes

[0091] The transgenes encode a HuPTM mAb, either as a full-length antibody or an antigen binding fragment thereof, e.g. a Fab fragment (an HuGlyFab) or a $F(ab')_2$, nanobody, or an scFv based upon a therapeutic antibody disclosed herein. In specific embodiments, the HuPTM mAb or antigen binding fragment, particularly the HuGlyFab, are engineered to contain additional glycosylation sites on the Fab domain (*e.g.*, see Courtois et al., 2016, mAbs 8: 99-112 which is incorporated by reference herein in its entirety for it description of sites of hyperglycosylation on a Fab domain). In addition, for the HuPTM mAb comprising an Fc domain, the Fc domain 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".

5.1.8.1 Constructs for Expression of Full length HuPTM mAb

[0092] In certain embodiments, the transgenes encode a full length heavy chain (including the heavy chain variable domain, the heavy chain constant domain 1 (C_H1), the hinge and Fc domain) and a full length light chain (light chain variable domain and light chain constant domain) that upon expression associate to form antigen-binding antibodies with Fc domains. The recombinant AAV constructs express the intact (i.e., full length) or substantially intact HuPTM mAb in a cell, cell culture, or in a subject. ("Substantially intact" refers to mAb having a sequence that is at least 95% identical to the full-length mAb sequence.) The nucleotide sequences encoding the heavy and light chains 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. See for example, the codon optimized sequences of adalimumab (SEQ ID NOs: 46 to 60) of **Table 8**. The transgenes may encode any full-length antibody. In preferred embodiments, the transgenes encode a full-length form of any of the therapeutic antibodies disclosed herein, for example, the Fab fragment of which depicted in **FIGS. 2A-2C** or **3A-3H** herein and including, in certain embodiments, the associated Fc domain provided in **Table 6**.

[0093] The full length mAb encoded by the transgene described herein preferably have the Fc domain of the full-length therapeutic antibody or is an Fc domain of the same type of immunoglobulin as the therapeutic antibody to be expressed. In certain embodiments, the Fc region is an IgG Fc region, but in other embodiments, the Fc region may be an IgA, IgD, IgE, or IgM. The Fc domain is preferably

of the same isotype as the therapeutic antibody to be expressed, for example, if the therapeutic antibody is an IgG1 isotype, then the antibody expressed by the transgene comprises an IgG1 Fc domain. The antibody expressed from the transgene may have an IgG1, IgG2, IgG3 or IgG4 Fc domain.

[0094] The Fc region of the intact mAb 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 antibody or can be modified therefrom to add, enhance, modify, or inhibit one or more effector functions using the Fc modifications disclosed in Section 5.1.9, infra. In certain embodiments, the HuPTM mAb transgene encodes a mAb 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 antibodies described herein as set forth in **Table 6** for adalimumab, infliximab, and golimumab, or an exemplary Fc domain of an IgG1, IgG2 or IgG4 isotype as set forth in **Table 6**. In some embodiments, the HuPTM mAb comprises a Fc polypeptide of a sequence that is a variant of the Fc polypeptide sequence in **Table 6** in that the sequence has been modified with one or more of the techniques described in Section 5.1.9, *infra*, to alter the Fc polypeptide's effector function.

[0095] In some embodiments, provided are exemplary recombinant AAV constructs such as the constructs shown in **FIGS. 1A and 1B**, for gene therapy administration to a human subject in order to express an intact or substantially intact HuPTM mAb in the subject. Gene therapy constructs are designed such that both the heavy and light chains are expressed in tandem from the vector including the Fc domain polypeptide of the heavy chain. In certain embodiments, the transgene encodes a transgene with heavy and light chain Fab fragment polypeptides as shown in **Table 7**, yet have a heavy chain that further comprises an Fc domain polypeptide C terminal to the hinge region of the heavy chain (including an IgG1, IgG2 or IgG4 Fc domain or the adalimumab, infliximab, or golimumab Fc as in **Table 6**). In specific embodiments, the transgene is a nucleotide sequence that encodes the following: Signal sequence-heavy chain Fab portion (including hinge region)-heavy chain Fc polypeptide-Furin-2A linker-signal sequence-light chain Fab portion.

[0096] In specific embodiments for expressing an intact or substantially intact mAb in ocular tissue cell types, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) Control elements, which include a) an

inducible promoter, preferably a ocular-tissue specific promoter, b) optionally an intron, such as a chicken β-actin intron or VH4 intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy chain Fab of an anti-TNFα, anti-IL6, or anti-IL6R mAb (e.g. adalimumab, infliximab, golimumab, satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab); an Fc polypeptide associated with the therapeutic antibody (**Table 6**) or of the same isotype as the native form of the therapeutic antibody, such as an IgG isotype amino acid sequence from **Table 6**; and the light chain of an anti-TNFα, anti-IL6, or anti-IL6R mAb (e.g. adalimumab, infliximab, golimumab, satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab), wherein the heavy chain (Fab and Fc region) and the light chain are separated by a self-cleaving furin (F)/F2A or T2A or flexible linker, ensuring expression of equal amounts of the heavy and the light chain polypeptides. Exemplary constructs are provided in **FIGS. 1A and 1B.**

[0097] In specific embodiments, provided are AAV vectors comprising a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO:196); and an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding an intact or substantially intact anti-TNFα, anti-IL6, or anti-IL6R mAb; operably linked to one or more regulatory sequences that control expression of the transgene in ocular tissue type cells.

[0098] The rAAV vectors that encode and express the full-length therapeutic antibodies 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 antibodies. Also provided are methods of expressing HuPTM mAbs in human cells using the rAAV vectors and constructs encoding them.

5.1.8.2 Constructs for Expression of Antigen Binding Fragments

[0099] In some embodiments, the transgenes express antigen binding fragments, e.g. a Fab fragment (an HuGlyFab) or a $F(ab')_2$, nanobody, or an scFv based upon a therapeutic antibody disclosed herein. **FIGS. 2A-2C and 3A-3H** and section 5.4. provide the amino acid sequence of the heavy and light chains of the Fab fragments of the therapeutic antibodies (see also **Table 7**, which provides the amino acid sequences of the Fab heavy and light chains of the therapeutic antibodies).

[0100] Certain of these nucleotide sequences are codon optimized for expression in human cells. See for example, the codon optimized sequences of adalimumab (SEQ ID NOs: 46 to 60) in **Table 8**. The transgene may encode a Fab fragment using nucleotide sequences encoding the amino acid sequences provided in **Table 7**, but not including the portion of the hinge region on the heavy chain that forms interchain di-sulfide bonds (*e.g.*, the portion containing the sequence CPPCPA (SEQ ID NO:150)). Heavy chain Fab domain sequences that do not contain a CPPCP (SEQ ID NO:151) sequence of the hinge region at the C-terminus will not form intrachain disulfide bonds and, thus, will form Fab fragments with the corresponding light chain Fab domain sequences, whereas those heavy chain Fab domain sequences with a portion of the hinge region at the C-terminus containing the sequence CPPCP (SEQ ID NO:151) will form intrachain disulfide bonds and, thus, will form Fab_2 fragments. For example, in some embodiments, the transgene may encode a scFv comprising a light chain variable domain and a heavy chain variable domain connected by a flexible linker in between (where the heavy chain variable domain may be either at the N-terminal end or the C-terminal end of the scFv), and optionally, may further comprise a Fc polypeptide (*e.g.*, IgG1, IgG2, IgG3, or IgG4) on the C-terminal end of the heavy chain. Alternatively, in other embodiments, the transgene may encode $F(ab')_2$ fragments comprising a nucleotide sequence that encodes the light chain and the heavy chain sequence that includes at least the sequence CPPCA (SEQ ID NO:152) of the hinge region, as depicted in **FIGS. 2A-2C and 3A-3H** which depict various regions of the hinge region that may be included at the C-terminus of the heavy chain sequence. Pre-existing anti-hinge antibodies (AHA) may cause immunogenicity and reduce efficacy. Thus, in certain embodiments, for the IgG1 isotype, C-terminal ends with D221 or ends with a mutation T225L or with L242 can reduce binding to AHA. (See, e.g., Brezski, 2008, J Immunol 181: 3183-92 and Kim, 2016, 8: 1536-1547). For IgG2, the risk of AHA is lower since the hinge region of IgG2 is not as susceptible to enzymatic cleavage required to generate endogenous AHA. (*See, e.g.*, Brezski, 2011, MAbs 3: 558-567).

Table 5. Hinge Regions

SEQ ID NO:	**Sequence**
150	CPPCP
151	CPPCPA
152	CPPCA
153	EPKSCDKTHTCPPCPAPELLGG
154	EPKSCDKTHLCPPCPAPELLGG

SEQ ID NO:	Sequence
155	EPKSCDKTHL
156	EPKSCDKTHT
157	EPKSCDKTHTCPPCPA
158	EPKSCDKTHLCPPCPA
159	EPKSCDKTHTCPPCPAPELLGGPSVFL
160	EPKSCDKTHLCPPCPAPELLGGPSVFL
161	EPKSCDKTHTCPPCPAPEAAGG
162	EPKSCDKTHTCPPCPAPEAAGGPSVFL
163	EPKSCDKTHLCPPCPAPEAAGGPSVFL
164	ERKSCVECPPCPAPPVAG
165	ERKSCVECPPCPA
166	ESKYGPPCPPCPAPEFLGG
167	ESKYGPPCPPCPA
168	ESKYGPPCPSCPA
150	ESKYGPPCPSCPAPEFLGGPSVFL
169	ESKYGPPCPPCPAPEFLGGPSVFL
170	ERKCCVECPPCPAPPVAG
171	ERKCCVECPPCPA
172	EPKSCDKTHTCPPCPAPELAGA
173	EPKSCDKTHTCPPCPAPELAGAPSVFL
174	EPKSCDKTHLCPPCPAPELAGAPSVFL
175	EPKSCDKTHTCPPCPAPEFEGG
176	EPKSCDKTHTCPPCPAPEFEGGPSVFL
177	EPKSCDKTHLCPPCPAPEFEGGPSVFL

[0101] 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 **1a**, and b) a sequence encoding the transgene (*e.g.*, a HuGlyFab). In certain embodiments, the sequence encoding the transgene comprises multiple ORFs separated by IRES elements. In certain embodiments, the ORFs encode the heavy and light chain domains of the HuGlyFab. In certain embodiments, the sequence encoding the transgene comprises multiple subunits in one ORF separated by F/F2A sequences or F/T2A sequences. In certain embodiments, the sequence comprising the transgene encodes the heavy and light chain domains of the HuGlyFab separated by an F/F2A sequence or a F/T2A sequence. In certain embodiments, the sequence comprising the transgene encodes the heavy and light chain variable domains of the

HuGlyFab separated by a flexible peptide linker (as an scFv). 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** or **1a**, and b) a sequence encoding the transgene (*e.g.*, a HuGlyFab), wherein the transgene comprises a nucleotide sequence encoding a signal peptide, a light chain and a heavy chain Fab portion separated by an IRES element. In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a constitutive or a hypoxia-inducible promoter sequence or regulatory element listed in **Table 1** or **1a**, and b) a sequence encoding the transgene comprising a signal peptide, a light chain and a heavy chain sequence separated by a cleavable F/F2A sequence (SEQ ID NOS:143 or 144) or a F/T2A sequence (SEQ ID NOS:141 or 142) or a flexible peptide linker.

[0102] In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a first ITR sequence, b) a first linker sequence, c) a constitutive or an inducible promoter sequence or a tissue specific promoter or regulatory region, d) a second linker sequence, e) an intron sequence, f) a third linker sequence, g) a first UTR sequence, h) a sequence encoding the transgene (*e.g.*, a HuGlyFab), i) a second UTR sequence, j) a fourth linker sequence, k) a poly A sequence, l) a fifth linker sequence, and m) a second ITR sequence.

[0103] In certain embodiments, the viral vectors provided herein comprise the following elements in the following order: a) a first ITR sequence, b) a first linker sequence, c) a constitutive or an inducible promoter sequence or a tissue specific regulatory region, d) a second linker sequence, e) an intron sequence, f) a third linker sequence, g) a first UTR sequence, h) a sequence encoding the transgene (*e.g.*, HuGlyFab), i) a second UTR sequence, j) a fourth linker sequence, k) a poly A sequence, l) a fifth linker sequence, and m) a second ITR sequence, wherein the transgene comprises a signal, and wherein the transgene encodes a light chain and a heavy chain sequence separated by a cleavable F/2A sequence.

5.1.9. Fc Region Modifications

[0104] In certain embodiments, the transgenes encode full length or substantially full length heavy and light chains that associate to form a full length or intact antibody. ("Substantially intact" or "substantially full length" refers to a mAb having a heavy chain sequence that is at least 95% identical

to the full-length heavy chain mAb amino acid sequence and a light chain sequence that is at least 95% identical to the full-length light chain mAb amino acid sequence). Accordingly, the transgenes comprise nucleotide sequences that encode, for example, the light and heavy chains of the Fab fragments including the hinge region of the heavy chain and C-terminal of the heavy chain of the Fab fragment, an Fc domain peptide. **Table 6** provides the amino acid sequence of the Fc polypeptides for adalimumab, infliximab, golimumab, satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, and tocilizumab. Alternatively, an IgG1, IgG2, or IgG4 Fc domain, the sequences of which are provided in **Table 6** may be utilized.

[0105] 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.

[0106] In certain embodiments, the Fc polypeptide is that of the therapeutic antibody or is the Fc polypeptide corresponding to the isotype of the therapeutic antibody). In still other embodiments, the Fc polypeptide is an IgG Fc polypeptide. The Fc polypeptide may be from the IgG1, IgG2, or IgG4 isotype (see **Table 6**) 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 6. Table of Fc Domain Amino Acid Sequences

Fc	Chain/ SEQ ID NO.	Sequence
IgG1	Fc domain /SEQ ID NO: 61	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLSLSPGK
IgG2	Fc domain /SEQ ID NO: 62	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDISVEWE SNGQPENNYK TTPPMLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
IgG4	Fc domain /SEQ ID NO: 63	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK
Adalimumab	Fc domain /SEQ ID NO: 64	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Infliximab	Fc domain	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ

Fc	Chain/ SEQ ID NO.	Sequence
	/SEQ ID NO: 65	VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Golimumab	Fc domain /SEQ ID NO: 66	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Satralizumab	Fc domain/ SEQ ID NO: 67	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG SFFLYSKLTV DKSRWQEGNV FSCSVMHEAL HAHYTQKSLS LSP
Sarilumab	Fc domain/ SEQ ID NO:185	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Siltuximab	Fc domain/ SEQ ID NO: 68	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Clazakizumab	Fc domain/ SEQ ID NO: 69	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYASTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Sirukumab	Fc domain/ SEQ ID NO: 70	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Olokizumab	Fc domain/	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ

Fc	Chain/ SEQ ID NO.	Sequence
	SEQ ID NO: 71	VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK
Tocilizumab	Fc domain/ SEQ ID NO: 72	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPG

[0107] In some embodiments, the recombinant vectors encode therapeutic antibodies 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).

[0108] "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.

[0109] 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.

[0110] "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.

[0111] "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.

[0112] "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.

[0113] 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. 6): 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.

[0114] 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. 6) 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.

[0115] 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.

[0116] 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);

[0117] 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 6).

[0118] 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).

[0119] 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).

[0120] 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.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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).

5.1.10 Manufacture and testing of vectors

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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. In addition, in vitro neutralization assays can be used to measure the activity of the transgene expressed from a vector described herein. For example, Vero-E6 cells, a cell line derived from the kidney of an African green monkey, or HeLa cells engineered to stably express the ACE2 receptor (HeLa-ACE2), can be used to assess neutralization activity of transgenes expressed from a vector described herein. In addition, other characteristics of the expressed product can be determined, for example determination of the glycosylation and tyrosine sulfation patterns associated with the HuGlyFab. Glycosylation patterns and methods of determining the same are discussed in Section 5.3, while tyrosine sulfation patterns and methods of determining the same are discussed in Section 5.3. In addition, benefits resulting from glycosylation/sulfation of the cell-expressed HuGlyFab can be determined using assays known in the art, *e.g.*, the methods described in Section 5.3.

[0129] 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.

5.1.11 Compositions

[0130] 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.

5.2 Methods of Treating Non-Infectious Uveitis

[0131] In another aspect, methods for treating non-infectious uveitis or other indication that can be treated with an anti-TNFα, anti-IL6, or anti-IL6R antibody in a subject in need thereof comprising the administration of recombinant AAV particles comprising an expression cassette encoding anti-TNFα, anti-IL6, or anti-IL6R antibodies and antibody-binding fragments and variants thereof, or peptides, 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 an anti-TNFα antibody. Subjects to whom such gene therapy is administered can be those responsive to anti-TNFα, e.g. adalimumab, infliximab, or golimumab, or anti-IL6, or anti-IL6R therapy e.g., satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab. 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, anti-IL6, or anti-IL6R antibody or considered a good candidate for therapy with an anti-TNFα, anti-IL6, or anti-IL6R antibody. In specific embodiments, the patients have previously been treated with an anti-TNFα, anti-IL6, or anti-IL6R antibody. To determine responsiveness, the anti-TNFα, anti-IL6, or anti-IL6R antibody or antigen-binding fragment transgene product (e.g., produced in human cell culture, bioreactors, etc.) may be administered directly to the subject.

[0132] In specific embodiments, provided are methods of treating non-infectious uveitis or other indication amenable to treatment with an anti-TNFα, anti-IL6, or anti-IL6R antibody 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 a substantially full-length or full-length anti-TNFα, anti-IL6, or anti-IL6R mAb having an Fc region, or an antigen-binding fragment thereof, 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.

[0133] Recombinant vectors and pharmaceutical compositions for treating diseases or disorders in a subject in need thereof are described in Section 5.1. 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:77 or 217), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 214-216), a human red opsin (RedO) promoter (SEQ ID NO: 212), a CAG promoter (SEQ ID NO: 74), a CB promoter or CBlong promoter (SEQ ID NO: 273 or 274) or a Best1/GRK1 tandem promoter (SEQ ID NO: 275) (see also Tables 1 and 1a).

5.3.N-GLYCOSYLATION, TYROSINE SULFATION, AND O-GLYCOSYLATION

[0134] The amino acid sequence (primary sequence) of HuGlyFabs or HuPTM Fabs, HuPTMmAbs, and HuPTM scFvs disclosed herein each comprises at least one site at which N-glycosylation or tyrosine sulfation takes place (see exemplary **FIG. 5**) for glycosylation and/or sulfation positions within the amino acid sequences of the Fab fragments of the therapeutic antibodies). Post-translational modification also occurs in the Fc domain of full length antibodies, particularly at residue N297 (by EU numbering, see **Table 6**).

[0135] Alternatively, mutations may be introduced into the Fc domain to alter the glycosylation site at residue N297 (EU numbering, see **Table 6**), 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.

5.3.1. N-Glycosylation

Reverse Glycosylation Sites

[0136] 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 HuGlyFabs and HuPTM scFvs disclosed herein comprise such reverse consensus sequences.

Non-Consensus Glycosylation Sites

[0137] 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 antibodies 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

[0138] In certain embodiments, a nucleic acid encoding a HuPTM mAb, HuGlyFab or HuPTM scFv 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 mAb, HuGlyFab or HuPTM scFv (*e.g.*, relative to the number of N-glycosylation sites associated with the HuPTM mAb, HuGlyFab or HuPTM scFv 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 antigen-binding fragment, or the antibody from which the antigen-binding fragment is derived (*e.g.*, the glycosylation sites are added, in full or in part), or by mutating existing amino acids in the antigen-binding fragment, or the antibody from which the antigen-binding fragment is derived, in order to generate the N-glycosylation sites (*e.g.*, amino acids are not added to the antigen-binding fragment/antibody, but selected amino acids of the antigen-binding fragment/antibody 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.

[0139] In a specific embodiment, a HuGlyMab or antigen-binding fragment is modified such that, when expressed in mammalian cells, such as retina, CNS, liver or muscle cells, it can be hyperglycosylated. See Courtois et al., 2016, mAbs 8:99-112 which is incorporated by reference herein in its entirety.

N-Glycosylation of HuPTM mAbs and HuPTM antigen-binding fragments

[0140] 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.

[0141] When a HuPTM mAb, HuGlyFab or HuPTM scFv is expressed in a human cell, the N-glycosylation sites of the antigen-binding fragment can be glycosylated with various different glycans. N-glycans of antigen-binding fragments and the Fc domain have been characterized in the art. For

example, Bondt et al., 2014, Mol. & Cell. Proteomics 13.11:3029-3039 (incorporated by reference herein in its entirety for its disclosure of Fab-associated N-glycans; see also, FIG. 22) characterizes glycans associated with Fabs, and demonstrates that Fab and Fc portions of antibodies comprise distinct glycosylation patterns, with Fab glycans being high in galactosylation, sialylation, and bisection (*e.g.*, with bisecting GlcNAc) but low in fucosylation with respect to Fc glycans. Like Bondt, Huang et al., 2006, Anal. Biochem. 349:197-207 (incorporated by reference herein in its entirety for it disclosure of Fab-associated N-glycans) found that most glycans of Fabs are sialylated. However, in the Fab of the antibody examined by Huang (which was produced in a murine cell background), the identified sialic residues were N-Glycolylneuraminic acid ("Neu5Gc" or "NeuGc") (which is not natural to humans) instead of N-acetylneuraminic acid ("Neu5Ac," the predominant human sialic acid). In addition, Song et al., 2014, Anal. Chem. 86:5661-5666 (incorporated by reference herein in its entirety for its disclosure of Fab-associated N-glycans) describes a library of N-glycans associated with commercially available antibodies.

[0142] Glycosylation of the Fc domain has been characterized and is a single N-linked glycan at asparagine 297 (EU numbering; see **Table 6**). 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, 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 mAbs 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.

[0143] Importantly, when the HuPTM mAb, HuGlyFab or HuPTM scFv 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 mAb, HuGlyFab or HuPTM scFv 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.

[0144] Assays for determining the glycosylation pattern of antibodies, including antigen-binding fragments 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 antigen-binding fragments include those described by Bondt et al., 2014, Mol. & Cell. Proteomics 13.11:3029-3039, Huang et al., 2006, Anal. Biochem. 349:197-207, and/or Song et al., 2014, Anal. Chem. 86:5661-5666.

[0145] Homogeneity or heterogeneity of the glycan patterns associated with antibodies (including antigen-binding fragments), 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.

[0146] In certain embodiments, the HuPTM mAbs, or antigen binding fragments thereof, 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 mAb or antigen-binding fragment, 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

[0147] N-glycosylation confers numerous benefits on the HuPTM mAb, HuGlyFab or HuPTM scFv described herein. Such benefits are unattainable by production of antigen-binding fragments 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 HuGlyFab of HuPTM scFv described herein should reduce immunogenicity of the transgene product and improve efficacy.

[0148] While non-canonical glycosylation sites usually result in low level glycosylation (*e.g.*, 1-5%) of the antibody population, the functional benefits may be significant (*See, e.g.*, van de Bovenkamp et al., 2016, J. Immunol. 196:1435-1441). For example, Fab glycosylation may affect the stability, half-life, and binding characteristics of an antibody. To determine the effects of Fab glycosylation on the affinity of the antibody 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 Fab glycosylation on the half-life of the antibody, 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 Fab glycosylation on the stability, for example, levels of aggregation or protein unfolding, of the antibody, 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.

[0149] The presence of sialic acid on HuPTM mAb, HuGlyFab or HuPTM scFv used in the methods described herein can impact clearance rate of the HuPTM mAb, HuGlyFab or HuPTM scFv. Accordingly, sialic acid patterns of a HuPTM mAb, HuGlyFab or HuPTM scFv can be used to generate a therapeutic having an optimized clearance rate. Methods of assessing antigen-binding fragment clearance rate are known in the art. *See, e.g.*, Huang et al., 2006, Anal. Biochem. 349:197-207.

[0150] 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 antigen-binding fragment used herein or engineered into an antigen-binding fragment used herein, resulting in HuGlyFab or HuPTM scFv 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.

[0151] 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 HuPTM mAb, HuGlyFab or HuPTM scFv that is less prone to immunogenicity when expressed, *e.g.*, expressed in human ocular tissue cells, human CNS cells, human liver cells or human muscle cells.

[0152] 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.

[0153] In another specific embodiment, a benefit conferred by N-glycosylation is altered binding affinity. It is known in the art that the presence of N-glycosylation sites in the variable domains

of an antibody can increase the affinity of the antibody for its antigen. *See, e.g.*, Bovenkamp et al., 2016, J. Immunol. 196:1435-1441. Assays for measuring antibody binding affinity are known in the art. *See, e.g.*, Wright et al., 1991, EMBO J. 10:2717-2723; and Leibiger et al., 1999, Biochem. J. 338:529-538.

5.3.2 Tyrosine Sulfation

[0154] Tyrosine sulfation occurs at tyrosine (Y) residues with glutamate (E) or aspartate (D) within +5 to -5 position of Y, and where position -1 of Y is a neutral or acidic charged amino acid, but not a basic amino acid, *e.g.*, arginine (R), lysine (K), or histidine (H) that abolishes sulfation. The HuGlyFabs and HuPTM scFvs described herein comprise tyrosine sulfation sites (see exemplary FIG. 2).

[0155] Importantly, tyrosine-sulfated antigen-binding fragments cannot be produced in *E. coli*, which naturally does not possess the enzymes required for tyrosine-sulfation. Further, CHO cells are deficient for tyrosine sulfation–they are not secretory cells and have a limited capacity for post-translational tyrosine-sulfation. *See, e.g.*, Mikkelsen & Ezban, 1991, Biochemistry 30: 1533-1537. Advantageously, the methods provided herein call for expression of HuPTM Fab in human cells that are secretory and have capacity for tyrosine sulfation.

[0156] Tyrosine sulfation is advantageous for several reasons. For example, tyrosine-sulfation of the antigen-binding fragment of therapeutic antibodies against targets has been shown to dramatically increase avidity for antigen and activity. *See, e.g.*, Loos et al., 2015, PNAS 112: 12675-12680, and Choe et al., 2003, Cell 114: 161-170. Assays for detection tyrosine sulfation are known in the art. *See, e.g.*, Yang et al., 2015, Molecules 20:2138-2164.

5.3.3 O-Glycosylation

[0157] 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. In certain embodiments, the HuGlyFab 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 HuGlyFab 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.) O-glycosylated HuGlyFab, by virtue of possessing glycans, shares advantageous characteristics with N-glycosylated HuGlyFab (as discussed above).

5.4 Anti-TNFα HuPTM Constructs and Formulations for Non-Infectious Uveitis

[0158] Compositions and methods are described for the delivery of HuPTM mAb or the antigen-binding fragment thereof, such as HuPTM Fab, that bind to TNFα, derived from an anti-TNFα antibody and indicated for treating non-infectious uveitis. In certain embodiments, the HuPTM mAb has the amino acid sequence of adalimumab, infliximab, or golimumab or an antigen binding fragment thereof. The amino acid sequence of Fab fragment of these antibodies is provided in **FIGS. 2A-2C**. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an TNFα-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with non-infectious uveitis to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0159] Provided are recombinant vectors containing a transgene encoding a HuPTM mAb or HuPTM Fab (or other antigen binding fragment of the HuPTM mAb) that binds to TNFα that can be administered to deliver the HuPTM mAb or antigen binding fragment in a patient. The transgene is a nucleic acid comprising the nucleotide sequences encoding an antigen binding fragment of an antibody that binds to TNFα, such as adalimumab, infliximab, or golimumab, or variants thereof as detailed herein. The transgene may also encode an anti-TNFα antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0160] In certain embodiments, the anti-TNFα antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of adalimumab (having amino acid sequences of SEQ ID NOs. 1 and 2, respectively, see **Table 7** 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: 26 (encoding the adalimumab

heavy chain Fab portion) and SEQ ID NO: 27 (encoding the adalimumab light chain Fab portion) as set forth in **Table 8**. The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0161] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-TNFα-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 1 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:153), and specifically, EPKSCDKTHL (SEQ ID NO:155), EPKSCDKTHT (SEQ ID NO:156), EPKSCDKTHTCPPCPA (SEQ ID NO:157), EPKSCDKTHLCPPCPA (SEQ ID NO:158), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:159) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:160) as set forth in **FIG. 2A**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 26 by the hinge region encoding sequences set forth in **Table 7** (SEQ ID NO: 26). In another embodiment, the transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g., having an amino acid sequence of SEQ ID NO: 64 (**Table 6**) or an IgG1 Fc domain, such as SEQ ID No. 61 or as depicted in **FIG. 6**, 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 5.1.9, infra.

[0162] In specific embodiments, provided are constructs encoding a full length adalimumab, including the Fc domain, particularly nucleotide sequence of CAG.adalimumab.IgG (SEQ ID NOs: 46, 47, or 48), GRK1.adalimumab.IgG (SEQ ID NOs: 52 or 53), CB.VH4.adalimumab (SEQ ID NO: 276 or 277), Best1.GRK1.VH4.adalimumab, or an antigen-binding fragment of adalimumab,

particularly CAG.adalimumab.Fab (SEQ ID NOS: 49 or 50), mU1a.adalimumab.Fab (SEQ ID NOS:224 or 225), and EF1a.adalimumab.Fab (SEQ ID NOs:222 or 223) as set forth in **Table 8**, herein, in certain cases depleted for CpG dimers. The transgene may also comprises a nucleotide sequence that encodes a signal peptide MYRMQLLLLIALSLALVTNS (SEQ ID NO:85); for example at the N-terminal of the heavy and/or the light chain) which may be encoded by the nucleotide sequence of SEQ ID NO:86. The nucleotide sequences encoding the light chain and heavy chain may be separated by a Furin-2A linker (SEQ ID NOs:146-149, see also amino acid sequences of SEQ ID NOs:142 and 144) to create a bicistronic vector. Alternatively, the nucleotide sequences of the light chain and heavy chain are separated by a Furin-T2A linker, such as SEQ ID NO:145. Expression of the adalimumab may be directed by a constitutive or a tissue specific promoter. In certain embodiments, the transgene contains a CAG promoter (SEQ ID NO: 74), a CB promoter or CB long promoter (SEQ ID NO: 273 or 274), a GRK1 (SEQ ID NO:77) 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:77 or 217), (a mouse cone arresting (CAR) promoter (SEQ ID NOS: 214-216), a human red opsin (RedO) promoter (SEQ ID NO: 212) or a Best1/GRK1 tandem promoter (SEQ ID NO: 275). In embodiments, a intron sequence is positioned between the promoter and the coding sequence, for example a VH4 intron sequence (SEQ ID NO: 70). The transgenes may contain elements provided in **Table 1** or **1a**. Exemplary transgenes encoding full length adalimumab are provided in **Table 8** and include CAG.Adalimumab.T2A (SEQ ID NO: 46 to 48); GRK1.Adalimumab (SEQ ID NO: 52 and 53). ITR sequences are added to the 5' and 3' ends of the constructs to generate the genomes. including pAAV.CB.VH4.adalimumab (SEQ ID NO: 277), pAAV.CBlong.VH4.adalimumab, or pAAV.Best1.GRK1.VH4 adalimumab. The transgenes may be packaged into AAV, particularly AAV8.

[0163] In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes an TNFα antigen-binding fragment comprising a light chain 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 anti-TNFα antigen-binding fragment transgene encodes an TNFα antigen-binding fragment comprising a heavy chain 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 anti-TNFα antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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 and a heavy chain 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 specific embodiments, the TNFα antigen binding fragment comprises a heavy chain 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, e.g., in the framework regions (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in **FIG. 2A**). In specific embodiments, the TNFα antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 2 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in **FIG. 2A**).

[0164] In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes a hyperglycosylated adalimumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 1 and 2, respectively, with one or more of the following mutations: L116N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 14A (heavy chain) and 14B (light chain)).

[0165] In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six adalimumab CDRs which are underlined in the heavy and light chain variable domain sequences of **FIG. 2A** which are spaced between framework regions, generally human framework regions, and associated with constant domains depending upon the form of the antigen-binding molecule, as is known in the art to form the heavy and/or light chain variable domain of an anti-TNFα antibody or antigen-binding fragment thereof.

[0166] In certain embodiments, the anti-TNFα antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of infliximab (having amino acid sequences of SEQ ID NOs. 3 and 4, respectively, see **Table 7** and **FIG. 2B**). 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: 28 (encoding the infliximab heavy chain Fab portion) and SEQ ID NO: 29 (encoding the infliximab light chain Fab portion) as set forth in **Table 8**. The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0167] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-TNFα-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 3 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:153), and specifically, EPKSCDKTHL (SEQ ID NO:155), EPKSCDKTHT (SEQ ID NO:156), EPKSCDKTHTCPPCPA (SEQ ID NO:157), EPKSCDKTHLCPPCPA (SEQ ID NO:158), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:159) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:160) as set forth in **FIG. 2B**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 28 by the hinge region encoding sequences set forth in **Table 8** (SEQ ID NO: 28). In another embodiment, the transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g. having an amino acid sequence of SEQ ID NO: 65 (**Table 7**) or an IgG1 Fc domain, such as SEQ ID No. 61 or as depicted in **FIG. 6**, 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 5.1.9, *infra*.

[0168] In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes an TNFα antigen-binding fragment comprising a light chain 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: 4. In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes an TNFα antigen-binding fragment comprising a heavy chain 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, the anti-TNFα antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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: 4 and a heavy chain 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 specific embodiments, the TNFα antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 3 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 2B) or are substitutions with an amino acid present at that position in the heavy chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9A. In specific embodiments, the TNFα antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 4 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, for example, in the framework regions (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 2B) or are substitutions with an amino acid present at that position in the light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9B.

[0169] In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes a hyperglycosylated infliximab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 3 and 4, respectively, with one or more of the following mutations: T115N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 9A (heavy chain) and 9B (light chain)).

[0170] In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six infliximab CDRs

which are underlined in the heavy and light chain variable domain sequences of FIG. 2B which are spaced between framework regions, generally human framework regions, and associated with constant domains depending upon the form of the antigen-binding molecule, as is known in the art to form the heavy and/or light chain variable domain of an anti-TNFα antibody or antigen-binding fragment thereof.

[0171] In certain embodiments, the anti-TNFα antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of golimumab (having amino acid sequences of SEQ ID NOs. 5 and 6, respectively, see **Table 7** and **FIG. 2C**). 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: 30 (encoding the golimumab heavy chain Fab portion) and SEQ ID NO: 31 (encoding the golimumab light chain Fab portion) as set forth in **Table 6**. The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0172] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-TNFα-antigen binding domain has a heavy chain variable domain of SEQ ID NO: 5 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:153), and specifically, EPKSCDKTHL (SEQ ID NO:155), EPKSCDKTHT (SEQ ID NO:156), EPKSCDKTHTCPPCPA (SEQ ID NO:157), EPKSCDKTHLCPPCPA (SEQ ID NO:158), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:159) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:160) as set forth in **FIG. 2C**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 30 by the hinge region encoding sequences set forth in **Table 8** (SEQ ID NO: 30). In another embodiment, the

transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g., having an amino acid sequence of SEQ ID NO: 66 (**Table 6**) or an IgG1 Fc domain, such as SEQ ID No. 61 or as depicted in **FIG. 6**, 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 5.1.9, infra.

[0173] In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes an TNFα antigen-binding fragment comprising a light chain 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, the anti-TNFα antigen-binding fragment transgene encodes an TNFα antigen-binding fragment comprising a heavy chain 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: 5. In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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 and a heavy chain 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: 5. In specific embodiments, the TNFα antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 5 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, for example, in the framework regions (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 2C) or are substitutions with an amino acid present at that position in the heavy chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 149A. In specific embodiments, the TNFα antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 6 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 2C) or are substitutions

with an amino acid present at that position in the light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9B.

[0174] In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes a hyperglycosylated golimumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 5 and 6, respectively, with one or more of the following mutations: T124N (heavy chain), Q164N or Q164S (light chain), and/or E199N (light chain) (see FIGS. 9A (heavy chain) and 9B (light chain)).

[0175] In certain embodiments, the anti-TNFα antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six golimumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 2C which are spaced between framework regions, generally human framework regions, and associated with constant domains depending upon the form of the antigen-binding molecule, as is known in the art to form the heavy and/or light chain variable domain of an anti-TNFα antibody or antigen-binding fragment thereof. **Table 7** provides the amino acid sequences of Fab heavy and light chains, the full length heavy chain for adalimumab and the amino acid sequence for the translation product of full length and Fab adalimumab (SEQ ID Nos: 1, 2 , 23, 24, 25). **Table 8** provides a nucleotide sequence encoding the Fab heavy and light chains of the antibodies disclosed herein, adalimumab full length heavy chain, expression cassettes and genomes.

Table 7. Amino Acid Sequences of Heavy and Light Chains

mAb	Chain/ SEQ ID NO:	Sequences
Adalimumab	Heavy/ SEQ ID NO: 1	EVQLVESGGG LVQPGRSLRL SCAASGFTFD DYAMHWVRQA PGKGLEWVSA ITWNSGHIDY ADSVEGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAKVS YLSTASSLDY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKKVE PKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Adalimumab	Light/ SEQ ID NO: 2	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NYLAWYQQKP GKAPKLLIYA ASTLQSGVPS RFSGSGSGTD FTLTISSLQP EDVATYYCQR YNRAPYTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ

mAb	Chain/ SEQ ID NO:	Sequences
		ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Infliximab	Heavy/ SEQ ID NO: 3	EVKLEESGGG LVQPGGSMKL SCVASGFIFS NHWMNWVRQS PEKGLEWVAE IRSKSINSAT HYAESVKGRF TISRDDSKSA VYLQMTDLRT EDTGVYYCSR NYYGSTYDYW GQGTTLTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCD +/- KTHT (or KTHL)+/- CPPCPA +/- PELLGGPSVFL
Infliximab	Light/ SEQ ID NO: 4	DILLTQSPAI LSVSPGERVS FSCRASQFVG SSIHWYQQRT NGSPRLLIKY ASESMSGIPS RFSGSGSGTD FTLSINTVES EDIADYYCQQ SHSWPFTFGS GTNLEVKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Golimumab	Heavy/ SEQ ID NO: 5	SKLQVQLVES GGGVVQPGRS LRLSCAASGF IFSSYAMHWV RQAPGNGLEW VAFMSYDGSN KKYADSVKGR FTISRDNSKN TLYLQMNSLR AEDTAVYYCA RDRGIAAGGN YYYYGMDVWG QGTTVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Golimumab	Light/ SEQ ID NO: 6	AGSEIVLTQS PATLSLSPGE RATLSCRASQ SVYSYLAWYQ QKPGQAPRLL IYDASNRATG IPARFSGSGS GTDFTLTISS LEPEDFAVYY CQQRSNWPPF TFGPGTKVDI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
Satralizumab	Heavy/ SEQ ID NO: 7	QVQLQESGPG LVKPSETLSL TCAVSGHSIS HDHAWSWVRQ PPGEGLEWIG FISYSGITNY NPSLQGRVTI SRDNSKNTLY LQMNSLRAED TAVYYCARSL ARTTAMDYWG EGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSNFGTQTY TCNVDHKPSN TKVDKTVERK SCVE +/- CPPCPA +/-P PVAG

mAb	Chain/ SEQ ID NO:	Sequences
Satralizumab	Light/ SEQ ID NO: 8	DIQMTQSPSS LSASVGDSVT ITCQASTDIS SHLNWYQQKP GKAPELLIYY GSHLLSGVPS RFSGSGSGTD FTFTISSLEA EDAATYYCGQ GNRLPYTFGQ GTKVEIERTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Sarilumab	Heavy/ SEQ ID NO: 9	EVQLVESGGG LVQPGRSLRL SCAASRFTFD DYAMHWVRQA PGKGLEWVSG ISWNSGRIGY ADSVKGRFTI SRDNAENSLF LQMNGLRAED TALYYCAKGR DSFDIWGQGT MVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD +/- KTHT (or KTHL)+ /- CPPCPA +/- PELLGGPSVFL
Sarilumab	Light/ SEQ ID NO: 10	DIQMTQSPSS VSASVGDRVT ITCRASQGIS SWLAWYQQKP GKAPKLLIYG ASSLESGVPS RFSGSGSGTD FTLTISSLQP EDFASYYCQQ ANSFPYTFGQ GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Siltuximab	Heavy/ SEQ ID NO: 11	EVQLVESGGK LLKPGGSLKL SCAASGFTFS SFAMSWFRQS PEKRLEWVAE ISSGGSYTYY PDTVTGRFTI SRDNAKNTLY LEMSSLRSED TAMYYCARGL WGYYALDYWG QGTSVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCD *+/- KTHT (or KTHL) +/- CPPCPA +/- PELLGG*PSVFL
Siltuximab	Heavy/ SEQ ID NO: 12	QIVLIQSPAI MSASPGEKVT MTCSASSSVS YMYWYQQKPG SSPRLLIYDT SNLASGVPVR FSGSGSGTSY SLTISRMEAE DAATYYCQQW SGYPYTFGGG TKLEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC
Clazakizumab	Heavy/ SEQ ID NO: 13	EVQLVESGGG LVQPGGSLRL SCAASGFSLS NYYVTWVRQA PGKGLEWVGI IYGSDETAYA TSAIGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARDDS SDWDAKFNLW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS

mAb	Chain/ SEQ ID NO:	Sequences
		WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Clazakizumab	Light/ SEQ ID NO: 14	AIQMTQSPSS LSASVGDRVT ITCQASQSIN NELSWYQQKP GKAPKLLIYR ASTLASGVPS RFSGSGSGTD FTLTISSLQP DDFATYYCQQ GYSLRNIDNA FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC
Sirukumab	Heavy/ SEQ ID NO: 15	EVQLVESGGG LVQPGGSLRL SCAASGFTFS PFAMSWVRQA PGKGLEWVAK ISPGGSWTYY SDTVTGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARQL WGYYALDIWG QGTTVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCD +-/ KTHT (or KTHL) +/- CPPCPA +-/ PELLGGPSVFL
Sirukumab	Light/ SEQ ID NO: 16	EIVLTQSPAT LSLSPGERAT LSCSASISVS YMYWYQQKPG QAPRLLIYDM SNLASGIPAR FSGSGSGTDF TLTISSLEPE DFAVYYCMQW SGYPYTFGGG TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC
Olokizumab	Heavy/ SEQ ID NO: 17	EVQLVESGGG LVQPGGSLRL SCAASGFNFN DYFMNWVRQA PGKGLEWVAQ MRNKNYQYGT YYAESLEGRF TISRDDSKNS LYLQMNSLKT EDTAVYYCAR ESYYGFTSYW GQGTLVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KY +/- GPPCPPCPA (or GPPCPSCPA) +/- PEFLGGPSVFL
Olokizumab	Light/ SEQ ID NO: 18	DIQMTQSPSS LSASVGDRVT ITCQASQDIG ISLSWYQQKP GKAPKLLIYN ANNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCLQ HNSAPYTFGQ GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

mAb	Chain/ SEQ ID NO:	Sequences
Gerilizumab	Heavy/ SEQ ID NO: 19	EVQLQESGPG LVKPSQTLSL TCTVSGGSIT SRYYAWSWIR QPPGKGLEWI GVIDYDGDTY YSPSLKSRVS ISWDTSKNQF SLKLSSVTPA DTAVYYCARD PDVVTGFHYD YWGQGTMVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKKV EPKSCD +/- KTHT (or KTHL) +/- CPPCPA +-/ PELLGGPSVFL
Gerilizumab	Light/ SEQ ID NO: 20	QSALTQPPSV SGTPGQSVTI SCAGANNDIG TYAYVSWYQQ LPGTAPKLMI YKVTTRASGI PDRFSGSKSG NTASLTISGL QAEDEADYYC ASYRNFNNAV FGTGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS
Tocilizumab	Heavy/ SEQ ID NO: 21	QVQLQESGPG LVRPSQTLSL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG YISYSGITTY NPSLKSRVTM LRDTSKNQFS LRLSSVTAAD TAVYYCARSL ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Tocilizumab	Light/ SEQ ID NO: 22	DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY TSRLHSGVPS RFSGSGSGTD FTFTISSLQP EDIATYYCQQ GNTLPYTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Adalimumab Heavy Chain *(IgG1 Fc: CH1-hinge-CH2)*	Heavy/ SEQ ID NO: 23	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGK GLEWVSAITWNSGHIDYADSVEGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCAKVSYLSTASSLDYWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK

mAb	Chain/ SEQ ID NO:	Sequences
Adalimumab Vectorized IgG-fully encoded protein	SEQ ID NO: 24	**MYRMQLLLLLIALSLALVTNS**EVQLVESGGGLVQPGRSLRLSCA ASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSVEG RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLD YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV*EPKSCDKTHTCPPCPAPEL* *LGGPSVFL*FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKRK RRGSGEGRGSLLTCGDVEENPGP**MYRMQLLLLLIALSLALVTNS** DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKA PKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDVATY YCQRYNRAPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC Leaders are shown in bold; Furin-2A linker is underlined; hinge region is shown in italic
Adalimumab Vectorized Fab-fully encoded protein	SEQ ID NO: 25	**MYRMQLLLLLIALSLALVTNS**EVQLVESGGGLVQPGRSLRLSCA ASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSVEG RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKVSYLSTASSLD YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKV*EPKSCDKTH*RKRRGSGEGR GSLLTCGDVEENPGP**MYRMQLLLLLIALSLALVTNS**DIQMTQSP SSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIYAA STLQSGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQRYNRA PYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC Leaders are shown in bold; Furin-2A linker is underlined; hinge region is shown in italic

Table 8. Nucleotide Sequences of Heavy and Light Chains, Expression Cassettes and Genomes

mAb or construct name	Chain/ SEQ ID NO:	Sequences
Adalimumab	Heavy/ SEQ ID NO: 26	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCG GCAGGAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTT CGACGACTACGCCATGCACTGGGTGAGGCAGGCCCCCGGCAAG GGCCTGGAGTGGGTGAGCGCCATCACCTGGAACAGCGGCCACA TCGACTACGCCGACAGCGTGGAGGGCAGGTTCACCATCAGCAG GGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTG AGGGCCGAGGACACCGCCGTGTACTACTGCGCCAAGGTGAGCT ACCTGAGCACCGCCAGCAGCCTGGACTACTGGGGCCAGGGCAC CCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTG TTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCG CCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGT GACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCAC ACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGA GCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGAC CTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTT CCTG
Adalimumab	Light/ SEQ ID NO: 27	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCG TGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGGGCAT CAGGAACTACCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCC CCCAAGCTGCTGATCTACGCCGCCAGCACCCTGCAGAGCGGCG TGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCAC CCTGACCATCAGCAGCCTGCAGCCCGAGGACGTGGCCACCTAC TACTGCCAGAGGTACAACAGGGCCCCCTACACCTTCGGCCAGG GCACCAAGGTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGT GTTCATCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACC GCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCAGGGAGG CCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAA CAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACC TACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACG AGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
Infliximab	Heavy/ SEQ ID NO: 28	GAGGTGAAGCTGGAGGAGAGCGGCGGCGGCCTGGTGCAGCCCG GCGGCAGCATGAAGCTGAGCTGCGTGGCCAGCGGCTTCATCTT CAGCAACCACTGGATGAACTGGGTGAGGCAGAGCCCCGAGAAG GGCCTGGAGTGGGTGGCCGAGATCAGGAGCAAGAGCATCAACA GCGCCACCCACTACGCCGAGAGCGTGAAGGGCAGGTTCACCAT CAGCAGGGACGACAGCAAGAGCGCCGTGTACCTGCAGATGACC GACCTGAGGACCGAGGACACCGGCGTGTACTACTGCAGCAGGA ACTACTACGGCAGCACCTACGACTACTGGGGCCAGGGCACCAC

mAb or construct name	Chain/ SEQ ID NO:	Sequences
		CCTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTC CCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCG CCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGAC CGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACC TTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCA GCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTA CATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC AAGAAGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCG TGTTCCTG
Infliximab	Light/ SEQ ID NO: 29	GACATCCTGCTGACCCAGAGCCCCGCCATCCTGAGCGTGAGCC CCGGCGAGAGGGTGAGCTTCAGCTGCAGGGCCAGCCAGTTCGT GGGCAGCAGCATCCACTGGTACCAGCAGAGGACCAACGGCAGC CCCAGGCTGCTGATCAAGTACGCCAGCGAGAGCATGAGCGGCA TCCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCAC CCTGAGCATCAACACCGTGGAGAGCGAGGACATCGCCGACTAC TACTGCCAGCAGAGCCACAGCTGGCCCTTCACCTTCGGCAGCG GCACCAACCTGGAGGTGAAGAGGACCGTGGCCGCCCCCAGCGT GTTCATCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACC GCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCAGGGAGG CCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAA CAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACC TACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACG AGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
Golimumab	Heavy/ SEQ ID NO: 30	AGCAAGCTGCAGGTGCAGCTGGTGGAGAGCGGCGGCGGCGTGG TGCAGCCCGGCAGGAGCCTGAGGCTGAGCTGCGCCGCCAGCGG CTTCATCTTCAGCAGCTACGCCATGCACTGGGTGAGGCAGGCC CCCGGCAACGGCCTGGAGTGGGTGGCCTTCATGAGCTACGACG GCAGCAACAAGAAGTACGCCGACAGCGTGAAGGGCAGGTTCAC CATCAGCAGGGACAACAGCAAGAACACCCTGTACCTGCAGATG AACAGCCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCA GGGACAGGGGCATCGCCGCCGGCGGCAACTACTACTACTACGG CATGGACGTGTGGGGCCAGGGCACCACCGTGACCGTGAGCAGC GCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCA GCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGT GAAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAACAGC GGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGC AGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCC CAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAAC CACAAGCCCAGC+/- AAGACCCACACC (or

mAb or construct name	Chain/ SEQ ID NO:	Sequences
		AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTG CTGGGCGGCCCCAGCGTGTTCCTG
Golimumab	Light/ SEQ ID NO: 31	GCCGGCAGCGAGATCGTGCTGACCCAGAGCCCCGCCACCCTGA GCCTGAGCCCCGGCGAGAGGGCCACCCTGAGCTGCAGGGCCAG CCAGAGCGTGTACAGCTACCTGGCCTGGTACCAGCAGAAGCCC GGCCAGGCCCCCAGGCTGCTGATCTACGACGCCAGCAACAGGG CCACCGGCATCCCCGCCAGGTTCAGCGGCAGCGGCAGCGGCAC CGACTTCACCCTGACCATCAGCAGCCTGGAGCCCGAGGACTTC GCCGTGTACTACTGCCAGCAGAGGAGCAACTGGCCCCCCTTCA CCTTCGGCCCCGGCACCAAGGTGGACATCAAGAGGACCGTGGC CGCCCCCAGCGTGTTCATCTTCCCCCCCAGCGACGAGCAGCTG AAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCT ACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCT GCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGC AAGGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCA AGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGAC CCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGCTTCAACAGG GGCGAGTGC
Satralizumab	Heavy/ SEQ ID NO: 32	CAGGTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCA GCGAGACCCTGAGCCTGACCTGCGCCGTGAGCGGCCACAGCAT CAGCCACGACCACGCCTGGAGCTGGGTGAGGCAGCCCCCCGGC GAGGGCCTGGAGTGGATCGGCTTCATCAGCTACAGCGGCATCA CCAACTACAACCCCAGCCTGCAGGGCAGGGTGACCATCAGCAG GGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTG AGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGAGCCTGG CCAGGACCACCGCCATGGACTACTGGGGCGAGGGCACCCTGGT GACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCC CTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCC TGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGT GAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTC CCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCG TGGTGACCGTGCCCAGCAGCAACTTCGGCACCCAGACCTACAC CTGCAACGTGGACCACAAGCCCAGCAACACCAAGGTGGACAAG ACCGTGGAGAGGAAGAGCTGCGTGGAG +/- TGCCCCCCCTGCCCCGCC +/- CCCCCCGTGGCCGGC
Satralizumab	Light/ SEQ ID NO: 33	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCG TGGGCGACAGCGTGACCATCACCTGCCAGGCCAGCACCGACAT CAGCAGCCACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCC CCCGAGCTGCTGATCTACTACGGCAGCCACCTGCTGAGCGGCG TGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCAC CTTCACCATCAGCAGCCTGGAGGCCGAGGACGCCGCCACCTAC TACTGCGGCCAGGGCAACAGGCTGCCCTACACCTTCGGCCAGG

mAb or construct name	Chain/ SEQ ID NO:	Sequences
		GCACCAAGGTGGAGATCGAGAGGACCGTGGCCGCCCCCAGCGT GTTCATCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACC GCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCAGGGAGG CCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAA CAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACC TACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACG AGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
Sarilumab	Heavy/ SEQ ID NO: 34	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCG GCAGGAGCCTGAGGCTGAGCTGCGCCGCCAGCAGGTTCACCTT CGACGACTACGCCATGCACTGGGTGAGGCAGGCCCCCGGCAAG GGCCTGGAGTGGGTGAGCGGCATCAGCTGGAACAGCGGCAGGA TCGGCTACGCCGACAGCGTGAAGGGCAGGTTCACCATCAGCAG GGACAACGCCGAGAACAGCCTGTTCCTGCAGATGAACGGCCTG AGGGCCGAGGACACCGCCCTGTACTACTGCGCCAAGGGCAGGG ACAGCTTCGACATCTGGGGCCAGGGCACCATGGTGACCGTGAG CAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCC AGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCC TGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAA CAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTG CTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCG TGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGT GAACCACAAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAG CCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Sarilumab	Light/ SEQ ID NO: 35	GACATCCAGATGACCCAGAGCCCCAGCAGCGTGAGCGCCAGCG TGGGCGACAGGGTGACCATCACCTGCAGGGCCAGCCAGGGCAT CAGCAGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCC CCCAAGCTGCTGATCTACGGCGCCAGCAGCCTGGAGAGCGGCG TGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACTTCAC CCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCAGCTAC TACTGCCAGCAGGCCAACAGCTTCCCCTACACCTTCGGCCAGG GCACCAAGCTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGT GTTCATCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACC GCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCAGGGAGG CCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAA CAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACC TACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACG AGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC

mAb or construct name	Chain/ SEQ ID NO:	Sequences
Siltuximab	Heavy/ SEQ ID NO: 36	gaagtgcagctggtggaaagcggcggcaaactgctgaaaccgg gcggcagcctgaaactgagctgcgcggcgagcggctttacctt tagcagctttgcgatgagctggtttcgccagagcccggaaaaa cgcctggaatgggtggcggaaattagcagcggcggcagctata cctattatccggataccgtgaccggccgctttaccattagccg cgataacgcgaaaaacaccctgtatctggaaatgagcagcctg cgcagcgaagataccgcgatgtattattgcgcgcgcggcctgt ggggctattatgcgctggattattggggccagggcaccagcgt gaccgtgagcagcgcgagcaccaaaggcccgagcgtgtttccg ctggcgccgagcagcaaaagcaccagcggcggcaccgcggcgc tgggctgcctggtgaaagattattttccggaaccggtgaccgt gagctggaacagcggcgcgctgaccagcggcgtgcatacctttt ccggcggtgctgcagagcagcggcctgtatagcctgagcagcg tggtgaccgtgccgagcagcagcctgggcacccagacctatat ttgcaacgtgaaccataaaccgagcaacaccaaagtggataaa aaagtggaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Siltuximab	Light/ SEQ ID NO: 37	cagattgtgctgattcagagcccggcgattatgagcgcgagcc cgggcgaaaaagtgaccatgacctgcagcgcgagcagcagcgt gagctatatgtattggtatcagcagaaaccgggcagcagcccg cgcctgctgatttatgataccagcaacctggcgagcggcgtgc cggtgcgctttagcggcagcggcagcggcaccagctatagcct gaccattagccgcatggaagcggaagatgcggcgacctattat tgccagcagtggagcggctatccgtatacctttggcggcggca ccaaactggaaattaaacgcaccgtggcggcgccgagcgtgtt tatttttccgccgagcgatgaacagctgaaaagcggcaccgcg agcgtggtgtgcctgctgaacaacttttatccgcgcgaagcga aagtgcagtggaaagtggataacgcgctgcagagcggcaacag ccaggaaagcgtgaccgaacaggatagcaaagatagcacctat agcctgagcagcaccctgaccctgagcaaagcggattatgaaa aacataaagtgtatgcgtgcgaagtgacccatcagggcctgag cagcccggtgaccaaaagctttaaccgcggcgaatgc
Clazakizumab	Heavy/ SEQ ID NO: 38	gaagtgcagctggtggaaagcggcggcggcctggtgcagccgg gcggcagcctgcgcctgagctgcgcggcgagcggctttagcct gagcaactattatgtgacctgggtgcgccaggcgccgggcaaa ggcctggaatgggtgggcattatttatggcagcgatgaaaccg cgtatgcgaccagcgcgattggccgctttaccattagccgcga taacagcaaaaacaccctgtatctgcagatgaacagcctgcgc gcggaagataccgcggtgtattattgcgcgcgcgatgatagca gcgattgggatgcgaaatttaacctgtggggccagggcaccct

mAb or construct name	Chain/ SEQ ID NO:	Sequences
		ggtgaccgtgagcagcgcgagcaccaaaggcccgagcgtgttt ccgctggcgccgagcagcaaaagcaccagcggcggcaccgcgg cgctgggctgcctggtgaaagattattttccggaaccggtgac cgtgagctggaacagcggcgcgctgaccagcggcgtgcatacc tttccggcggtgctgcagagcagcggcctgtatagcctgagca gcgtggtgaccgtgccgagcagcagcctgggcacccagaccta tatttgcaacgtgaaccataaaccgagcaacaccaaagtggat aaacgcgtggaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Clazakizumab	Light/ SEQ ID NO: 39	gcgattcagatgacccagagcccgagcagcctgagcgcgagcg tgggcgatcgcgtgaccattacctgccaggcgagccagagcat taacaacgaactgagctggtatcagcagaaaccgggcaaagcg ccgaaactgctgatttatcgcgcgagcaccctggcgagcggcg tgccgagccgctttagcggcagcggcagcggcaccgattttac cctgaccattagcagcctgcagccggatgattttgcgacctat tattgccagcagggctatagcctgcgcaacattgataacgcgt ttggcggcggcaccaaagtggaaattaaacgcaccgtggcggc gccgagcgtgtttatttttccgccgagcgatgaacagctgaaa agcggcaccgcgagcgtggtgtgcctgctgaacaacttttatc cgcgcgaagcgaaagtgcagtggaaagtggataacgcgctgca gagcggcaacagccaggaaagcgtgaccgaacaggatagcaaa gatagcacctatagcctgagcagcaccctgaccctgagcaaag cggattatgaaaaacataaagtgtatgcgtgcgaagtgaccca tcagggcctgagcagcccggtgaccaaaagctttaaccgcggc gaatgcgaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Sirukumab	Heavy/ SEQ ID NO: 40	Gaagtgcagctggtggaaagcggcggcggcctggtgcagccgg gcggcagcctgcgcctgagctgcgcggcgagcggctttacctt tagcccgtttgcgatgagctgggtgcgccaggcgccgggcaaa ggcctggaatgggtggcgaaaattagcccgggcggcagctgga cctattatagcgataccgtgaccggccgctttaccattagccg cgataacgcgaaaaacagcctgtatctgcagatgaacagcctg cgcgcggaagataccgcggtgtattattgcgcgcgccagctgt ggggctattatgcgctggatatttggggccagggcaccaccgt gaccgtgagcagcgcgagcaccaaaggcccgagcgtgtttccg ctggcgccgagcagcaaaagcaccagcggcggcaccgcggcgc tgggctgcctggtgaaagattattttccggaaccggtgaccgt gagctggaacagcggcgcgctgaccagcggcgtgcatacctttt

mAb or construct name	Chain/ SEQ ID NO:	Sequences
		ccggcggtgctgcagagcagcggcctgtatagcctgagcagcg tggtgaccgtgccgagcagcagcctgggcacccagacctatat ttgcaacgtgaaccataaaccgagcaacaccaaagtggataaa aaagtggaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Sirukumab	Light/ SEQ ID NO: 41	gaaattgtgctgacccagagcccggcgaccctgagcctgagcc cgggcgaacgcgcgaccctgagctgcagcgcgagcattagcgt gagctatatgtattggtatcagcagaaaccgggccaggcgccg cgcctgctgatttatgatatgagcaacctggcgagcggcattc cggcgcgctttagcggcagcggcagcggcaccgattttaccct gaccattagcagcctggaaccggaagattttgcggtgtattat tgcatgcagtggagcggctatccgtatacctttggcggcggca ccaaagtggaaattaaacgcaccgtggcggcgccgagcgtgtt tatttttccgccgagcgatgaacagctgaaaagcggcaccgcg agcgtggtgtgcctgctgaacaacttttatccgcgcgaagcga aagtgcagtggaaagtggataacgcgctgcagagcggcaacag ccaggaaagcgtgaccgaacaggatagcaaagatagcacctat agcctgagcagcaccctgaccctgagcaaagcggattatgaaa aacataaagtgtatgcgtgcgaagtgacccatcagggcctgag cagcccggtgaccaaaagctttaaccgcggcgaatgc
Olokizumab	Heavy/ SEQ ID NO:42	Gaagtgcagctggtggaaagcggcggcggcctggtgcagccgg gcggcagcctgcgcctgagctgcgcggcgagcggctttaactt taacgattattttatgaactgggtgcgccaggcgccgggcaaa ggcctggaatgggtggcgcagatgcgcaacaaaaactatcagt atggcacctattatgcggaaagcctggaaggccgctttaccat tagccgcgatgatagcaaaaacagcctgtatctgcagatgaac agcctgaaaaccgaagataccgcggtgtattattgcgcgcgcg aaagctattatggctttaccagctattggggccagggcaccct ggtgaccgtgagcagcgcgagcaccaaaggcccgagcgtgttt ccgctggcgccgtgcagccgcagcaccagcgaaagcaccgcgg cgctgggctgcctggtgaaagattattttccggaaccggtgac cgtgagctggaacagcggcgcgctgaccagcggcgtgcatacc tttccggcggtgctgcagagcagcggcctgtatagcctgagca gcgtggtgaccgtgccgagcagcagcctgggcaccaaaaccta tacctgcaacgtggatcataaaccgagcaacaccaaagtggat aaacgcgtgGAGAGCAAGTAC +/- GGCCCCCCCTGCCCCCCCTG CCCCGCC (GGCCCCCCCCTGCCCCAGCTGCCCCGCC)+/- CCCGAGTTCCTGGGCGGCCCCAGCGTGTTCCTG

mAb or construct name	Chain/ SEQ ID NO:	Sequences
Olokizumab	Light/ SEQ ID NO: 43	gatattcagatgacccagagcccgagcagcctgagcgcgagcg tgggcgatcgcgtgaccattacctgccaggcgagccaggatat tggcattagcctgagctggtatcagcagaaaccgggcaaagcg ccgaaactgctgatttataacgcgaacaacctggcggatggcg tgccgagccgctttagcggcagcggcagcggcaccgattttac cctgaccattagcagcctgcagccggaagattttgcgacctat tattgcctgcagcataacagcgcgccgtatacctttggccagg gcaccaaactggaaattaaacgcaccgtggcggcgccgagcgt gtttatttttccgccgagcgatgaacagctgaaaagcggcacc gcgagcgtggtgtgcctgctgaacaacttttatccgcgcgaag cgaaagtgcagtggaaagtggataacgcgctgcagagcggcaa cagccaggaaagcgtgaccgaacaggatagcaaagatagcacc tatagcctgagcagcaccctgaccctgagcaaagcggattatg aaaaacataaagtgtatgcgtgcgaagtgacccatcagggcct gagcagcccggtgaccaaaagctttaaccgcggcgaatgc
Gerilimzumab	Heavy/ SEQ ID NO: 44	Gaagtgcagctgcaggaaagcggcccgggcctggtgaaaccga gccagaccctgagcctgacctgcaccgtgagcggcggcagcat taccagccgctattatgcgtggagctggattcgccagccgccg ggcaaaggcctggaatggattggcgtgattgattatgatggcg atacctattatagcccgagcctgaaaagccgcgtgagcattag ctgggataccagcaaaaaccagtttagcctgaaactgagcagc gtgaccccggcggataccgcggtgtattattgcgcgcgcgatc cggatgtggtgaccggctttcattatgattattggggccaggg caccatggtgaccgtgagcagcgcgagcaccaaaggcccgagc gtgtttccgctggcgccgagcagcaaaagcaccagcggcggca ccgcggcgctgggctgcctggtgaaagattattttccggaacc ggtgaccgtgagctggaacagcggcgcgctgaccagcggcgtg cataccttccggcggtgctgcagagcagcggcctgtatagcc tgagcagcgtggtgaccgtgccgagcagcagcctgggcaccca gacctatatttgcaacgtgaaccataaaccgagcaacaccaaa gtggataaaaaagtggaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Gerilimzumab	Light/ SEQ ID NO: 45	cagagcgcgctgacccagccgccgagcgtgagcggcaccccgg gccagagcgtgaccattagctgcgcgggcgcgaacaacgatat tggcacctatgcgtatgtgagctggtatcagcagctgccgggc accgcgccgaaactgatgatttataaagtgaccacccgcgcga gcggcattccggatcgctttagcggcagcaaaagcggcaacac cgcgagcctgaccattagcggcctgcaggcggaagatgaagcg gattattattgcgcgagctatcgcaactttaacaacgcggtgt ttggcaccggcaccaaactgaccgtgctgggccagccgaaagc

mAb or construct name	Chain/ SEQ ID NO:	Sequences
		ggcgccgagcgtgaccctgtttccgccgagcagcgaagaactg caggcgaacaaagcgaccctggtgtgcctgattagcgattttt atccgggcgcggtgaccgtggcgtggaaagcggatagcagccc ggtgaaagcgggcgtggaaaccaccaccccgagcaaacagagc aacaacaaatatgcggcgagcagctatctgagcctgaccccgg aacagtggaaaagccatcgcagctatagctgccaggtgaccca tgaaggcagcaccgtggaaaaaaccgtggcgccgaccgaatgc agc
Tocilizumab	Heavy/ SEQ ID NO:183	Caggtgcagctgcaggaaagcggcccgggcctggtgcgcccga gccagaccctgagcctgacctgcaccgtgagcggctatagcat taccagcgatcatgcgtggagctgggtgcgccagccgccgggc cgcggcctggaatggattggctatattagctatagcggcatta ccacctataacccgagcctgaaaagccgcgtgaccatgctgcg cgataccagcaaaaaccagtttagcctgcgcctgagcagcgtg accgcggcggataccgcggtgtattattgcgcgcgcagcctgg cgcgcaccaccgcgatggattattggggccagggcagcctggt gaccgtgagcagcgcgagcaccaaaggcccgagcgtgtttccg ctggcgccgagcagcaaaagcaccagcggcggcaccgcggcgc tgggctgcctggtgaaagattattttccggaaccggtgaccgt gagctggaacagcggcgcgctgaccagcggcgtgcatacctttt ccggcggtgctgcagagcagcggcctgtatagcctgagcagcg tggtgaccgtgccgagcagcagcctgggcacccagacctatat ttgcaacgtgaaccataaaccgagcaacaccaaagtggataaa aaagtggaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Tocilizumab	Light/ SEQ ID NO:184	gatattcagatgacccagagcccgagcagcctgagcgcgagcg tgggcgatcgcgtgaccattacctgccgcgcgagccaggatat tagcagctatctgaactggtatcagcagaaaccgggcaaagcg ccgaaactgctgatttattataccagccgcctgcatagcggcg tgccgagccgctttagcggcagcggcagcggcaccgattttac ctttaccattagcagcctgcagccggaagatattgcgacctat tattgccagcagggcaacaccctgccgtatacctttggccagg gcaccaaagtggaaattaaacgcaccgtggcggcgccgagcgt gtttatttttccgccgagcgatgaacagctgaaaagcggcacc gcgagcgtggtgtgcctgctgaacaacttttatccgcgcgaag cgaaagtgcagtggaaagtggataacgcgctgcagagcggcaa cagccaggaaagcgtgaccgaacaggatagcaaagatagcacc tatagcctgagcagcaccctgaccctgagcaaagcggattatg aaaaacataaagtgtatgcgtgcgaagtgacccatcagggcct gagcagcccggtgaccaaaagctttaaccgcggcgaatgc

mAb or construct name	Chain/ SEQ ID NO:	Sequences
pAAV.CAG. Adalimumab. IgG *(5'-ITR to 3--ITR)*	SEQ ID NO: 46	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccg ggcgtcgggcgacctttggtcgcccggcctcagtgagcgagcg agcgcgcagagagggagtggccaactccatcactaggggttcc ttgtagttaatgattaacccgccatgctacttatctaccaggg taatggggatcctctagaactatagctagtcgacattgattat tgactagttattaatagtaatcaattacggggtcattagttca tagcccatatatggagttccgcgttacataacttacggtaaat ggcccgcctggctgaccgcccaacgacccccgcccattgacgt caataatgacgtatgttcccatagtaacgccaatagggactt ccattgacgtcaatgggtggagtatttacggtaaactgcccac ttggcagtacatcaagtgtatcatatgccaagtacgccccta ttgacgtcaatgacggtaaatggcccgcctggcattatgccca gtacatgaccttatgggactttcctacttggcagtacatctac gtattagtcatcgctattaccatggtcgaggtgagccccacgt tctgcttcactctccccatctccccccccctccccacccccaat tttgtatttatttatttttaattattttgtgcagcgatgggg gcgggggggggggggggcgcgcgccaggcggggcggggcggg gcgaggggcggggcggggcgaggcggagaggtgcggcggcagc caatcagagcggcgcgctccgaaagtttccttttatggcgagg cggcggcggcggcggccctataaaaagcgaagcgcgcggcggg cgggagtcgctgcgcgctgccttcgccccgtgccccgctccgc cgccgcctcgcgccgcccgccccggctctgactgaccgcgtta ctcccacaggtgagcgggcgggacggcccttctcctccgggct gtaattagcgcttggtttaatgacggcttgtttcttttctgtg gctgcgtgaaagccttgaggggctccgggagggccctttgtgc ggggggagcggctcgggggggtgcgtgcgtgtgtgtgtgcgtgg ggagcgccgcgtgcggctccgcgctgcccggcggctgtgagcg ctgcgggcgcggcgcggggctttgtgcgctccgcagtgtgcgc gaggggagcgcggccgggggcggtgccccgcggtgcgggggggg gctgcgaggggaacaaaggctgcgtgcggggtgtgtgcgtggg ggggtgagcagggggtgtgggcgcgtcggtcgggctgcaaccc cccctgcaccccccctccccgagttgctgagcacggcccggctt cgggtgcggggctccgtacggggcgtggcgcggggctcgccgt gccgggcgggggggtggcggcaggtgggggtgccgggcggggcg gggccgcctcgggccggggagggctcgggggaggggcgcggcg gcccccggagcgccggcggctgtcgaggcgcggcgagccgcag ccattgcctttttatggtaatcgtgcgagagggcgcagggactt cctttgtcccaaatctgtgcggagccgaaatctgggaggcgcc gccgcacccccctctagcgggcgcggggcgaagcggtgcggcgc cggcaggaaggaaatgggcggggagggccttcgtgcgtcgccg cgccgccgtccccttctccctctccagcctcggggctgtccgc gggggggacggctgccttcgggggggggacggggcagggcggggtt

mAb or construct name	Chain/ SEQ ID NO:	Sequences
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pAAV.CAG. Adalimumab. Fab cassette *(promoter to polyA)*	SEQ ID NO: 50	gacattgattattgactagttattaatagtaatcaattacggg gtcattagttcatagcccatatatggagttccgcgttacataa cttacggtaaatggcccgcctggctgaccgcccaacgacccccc gcccattgacgtcaataatgacgtatgttcccatagtaacgcc aatagggactttccattgacgtcaatgggtggagtatttacgg taaactgcccacttggcagtacatcaagtgtatcatatgccaa gtacgcccccctattgacgtcaatgacggtaaatggcccgcctg gcattatgcccagtacatgaccttatgggactttcctacttgg cagtacatctacgtattagtcatcgctattaccatggtcgagg tgagccccacgttctgcttcactctccccatctccccccccctc cccaccccccaattttgtatttatttatttttttaattattttgt gcagcgatgggggcgggggggggggggggcgcgcgccaggcg gggcggggcggggcgaggggcggggcggggcgaggcggagagg tgcggcggcagccaatcagagcggcgcgctccgaaagtttcct tttatggcgaggcggcggcggcggcggccctataaaaagcgaa gcgcgcggcgggcgggagtcgctgcgcgctgccttcgccccgt gccccgctccgccgccgcctcgcgccgcccgccccggctctga ctgaccgcgttactcccacaggtgagcgggcgggacggcccct ctcctccgggctgtaattagcgcttggtttaatgacggcttgt ttcttttctgtggctgcgtgaaagccttgaggggctccgggag ggccctttgtgcgggggggagcggctcgggggggtgcgtgcgtgt gtgtgtgcgtggggagcgccgcgtgcggctccgcgctgcccgg cggctgtgagcgctgcgggcgcggcgcggggctttgtgcgctc cgcagtgtgcgcgaggggagcgcggccgggggcggtgccccgc ggtgcgggggggggctgcgaggggaacaaaggctgcgtgcgggg tgtgtgcgtgggggggtgagcagggggtgtgggcgcgtcggtc gggctgcaaccccccctgcaccccccctccccgagttgctgagc acggcccggcttcgggtgcggggctccgtacggggcgtggcgc ggggctcgccgtgccgggcgggggggtggcggcaggtgggggtg ccgggcgggggcgggggccgcctcgggccgggggagggctcgggggg aggggcgcggcggcccccggagcgccggcggctgtcgaggcgc ggcgagccgcagccattgccttttatggtaatcgtgcgagagg gcgcagggacttcctttgtcccaaatctgtgcggagccgaaat ctgggaggcgccgccgcacccccctctagcgggcgcggggcgaa gcggtgcggcgccggcaggaaggaaatgggcggggagggcctt cgtgcgtcgccgcgccgccgtcccccttctccctctccagcctc

mAb or construct name	Chain/ SEQ ID NO:	Sequences
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mAb or construct name	Chain/ SEQ ID NO:	Sequences
		cttctggctaataaaggaaatttattttcattgcaatagtgtg ttggaatttttgtgtctctcactcg
Adalimumab Fab single chain construct transgene (HC-Furin-linker-T2A-LC)	SEQ ID NO: 51	ATGTACAGAATGCAGCTGCTGCTGCTCATTGCCCTGTCTCTGG CCCTGGTCACCAATTCTGAAGTGCAGCTGGTGGAAAGTGGTGG TGGACTGGTGCAGCCTGGCAGAAGCCTGAGACTGTCTTGTGCT GCCTCTGGCTTCACCTTTGATGACTATGCCATGCACTGGGTCA GACAGGCCCCTGGCAAAGGACTGGAATGGGTGTCAGCCATCAC CTGGAACTCTGGCCACATTGACTATGCTGACTCTGTGGAAGGC AGATTCACCATCAGCAGAGACAATGCCAAGAACAGCCTGTACC TGCAGATGAACTCCCTGAGAGCTGAGGACACAGCAGTGTACTA CTGTGCCAAGGTGTCCTACCTGAGCACAGCCAGCAGCCTGGAT TATTGGGGCCAGGGCACACTGGTTACAGTGTCCTCTGCCAGCA CAAAGGGCCCCTCTGTTTTTCCACTGGCTCCCAGCAGCAAGAG CACCAGTGGTGGAACAGCTGCCCTGGGCTGTCTGGTCAAGGAT TACTTCCCTGAGCCTGTGACAGTGTCTTGGAACTCAGGGGCTC TGACCTCTGGGGTGCACACATTTCCAGCTGTGCTGCAGTCCTC TGGCCTGTACTCTCTGTCCTCTGTGGTCACAGTGCCTAGCTCT AGCCTGGGCACCCAGACCTACATCTGCAATGTGAACCACAAGC CTAGCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGAGCTG TGACAAGACCCACAGAAAGAGAAGAGGCTCTGGAGAAGGCAGA GGCTCCCTGCTGACATGTGGGGATGTTGAAGAGAATCCTGGGC CTATGTATAGGATGCAACTGCTCCTCCTGATTGCTCTGAGCCT GGCTCTTGTGACCAACTCTGACATCCAGATGACACAGAGCCCT AGCAGCCTGTCTGCTTCTGTGGGAGACAGAGTGACCATCACAT GCAGAGCCAGCCAGGGCATCAGAAACTACCTGGCCTGGTATCA GCAGAAGCCAGGCAAGGCCCCTAAGCTGCTGATCTATGCAGCC AGCACACTGCAGAGTGGGGTGCCAAGCAGATTTTCAGGCTCTG GCTCTGGCACAGACTTCACCCTGACCATTTCTAGCCTGCAGCC TGAGGATGTGGCCACCTACTACTGCCAGAGATACAACAGAGCC CCATACACCTTTGGACAGGGCACAAAGGTGGAAATCAAGAGAA CAgttgcagcaccctcagttttcatcttccccccctcagatga acagCTGAAGTCTGGCACTGCCTCTGTTGTGTGCCTGCTGAAC AACTTCTACCCCAGAGAAGCCAAGGTGCAGTGGAAGGTTGACA ATGCCCTGCAGTCAGGCAACAGCCAAGAATCTGTGACTGAACA GGATTCCAAGGATAGCACCTACAGCCTGAGCAGCACCCTGACA CTGAGCAAGGCTGACTATGAGAAGCACAAAGTGTATGCCTGTG AAGTGACCCACCAGGGACTGAGCAGCCCAGTGACCAAGAGCTT CAACAGGGGAGAGTGCTGA
pAAV.GRK1. Vh4i. Adalimumab.	SEQ ID NO: 52	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccg ggcgtcgggcgacctttggtcgcccggcctcagtgagcgagcg agcgcgcagagagggagtggccaactccatcactaggggttcc ttgtagttaatgattaacccgccatgctacttatctaccaggg

mAb or construct name	Chain/ SEQ ID NO:	Sequences
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mAb or construct name	Chain/ SEQ ID NO:	Sequences
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pAAV.GRK1. Vh4i. Adalimumab. IgG *(promoter to polyA)*	SEQ ID NO: 53	GGGCCCCAGAAGCCTGGTGGTTGTTTGTCCTTCTCAGGGGAAA AGTGAGGCGGCCCCTTGGAGGAAGGGGCCGGGCAGAATGATCT AATCGGATTCCAAGCAGCTCAGGGGATTGTCTTTTTCTAGCAC CTTCTTGCCACTCCTAAGCGTCCTCCGTGACCCCGGCTGGGAT TTAGCCTGGTGCTGTGTCAGCCCCGGGCTCCCAGGGGCTTCCC AGTGGTCCCCAGGAACCCTCGACAGGGCCAGGGCGTCTCTCTC GTCCAGCAAGGGCAGGGACGGGCCACAGGCCAAGGGCCAGGTG AGTATCTCAGGGATCCAGACATGGGGATATGGGAGGTGCCTCT GATCCCAGGGCTCACTGTGGGTCTCTCTGTTCACAGGTTGAAT TCGCCACCATGTACAGAATGCAGCTGCTGCTGCTCATTGCCCT GTCTCTGGCCCTGGTCACCAATTCTGAAGTGCAGCTGGTGGAA AGTGGTGGTGGACTGGTGCAGCCTGGCAGAAGCCTGAGACTGT CTTGTGCTGCCTCTGGCTTCACCTTTGATGACTATGCCATGCA CTGGGTCAGACAGGCCCCTGGCAAAGGACTGGAATGGGTGTCA

mAb or construct name	Chain/ SEQ ID NO:	Sequences
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mAb or construct name	Chain/ SEQ ID NO:	Sequences
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mAb or construct name	Chain/ SEQ ID NO:	Sequences
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pAAV.sc.EF1ac.Vh4i.Adalimumab.Fab *(promoter to polyA)*	SEQ ID NO:223	GGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGG AGGGGTCGGCAATTGAACGGGTGCCTAGAGAAGGTGGCGCGGG GTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTC CCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGT GAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACACAGCAG GTGAGTATCTCAGGGATCCAGACATGGGGATATGGGAGGTGCC TCTGATCCCAGGGCTCACTGTGGGTCTCTCTGTTCACAGGTTa ccggtGCCACCATGTACAGAATGCAGCTGCTGCTGCTCATTGC CCTGTCTCTGGCCCTGGTCACCAATTCTGAAGTGCAGCTGGTG GAAAGTGGTGGTGGACTGGTGCAGCCTGGCAGAAGCCTGAGAC TGTCTTGTGCTGCCTCTGGCTTCACCTTTGATGACTATGCCAT GCACTGGGTCAGACAGGCCCCTGGCAAAGGACTGGAATGGGTG TCAGCCATCACCTGGAACTCTGGCCACATTGACTATGCTGACT CTGTGGAAGGCAGATTCACCATCAGCAGAGACAATGCCAAGAA CAGCCTGTACCTGCAGATGAACTCCCTGAGAGCTGAGGACACA GCAGTGTACTACTGTGCCAAGGTGTCCTACCTGAGCACAGCCA GCAGCCTGGATTATTGGGGCCAGGGCACACTGGTTACAGTGTC CTCTGCCAGCACAAAGGGCCCCTCTGTTTTTCCACTGGCTCCC AGCAGCAAGAGCACCAGTGGTGGAACAGCTGCCCTGGGCTGTC TGGTCAAGGATTACTTCCCTGAGCCTGTGACAGTGTCTTGGAA CTCAGGGGCTCTGACCTCTGGGGTGCACACATTTCCAGCTGTG CTGCAGTCCTCTGGCCTGTACTCTCTGTCCTCTGTGGTCACAG

mAb or construct name	Chain/ SEQ ID NO:	Sequences
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mAb or construct name	Chain/ SEQ ID NO:	Sequences
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mAb or construct name	Chain/ SEQ ID NO:	Sequences
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mAb or construct name	Chain/ SEQ ID NO:	Sequences
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mAb or construct name	Chain/ SEQ ID NO:	Sequences
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mAb or construct name	Chain/ SEQ ID NO:	Sequences
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IgG1 CH1	SEQ ID NO: 56	gccagcacaaagggcccctctgttttccactggctcccagca gcaagagcaccagtggtggaacagctgccctgggctgtctggt caaggattacttccctgagcctgtgacagtgtcttggaactca ggggctctgacctctggggtgcacacatttccagctgtgctgc agtcctctggcctgtactctctgtcctctgtggtcacagtgcc tagctctagcctgggcacccagacctacatctgcaatgtgaac cacaagcctagcaacaccaaggtggacaagaaggtg
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mAb or construct name	Chain/ SEQ ID NO:	Sequences
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Adalimumab Light chain C-Domain (CL)	SEQ ID NO: 60	agaacagttgcagcaccctcagttttcatcttcccccccctcag atgaacagctgaagtctggcactgcctctgttgtgtgcctgct gaacaacttctaccccagagaagccaaggtgcagtggaaggtt gacaatgccctgcagtcaggcaacagccaagaatctgtgactg

mAb or construct name	Chain/ SEQ ID NO:	Sequences
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Gene Therapy Methods

[0176] Provided are methods of treating human subjects for non-infectious uveitis by administration of a viral vector containing a transgene encoding an anti-TNFα antibody, or antigen binding fragment thereof. The antibody may be adalimumab, infliximab, or golimumab and is, e.g., a full length or substantially full length antibody or Fab fragment thereof, or other antigen-binding fragment thereof.

[0177] 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 5.1 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 AAV8, AAV3B or AAVrh73 capsid. The recombinant vectors, such as shown in **FIGS. 2A-2C**, can be administered in any manner such that the recombinant vector enters one or more ocular tissue cells. In particular embodiments, the transgene is CAG.Adalimumab.T2A.IgG (SEQ ID NO: 48); CAG.Adalimumab.Fab (SEQ ID NO: 51); GRK1.Vh4i.Adalimumab.IgG (SEQ ID NO: 53), mU1a.Vh4i.Adalimumab.Fab (SEQ ID NO:224), EF1a.Vh4i.Adalimumab.Fab (SEQ ID NO:222), CB.VH4.adalimumab (SEQ ID NO: 276), CBlong.VH4.adalimumab or Best1.GRK1.VH4i.adalimumab in an AAV8 vector.

[0178] 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 Antibodies

[0179] The production of the anti-TNFα HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of angioedema accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-TNFα HuPTM Fab, subretinally, intravitreally, intracamerally, suprachoroidally, or intravenously to human subjects (patients) diagnosed with or having one or more symptoms of non-infectious uveitis, to create a permanent depot in the eye (and/or liver and/or muscle) that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced ocular tissue cells.

[0180] In specific embodiments, the anti-TNFα HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab portions of adalimumab as set forth in FIG. 2A (with glutamine (Q) glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N54, Q113, and/or N163 of the heavy chain (SEQ ID NO: 1) or Q100, N158, and/or N210 of the light chain (SEQ ID NO: 2). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of adalimumab has a sulfation group at Y32, Y94 and/or Y95 of the heavy chain (SEQ ID NO: 1) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 2). In other embodiments, the anti-TNFα HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0181] In specific embodiments, the anti-TNFα HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab

portions of infliximab as set forth in FIG. 2B (with glutamine (Q) glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N57, N101, Q112 and/or N162 of the heavy chain (SEQ ID NO: 3) or N41, N76, N158 and/or N210 of the light chain (SEQ ID NO: 4). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of infliximab has a sulfation group at Y96 and/or Y97 of the heavy chain (SEQ ID NO: 3) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 4). In other embodiments, the anti-TNFα HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0182] In specific embodiments, the anti-TNFα HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab portions of golimumab as set forth in FIG. 2C (with glutamine (Q) glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N80, Q121, and/or N171 of the heavy chain (SEQ ID NO: 5) or N162 and/or N214 of the light chain (SEQ ID NO: 6). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of golimumab has a sulfation group at Y112, Y113 and/or Y114 of the heavy chain (SEQ ID NO: 5) and/or Y89 and/or Y90 of the light chain (SEQ ID NO: 6). In other embodiments, the anti-TNFα HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0183] In certain embodiments, the HuPTM mAb or Fab 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.

[0184] Combinations of delivery of the anti-TNFα HuPTM mAb or antigen-binding fragment thereof, to the eye, liver and/or muscles 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 adalimumab, infliximab, or golimumab.

5.4.2. Dose Administration of anti-TNFα Antibodies

[0185] Section 5.2. and 5.4.1 describe recombinant vectors that contain a transgene encoding a HuPTM mAb or HuPTM Fab (or other antigen binding fragment of the HuPTM mAb) that binds to TNFα. 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, intracameral, suprachoroidal administration should result in expression of the soluble transgene product in cells of the eye. The expression of the transgene encoding an anti-TNFα antibody creates a permanent depot in one or more ocular tissue cells of the patient that continuously supplies the anti-TNFα HuPTM mAb, or antigen binding fragment of the anti- TNFα mAb to ocular tissues of the subject.

[0186] In specific embodiments, doses that maintain a plasma concentration of the anti-TNFα antibody transgene product at a C_{min} of at least .5 μg/mL or at least 1 μg/mL (e.g., C_{min} of 1 to 10 μg/ml, 3 to 30 μg/ml or 5 to 15 μg/mL or 5 to 30 μg/mL) are provided.

[0187] In specific embodiments, doses that maintain a plasma concentration of the adalimumab antibody, or antigen-binding fragment thereof, at a C_{min} of at least 5 μg/mL (e.g., C_{min} of 5 to 10 μg/ml or 10 to 20 μg/ml), preferably a C_{min} of about 8 μg/mL to 9 μg/mL are provided.

[0188] In specific embodiments, doses that maintain a plasma concentration of the infliximab antibody, or antigen-binding fragment thereof, at a Cmin of at least 2 μg/mL (e.g., C_{min} of 2 to 10 μg/ml or 10 to 20 μg/ml), preferably at a C_{min} of about 5 μg/mL to 6 μg/mL, are provided.

[0189] However, in all cases because the transgene product is continuously produced, maintenance of lower concentrations can be effective. Notwithstanding, because the transgene product is continuously produced, maintenance of lower concentrations can be effective. The concentration of the transgene product can be measured in patient blood serum samples.

[0190] Pharmaceutical compositions suitable for intravenous, intramuscular, subcutaneous or hepatic administration comprise a suspension of the recombinant vector comprising the transgene encoding the anti-TNFα antibody, or antigen-binding fragment thereof, 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.

5.5 Anti-IL6 and anti-IL6R HuPTM Constructs and Formulations for Non-Infectious Uveitis

[0191] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to interleukin-6 receptor (IL6R) or interleukin-6 (IL6) derived from an anti-IL6R or anti-IL6 antibody, such as satralizumab**,** sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, or gerilizumab (**FIGS. 3A-3H**), indicated for treating non-infectious uveitis. In certain embodiments, the HuPTM mAb has the amino acid sequence of satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, or gerilizumab, or an antigen binding fragment thereof. Amino acid sequences of Fab fragments of the antibody are provided in **FIGS. 3A-3H**. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an IL6R-binding or IL6-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with one or more symptoms of non-infectious uveitis, or alternatively in need of treating, inhibiting or ameliorating a

detrimental immune response to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0192] Provided are recombinant vectors containing a transgene encoding a HuPTM mAb or HuPTM Fab (or other antigen binding fragment of the HuPTM mAb) that binds to IL6R or IL6 that can be administered to deliver the HuPTM mAb or antigen binding fragment in a patient. The transgene is a nucleic acid comprising the nucleotide sequences encoding an antigen binding fragment of an antibody that binds to IL6R or IL6, such as satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, or gerilizumab, or variants thereof as detailed herein. The transgene may also encode an anti-IL6R or IL6 antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0193] In certain embodiments, the anti-IL6R antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of satralizumab (having amino acid sequences of SEQ ID NOs. 7 and 8, respectively, see **Table 7** and **FIG. 3A**). 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: 32 (encoding the satralizumab heavy chain Fab portion) and SEQ ID NO: 33 (encoding the satralizumab light chain Fab portion) as set forth in **Table 8**. The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0194] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-IL6R-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 7 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence

ERKSCVECPPCPAPPVAG (SEQ ID NO:163) or ERKSCVECPPCPA (SEQ ID NO:164) as set forth in **FIG. 3A**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 32 by the hinge region encoding sequences set forth in **Table 6** (SEQ ID NO: 32). In another embodiment, the transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g., having an amino acid sequence of SEQ ID NO: 67 (**Table 6**) or an IgG2 Fc domain, such as SEQ ID No. 62 or as depicted in **FIG. 6**, 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 5.1.9, infra.

[0195] In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an IL6R antigen-binding fragment comprising a light chain 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: 8. In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an IL6R antigen-binding fragment comprising a heavy chain 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: 7. In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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: 8 and a heavy chain 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: 7. In specific embodiments, the IL6R antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 7 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 (*e.g.,* those regions outside of the CDRs, which CDRs are underlined in **FIG. 3A**) or are substitutions with an amino acid present at that position in the heavy chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in **FIG. 9A**. In specific embodiments, the IL6R antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 8 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 (*e.g.,* those regions outside of the CDRs, which CDRs are underlined in **FIG. 3A**) or are substitutions with an amino acid present at that position in the light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in **FIG. 9B**.

[0196] In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes a hyperglycosylated satralizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 7 and 8, respectively, with one or more of the following mutations: L114N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 9A (heavy chain) and 9B (light chain)).

[0197] In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six satralizumab CDRs which are underlined in the heavy and light chain variable domain sequences of **FIG. 3A** which are spaced between framework regions, generally human framework regions, and associated with constant domains depending upon the form of the antigen-binding molecule, as is known in the art to form the heavy and/or light chain variable domain of an anti-IL6R antibody or antigen-binding fragment thereof.

[0198] In certain embodiments, the anti-IL6R antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of sarilumab (having amino acid sequences of SEQ ID NOs. 9 and 10, respectively, see **Table 7** and **FIG. 3B**). 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: 34 (encoding the sarilumab heavy chain Fab portion) and SEQ ID NO: 35 (encoding the sarilumab light chain Fab portion) as set forth in **Table 8**. The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0199] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-IL6R-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 9 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:153), and specifically, EPKSCDKTHL (SEQ ID NO:155), EPKSCDKTHT (SEQ ID NO:156), EPKSCDKTHTCPPCPA (SEQ ID NO:157), EPKSCDKTHLCPPCPA (SEQ ID NO:158), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:159) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:160) as set forth in **FIG. 3B**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 34 by the hinge region encoding sequences set forth in **Table 8** (SEQ ID NO: 34). In another embodiment, the transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g. having an amino acid sequence of SEQ ID NO:185 (**Table 6**) or an IgG1 Fc domain, such as SEQ ID No. 61 or as depicted in **FIG. 6**, 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 5.1.9, infra.

[0200] In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an IL6R antigen-binding fragment comprising a light chain 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. In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an IL6R antigen-binding fragment comprising a heavy chain 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: 9. In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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 and a heavy chain 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: 9. In specific embodiments, the IL6R antigen binding fragment comprises a heavy chain

comprising an amino acid sequence of SEQ ID NO: 9 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in **FIG. 3B**) or are substitutions with an amino acid present at that position in the heavy chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in **FIG. 9A**. In specific embodiments, the IL6R antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 10 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in **FIG. 3B**) or are substitutions with an amino acid present at that position in the light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in **FIG. 9B**.

[0201] In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes a hyperglycosylated sarilumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 9 and 10, respectively, with one or more of the following mutations: M111N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 9A (heavy chain) and 9B (light chain)).

[0202] In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six sarilumab CDRs which are underlined in the heavy and light chain variable domain sequences of **FIG. 3B** which are spaced between framework regions, generally human framework regions, and associated with constant domains depending upon the form of the antigen-binding molecule, as is known in the art to form the heavy and/or light chain variable domain of an anti-IL6R antibody or antigen-binding fragment thereof.

[0203] In certain embodiments, the anti-IL6R antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of tocilizumab (having amino acid sequences of SEQ ID NOs. 21 and 22, respectively, see **Table 7** and **FIG. 3H**). 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:183 (encoding the tocilizumab heavy chain Fab portion) and SEQ ID NO:184 (encoding the tocilizumab light chain Fab portion) as

set forth in **Table 8**. The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0204] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-IL6R-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 21 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:153), and specifically, EPKSCDKTHL (SEQ ID NO:155), EPKSCDKTHT (SEQ ID NO:156), EPKSCDKTHTCPPCPA (SEQ ID NO:157), EPKSCDKTHLCPPCPA (SEQ ID NO:158), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:159) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:160) as set forth in **FIG. 3H**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO:183 by the hinge region encoding sequences set forth in **Table 8** (SEQ ID NO:183). In another embodiment, the transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g., having an amino acid sequence of SEQ ID NO: 72 (**Table 6**) or an IgG1 Fc domain, such as SEQ ID No. 61 or as depicted in FIG. 6, 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 5.1.9, infra.

[0205] In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an IL6R antigen-binding fragment comprising a light chain 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: 22. In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an IL6R antigen-binding fragment comprising a heavy chain 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: 21. In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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: 22 and a heavy chain 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: 21. In specific embodiments, the IL6R antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 21 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 3H) or are substitutions with an amino acid present at that position in the heavy chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9A. In specific embodiments, the IL6R antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 22 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 3H) or are substitutions with an amino acid present at that position in the light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9B.

[0206] In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes a hyperglycosylated tocilizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 21 and 22, respectively, with one or more of the following mutations: L115N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 9A (heavy chain) and 9B (light chain)).

[0207] In certain embodiments, the anti-IL6R antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six tocilizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 3H which are spaced between framework regions, generally human framework regions, and associated with constant domains depending upon the form of the antigen-binding molecule, as is known in the art to form the

heavy and/or light chain variable domain of an anti-IL6R antibody or antigen-binding fragment thereof.

[0208] In certain embodiments, the anti-IL6 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of siltuximab (having amino acid sequences of SEQ ID NOs. 11 and 12, respectively, see **Table 7** and **FIG. 3C**). 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: 36 (encoding the siltuximab heavy chain Fab portion) and SEQ ID NO: 37 (encoding the siltuximab light chain Fab portion) as set forth in **Table 8.** The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0209] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-IL6-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 11 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:153), and specifically, EPKSCDKTHL (SEQ ID NO:155), EPKSCDKTHT (SEQ ID NO:156), EPKSCDKTHTCPPCPA (SEQ ID NO:157), EPKSCDKTHLCPPCPA (SEQ ID NO:158), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:159) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:160) as set forth in **FIG. 3C**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 36 by the hinge region encoding sequences set forth in **Table 8** (SEQ ID NO: 36). In another embodiment, the transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g. having an amino acid sequence of SEQ ID NO: 68 (**Table 6**) or an IgG1 Fc domain, such as SEQ

ID No. 61 or as depicted in **FIG. 6**, 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 5.1.9, infra.

[0210] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an IL6 antigen-binding fragment comprising a light chain 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 certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an IL6 antigen-binding fragment comprising a heavy chain 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: 11. In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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 and a heavy chain 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: 11. In specific embodiments, the IL6 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 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, e.g., in the framework regions (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 3C) or are substitutions with an amino acid present at that position in the heavy chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9A. In specific embodiments, the IL6 antigen binding fragment comprises a light chain comprising 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 3C) or are substitutions with an amino acid present at that position in the light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9B.

[0211] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes a hyperglycosylated siltuximab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 11 and 12, respectively, with one or more of the following mutations: S114N (heavy chain), Q159N or Q159S (light chain), and/or E194N (light chain) (see FIGS. 9A (heavy chain) and 9B (light chain)).

[0212] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six siltuximab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 3C which are spaced between framework regions, generally human framework regions, and associated with constant domains depending upon the form of the antigen-binding molecule, as is known in the art to form the heavy and/or light chain variable domain of an anti-IL6 antibody or antigen-binding fragment thereof.

[0213] In certain embodiments, the anti-IL6 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of clazakizumab (having amino acid sequences of SEQ ID NOs. 13 and 14, respectively, see **Table 7** and **FIG. 3D**). 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: 38 (encoding the clazakizumab heavy chain Fab portion) and SEQ ID NO: 39 (encoding the clazakizumab light chain Fab portion) as set forth in **Table 8**. The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0214] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-IL6-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 13 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:153), and specifically, EPKSCDKTHL (SEQ ID

NO:155), EPKSCDKTHT (SEQ ID NO:156), EPKSCDKTHTCPPCPA (SEQ ID NO:157), EPKSCDKTHLCPPCPA (SEQ ID NO:158), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:159) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:160) as set forth in **FIG. 3D**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 38 by the hinge region encoding sequences set forth in **Table 8** (SEQ ID NO: 38). In another embodiment, the transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g. having an amino acid sequence of SEQ ID NO: 69 (**Table 6**) or an IgG1 Fc domain, such as SEQ ID No. 61 or as depicted in **FIG. 6**, 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 5.1.9, infra.

[0215] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an IL6 antigen-binding fragment comprising a light chain 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: 14. In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an IL6 antigen-binding fragment comprising a heavy chain 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: 13. In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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: 14 and a heavy chain 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: 13. In specific embodiments, the IL6 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 13 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 3D) or are substitutions with an amino acid present at that position in the heavy chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9A. In specific embodiments, the IL6 antigen binding fragment comprises a light

chain comprising an amino acid sequence of SEQ ID NO: 14 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 3D) or are substitutions with an amino acid present at that position in the light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9B.

[0216] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes a hyperglycosylated clazakizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 13 and 14, respectively, with one or more of the following mutations: L115N (heavy chain), Q163N or Q163S (light chain), and/or E198N (light chain) (see FIGS. 9A (heavy chain) and 9B (light chain)).

[0217] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six clazakizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 3D which are spaced between framework regions, generally human framework regions, and associated with constant domains depending upon the form of the antigen-binding molecule, as is known in the art to form the heavy and/or light chain variable domain of an anti-IL6 antibody or antigen-binding fragment thereof.

[0218] In certain embodiments, the anti-IL6 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of sirukumab (having amino acid sequences of SEQ ID NOs. 15 and 16, respectively, see **Table 7** and **FIG. 3E**). 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: 40 (encoding the sirukumab heavy chain Fab portion) and SEQ ID NO: 41 (encoding the sirukumab light chain Fab portion) as set forth in **Table 8**. The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0219] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-IL6-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 15 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:153), and specifically, EPKSCDKTHL (SEQ ID NO:155), EPKSCDKTHT (SEQ ID NO:156), EPKSCDKTHTCPPCPA (SEQ ID NO:157), EPKSCDKTHLCPPCPA (SEQ ID NO:158), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:159) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:160) as set forth in **FIG. 3E**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 40 by the hinge region encoding sequences set forth in **Table 8** (SEQ ID NO: 40). In another embodiment, the transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g. having an amino acid sequence of SEQ ID NO: 70 (**Table 6**) or an IgG1 Fc domain, such as SEQ ID No. 61 or as depicted in FIG. 6, 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 5.1.9, infra.

[0220] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an IL6 antigen-binding fragment comprising a light chain 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: 16. In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an IL6 antigen-binding fragment comprising a heavy chain 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: 15. In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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: 16

and a heavy chain 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: 15. In specific embodiments, the IL6 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 15 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 (*e.g.,* those regions outside of the CDRs, which CDRs are underlined in FIG. 3E) or are substitutions with an amino acid present at that position in the heavy chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9A. In specific embodiments, the IL6 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 16 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 (*e.g.,* those regions outside of the CDRs, which CDRs are underlined in FIG. 3E) or are substitutions with an amino acid present at that position in the light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9B.

[0221] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes a hyperglycosylated sirukumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 15 and 16, respectively, with one or more of the following mutations: T114N (heavy chain), Q159N or Q159S (light chain), and/or E194N (light chain) (see FIGS. 9A (heavy chain) and 9B (light chain)).

[0222] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six sirukumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 3E which are spaced between framework regions, generally human framework regions, and associated with constant domains depending upon the form of the antigen-binding molecule, as is known in the art to form the heavy and/or light chain variable domain of an anti-IL6 antibody or antigen-binding fragment thereof.

[0223] In certain embodiments, the anti-IL6 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of olokizumab (having amino acid sequences of SEQ ID NOs. 17 and 18, respectively, see **Table 7** and **FIG. 3F**). 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: 42 (encoding the olokizumab heavy chain Fab portion) and SEQ ID NO: 43 (encoding the olokizumab light chain Fab portion) as set forth in **Table 8**. The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0224] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-IL6-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 17 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence ESKYGPPCPPCPAPEFLGG (SEQ ID NO:165), and specifically, ESKYGPPCPPCPA (SEQ ID NO:166), ESKYGPPCPSCPA (SEQ ID NO:167), ESKYGPPCPSCPAPEFLGGPSVFL (SEQ ID NO:168), or ESKYGPPCPPCPAPEFLGGPSVFL (SEQ ID NO:169) as set forth in **FIG 4F**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 42 by the hinge region encoding sequences set forth in **Table 8** (SEQ ID NO: 42). In another embodiment, the transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g. having an amino acid sequence of SEQ ID NO: 71 (**Table 6**) or an IgG4 Fc domain, such as SEQ ID No. 63 or as depicted in FIG. 6, 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 5.1.9, infra.

[0225] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an IL6 antigen-binding fragment comprising a light chain 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: 18. In certain embodiments, the anti-IL6 antigen-binding

fragment transgene encodes an IL6 antigen-binding fragment comprising a heavy chain 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: 17. In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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: 18 and a heavy chain 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: 17. In specific embodiments, the IL6 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 17 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 3F) or are substitutions with an amino acid present at that position in the heavy chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9A. In specific embodiments, the IL6 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 18 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 (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 3F) or are substitutions with an amino acid present at that position in the light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9B.

[0226] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes a hyperglycosylated olokizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 17 and 18, respectively, with one or more of the following mutations: L115N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 9A (heavy chain) and 9B (light chain)).

[0227] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six olokizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 3F which are spaced between framework regions, generally human framework regions, and associated with constant

domains depending upon the form of the antigen-binding molecule, as is known in the art to form the heavy and/or light chain variable domain of an anti-IL6 antibody or antigen-binding fragment thereof.

[0228] In certain embodiments, the anti-IL6 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of gerilizumab (having amino acid sequences of SEQ ID NOs. 19 and 20, respectively, see **Table** 7 and FIG. 2G). 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: 44(encoding the gerilizumab heavy chain Fab portion) and SEQ ID NO: 45 (encoding the gerilizumab light chain Fab portion) as set forth in **Table 8**. The heavy and light chain sequences both have a signal or leader sequence at the N-terminus appropriate for expression and secretion in human cells, in particular, human ocular tissue cells (e.g., retinal cells) or liver and/or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). 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 ocular tissue cell types. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in **Tables 3** and **4** *infra*.

[0229] In addition to the heavy and light chain variable domain and C_H1 and C_L domain sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-IL6-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 19 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO:153), and specifically, EPKSCDKTHL (SEQ ID NO: 160), EPKSCDKTHT (SEQ ID NO:156), EPKSCDKTHTCPPCPA (SEQ ID NO:157), EPKSCDKTHLCPPCPA (SEQ ID NO:158), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO:159) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO:160) as set forth in **FIG. 3G**. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 44 by the hinge region encoding sequences set forth in **Table 8** (SEQ ID NO: 44). In another embodiment, the transgenes comprise the amino acid sequences encoding the full length (or substantially full length) heavy and light chains of the antibody, comprising the Fc domain at the C terminus of the heavy chain, e.g. having an IgG1 Fc domain, such as SEQ ID No. 72 (**Table 6**) or 61 (depicted in FIG. 6), 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 5.1.9, infra.

[0230] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an IL6 antigen-binding fragment comprising a light chain 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: 20. In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an IL6 antigen-binding fragment comprising a heavy chain 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: 19. In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment comprising a light chain 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: 20 and a heavy chain 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: 19. In specific embodiments, the IL6 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 19 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 (*e.g.,* those regions outside of the CDRs, which CDRs are underlined in FIG. 3G) or are substitutions with an amino acid present at that position in the heavy chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9. In specific embodiments, the IL6 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 20 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 (*e.g.,* those regions outside of the CDRs, which CDRs are underlined in FIG. 3G) or are substitutions with an amino acid present at that position in the light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 9B.

[0231] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes a hyperglycosylated gerilizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 19

and 20, respectively, with one or more of the following mutations: M117N (heavy chain), and/or Q198N (light chain) (see FIGS. 9A (heavy chain) and 9B (light chain)).

[0232] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six gerilizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 3G which are spaced between framework regions, generally human framework regions, and associated with constant domains depending upon the form of the antigen-binding molecule, as is known in the art to form the heavy and/or light chain variable domain of an anti-IL6 antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0233] Provided are methods of treating human subjects for non-infectious uveitis by administration of a viral vector containing a transgene encoding an anti-IL6R or anti-IL6 antibody, or antigen binding fragment thereof. The antibody may be satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, or gerilizumab, and is, e.g., a full length, substantially full length or Fab fragment thereof, or other antigen-binding fragment thereof.

[0234] 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 5.1 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 AAV8, AAV3B or AAVrh73 capsid. The recombinant vectors, such as shown in **FIGS. 3A-3H**, can be administered in any manner such that the recombinant vector enters one or more ocular tissue cells, e.g., by introducing the recombinant vector into the eye, for example by subretinal, intravitreal, intracameral, or suprachoroidal administration, or into the bloodstream, for example by intravenous or intramuscular administration. See below for details regarding the methods of treatment.

Subjects to whom such gene therapy is administered can be those responsive to anti-IL6R or anti-IL6 therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with one or more ocular disorders, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-IL6R or anti-IL6 antibody or considered a good candidate for therapy with an anti-IL6 or anti-IL6 antibody. In specific embodiments, the patients have previously

been treated with satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, or gerilizumab, and have been found to be responsive to satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, or gerilizumab. In other embodiments, the patients have been previously treated with an anti-IL6R or anti-IL6 antibody. To determine responsiveness, the anti-IL6R or anti-IL6 antibody or antigen-binding fragment transgene product (e.g., produced in cell culture, bioreactors, etc.) may be administered directly to the subject.

Human Post Translationally Modified Antibodies

[0235] The production of anti-IL6R or anti-IL6 HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of angioedema accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-IL6 or anti-IL6R HuPTM Fab, subretinally, intravitreally, intracamerally, suprachoroidally, or intravenously to human subjects (patients) diagnosed with or having one or more symptoms of non-infectious uveitis, to create a permanent depot in the eye (and/or liver and/or muscle) that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced ocular tissue cells.

[0236] In specific embodiments, the anti-IL6R HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab portions of satralizumab as set forth in FIG. 3A (with glutamine (Q) glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N77, N161, N194, and/or N203 of the heavy chain (SEQ ID NO: 7) or Q100, N158, and/or N210 of the light chain (SEQ ID NO: 8). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of satralizumab has a sulfation group at Y94, Y95, and/or Y200 of the heavy chain (SEQ ID NO: 7) and/or Y49, Y50, Y86, and/or Y87 of the light chain (SEQ ID NO: 8). In other embodiments, the anti-IL6R HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0237] In specific embodiments, the anti-IL6R HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab portions of sarilumab as set forth in FIG. 3B (with glutamine (Q) glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N54, Q108, and/or N158 of the heavy chain (SEQ ID NO: 9) or Q100, N158, and/or N210 of the light chain (SEQ ID NO: 10). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of sarilumab has a sulfation group at Y32, Y94, and/or Y95 of the heavy chain (SEQ ID NO: 9) and/or Y86, Y87, and/or Y192 of the light chain (SEQ ID NO: 10). In other embodiments, the anti-IL6R HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0238] In specific embodiments, the anti-IL6R HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab portions of tocilizumab as set forth in FIG. 3H (with glutamine (Q) glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N61, N77, and/or N161 of the heavy chain (SEQ ID NO: 21) or Q100, N158, and/or N210 of the light chain (SEQ ID NO: 22). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of satralizumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 21) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 22). In other embodiments, the anti-IL6R HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0239] In specific embodiments, the anti-IL6 HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab portions of siltuximab as set forth in FIG. 3C (with glutamine (Q) glycosylation sites; asparaginal (N)

glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions Q111 and/or N161 of the heavy chain (SEQ ID NO: 11) or N60, N157, and/or N209 of the light chain (SEQ ID NO: 12). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of siltuximab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 11) and/or Y85 and/or Y86 of the light chain (SEQ ID NO: 12). In other embodiments, the anti-IL6 HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0240] In specific embodiments, the anti-IL6 HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab portions of clazakizumab as set forth in FIG. 3D (with glutamine (Q) glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N76, Q112, and/or N162 of the heavy chain (SEQ ID NO: 13) or N30, N161, and/or N213 of the light chain (SEQ ID NO: 14). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of clazakizumab has a sulfation group at Y93 and/or Y94 of the heavy chain (SEQ ID NO: 13) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 14). In other embodiments, the anti-IL6 HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0241] In specific embodiments, the anti-IL6 HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab portions of sirukumab as set forth in FIG. 3E (with glutamine (Q) glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions Q111 and/or N161 of the heavy chain (SEQ ID NO: 15) or N157 and/or N209

of the light chain (SEQ ID NO: 16). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of sirukumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 15) and/or Y85 and/or Y86 of the light chain (SEQ ID NO: 16). In other embodiments, the anti-IL6 HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0242] In specific embodiments, the anti-IL6 HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab portions of olokizumab as set forth in FIG. 3F (with glutamine (Q) glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N79, Q112, N162, and/or N204 of the heavy chain (SEQ ID NO: 17) or Q100, N158 and/or N210 of the light chain (SEQ ID NO: 18). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of olokizumab has a sulfation group at Y96 and/or Y97 of the heavy chain (SEQ ID NO: 17) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 18). In other embodiments, the anti-IL6 HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0243] In specific embodiments, the anti-IL6 HuPTM mAb or antigen-binding fragment thereof has heavy and light chains with the amino acid sequences of the heavy and light chain Fab portions of gerilizumab as set forth in FIG. 3G (with glutamine (Q) glycosylation sites; asparaginal (N) glycosylation sites, non-consensus asparaginal (N) glycosylation sites; and tyrosine-O-sulfation sites (Y) are as indicated in the legend) has a glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N78, Q114, N164 of the heavy chain (SEQ ID NO: 19) or N71 and/or N174 of the light chain (SEQ ID NO: 20). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of gerilizumab has a sulfation group at Y95 and/or Y96 of the heavy chain (SEQ ID NO: 19) and/or Y88 and/or Y89

of the light chain (SEQ ID NO: 20). In other embodiments, the anti-IL6 HuPTM mAb or antigen-binding fragment thereof does not contain any detectable NeuGc moieties and/or does not contain any detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0244] In certain embodiments, the HuPTM mAb or Fab 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. Efficacy may be monitored by measuring a reduction in pain, redness, and/or photophobia and/or an improvement in vision from baseline.

[0245] Combinations of delivery of the anti-IL6R or anti-IL6 HuPTM mAb or antigen-binding fragment thereof, to one or more ocular tissues 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-IL6R or anti-IL6, including but not limited to sarilumab, satralizumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, or gerilizumab.

5.6. Monitoring of Efficacy

[0246] 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.

[0247] 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).

[0248] 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: Adalimumab Fab cDNA-Based Vector

[0249] An adalimumab Fab cDNA-based vector was constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of adalimumab (amino acid sequences being SEQ ID NOs. 1 and 2, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is the nucleotide sequence of SEQ ID NOs. 26 and 27, respectively. Alternatively, the nucleotide sequence of representative adalimumab Fab transgene cassettes are exemplified in the nucleotide sequence of SEQ ID NOs. 49-51 or 222-225. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g.,

MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.2. EXAMPLE 2: Infliximab Fab cDNA-Based Vector

[0250] An infliximab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of infliximab (amino acid sequences being SEQ ID NOs. 3 and 4, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 28 and 29, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.3. EXAMPLE 3: Golimumab Fab cDNA-Based Vector

[0251] A golimumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of golimumab (amino acid sequences being SEQ ID NOs. 5 and 6, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 30 and 31, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector

additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.4. EXAMPLE 4: Satralizumab Fab cDNA-Based Vector

[0252] An satralizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of satralizumab (amino acid sequences being SEQ ID NOs. 7 and 8, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 32 and 33, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.5. EXAMPLE 5: Sarilumab Fab cDNA-Based Vector

[0253] A sarilumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of sarilumab (amino acid sequences being SEQ ID NOs. 9 and 10, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 34 and 35, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.6. EXAMPLE 6: Siltuximab Fab cDNA-Based Vector

[0254] A siltuximab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of siltuximab (amino acid sequences being SEQ ID NOs. 11 and 12, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 36 and 37, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.6. EXAMPLE 6: Clazakizumab Fab cDNA-Based Vector

[0255] A clazakizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of clazakizumab (amino acid sequences being SEQ ID NOs. 13 and 14, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 38 and 39, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.7. EXAMPLE 7: Sirukumab Fab cDNA-Based Vector

[0256] An sirukumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of

sirukumab (amino acid sequences being SEQ ID NOs. 15 and 16, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 40 and 41, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.8. EXAMPLE 8: Olokizumab Fab cDNA-Based Vector

[0257] An olokizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of olokizumab (amino acid sequences being SEQ ID NOs. 17 and 18, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 42 and 43, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.9. EXAMPLE 9: Gerilizumab Fab cDNA-Based Vector

[0258] A gerilizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of gerilizumab (amino acid sequences being SEQ ID NOs. 19 and 20, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 44 and 45, respectively. The transgene also comprises nucleotide sequences that

encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.10. EXAMPLE 10: Tocilizumab Fab cDNA-Based Vector

[0259] A tocilizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of tocilizumab (amino acid sequences being SEQ ID NOs. 21 and 22, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs:183 and 184, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO:85). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (See **Table 4**, particularly, SEQ ID NO:142 or 144) to create a bicistronic vector. The vector additionally includes a constitutive promoter, such as CAG, mU1a, EF1a, CB7, a CB or CB long promoter, a tissue-specific promoter, such as a ocular tissue-specific promoter, particularly GRK1 promoter (SEQ ID NO:77), or a BEST1/GRK1 tandem promoter (SEQ ID NO: 275), or an inducible promoter, such as a hypoxia-inducible promoter.

6.11 EXAMPLE 11: Vectorized adalimumab IgG and Fab cassettes: design and characterization

[0260] An AAV transgene cassette was constructed (SEQ ID NOs: 46 and 47) that drives ubiquitous expression of vectorized adalimumab IgG (SEQ ID NO: 48). The protein coding sequence is composed of the heavy and light chains of adalimumab separated by a Furin cleavage site (SEQ ID NO:146), Gly-Ser-Gly (GSG) linker (SEQ ID NO:148), and T2A self-processing peptide sequence (SEQ ID NO:149). The specific sequence configuration yields expression of separate heavy and light chain peptides. The entire reading frame is codon-optimized and depleted of CpG dinucleotides. Expression is driven by the CAG promoter (SEQ ID NO: 74). Alternatively, an AAV transgene cassette

was constructed (SEQ ID NOs: 52 and 53) that drives tissue-specific expression of vectorized adalimumab IgG (SEQ ID NO: 48) driven by the GRK1 promoter (SEQ ID NO:77). In addition, constructs are provided where the CB promoter (SEQ ID NO: 273) or the tandem Best1/GRK promoter (SEQ ID NO: 275) drives expression, and, optionally, the construct includes the VH4 intron (SEQ ID NO: 80), including constructs pAAV.CB.VH4.adalimumab (SEQ ID Nos: 276 and 277) or pAAV.CBlong.VH4.adalimumab, pAAV.Best1.GRK1.VH4.adalimumab. Similarly, an additional cassette was developed (SEQ ID NOs: 49 and 50) that drives expression of a Fab containing the adalimumab variable regions (SEQ ID NO: 51). Constructs are outlined in **FIGS. 1A and 1B**, and sequences are provided in **Table 8**.

[0261] Plasmid expression of adalimumab IgG and Fab fragment from pAAV.CAG.adalimumab.IgG (SEQ ID NO: 46) or pAAV.CAG.adalimumab.Fab (SEQ ID NO: 49) in the supernatant of transfected 293T cells was characterized via western blot and ELISA with recombinant human TNFα. Western blot analysis confirmed expression of heavy and light chains of the full length adalimumab and the light chain of the Fab fragment using goat anti-human Fc domain (1:3000) to detect the full length heavy chain and goat anti-human kappa light chain (1:3000) to detect the light chain, as compared to a control antibody. Both vectors produced adalimumab that bound human TNFα in an ELISA assay. In addition, the pAAV.CAG.adalimumab.IgG (SEQ ID NO: 46) and pAAV.CAG.adalimumab.Fab (SEQ ID NO: 49) plasmids were used to produce recombinant AAV8 vectors. Expression and TNFα binding activity of adalimumab produced from these recombinant AAV8 were confirmed by western blot and ELISA at 1E4 and 1E5 multiplicity of infection (MOI) with the aforementioned assays.

6.12 EXAMPLE 12: Self-complementary adalimumab Fab transgene cassettes: design and characterization

[0262] Two self-complementary AAV (scAAV) transgene cassettes encoding vectorized adalimumab Fab were generated (SEQ ID NOS:222, 223, 224, and 225). The transgenes are driven by the ubiquitous mU1a (SEQ ID NO: 75) or EF-1α (SEQ ID NO: 76) core promoters. These plasmids were compared for Fab expression via transfection into 293T cells. The mU1a-driven vector displayed a higher absorbance value suggesting higher Fab concentration within the cell supernatant.

6.13 EXAMPLE 13: TNFα binding across model species with vectorized adalimumab IgG and Fab

[0263] Vectorized adalimumab candidates were assessed for binding to TNFα isolated from model species including human, mouse, and rat. 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 human, mouse and rat. 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 reduced binding to rat TNFα as compared to mouse or human.

6.14 EXAMPLE 14: In vivo Study 1

[0264] In this study, full length adalimumab AAV8.CAG.adalimumab.IgG was evaluated for AAV-mediated antibody expression *in vivo* in mouse ocular tissues via local administration (subretinal, SR). AAV8.GFP and vehicle served as a controls.

Table 9. Study Layout

Group	Vector	ROA	Inj. Volume (µL)	Dose (vg/eye)	N (animals)
1	AAV8.CAG.Adalimumab.IgG	SR	1	1.00E+07	3
2		SR	1	1.00E+08	3
3		SR	1	1.00E+09	3
4	AAV8.GFP	SR	1	1.00E+08	3
5	Vehicle	SR	1	-	3

[0265] Young adult C57BL/6 (8-10 weeks old) were used for this study. The AAV8.CAG.adalimumab.IgG and AAV8.CAG.GFP vectors were 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 (**Table 9**). Fundus and OCT imaging were performed at days 6 and 16 after SR injection. Ocular samples were collected at 21 days post administration. Levels of antibody protein expression in ocular tissues (RPE, Retina and Anterior Segment) were quantified by ELISA (**FIG. 7**). Cell type specificity was determined by immunofluorescent staining with various retinal cell markers. Retina structure

changes and neuron survival were evaluated by histology and immunofluorescent staining at 6 and 16 days post administration.

[0266] Subretinal injection of at different doses ($1x10^7$, $1x10^8$ and $1x10^9$ vg/eye) of vectorized full-length adalimumab (AAV8.CAG.Adalimumab.IgG) resulted in dose-dependent transgene expression (**FIGs. 7** and **8**) and retinal inflammation (**Table 10**). At each dose, expression levels were found to be highest in the retina followed by the RPE and anterior segment. Retinal inflammation was detected in 5 out of 6 mice injected with a dose of $1x10^9$ vg/eye at 16 days post administration. No signs of inflammation were detected in mice receiving lower doses. Retinal inflammation/toxicity may be the cause for the lower expression levels detected in mice receiving $1x10^9$ vg/eye (120.9 ng adalimumab/g protein, or adalimumab concentration of 202.7 ng/ml in the retina) compared to $1x10^8$ vg/eye (288.9 ng adalimumab/g protein in the retina, which is equivalent to an adalimumab concentration of 439.3 mg/ml). Adalimumab expression levels are depicted as adalimumab levels (ng) per total protein (g) (**FIG. 7**) or adalimumab concentration ng per mL (**FIG. 8**).

[0267] Immunofluorescence double staining confirmed expression of adalimumab (as determined by using an antibody against human IgG) in the RPE.

Table 10.

	Ocular/retinal inflammation			
Time points/ treatment	**Vehicle**	**AAV8.CAG.Adalimumab.IgG**		
Day 6	**N**	**N**	**N**	**N**
Day 16	**N**	**N**	**N**	**Yes *5/6)**

6.15 EXAMPLE 15: In vivo Study 2

[0268] In this study, full length and Fab adalimumab antibody in an adeno-associated virus (AAV) vector (AAV8.CAG.adalimumab.IgG and AAV8.CAG.adalimumab.Fab), as well as etanercept Fc fusion protein (AAV8.CAG.etanercept), were evaluated for AAV-mediated antibody expression *in vivo* in mouse ocular tissues via local administration (subretinal (SR), **Table 11**).

Table 11. Study Layout

Group	Vector	ROA	Inj. Volume (µL)	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

[0269] 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 (SEQ ID NO: 46), AAV8.CAG.adalimumab.Fab (SEQ ID NO: 49), AAV8.CAG.etanercept, and vehicle were 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 11**).

[0270] Fundus and OCT imaging was 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 were quantified by ELISA. Cell type specificity was determined by immunofluorescent staining with various retinal cell markers. Retina structure changes and neuron survival were evaluated by histology and immunofluorescent staining at 2 and 4 weeks post administration.

[0271] AAV8.CAG.adalimumab.IgG was well up to the $1x10^9$ dose level (data not shown).

6.16 EXAMPLE 16: *In vivo* Study 3

[0272] In this study, full length and Fab adalimumab antibody in an adeno-associated virus (AAV) vector (AAV8.CAG.adalimumab.IgG and AAV8.GRK1.adalimumab.Fab, as well as control AAV8.CAG.GFP and AAV9.CAG.GFP were evaluated for AAV-mediated antibody expression *in vivo* in mouse ocular tissues via local administration (**Table 12**).

Table 12. Study Layout

Group	Vector	ROA	Inj. Volume (µL)	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.GRK1.Adalimumab.Fab	SR	1	1.00E+09	3	6
4		SR	1	1.00E+08	3	6
5	AAV8.GFP	SR	1	1.00E+09	2	4
6		SR	1	1.00E+08	2	4
7	AAV9.GFP	SR	1	1.00E+09	2	4
8		SR	1	1.00E+08	2	4
9	Vehicle	SR	1	-	2	4

[0273] Vectorized adalimumab 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 (SEQ ID NO: 46), AAV8.GRK1.adalimumab.Fab (SEQ ID NO: 49), AAV8.GFP, and AAV9.GFP were 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 12**).

[0274] Fundus and OCT imaging was performed at 2 and 4 weeks after SR injection. Ocular samples were collected at 4 weeks post administration. Levels of antibody or GFP expression in ocular tissues were quantified by ELISA. Cell type specificity was determined by immunofluorescent staining with various retinal cell markers. Retina structure changes and neuron survival were evaluated by histology and immunofluorescent staining at 2 and 4 weeks post administration.

6.17 Example 17: Evaluation of Vector-expressed Adalimumab Binding Kinetics

[0275] Expression and purification of vectorized Adalimumab from AAV produced in mouse eyes was assessed. The purified vectorized adalimumab kinetics of binding to various species of TNFα protein was compared to commercially produced adalimumab in various ligand binding assays.

[0276] *Binding affinity using Biacore™ (surface plasmon resonance (SPR)) assays*: A study was performed to measure the binding affinity of different TNF-alpha (TNFα) molecules to purified antibodies using BiacoreT200. First, binding affinity of TNFα to pAAV.CAG.Adalimumab-produced

antibody and was compared to binding of TNFα to commercial adalimumab antibody. Second, binding affinity of TNFα from different species were tested in order to determine the suitability of various species TNFα proteins for later animal model studies. The Biacore assay was performed at 25°C using HBS-EP+ as the running buffer. Diluted antibodies were 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) were tested individually as the analyte, followed by injecting running buffer in the dissociation phase. Dissociation rates were calculated [K_{off}= K_d= antibody dissociation rate; K_{on}= K_a= antibody association rate; K_D = K_{off}/K_{on}], and smaller (lower) K_D values indicated the greater the affinity of the antibody for its target.

Table 13.

Ligand	**Analyte**	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**
Adalimumab	Human TNFα	4.08E+05	1.87E-04	4.58E-10
pAAV.CAG.Adalimumab	Human TNFα	3.98E+05	1.70E-04	4.28E-10
Adalimumab	Macaque TNFα	2.60E+05	2.01E-04	7.72E-10
pAAV.CAG. Adalimumab	Macaque TNFα	2.46E+05	1.77E-04	7.20E-10
Adalimumab	Porcine TNFα	3.03E+05	6.59E-04	2.17E-09
pAAV.CAG. Adalimumab	Porcine TNFα	2.69E+05	5.52E-04	2.05E-09
Adalimumab	Mouse TNFα	1.39E+05	3.16E-04	2.27E-09
pAAV.CAG. Adalimumab	Mouse TNFα	1.51E+05	3.23E-04	2.13E-09
Adalimumab	Canine TNFα	1.42E+05	2.11E-04	1.49E-09
pAAV.CAG. Adalimumab	Canine TNFα	1.47E+05	2.27E-04	1.54E-09
Adalimumab	Rabbit TNFα	ND	ND	5.28E-07
pAAV.CAG. Adalimumab	Rabbit TNFα	ND	ND	6.14E-07
Adalimumab	Rat TNFα	ND	ND	6.81E-07
pAAV.CAG. Adalimumab	Rat TNFα	ND	ND	7.26E-07

ND: not detectable

[0277] *Binding Kinetics by Competitive ELISA*: Binding to various concentrations of mouse or human TNFα was compared in a competitive ELISA assay for both vector-expressed adalimumab extracted from mouse eye (following SR administration) and commercial adalimumab (**FIG 10A** and **10B**, respectively).

[0278] In the Biacore assays, each species TNF-alpha bound to adalimumab produced by CHO cells transfected with *cis* plasmids expressing adalimumab and commercial adalimumab at essentially the same level. Binding affinity (KD) of different species TNFα to vectorized adalimumab/adalimumab was ranked as follows: Human ≥ Macaque > Porcine = Mouse = Canine > Rabbit > Rat. Rat TNFα is not expected to compete with human TNFα in a rat model of uveitis (where IVT injection of human TNFα is introduced to induce uveitis).

[0279] According to the competitive ELISA assay data, the human TNFα displayed >100X higher affinity to adalimumab compared to mouse TNFα. In the Biacore studies, the human TNFα displayed 5X higher affinity to adalimumab compared to mouse TNFα. Adalimumab binding affinity to rat TNFα was negligible, as reported in the literature for HUMIRA.

6.18 Example 18: Measurement of Antibody Effector Function

[0280] Antibody effector functions, antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), of the vector-produced adalimumab were evaluated by *in vitro* assays and compared to commercially produced adalimumab (HUMIRA).

Materials and Methods

[0281] Target cells (CHO/DG44-tm TNFα; GenScript Cat. #RD00746) were maintained with corresponding complete culture medium at 37°C with 5% CO2. Effector cells (peripheral blood mononuclear cells, PBMCs; Saily Bio Cat. # XFB-HP100B) were thawed at 37℃ and maintained with 1640 complete culture medium at 37℃ with 5% CO_2.

[0282] For the ADCC dose-response assay, CHO/DG44-tm TNFα and PBMCs were target and effector cells, respectively. With the E/T (effector cell to target cell) ratio at 25:1, adalimumab (commercial) and human IgG1 against CHO/DG44-tm TNFα were used as positive and negative control, respectively. Briefly, the method steps were:

CHO/DG44-tm TNFα (target cells)

+

Samples

+

PBMC (effector cells)

↓

% target cell lysis

[0283] Effector cells (PBMCs) were thawed and resuspended with assay buffer (CellTiter-Glo®Detection Kit (Promega, Cat.#G7573). Target cells were 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 were transferred to the assay plate as well, and the assay plate incubated at RT for 30 minutes. The effector cell density was adjusted according to the E/T ratio, then the effector cell suspension was transferred to the assay plate. The assay plate was then incubated in a cell incubator (37°C/5%CO_2) for 6 hours, removed, then the supernatant of corresponding wells of the assay plate were transferred to another 96-well assay plate. LDH Mixture (LDH Cytotoxicity Detection Kit, Roche Cat# 11644793001) was transferred to the corresponding wells of the second 96-well assay plate and luminescence/ absorbance was read with a PHERAStar® (BMG LABTECH) plate reader.

[0284] For the CDC dose-response study, CHO/DG44-tm TNFα was used as the target cell. With 5% NHSC (normal human serum complement), adalimumab and human IgG1 against CHO/DG44-tm TNFα were used as positive and negative control, respectively. Briefly, the CDC assay method steps were:

CHO/DG44-tm TNFα (target cells)

+

Samples

+

NHSC

↓

% target cell lysis

[0285] Target cells were harvested by centrifugation and resuspended with assay buffer (CellTiter-Glo®Detection Kit (Promega, Cat.#G7573). Samples and controls were 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 were also transferred to the assay plate, and then assay plate was incubated at RT for 30 minutes, before the Normal Human Serum Complement (NHSC) working solution (Quidel, Cat. # A113) was added to the assay plate. The assay plate was incubated in the cell incubator (37°C/5%CO_2) for 4 hours, removed, and the Cell Titer-Glo® working solution was added to the corresponding wells and the plate incubated for about 10-30 minutes at RT. Luminescence data was read on a PHERAStar® FSX (BMG LABTECH) plate reader to determine the number of viable cells. Raw data of ADCC and CDC study were 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 were 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.

[0286] With E/T ratio at 25:1, CHO/DG44-tm TNFα cells were used as the target cells in ADCC dose-response study. Dose-responses and Best-fit values of positive control (Adalimumab), samples and negative control (Human IgG1) are provided in **Table 14** and shown in **FIG. 11A**. EC50 value of Adalimumab was 0.01288 μg/mL.

Table 14: ADCC assay.

log(agonist) vs. response – Variable slope (four parameters)			
Best-fit values			
ID	**Adalimumab**	**Human IgG1**	**AAV-Adalimumab**
Bottom	-2.723	N/A	-3.469
Top	46.74		30.26
LogEC50	-1.89		-1.775

HillSlope	1.681		~1.800
EC50	**0.01288**		**0.01678**
Span	49.46		33.73

[0287] With 5% NHSC, CHO/DG44-tm TNFα cells were used as the target cells in CDC dose-response study. Dose-responses and Best-fit values of positive control (Adalimumab), samples and negative control (Human IgG1) are provided in **Table 15** and shown in **FIG. 11B**. EC_{50} value of Adalimumab was 0.4402 μg/mL.

Table 15. CDC Assay.

log(agonist) vs. response – Variable slope (four parameters)			
Best-fit values			
ID	**Adalimumab**	**Human IgG1**	**AAV-Adalimumab**
Bottom	4.576	N/A	3.099
Top	96.68		89.35
LogEC50	-0.1203		0.9249
HillSlope	2.343		2.033
EC50	**0.7580**		**8.413**
Span	92.11		86.25

Results and Conclusions:

[0288] EC50 value of the positive control (adalimumab) in the ADCC assay was 0.01288 μg/mL and EC50 value of positive control in the CDC assay was 0.758 μg/mL. Under the experimental conditions, both test samples effectively mediated ADCC and CDC activity, and the negative control (human IgG1) was not observed to induce ADCC and CDC activity against CHO/DG44-tm TNFα cells. AAV-adalimumab displayed lower ADCC and CDC activity compared to Adalimumab (HUMIRA®). Without being bound to any one theory, the difference may be due to the post-translational modification such as glycosylation which is expected to differ in manufacturing cell

culture. Lower ADCC/CDC-mediated cell lysis with adalimumab from pAAV.CAG.adalimumab transfected cells compared to HUMIRA® at the same dose may be beneficial in terms of immunogenicity for an ocular administered AAV-adalimumab.

6.19 Example 19: Human TNF-alpha target engagement model characterization (TNF Target Engagement Animal Model)

[0289] Binding affinity evaluations confirmed (Example 17, **Table 13**) that mouse TNFα binds considerably weaker than human TNFα, and adalimumab does not bind rat TNFα. Therefore, target (TNFα) enrichment in this model can be accomplished by injecting human TNFα into a rat eye where endogenous TNFα if stimulated will not be blocked (neutralized) or engaged by exogenous adalimumab, thus allowing normal endogenous receptor activation. In this model, the excess human TNFα target injected into the eye induces local inflammation and can be measured before and after engagement with exogenous antibody (adalimumab or AAV-adalimumab) by ophthalmic exams. The effect of adalimumab or AAV-adalimumab on uveitis caused by the TNF-induced inflammation will also be observed and measured by ophthalmic examination and tissue analysis.

[0290] To characterize a dose response and time-course of IVT-administered human TNFα, three (3) doses of human TNFα were given to the eyes of female Lewis rats: low dose/50 ng/eye, middle dose/100 ng/eye and high dose/170 ng/eye. Ocular samples were collected at each time point: 4 hours, 24 hours, 72 hours (Day 3), and 168 hours (Day 7), and human TNFα was measured in each sample.

Table 16. Details of the hTNFα target engagement model characterization study

Group	# of Animals	Induction Agent (does, per eye)	Route and Volume (OU)	Experimental Endpoints (to Day 21)
1	8	Vehicle	Intravitreal (5uL)	-*Body weights*: prior to dose and at necropsy -*Ophthalmic exams*: Baseline, 4 hrs, 7 hrs, Day 3 and Day 7 -*Ocular tissues (whole eyeballs)*: collected from two animals at each time point after injection (4 hrs, 7 hrs, Day 3 and Day 7). Both eyes stored frozen at -80°C until analysis.
2	8	hTNFα (50 ng)		
3	8	hTNFα (100 ng)		
4	8	hTNFα (170 ng)		
5	2	Naïve	N/A	Ocular tissues (whole eyeballs) were collected, and served as baseline samples

Female Lewis rats (6-8 weeks) were used; eyeballs were collected fresh, weighed and snap frozen (-80℃).

[0291] The ability of human TNFα to induce inflammation in the rat eye was measured upon examination of the eye per the Clinical Grading of EAU guidelines of Agarwal, RJ et al. ("Rodent Models of Experimental Autoimmune Uveitis." *Methods in Molecular Medicine*. 2004: Vol. 102, pp 395-419), as described in **Table 17**.

Table 17

Clinical Grading of EAU in the Rat	
Grade[a]	Criteria
0	No disease; eye is translucent and reflects light (red reflex)
0.5 (trace)	Dilated blood vessels in the iris
1	Engorged blood vessels in the iris; abnormal pupil contraction
2	Hazy anterior chamber; decreased red reflux
3	Moderately opaque anterior chamber, but pupil still visible; dull red reflex
4	Opaque anterior chamber and obscured pupil; red reflex absent; proptosis
[a] Each higher grade includes the criteria of the preceding one.	
Agarwal, RJ, et al. Rodent Models of Experimental Autoimmune Uveitis. Methods in Molecular Medicine. 2004: Vol 102, pp 395-419.	

[0292] The study shows total EAU scores over time for 3 (rat) groups administered with varying doses of hTNFα. The highest EAU score was approximately 2 for a dose of 170ng hTNFα administered IVT. After the 24 hour mark, the grade decreases over time to an EAU score of a 1 by 168 hours. See **FIG. 12**.

6.20. Example 20: Human TNF-alpha induced uveitis (target engagement model)

[0293] TNFα is an inflammatory cytokine produced by T cells and macrophages/monocytes during acute inflammation. TNF-α is thought to play a key role in uveitic inflammation, such as mediating reactive oxygen species, promotion of angiogenesis, breakdown of the blood-retinal barrier–Retinal cell death–T cell activation and migration. hTNFα is elevated in the aqueous humor and serum in patients with non-infectious uveitis, and is considered a "master regulator" of the inflammatory (immune) response in many organ systems (Tracey D. et al., *Pharmacology & Therapeutics* 2008, 117, 244–27, Forrester JV et al., *American J Ophthalmology*, 2018,189: 77-85; Lee RW et al., *Semin Immunopathol*, 2014 36:581–59)

[0294] *Tolerability and Dose Response in normal rats:* Three dose cohorts of Lewis rats (low dose/1.0E+7 GC/eye, mid dose/3.0E+8 GC/eye and high dose /1.0E+9 GC/eye) were administered AAV8.CAG.adalimumab subretinally (2.5 µL volume injections). Ophthalmic examinations were performed at day 7, 14 and 21 post-administration. For each rat, one eye was dissected and evaluated at the end of study (21 days) for measurement of adalimumab (e.g. ELISA), and one eye for histology.

[0295] Adalimumab was measured by ELISA with wells coated with recombinant human TNF (as in previous Example). Subretinal injection with AAV8.CAG.Adalimumab at 1.0E+9 GC/eye and 3.0E+8 GC/eye have 86.0 ng/eye and 17.1 ng/eye of adalimumab/eye, respectively, at 21 days post-administration (Lewis rats). See **FIG. 13**.

[0296] The averaged clinical score of dose-dependent hTNFα-induced inflammation was measured at several timepoints in the TNFα model characterization study (see Example 19 above). In order to further demonstrate by different routes of administration (*e.g.* subretinal or suprachoroidal injection) that AAV-delivered vectorized adalimumab can attenuate the intravitreally-injected hTNFα in a rat eye, further dose characterization was performed in order to select appropriate doses for the TNF model.

[0297] *Time course evaluation of peak ocular hTNFα levels and adalimumab levels:* To further evaluate hTNFα levels at 24 hours following IVT administration in the rat (see Example 19: Human TNFα engagement characterization study), a minimal dilution (matrix) effect was examined.

[0298] A solid phase ELISA designed to measure human TNFα in cell culture supernatants (Quantikine Human TNF-alpha Immunoassay, R&D Systems, Cat. # DTA00D) was used to measure hTNFα in spiked samples vs. serial dilutions from 1:2 through 1:256 of hTNFα (170 ng) samples taken from the 24 hour eye sample in the previous characterization study (Example 19).

[0299] hTNFα-induced Uveitis models at 170 ng hTNFα/eye quickly decreased to ~2.8 ng/eye hTNF-α at 24 hours post IVT injection. It has been reported that Adalimumab –TNF complexes are most likely formed in a 3:1 ratio (Bloemendaal et al. *J. Crohns and Colitis*, Volume 12, Issue 9, September 2018, pp. 1122–1130; Hu et al. *J. Biol. Chem.* 288, 27059–27067 (2013); Berkhout et al., Sci Transl Med.11(477), 2019). Adalimumab has a molecular weight (MW) of 148 KDa, and hTNFα has a subunit molecular mass of 17.3 KDa (with homotrimer MW = 51.9 KDa).

[0300] Based on adalimumab expression at the highest dose, 1.0E+9 GC/eye of vectorized adalimumab, 50 ng hTNF was selected for model induction.

[0301] *Efficacy of vectorized AAV-adalimumab in TNFα model:* This study is designed to determine potential efficacy and distribution of AAV.adalimumab in a hTNFα-induced engagement model in the rat. The number of animals, data collection time points and parameters for measurement were chosen based on the minimum required to meet the objectives of the study.

[0302] Briefly, to evaluate the efficacy of vectorized adalimumab treatment: (i) vector (AAV8.CAG.adalimumab) is administered subretinally (SR) in both eyes (OU) at a dose of 1.0E+9 GC/eye at day -21 (21 days before TNF-α administration), or (ii) 100, 150, 200 or 500 ng/eye commercial adalimumab (in 5μL) administered IVT at day -1 (1 day prior to TNF-α administration), followed by 50 ng hTNF alpha (induction) administered to Lewis rats by intravitreal (IVT) injection at day 0. Body Weights are measured prior to dose and at necropsy; Ophthalmic Exams are done at baseline, 4, 24 hours and Day 3, and Day 7. Necropsy will be performed at Day 7, whereas one eye per animal/group is analyzed for transgene/TNFα levels, and one eye per animal/group is analyzed for histopathology. The study is summarized in **Table 18**.

Table 18. Rat TNF-α Target Enrichment Experimental Design:

Group	# of Animals	Treatment Route, (OU) 5 μL/eye	Induction Agent Route, (OU)	Experimental Endpoints	Necropsy
1	10	Formulation Buffer, IVT (5 μL/eye) Day -1	hTNFα, IVT (50 ng, 5 μL/eye)	• Body Weights: Prior to dose and at necropsy • Ophthalmic Exams: Baseline, 4, 24 hours and Days 3, and 7	**Day 7** •One eye per animal/group for transgene/TNFα levels •One eye per animal/group for histopathology
2	10	Formulation Buffer, SR (2.5 μL/eye) Day -21			
3	10	Adalimumab, IVT (5 μL/eye, 500 ng) Day -1			
4	10	AAV.Adalimumab, SR (2.5 μL/eye, 1.00E09) Day -21			
5*	4	Saline, IVT Day -14	NA	• Body Weights: Prior to dose and at necropsy	**24 & 48 Hours Post-Dose**

Group	# of Animals	Treatment Route, (OU) 5 µL/eye	Induction Agent Route, (OU)	Experimental Endpoints	Necropsy
6*	4	Adalimumab, IVT (100 ng/eye) Day -14		• Ophthalmic Exams: baseline, Day -13, Day -12 • Ocular tissues (whole eyes): 24 and 48 hours (n=2 animals OU per timepoint) post IVT injection (Day -13 and Day -12) • Serum: 24 and 48 hours (terminal animals) post IVT injection (Day -13 and Day -12)	•Both eyes from n=2 animals/group for adalimumab tissue levels •Serum from terminal animals (n=2 animals/group/time point) for systemic adalimumab levels
7*	4	Adalimumab, IVT (150 ng/eye) Day -14			
8*	4	Adalimumab, IVT (200 ng/eye) Day -14			
9	4	Adalimumab, IVT (500 ng/eye) Day -14			

** Note, animals in Group 5-9 will be dosed prior to Groups 1 & 3 to determine dose level needed for Group 3.*

[0303] Tissue Collections Groups 1-4 (One eye), Groups 5-8 (All eyes): At the timepoints specified in the experimental design table, animals will be euthanized (protocols will be approved by IACUC). Post euthanasia, aqueous humor (AH) will be collected from both (OU) eyes using a 31-gauge insulin syringe. The AH (10-15 µL) will be dispensed into a polypropylene tube, briefly centrifuged to collect the fluid into the bottom of the tube, and then 10 µL will be transferred to a pre-labelled, 2 mL screw-cap, polypropylene tube. Tubes will then be snap-frozen and stored at -80°C until analysis. After AH collection, eyes will be enucleated and snap frozen in individual tubes and subsequently stored at -80°C.

6.21 Example 21: Evaluation of regulatory elements (promoters) in retinal cells

[0304] Several AAV constructs were made with GFP or adalimumab under the control of different promoters and optionally a VH4 intron, as such:

- AAV8.CAG.GFP or adalimumab
- AAV8.U1a.VH4.GFP or adalimumab
- AAV8.CB.VH4.GFP or adalimumab
- AAV8.CBlong.VH4.GFP or adalimumab
- AAV8.GRK1.VH4.GFP or adalimumab

- AAV8.Best1.VH4.GFP or adalimumab
- AAV8.Best1.GRK1.VH4.GFP or adalimumab

[0305] The sequence of each promoter is provided in **Table 1** (*supra*). CAG is considered a strong ubiquitous promoter, while U1a or CB drive expression at a medium level and are ubiquitous with respect to cell type. CB long (CB promoter extended +100 nucleotides of 5'UTR from the chicken beta-actin promoter) will also be tested for promoter strength under the test conditions. BEST1 is considered an RPE specific promoter, whereas GRK1 displays specificity for transcriptional control in photoreceptor cells. A BEST1/GRK1 tandem promoter was also made. The tandem promoter contains a modified GRK1 sequence, such that any start codons (ATG) are modified (T removed) to prevent unintended or aberrant transcripts. An intron is optionally placed proximal to the promoter, upstream of the coding sequence. Sequences of the adalimumab IgG constructs are provided in **Table 8**.

[0306] AAV8.CAG.adalimumab and AAV8.GRK1.adalimumab were tested in a mouse model following subretinal vector administration at two different doses (1.0E=8 or 1.0E+09), and total adalimumab was extracted and measured. Ophthalmic tests (fundus and OCT imaging) were performed at various time points. Animals were euthanized and necropsied at week 4-5 after injection, and eyeballs were collected. Ocular tissues (retinas, RPE & Choroid, and anterior segments) were collected into separate tubes and snap frozen in liquid nitrogen. Tubes were stored at -80°C until analysis. The right eyes were fixed in 4% paraformaldehyde (PFA) for 1-2 hours, then transferred to 1x PBS. Under the current conditions, Adalimumab concentrations were highest in RPE when driven by CAG promoter at the 1.0E+8 dose.

[0307] Additionally, ARPE-19 retinal cells were transfected with AAV receptor (AAVR; Pillay et al. *Curr Opin Virol*. 2017 June; 24: 124–131. doi:10.1016/j.coviro.2017.06.003). ARPE-AAVR cells were then transfected with AAV *cis* plasmids expressing GFP under the control of different promoters, and examined for GFP expression. Strong CB promoter-driven expression of GFP is observed in ARPE cells, whereas BEST1, GRK1 and BEST1/GRK promoter-driven genes were comparable, in the tested conditions.

EQUIVALENTS

[0308] 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.

[0309] 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:

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

(d) an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding a heavy chain and a light chain of a substantially full-length or full-length anti-TNFα mAb, anti-IL6 mAb, or anti-IL6R mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue 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 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).
3. The pharmaceutical composition of claims 1 or 2, wherein the AAV capsid is AAV8, AAV3B, AAV2.7m8, or AAVrh73.
4. The pharmaceutical composition of claims 1 to 3, 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.
5. The pharmaceutical composition of claims 1 to 4, wherein the regulatory sequence includes a regulatory sequence from Table 1.

6. The pharmaceutical composition of claim 5, wherein the regulatory sequence is a CAG promoter (SEQ ID NO: 74), a CB promoter (SEQ ID NO: 273 or 274), a human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:77 or 217), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 214-216), a human red opsin (RedO) promoter (SEQ ID NO: 212) or a Best1/GRK1 tandem promoter (SEQ ID NO: 275).

7. The pharmaceutical composition of any of claims 1 to 6, wherein the transgene comprises a Furin/2A linker between the nucleotide sequences coding for the heavy and light chains of said mAb.

8. The pharmaceutical composition of claim 7, wherein said Furin 2A linker is a Furin/T2A linker having the amino acid sequence RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NOS:143 or 144).

9. The pharmaceutical composition of any of claims 1 to 8, wherein the transgene encodes a signal sequence at the N-terminus of the heavy chain and the light chain of said antigen-binding fragment that directs secretion and post translational modification in said human ocular tissue cells.

10. The pharmaceutical composition of claim 9, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO:85) or a signal sequence from Table 2.

11. The pharmaceutical composition of any of claims 1 to 10, wherein transgene has the structure: signal sequence– Heavy chain – Furin site – 2A site – signal sequence– Light chain – PolyA.

12. The pharmaceutical composition of any of claims 1 to 11, wherein the anti-TNFα antibody is adalimumab, infliximab, or golimumab, or an antigen binding fragment thereof.

13. The pharmaceutical composition of any of claims 1 to 12, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 1 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 64 and a light chain with an amino acid sequence of SEQ ID NO: 2; a heavy chain with an amino acid sequence of SEQ ID NO: 3 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 4; or a heavy chain with an

amino acid sequence of SEQ ID NO: 5 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 6.

14. The pharmaceutical composition of any of claims 1 to 13 , wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 26 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 27 encoding the light chain; a nucleotide sequence of SEQ ID NO: 28 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 29 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 30 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 31 encoding the light chain.

15. The pharmaceutical composition of any of claims 1 to 11, wherein the antiIL6 or anti-IL6R antibody is satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab, or an antigen binding fragment thereof.

16. The pharmaceutical composition of any of claims 1 to 11 or 15, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 7 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 67 and a light chain with an amino acid sequence of SEQ ID NO: 8; a heavy chain with an amino acid sequence of SEQ ID NO: 9 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO:185 and a light chain with an amino acid sequence of SEQ ID NO: 10; a heavy chain with an amino acid sequence of SEQ ID NO: 11 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 68 and a light chain with an amino acid sequence of SEQ ID NO: 12; comprises a heavy chain with an amino acid sequence of SEQ ID NO: 13 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 69 and a light chain with an amino acid sequence of SEQ ID NO: 14; a heavy chain with an amino acid sequence of SEQ ID NO: 15 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 70 and a light chain with an amino acid sequence of SEQ ID NO: 16; a heavy chain with an amino acid sequence of SEQ ID NO: 17 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 71 and a light chain with an amino acid sequence of SEQ ID NO: 18; a heavy chain with an amino acid sequence of SEQ ID NO: 19 and a light chain with an amino acid sequence of SEQ ID NO: 20; or a heavy chain with an amino acid sequence of SEQ ID NO:

21 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 72 and a light chain with an amino acid sequence of SEQ ID NO: 22.

17. The pharmaceutical composition of any of claims 1, 11 or 15-16, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 32 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 33 encoding the light chain; a nucleotide sequence of SEQ ID NO: 34 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 35 encoding the light chain; a nucleotide sequence of SEQ ID NO: 36 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 37 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 38 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 39 encoding the light chain; a nucleotide sequence of SEQ ID NO: 40 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 41 encoding the light chain; a nucleotide sequence of SEQ ID NO: 42 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 43 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 44 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 45 encoding the light chain; or a nucleotide sequence of SEQ ID NO:183 encoding the heavy chain and a nucleotide sequence of SEQ ID NO:184 encoding the light chain.

18. The pharmaceutical composition of claims1 to 17, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

19. The pharmaceutical composition of any of claims 1 to 18, wherein the mAb or the antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

20. The pharmaceutical composition of any of claims 1 to 19, wherein the artificial genome is self complementary.

21. The pharmaceutical composition of any of claims 1 to 20 wherein the artificial genome is the construct EF1ac.Vh4i.Adalimumab.Fab scAAV, mU1a.Vh4i.Adalimumab.Fab scAAV, CAG.Adalimumab.IgG, CAG.Adalimumab.Fab, GRK1.Vh4i.Adalimumab.IgG, CB.VH4i.adalimumab.IgG, or Best1/GRK1.VH4i.adalimumab.IgG.

22. 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 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); and

b. an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding a heavy and a light chain of a substantially full-length or full-length anti-TNFα mAb anti-IL6 antibody or anti-IL6R antibody, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that promote expression of the transgene in human ocular tissue cells;

c. wherein the transgene encodes a signal sequence at the N-terminus of the heavy chain and the light chain of said mAb that directs secretion and post translational modification of said mAb in ocular tissue cells.

23. The composition of claim 22, 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.

24. The composition of claims 22 or 23, wherein the AAV capsid is AAV2.7m8, AAV8, AAV3B, or AAVrh73.

25. The composition of claims 22 to 24, wherein the anti-TNFα antibody is adalimumab, infliximab, or golimumab, or an antigen binding fragment thereof.

26. The pharmaceutical composition of any of claims 22 to 25, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 1 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 64 and a light chain with an amino acid sequence of SEQ ID NO: 2; a heavy chain with an amino acid sequence of SEQ ID NO: 3 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 4; or a heavy chain with an

amino acid sequence of SEQ ID NO: 5 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 6.

27. The pharmaceutical composition of claims 22 to 26, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 26 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 27 encoding the light chain; a nucleotide sequence of SEQ ID NO: 28 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 29 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 30 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 31 encoding the light chain.

28. The pharmaceutical composition of any of claims 22 to 27, wherein the antiIL6 or anti-IL6R antibody is satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab, or an antigen binding fragment thereof.

29. The pharmaceutical composition of any of claims 22 to 24 or 27, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 7 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 67 and a light chain with an amino acid sequence of SEQ ID NO: 8; a heavy chain with an amino acid sequence of SEQ ID NO: 9 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO:185 and a light chain with an amino acid sequence of SEQ ID NO: 10; a heavy chain with an amino acid sequence of SEQ ID NO: 11 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 68 and a light chain with an amino acid sequence of SEQ ID NO: 12; comprises a heavy chain with an amino acid sequence of SEQ ID NO: 13 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 69 and a light chain with an amino acid sequence of SEQ ID NO: 14; a heavy chain with an amino acid sequence of SEQ ID NO: 15 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 70 and a light chain with an amino acid sequence of SEQ ID NO: 16; a heavy chain with an amino acid sequence of SEQ ID NO: 17 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 71 and a light chain with an amino acid sequence of SEQ ID NO: 18; a heavy chain with an amino acid sequence of SEQ ID NO: 19 and a light chain with an amino acid sequence of SEQ ID NO: 20; or a heavy chain with an amino acid sequence of SEQ ID NO:

21 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 72 and a light chain with an amino acid sequence of SEQ ID NO: 22.

30. The pharmaceutical composition of any of claims 22-24 or 28-29, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 32 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 33 encoding the light chain; a nucleotide sequence of SEQ ID NO: 34 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 35 encoding the light chain; a nucleotide sequence of SEQ ID NO: 36 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 37 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 38 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 39 encoding the light chain; a nucleotide sequence of SEQ ID NO: 40 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 41 encoding the light chain; a nucleotide sequence of SEQ ID NO: 42 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 43 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 44 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 45 encoding the light chain; or a nucleotide sequence of SEQ ID NO:183 encoding the heavy chain and a nucleotide sequence of SEQ ID NO:184 encoding the light chain.

31. The composition of any of claims 22 to 30, wherein the transgene comprises a Furin/2A linker between the nucleotide sequences coding for the heavy and light chains of said mAb.

32. The composition of any of claims 22 to 31, wherein the nucleic acid encoding a Furin 2A linker is incorporated into the expression cassette in between the nucleotide sequences encoding the heavy and light chain sequences, resulting in a construct with the structure: Signal sequence – Heavy chain – Furin site – 2A site – Signal sequence – Light chain – PolyA.

33. The composition of claims 22 to 32, wherein said Furin 2A linker is a Furin/T2A linker having the amino acid sequence RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NOS:143 or 144).

34. The composition of any of claims 22 to 33, wherein said signal sequence is MYRMQLLLLLIALSLALVTNS (SEQ ID NO:85) or a signal sequence from Table 2.

35. The composition of any of claims 22 to 34, wherein the artificial genome is self complementary.

36. The composition of any of claims 22 to 27 or 31 to 35, wherein the artificial genome is the construct EF1ac.Vh4i.Adalimumab.Fab scAAV, mU1a.Vh4i.Adalimumab.Fab scAAV, CAG.Adalimumab.IgG, CAG.Adalimumab.Fab, GRK1.Vh4i.Adalimumab.IgG, CB.VH4i.adalimumab.IgG, or Best1/GRK1.VH4i.adalimumab.IgG.

37. 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 mAb, anti-IL6 mAb, or anti-IL6R mAb, or antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in ocular tissue cells.

38. 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 mAb, anti-IL6 mAb, or anti-IL6R mAb, or antigen-binding fragment thereof, 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 mAb, anti-IL6 mAb, or anti-IL6R mAb or antigen-binding fragment thereof.

39. The method of claims 37 or 38 wherein the anti-TNFα mAb is adalimumab, infliximab or golimumab.

40. The method of claims 37 to 39, wherein the full-length anti-TNFα mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 1 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 64 and a light chain with an amino acid sequence of SEQ ID NO: 2; or a heavy chain with an amino acid sequence of SEQ ID NO: 3 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 4; a heavy chain with an amino acid sequence of SEQ ID NO: 5 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 65 and a light chain with an amino acid sequence of SEQ ID NO: 6.

41. The method of claims 37 to 40, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 26 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 27 encoding the light chain; a nucleotide sequence of SEQ ID NO: 28 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 29 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 30 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 31 encoding the light chain.

42. The method of any of claims 37 to 38, wherein the antiIL6 or anti-IL6R antibody is satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab, or an antigen binding fragment thereof.

43. The method of any of claims 37 to 38 or 42, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 7 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 67 and a light chain with an amino acid sequence of SEQ ID NO: 8; a heavy chain with an amino acid sequence of SEQ ID NO: 9 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO:185 and a light chain with an amino acid sequence of SEQ ID NO: 10; a heavy chain with an amino acid sequence of SEQ ID NO: 11 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 68 and a light chain with an amino acid sequence of SEQ ID NO: 12; comprises a heavy chain with an amino acid sequence of SEQ ID NO: 13 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 69 and a light chain with an amino acid sequence of SEQ ID NO: 14; a heavy chain with an amino acid sequence of SEQ ID NO: 15 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 70 and a light chain with an amino acid sequence of SEQ ID NO: 16; a heavy chain with an amino acid sequence of SEQ ID NO: 17 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 71 and a light chain with an amino acid sequence of SEQ ID NO: 18; a heavy chain with an amino acid sequence of SEQ ID NO: 19 and a light chain with an amino acid sequence of SEQ ID NO: 20; or a heavy chain with an amino acid sequence of SEQ ID NO: 21 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 72 and a light chain with an amino acid sequence of SEQ ID NO: 22.

44. The method of any of claims 37 to 38 or 42 to 43, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 32 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 33 encoding the light chain; a nucleotide sequence of SEQ ID NO: 34 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 35 encoding the light chain; a nucleotide sequence of SEQ ID NO: 36 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 37 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 38 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 39 encoding the light chain; a nucleotide sequence of SEQ ID NO: 40 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 41 encoding the light chain; a nucleotide sequence of SEQ ID NO: 42 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 43 encoding the light chain; wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 44 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 45 encoding the light chain; or a nucleotide sequence of SEQ ID NO:183 encoding the heavy chain and a nucleotide sequence of SEQ ID NO:184 encoding the light chain.

45. The method of claims 37 to 44, 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.

46. The method of any of claims 37 to 44 wherein the viral capsid is at least 95% identical to the amino acid sequence of an 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);

47. The method of any of claims 37 to 46, wherein the AAV capsid is AAV2.7m8, AAV8, AAV3B, or AAVrh73.

48. The method of any of claims 37 to 46, wherein the regulatory sequence includes a regulatory sequence from Table 1 or Table 1a.

49. The method of claim 48, wherein the regulator sequence is a CAG promoter (SEQ ID NO: 74), a CB promoter (SEQ ID NO: 273 or 274), human rhodopsin kinase (GRK1) promoter (SEQ ID NOS:77 or 217), a mouse cone arresting (CAR) promoter (SEQ ID NOS: 214-216), a human red opsin (RedO) promoter (SEQ ID NO: 212) or a Best1/GRK1 tandem promoter (SEQ ID NO: 275).

50. The method of any of claims 37 to 49, wherein the transgene comprises a Furin/2A linker between the nucleotide sequences coding for the heavy and light chains of said mAb.

51. The method of claim 50, wherein said Furin 2A linker is a Furin/T2A linker having the amino acid sequence RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NOS:143 or 144).

52. The method of any of claims 37 to 51, wherein the transgene encodes a signal sequence at the N-terminus of the heavy chain and the light chain of said antigen-binding fragment that directs secretion and post translational modification in said human ocular tissue cells.

53. The method of claim 52, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO:85) or a signal sequence from Table 2.

54. The method of any of claims 37 to 53, wherein transgene has the structure: Signal sequence– Heavy chain – Furin site – 2A site – Signal sequence– Light chain – PolyA.

55. The method of any of claims 37 to 54, wherein the mAb is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

56. The method of any of claims 37 to 55 wherein the mAb contains an alpha 2,6-sialylated glycan.

57. The method of any of claims 37 to 56 wherein the mAb is glycosylated but does not contain detectable NeuGc and/or α-Gal.

58. The method of any of claims 37 to 57 wherein the mAb contains a tyrosine sulfation.

59. The method of any of claims 37 to 58 in which production of said HuPTM form of said mAb or antigen-binding fragment thereof is confirmed by transducing human ocular tissue cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

60. The method of claims 37 or 59, wherein the therapeutically effective amount is determined to be sufficient to maintain a concentration of at least 10 ng/ml in aqueous humor, vitreous humor, RPE, retina, and/or anterior segment/chamber.

61. The method of claims 37 or 60, 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.

62. The method of any of claims 37 to 61, wherein the rAAV is self complementary.

63. The method of any of claims 37 to 62 wherein the transgene within the construct EF1ac.Vh4i.Adalimumab.Fab scAAV, mU1a.Vh4i.Adalimumab.Fab scAAV, CAG.Adalimumab.IgG, CAG.Adalimumab.Fab, GRK1.Vh4i.Adalimumab.IgG, CB.VH4i.adalimumab.IgG, or Best1/GRK1.VH4i.adalimumab.IgG.

64. 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 comprising a transgene encoding a substantially full-length or full-length anti-TNFα mAb, anti-IL6, or anti-IL6R or antigen-binding fragment thereof, 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 cell 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.

65. The method of claim 64, wherein the transgene encodes a substantially full-length or full-length mAb or antigen binding fragment that comprises the heavy and light chain variable domains of adalimumab, infliximab, golimumab, satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab wherein the AAV capsid protein is an AAV2.7m8, AAV8, AAV3B, or AAVrh73, capsid protein.

66. The method of claims 64 or 65, 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.

67. A host cell containing:

d. an artificial genome comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises comprising a transgene encoding a substantially full-length or full-length anti-TNFα mAb, anti-IL6 mAb or anti-IL6R mAb, or antigen-binding fragment thereof, 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 cell tropism;

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

68. The host cell of claim 67, wherein the transgene encodes a substantially full-length or full-length mAb or antigen binding fragment that comprises the heavy and light chain variable domains of adalimumab, infliximab, golimumab, satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilizumab, or tocilizumab.

69. The host cell of claim 67 or 68, wherein the AAV capsid protein is an AAV2.7m8, AAV8, AAV3B, or AAVrh73 capsid protein.

70. The host cell of claims 67 to 69, 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.

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<130> 38013.0015P1

<150> 63/106,832
<151> 2020-10-28

<160> 277

<170> PatentIn version 3.5

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val

```
    50                  55                  60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

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

Ala Lys Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

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

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

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

Gly Pro Ser Val Phe Leu
                245
```

<210> 2
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<213> Artificial Sequence

<220>
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<400> 2

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1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


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


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190
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Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195   200   205

Phe Asn Arg Gly Glu Cys
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<210> 3
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Glu Val Lys Leu Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Met Lys Leu Ser Cys Val Ala Ser Gly Phe Ile Phe Ser Asn His
            20   25   30

Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
        35   40   45

Ala Glu Ile Arg Ser Lys Ser Ile Asn Ser Ala Thr His Tyr Ala Glu
    50   55   60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ala
65   70   75   80

```
Val Tyr Leu Gln Met Thr Asp Leu Arg Thr Glu Asp Thr Gly Val Tyr
                85                  90                  95

Tyr Cys Ser Arg Asn Tyr Tyr Gly Ser Thr Tyr Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu
                245
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<210> 4
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<223> synthetic construct; light chain Infliximab

<400> 4

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Asp Ile Leu Leu Thr Gln Ser Pro Ala Ile Leu Ser Val Ser Pro Gly
1               5                  10                  15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Phe Val Gly Ser Ser
            20                  25                  30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35                  40                  45

Lys Tyr Ala Ser Glu Ser Met Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Thr Val Glu Ser
65                  70                  75                  80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser His Ser Trp Pro Phe
                85                  90                  95

Thr Phe Gly Ser Gly Thr Asn Leu Glu Val Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
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210

<210> 5
<211> 254
<212> PRT
<213> Artificial Sequence

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<220>
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<223> amino acids 238 to 243 can be present or absent

<220>
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<220>
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<223> amino acids 244 to 254 can be present or absent

<400> 5

Ser Lys Leu Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
1 5 10 15

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

Ser Ser Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Asn Gly Leu
35 40 45

Glu Trp Val Ala Phe Met Ser Tyr Asp Gly Ser Asn Lys Lys Tyr Ala
50 55 60

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
65 70 75 80

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

Tyr Tyr Cys Ala Arg Asp Arg Gly Ile Ala Ala Gly Gly Asn Tyr Tyr
            100                 105                 110

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
        115                 120                 125

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
    130                 135                 140

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
145                 150                 155                 160

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
                165                 170                 175

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
            180                 185                 190

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
        195                 200                 205

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
    210                 215                 220

Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
225                 230                 235                 240

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
                245                 250
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<210> 6
<211> 218
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<220>
<223> synthetic construct; light chain Golimumab

<400> 6

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

Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val
            20                  25                  30

Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg
        35                  40                  45

Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg
    50                  55                  60

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
65                  70                  75                  80

Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn
                85                  90                  95

Trp Pro Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
            100                 105                 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
        195                 200                 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> 7
<211> 235
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<220>
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<223> amino acids 231 to 235 can be present or absent

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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp
20 25 30

His Ala Trp Ser Trp Val Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp
35 40 45

Ile Gly Phe Ile Ser Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser Leu
50 55 60

Gln Gly Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Glu Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

```
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140


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


Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175


Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190


Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
        195                 200                 205


Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Ser Cys Val Glu
    210                 215                 220


Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
225                 230                 235


<210>  8
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic construct; light chain Satralizumab

<400>  8

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


Asp Ser Val Thr Ile Thr Cys Gln Ala Ser Thr Asp Ile Ser Ser His
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Glu Leu Leu Ile
        35                  40                  45


Tyr Tyr Gly Ser His Leu Leu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

```
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65                  70                  75                  80


Glu Asp Ala Ala Thr Tyr Tyr Cys Gly Gln Gly Asn Arg Leu Pro Tyr
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


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

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<223>  amino acids 221 to 224 can be present or absent
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<400> 9

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Asp Asp Tyr
            20                  25                  30


Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60


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


Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95


Ala Lys Gly Arg Asp Ser Phe Asp Ile Trp Gly Gln Gly Thr Met Val
            100                 105                 110


Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125


Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140


Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160


Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
```

```
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205

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

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

Leu
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<210> 10
<211> 214
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<223> sythetic construct; light chain Sarilumab

<400> 10

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
```

```
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
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<210>  11
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<213>  Artificial Sequence

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<223>  amino acids 228 to 233 can be present or absent
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<220>
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<223> amino acids 234 to 244 can be present or absent

<400> 11

Glu Val Gln Leu Val Glu Ser Gly Gly Lys Leu Leu Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Ala Met Ser Trp Phe Arg Gln Ser Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Glu Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Thr Val
50 55 60

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

Leu Glu Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Leu Trp Gly Tyr Tyr Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

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

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195   200   205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210   215   220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225   230   235   240

Ser Val Phe Leu

<210> 12
<211> 213
<212> PRT
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<220>
<223> synthetic construct; light chain Siltuximab

<400> 12

Gln Ile Val Leu Ile Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1   5   10   15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20   25   30

Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Arg Leu Leu Ile Tyr
        35   40   45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50   55   60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65   70   75   80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Gly Tyr Pro Tyr Thr
                85   90   95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
            100   105   110

```
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205


Asn Arg Gly Glu Cys
    210


<210>  13
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<220>
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<220>
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<222>  (235)..(245)
<223>  amino acids 235 to 245 can be present or absent

<400>  13
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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
            20                  25                  30

Tyr Val Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser Ala Ile
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80

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

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
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210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu
245

<210> 14
<211> 217
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<400> 14

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Asn Asn Glu
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Leu Arg Asn
85 90 95

Ile Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
115 120 125

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro

```
    130                 135                 140

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
145                 150                 155                 160

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
                165                 170                 175

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
            180                 185                 190

Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
        195                 200                 205

Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  15
<211>  244
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<220>
<223>  synthetic construct; heavy chain Sirukumab


<220>
<221>  misc
<222>  (224)..(227)
<223>  amino acids 224 to 227 can be present or absent

<220>
<221>  misc
<222>  (228)..(233)
<223>  amino acids 228 to 233 can be present or absent

<220>
<221>  misc
<222>  (234)..(244)
<223>  amino acids 234 to 244 can be present or absent

<400>  15

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Pro Phe
```

```
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Lys Ile Ser Pro Gly Gly Ser Trp Thr Tyr Tyr Ser Asp Thr Val
    50                  55                  60

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

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

Ala Arg Gln Leu Trp Gly Tyr Tyr Ala Leu Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

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

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240
```

Ser Val Phe Leu

<210> 16
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; light chain Sirukumab

<400> 16

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

Glu Arg Ala Thr Leu Ser Cys Ser Ala Ser Ile Ser Val Ser Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45

Asp Met Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
65 70 75 80

Asp Phe Ala Val Tyr Tyr Cys Met Gln Trp Ser Gly Tyr Pro Tyr Thr
85 90 95

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

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

```
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205


Asn Arg Gly Glu Cys
    210


<210>  17
<211>  242
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic construct; heavy chain Olokizumab


<220>
<221>  mis
<222>  (223)..(231)
<223>  amino acids 223 to 231 can be present or absent

<220>
<221>  mis
<222>  (232)..(242)
<223>  amino acids 232 to 242 can be present or absent

<400>  17

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Phe Asn Asp Tyr
            20                  25                  30


Phe Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Gln Met Arg Asn Lys Asn Tyr Gln Tyr Gly Thr Tyr Tyr Ala Glu
    50                  55                  60
```

```
Ser Leu Glu Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65                  70                  75                  80

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

Tyr Cys Ala Arg Glu Ser Tyr Tyr Gly Phe Thr Ser Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
    210                 215                 220

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

Phe Leu
```

<210> 18
<211> 214
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; light chain Olokizumab

<400> 18

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Gly Ile Ser
            20                  25                  30


Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Asn Ala Asn Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Ala Pro Tyr
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205
```

Phe Asn Arg Gly Glu Cys
    210

<210> 19
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; heavy chain Gerilimzumab

<220>
<221> misc
<222> (227)..(230)
<223> amino acids 227 to 230 can be present or absent

<220>
<221> misc
<222> (231)..(236)
<223> amino acids 231 to 236 can be present or absent

<220>
<221> misc
<222> (237)..(247)
<223> amino acids 237 to 247 can be present or absent

<400> 19

Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Thr Ser Arg
            20   25   30

Tyr Tyr Ala Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
        35   40   45

Trp Ile Gly Val Ile Asp Tyr Asp Gly Asp Thr Tyr Tyr Ser Pro Ser
    50   55   60

Leu Lys Ser Arg Val Ser Ile Ser Trp Asp Thr Ser Lys Asn Gln Phe
65   70   75   80

Ser Leu Lys Leu Ser Ser Val Thr Pro Ala Asp Thr Ala Val Tyr Tyr
                85   90   95

```
Cys Ala Arg Asp Pro Asp Val Val Thr Gly Phe His Tyr Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

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

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu
                245
```

<210> 20
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; light chain Gerilimzumab

<400> 20

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

```
Ser Val Thr Ile Ser Cys Ala Gly Ala Asn Asn Asp Ile Gly Thr Tyr
            20                  25                  30

Ala Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Met Ile Tyr Lys Val Thr Thr Arg Ala Ser Gly Ile Pro Asp Arg Phe
    50                  55                  60

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Arg Asn Phe
                85                  90                  95

Asn Asn Ala Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
```

<210> 21
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; heavy chain Tocilizumab

<220>
<221> misc
<222> (224)..(227)
<223> amino acids 224 to 227 can be present or absent

<220>
<221> misc
<222> (228)..(233)
<223> amino acids 228 to 233 can be present or absent

<220>
<221> misc
<222> (234)..(244)
<223> amino acids 234 to 244 can be present or absent

<400> 21

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
20 25 30

His Ala Trp Ser Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ile Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Met Leu Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

```
Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125


Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140


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


Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175


Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190


Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205


Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220


Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240


Ser Val Phe Leu
```

<210> 22
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; light chain Tocilizumab

<400> 22

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
            20                  25                  30
```

```
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 23
<211> 451
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; Adalimumab Heavy Chain

<400> 23

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30


Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
    50                  55                  60


Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


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


Ala Lys Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125


Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140


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


Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175


Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190


Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205
```

```
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

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

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

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

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415
```

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Lys
450

<210> 24
<211> 730
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; Adalimumab Vectorized IgG- fully encoded protein

<400> 24

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

Val Thr Asn Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
20 25 30

Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
35 40 45

Phe Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly
50 55 60

Leu Glu Trp Val Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr
65 70 75 80

Ala Asp Ser Val Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
85 90 95

Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu
115 120 125

```
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
    130                 135                 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145                 150                 155                 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                165                 170                 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            180                 185                 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        195                 200                 205

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    210                 215                 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
225                 230                 235                 240

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
                245                 250                 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            260                 265                 270

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

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

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

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

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
```

```
            340                 345                 350

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

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

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385                 390                 395                 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                405                 410                 415

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

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        435                 440                 445

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

Leu Ser Leu Ser Pro Gly Lys Arg Lys Arg Arg Gly Ser Gly Glu Gly
465                 470                 475                 480

Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro
                485                 490                 495

Met Tyr Arg Met Gln Leu Leu Leu Leu Ile Ala Leu Ser Leu Ala Leu
            500                 505                 510

Val Thr Asn Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
        515                 520                 525

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
    530                 535                 540

Ile Arg Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
545                 550                 555                 560
```

```
Lys Leu Leu Ile Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser
                565                 570                 575

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
            580                 585                 590

Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg Tyr Asn
        595                 600                 605

Arg Ala Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
    610                 615                 620

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
625                 630                 635                 640

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
                645                 650                 655

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
            660                 665                 670

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
        675                 680                 685

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
    690                 695                 700

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
705                 710                 715                 720

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
                725                 730
```

<210> 25
<211> 507
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; Adalimumab Vectorized Fab- fully encoded protein

<400> 25

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

Val Thr Asn Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
            20                  25                  30

Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
        35                  40                  45

Phe Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly
    50                  55                  60

Leu Glu Trp Val Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr
65                  70                  75                  80

Ala Asp Ser Val Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
                85                  90                  95

Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
    130                 135                 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145                 150                 155                 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                165                 170                 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            180                 185                 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        195                 200                 205
```

```
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    210                 215                 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
225                 230                 235                 240

Pro Lys Ser Cys Asp Lys Thr His Arg Lys Arg Arg Gly Ser Gly Glu
                245                 250                 255

Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly
            260                 265                 270

Pro Met Tyr Arg Met Gln Leu Leu Leu Leu Ile Ala Leu Ser Leu Ala
        275                 280                 285

Leu Val Thr Asn Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
    290                 295                 300

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

Gly Ile Arg Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
                325                 330                 335

Pro Lys Leu Leu Ile Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro
            340                 345                 350

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
        355                 360                 365

Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg Tyr
    370                 375                 380

Asn Arg Ala Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
385                 390                 395                 400

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
                405                 410                 415

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            420                 425                 430
```

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        435   440   445

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    450   455   460

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
465   470   475   480

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                485   490   495

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            500   505

<210> 26
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (676)..(687)
<223> nucleotides 676 to 687 can be present or absent

<220>
<221> misc
<222> (688)..(705)
<223> nucleotides 688 to 705 can be present or absent

<220>
<221> misc
<222> (706)..(738)
<223> nucleotides706 to 738 can be present or absent

<400> 26

Gly Ala Gly Gly Thr Gly Cys Ala Gly Cys Thr Gly Gly Thr Gly Gly
1   5   10   15

Ala Gly Ala Gly Cys Gly Gly Cys Gly Gly Cys Gly Gly Cys Cys Thr
            20   25   30

```
Gly Gly Thr Gly Cys Ala Gly Cys Cys Cys Gly Gly Cys Ala Gly Gly
        35                  40                  45

Ala Gly Cys Cys Thr Gly Ala Gly Gly Cys Thr Gly Ala Gly Cys Thr
    50                  55                  60

Gly Cys Gly Cys Cys Gly Cys Cys Ala Gly Cys Gly Gly Cys Thr Thr
65                  70                  75                  80

Cys Ala Cys Cys Thr Thr Cys Gly Ala Cys Gly Ala Cys Thr Ala Cys
                85                  90                  95

Gly Cys Cys Ala Thr Gly Cys Ala Cys Thr Gly Gly Gly Thr Gly Ala
            100                 105                 110

Gly Gly Cys Ala Gly Gly Cys Cys Cys Cys Cys Gly Gly Cys Ala Ala
        115                 120                 125

Gly Gly Gly Cys Cys Thr Gly Gly Ala Gly Thr Gly Gly Gly Thr Gly
    130                 135                 140

Ala Gly Cys Gly Cys Cys Ala Thr Cys Ala Cys Cys Thr Gly Gly Ala
145                 150                 155                 160

Ala Cys Ala Gly Cys Gly Gly Cys Cys Ala Cys Ala Thr Cys Gly Ala
                165                 170                 175

Cys Thr Ala Cys Gly Cys Cys Gly Ala Cys Ala Gly Cys Gly Thr Gly
            180                 185                 190

Gly Ala Gly Gly Gly Cys Ala Gly Gly Thr Thr Cys Ala Cys Cys Ala
        195                 200                 205

Thr Cys Ala Gly Cys Ala Gly Gly Gly Ala Cys Ala Ala Cys Gly Cys
    210                 215                 220

Cys Ala Ala Gly Ala Ala Cys Ala Gly Cys Cys Thr Gly Thr Ala Cys
225                 230                 235                 240
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Cys Thr Gly Cys Ala Gly Ala Thr Gly Ala Ala Cys Ala Gly Cys Cys
                245                 250                 255

Thr Gly Ala Gly Gly Gly Cys Cys Gly Ala Gly Gly Ala Cys Ala Cys
            260                 265                 270

Cys Gly Cys Cys Gly Thr Gly Thr Ala Cys Thr Ala Cys Thr Gly Cys
        275                 280                 285

Gly Cys Cys Ala Ala Gly Gly Thr Gly Ala Gly Cys Thr Ala Cys Cys
    290                 295                 300

Thr Gly Ala Gly Cys Ala Cys Cys Gly Cys Cys Ala Gly Cys Ala Gly
305                 310                 315                 320

Cys Cys Thr Gly Gly Ala Cys Thr Ala Cys Thr Gly Gly Gly Gly Cys
                325                 330                 335

Cys Ala Gly Gly Gly Cys Ala Cys Cys Cys Thr Gly Gly Thr Gly Ala
            340                 345                 350

Cys Cys Gly Thr Gly Ala Gly Cys Ala Gly Cys Gly Cys Cys Ala Gly
        355                 360                 365

Cys Ala Cys Cys Ala Ala Gly Gly Gly Cys Cys Cys Cys Ala Gly Cys
    370                 375                 380

Gly Thr Gly Thr Thr Cys Cys Cys Cys Cys Thr Gly Gly Cys Cys Cys
385                 390                 395                 400

Cys Cys Ala Gly Cys Ala Gly Cys Ala Ala Gly Ala Gly Cys Ala Cys
                405                 410                 415

Cys Ala Gly Cys Gly Gly Cys Gly Gly Cys Ala Cys Cys Gly Cys Cys
            420                 425                 430

Gly Cys Cys Cys Thr Gly Gly Gly Cys Thr Gly Cys Cys Thr Gly Gly
        435                 440                 445

Thr Gly Ala Ala Gly Gly Ala Cys Thr Ala Cys Thr Thr Cys Cys Cys
    450                 455                 460
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Cys Gly Ala Gly Cys Cys Cys Gly Thr Gly Ala Cys Cys Gly Thr Gly
465                 470                 475                 480

Ala Gly Cys Thr Gly Gly Ala Ala Cys Ala Gly Cys Gly Gly Cys Gly
                485                 490                 495

Cys Cys Cys Thr Gly Ala Cys Cys Ala Gly Cys Gly Gly Cys Gly Thr
            500                 505                 510

Gly Cys Ala Cys Ala Cys Cys Thr Thr Cys Cys Cys Cys Gly Cys Cys
        515                 520                 525

Gly Thr Gly Cys Thr Gly Cys Ala Gly Ala Gly Cys Ala Gly Cys Gly
    530                 535                 540

Gly Cys Cys Thr Gly Thr Ala Cys Ala Gly Cys Cys Thr Gly Ala Gly
545                 550                 555                 560

Cys Ala Gly Cys Gly Thr Gly Gly Thr Gly Ala Cys Cys Gly Thr Gly
                565                 570                 575

Cys Cys Cys Ala Gly Cys Ala Gly Cys Ala Gly Cys Cys Thr Gly Gly
            580                 585                 590

Gly Cys Ala Cys Cys Cys Ala Gly Ala Cys Cys Thr Ala Cys Ala Thr
        595                 600                 605

Cys Thr Gly Cys Ala Ala Cys Gly Thr Gly Ala Ala Cys Cys Ala Cys
    610                 615                 620

Ala Ala Gly Cys Cys Cys Ala Gly Cys Ala Ala Cys Ala Cys Cys Ala
625                 630                 635                 640

Ala Gly Gly Thr Gly Gly Ala Cys Ala Ala Gly Ala Ala Gly Gly Thr
                645                 650                 655

Gly Gly Ala Gly Cys Cys Cys Ala Ala Gly Ala Gly Cys Thr Gly Cys
            660                 665                 670
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Gly Ala Cys Ala Ala Gly Ala Cys Cys Cys Ala Cys Ala Cys Cys Thr
        675                 680                 685

Gly Cys Cys Cys Cys Cys Cys Cys Thr Gly Cys Cys Cys Cys Gly Cys
    690                 695                 700

Cys Cys Cys Cys Gly Ala Gly Cys Thr Gly Cys Thr Gly Gly Gly Cys
705                 710                 715                 720

Gly Gly Cys Cys Cys Cys Ala Gly Cys Gly Thr Gly Thr Thr Cys Cys
                725                 730                 735

Thr Gly
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<210> 27
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody

<400> 27

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gacatccaga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagggtgacc       60

atcacctgca gggccagcca gggcatcagg aactacctgg cctggtacca gcagaagccc      120

ggcaaggccc ccaagctgct gatctacgcc gccagcaccc tgcagagcgg cgtgcccagc      180

aggttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagccc      240

gaggacgtgg ccacctacta ctgccagagg tacaacaggg ccccctacac cttcggccag      300

ggcaccaagg tggagatcaa gaggaccgtg gccgccccca gcgtgttcat cttcccccccc      360

agcgacgagc agctgaagag cggcaccgcc agcgtggtgt gcctgctgaa caacttctac      420

cccagggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag      480

gagagcgtga ccgagcagga cagcaaggac agcacctaca gcctgagcag caccctgacc      540

ctgagcaagg ccgactacga gaagcacaag gtgtacgcct gcgaggtgac ccaccagggc      600

ctgagcagcc ccgtgaccaa gagcttcaac aggggcgagt gc                         642
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<210> 28
<211> 734

<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (673)..(684)
<223> nucleotides 673 to 684 can be present or absent

<220>
<221> misc
<222> (685)..(702)
<223> nucleotides 685 to 702 can be present or absent

<220>
<221> misc
<222> (703)..(734)
<223> nucleotides 703 to 734 can be present or absent

<400> 28
gaggtgaagc tggaggagag cggcggcggc ctggtgcagc ccggcggcag catgaagctg 60

agctgcgtgg ccagcggctt catcttcagc aaccactgga tgaactgggt gaggcagagc 120

cccgagaagg gcctggagtg ggtggccgag atcaggagca agagcatcaa cagcgccacc 180

cactacgccg agagcgtgaa gggcaggttc accatcagca gggacgacag caagagcgcc 240

gtgtacctgc agatgaccga cctgaggacc gaggacaccg gcgtgtacta ctgcagcagg 300

aactactacg gcagcaccta cgactactgg ggccagggca ccaccctgac cgtgagcagc 360

gccagcacca agggccccag cgtgttcccc ctggccccca gcagcaagag caccagcggc 420

ggcaccgccg ccctgggctg cctggtgaag gactacttcc ccgagcccgt gaccgtgagc 480

tggaacagcg gcgccctgac cagcggcgtg cacaccttcc ccgccgtgct gcagagcagc 540

ggcctgtaca gcctgagcag cgtggtgacc gtgcccagca gcagcctggg cacccagacc 600

tacatctgca acgtgaacca caagcccagc aacaccaagg tggacaagaa ggtggagccc 660

aagagctgcg acaagaccca cacctgcccc ccctgccccg cccccgagct gctgggcggc 720

cccagcggtt cctg 734

<210> 29
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 29
gacatcctgc tgacccagag ccccgccatc ctgagcgtga gccccggcga gagggtgagc 60

ttcagctgca gggccagcca gttcgtgggc agcagcatcc actggtacca gcagaggacc 120

aacggcagcc ccaggctgct gatcaagtac gccagcgaga gcatgagcgg catccccagc 180

aggttcagcg gcagcggcag cggcaccgac ttcaccctga gcatcaacac cgtggagagc 240

gaggacatcg ccgactacta ctgccagcag agccacagct ggcccttcac cttcggcagc 300

ggcaccaacc tggaggtgaa gaggaccgtg gccgccccca gcgtgttcat cttcccccc 360

agcgacgagc agctgaagag cggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

cccagggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtga ccgagcagga cagcaaggac agcacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcacaag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgagcagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 30
<211> 720
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (659)..(669)
<223> amino acids 659 to 669 can be present or absent

<220>
<221> misc
<222> (670)..(687)
<223> amino acids 670 to 687 can be present or absent

<220>
<221> misc
<222> (688)..(720)
<223> amino acids 688 to 720 can be present or absent

<400> 30
agcaagctgc aggtgcagct ggtggagagc ggcggcggcg tggtgcagcc cggcaggagc 60

ctgaggctga gctgcgccgc cagcggcttc atcttcagca gctacgccat gcactgggtg 120

aggcaggccc ccggcaacgg cctggagtgg gtggccttca tgagctacga cggcagcaac 180

aagaagtacg ccgacagcgt gaagggcagg ttcaccatca gcagggacaa cagcaagaac 240

accctgtacc tgcagatgaa cagcctgagg gccgaggaca ccgccgtgta ctactgcgcc 300

agggacaggg gcatcgccgc cggcggcaac tactactact acggcatgga cgtgtggggc 360

cagggcacca ccgtgaccgt gagcagcgcc agcaccaagg gccccagcgt gttccccctg 420

gcccccagca gcaagagcac cagcggcggc accgccgccc tgggctgcct ggtgaaggac 480

tacttccccg agcccgtgac cgtgagctgg aacagcggcg ccctgaccag cggcgtgcac 540

accttccccg ccgtgctgca gagcagcggc ctgtacagcc tgagcagcgt ggtgaccgtg 600

cccagcagca gcctgggcac ccagacctac atctgcaacg tgaaccacaa gcccagcaag 660

acccacacct gcccccccctg ccccgccccc gagctgctgg gcggccccag cgtgttcctg 720

<210> 31
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 31
gccggcagcg agatcgtgct gacccagagc cccgccaccc tgagcctgag ccccggcgag 60

agggccaccc tgagctgcag ggccagccag agcgtgtaca gctacctggc ctggtaccag 120

cagaagcccg gccaggcccc caggctgctg atctacgacg ccagcaacag ggccaccggc 180

atccccgcca ggttcagcgg cagcggcagc ggcaccgact tcaccctgac catcagcagc 240

ctggagcccg aggacttcgc cgtgtactac tgccagcaga ggagcaactg gccccccttc 300

accttcggcc ccggcaccaa ggtggacatc aagaggaccg tggccgcccc cagcgtgttc 360

atcttccccc ccagcgacga gcagctgaag agcggcaccg ccagcgtggt gtgcctgctg 420

aacaacttct accccaggga ggccaaggtg cagtggaagg tggacaacgc cctgcagagc 480

ggcaacagcc aggagagcgt gaccgagcag gacagcaagg acagcaccta cagcctgagc 540

agcaccctga ccctgagcaa ggccgactac gagaagcaca aggtgtacgc ctgcgaggtg 600

acccaccagg gcctgagcag ccccgtgacc aagagcttca acaggggcga gtgc 654

<210> 32
<211> 705
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (673)..(690)
<223> amino acids 673 to 690 can be present or absent

<220>
<221> misc
<222> (691)..(705)
<223> amino acids 691 to 705 can be present or absent

<400> 32
caggtgcagc tgcaggagag cggccccggc ctggtgaagc ccagcgagac cctgagcctg 60

acctgcgccg tgagcggcca cagcatcagc cacgaccacg cctggagctg ggtgaggcag 120

ccccccggcg agggcctgga gtggatcggc ttcatcagct acagcggcat caccaactac 180

aaccccagcc tgcagggcag ggtgaccatc agcagggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcgc caggagcctg 300

gccaggacca ccgccatgga ctactggggc gagggcaccc tggtgaccgt gagcagcgcc 360

agcaccaagg gccccagcgt gttccccctg gcccccagca gcaagagcac cagcggcggc 420

accgccgccc tgggctgcct ggtgaaggac tacttccccg agcccgtgac cgtgagctgg 480

aacagcggcg ccctgaccag cggcgtgcac accttccccg ccgtgctgca gagcagcggc 540

ctgtacagcc tgagcagcgt ggtgaccgtg cccagcagca acttcggcac ccagacctac 600

acctgcaacg tggaccacaa gcccagcaac accaaggtgg acaagaccgt ggagaggaag 660

agctgcgtgg agtgcccccc ctgccccgcc ccccccgtgg ccggc 705

<210> 33
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 33
gacatccaga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagcgtgacc 60

atcacctgcc aggccagcac cgacatcagc agccacctga actggtacca gcagaagccc 120

ggcaaggccc ccgagctgct gatctactac ggcagccacc tgctgagcgg cgtgcccagc 180

aggttcagcg gcagcggcag cggcaccgac ttcaccttca ccatcagcag cctggaggcc 240

gaggacgccg ccacctacta ctgcggccag ggcaacaggc tgccctacac cttcggccag 300

ggcaccaagg tggagatcga gaggaccgtg gccgccccca gcgtgttcat cttcccccc 360

agcgacgagc agctgaagag cggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

cccagggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtga ccgagcagga cagcaaggac agcacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcacaag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgagcagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 34
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (661)..(672)
<223> nucleotids 661 to 672 can be present or absent

<220>
<221> misc
<222> (673)..(690)
<223> nucleotids 673 to 690 can be present or absent

<220>
<221> misc
<222> (691)..(723)
<223> nucleotids 691 to 723 can be present or absent

<400> 34
gaggtgcagc tggtggagag cggcggcggc ctggtgcagc ccggcaggag cctgaggctg 60

agctgcgccg ccagcaggtt caccttcgac gactacgcca tgcactgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtgagcggc atcagctgga acagcggcag gatcggctac 180

gccgacagcg tgaagggcag gttcaccatc agcagggaca acgccgagaa cagcctgttc 240

ctgcagatga acggcctgag ggccgaggac accgccctgt actactgcgc caagggcagg 300

gacagcttcg acatctgggg ccagggcacc atggtgaccg tgagcagcgc cagcaccaag 360

ggccccagcg tgttcccccc ggcccccagc agcaagagca ccagcggcgg caccgccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagcccgtga ccgtgagctg gaacagcggc 480

gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540

ctgagcagcg tggtgaccgt gcccagcagc agcctgggca cccagaccta catctgcaac 600

gtgaaccaca agcccagcaa caccaaggtg gacaagaagg tggagcccaa gagctgcgac 660

aagacccaca cctgcccccc ctgccccgcc cccgagctgc tgggcggccc cagcgtgttc 720

ctg 723

<210> 35
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 35
gacatccaga tgacccagag ccccagcagc gtgagcgcca gcgtgggcga cagggtgacc 60

atcacctgca gggccagcca gggcatcagc agctggctgg cctggtacca gcagaagccc 120

ggcaaggccc ccaagctgct gatctacggc gccagcagcc tggagagcgg cgtgcccagc 180

aggttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagccc 240

gaggacttcg ccagctacta ctgccagcag gccaacagct tcccctacac cttcggccag 300

ggcaccaagc tggagatcaa gaggaccgtg gccgccccca gcgtgttcat cttccccccc 360

agcgacgagc agctgaagag cggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420

cccagggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480

gagagcgtga ccgagcagga cagcaaggac agcacctaca gcctgagcag caccctgacc 540

ctgagcaagg ccgactacga gaagcacaag gtgtacgcct gcgaggtgac ccaccagggc 600

ctgagcagcc ccgtgaccaa gagcttcaac aggggcgagt gc 642

<210> 36
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (670)..(681)
<223> nucleotides 670 to 681 can be present or absent

<220>
<221> misc
<222> (682)..(699)
<223> nucleotides 682 to 699 can be present or absent

<220>
<221> misc
<222> (700)..(732)
<223> nucleotides 700 to 732 can be present or absent

<400> 36
gaagtgcagc tggtggaaag cggcggcaaa ctgctgaaac cgggcggcag cctgaaactg 60

agctgcgcgg cgagcggctt tacctttagc agctttgcga tgagctggtt tcgccagagc 120

ccggaaaaac gcctggaatg ggtggcggaa attagcagcg gcggcagcta tacctattat 180

ccggataccg tgaccggccg ctttaccatt agccgcgata acgcgaaaaa caccctgtat 240

ctggaaatga gcagcctgcg cagcgaagat accgcgatgt attattgcgc gcgcggcctg 300

tggggctatt atgcgctgga ttattggggc cagggcacca gcgtgaccgt gagcagcgcg 360

agcaccaaag gcccgagcgt gtttccgctg gcgccgagca gcaaaagcac cagcggcggc 420

accgcggcgc tgggctgcct ggtgaaagat tattttccgg aaccggtgac cgtgagctgg 480

aacagcggcg cgctgaccag cggcgtgcat acctttccgg cggtgctgca gagcagcggc 540

ctgtatagcc tgagcagcgt ggtgaccgtg ccgagcagca gcctgggcac ccagacctat 600

atttgcaacg tgaaccataa accgagcaac accaaagtgg ataaaaaagt ggaaccgaaa 660

agctgcgata agacccacac ctgccccccc tgccccgccc ccgagctgct gggcggcccc 720

agcgtgttcc tg 732

<210> 37

<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 37
cagattgtgc tgattcagag cccggcgatt atgagcgcga gcccgggcga aaaagtgacc 60

atgacctgca gcgcgagcag cagcgtgagc tatatgtatt ggtatcagca gaaaccgggc 120

agcagcccgc gcctgctgat ttatgatacc agcaacctgg cgagcggcgt gccggtgcgc 180

tttagcggca gcggcagcgg caccagctat agcctgacca ttagccgcat ggaagcggaa 240

gatgcggcga cctattattg ccagcagtgg agcggctatc cgtatacctt tggcggcggc 300

accaaactgg aaattaaacg caccgtggcg gcgccgagcg tgtttatttt tccgccgagc 360

gatgaacagc tgaaaagcgg caccgcgagc gtggtgtgcc tgctgaacaa cttttatccg 420

cgcgaagcga aagtgcagtg gaaagtggat aacgcgctgc agagcggcaa cagccaggaa 480

agcgtgaccg aacaggatag caaagatagc acctatagcc tgagcagcac cctgaccctg 540

agcaaagcgg attatgaaaa acataaagtg tatgcgtgcg aagtgaccca tcagggcctg 600

agcagcccgg tgaccaaaag ctttaaccgc ggcgaatgc 639

<210> 38
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (673)..(684)
<223> nucleotides 673 to 684 can be present or absent

<220>
<221> misc
<222> (685)..(702)
<223> nucleotides 685 to 702 can be present or absent

<220>
<221> misc
<222> (703)..(735)
<223> nucleotides 703 to 735 can be present or absent

<400> 38
gaagtgcagc tggtggaaag cggcggcggc ctggtgcagc cgggcggcag cctgcgcctg 60

agctgcgcgg cgagcggctt tagcctgagc aactattatg tgacctgggt gcgccaggcg 120

ccgggcaaag gcctggaatg ggtgggcatt atttatggca gcgatgaaac cgcgtatgcg 180

accagcgcga ttggccgctt taccattagc cgcgataaca gcaaaaacac cctgtatctg 240

cagatgaaca gcctgcgcgc ggaagatacc gcggtgtatt attgcgcgcg cgatgatagc 300

agcgattggg atgcgaaatt taacctgtgg ggccagggca ccctggtgac cgtgagcagc 360

gcgagcacca aaggcccgag cgtgtttccg ctggcgccga gcagcaaaag caccagcggc 420

ggcaccgcgg cgctgggctg cctggtgaaa gattattttc cggaaccggt gaccgtgagc 480

tggaacagcg gcgcgctgac cagcggcgtg cataccttтc cggcggtgct gcagagcagc 540

ggcctgtata gcctgagcag cgtggtgacc gtgccgagca gcagcctggg cacccagacc 600

tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaacg cgtggaaccg 660

aaaagctgcg ataagaccca cacctgcccc ccctgccccg cccccgagct gctgggcggc 720

cccagcgtgt tcctg 735

<210> 39
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (670)..(681)
<223> nucleotides 670 to 681 can be present or absent

<220>
<221> misc
<222> (682)..(699)
<223> nucleotides 682 to 699 can be present or absent

<220>
<221> misc
<222> (700)..(732)
<223> nucleotides 700 to 732 can be present or absent

<400> 39

gcgattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgcc aggcgagcca gagcattaac aacgaactga gctggtatca gcagaaaccg 120

ggcaaagcgc cgaaactgct gatttatcgc gcgagcaccc tggcgagcgg cgtgccgagc 180

cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240

gatgattttg cgacctatta ttgccagcag ggctatagcc tgcgcaacat tgataacgcg 300

tttggcggcg gcaccaaagt ggaaattaaa cgcaccgtgg cggcgccgag cgtgtttatt 360

tttccgccga gcgatgaaca gctgaaaagc ggcaccgcga gcgtggtgtg cctgctgaac 420

aacttttatc cgcgcgaagc gaaagtgcag tggaaagtgg ataacgcgct gcagagcggc 480

aacagccagg aaagcgtgac cgaacaggat agcaaagata gcacctatag cctgagcagc 540

accctgaccc tgagcaaagc ggattatgaa aaacataaag tgtatgcgtg cgaagtgacc 600

catcagggcc tgagcagccc ggtgaccaaa agctttaacc gcggcgaatg cgaaccgaaa 660

agctgcgata agacccacac ctgcccccc tgccccgccc ccgagctgct gggcggcccc 720

agcgtgttcc tg 732

<210> 40
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (670)..(681)
<223> nucleotides 670 to 681 can be present or absent

<220>
<221> misc
<222> (682)..(699)
<223> nucleotides 682 to 699 can be present or absent

<220>
<221> misc
<222> (700)..(732)
<223> nucleotides 700 to 732 can be present or absent

<400> 40
gaagtgcagc tggtggaaag cggcggcggc ctggtgcagc cgggcggcag cctgcgcctg 60

agctgcgcgg cgagcggctt tacctttagc ccgtttgcga tgagctgggt gcgccaggcg 120

ccgggcaaag gcctggaatg ggtggcgaaa attagcccgg gcggcagctg gacctattat 180

agcgataccg tgaccggccg ctttaccatt agccgcgata acgcgaaaaa cagcctgtat 240

ctgcagatga acagcctgcg cgcggaagat accgcggtgt attattgcgc gcgccagctg 300

tggggctatt atgcgctgga tatttggggc cagggcacca ccgtgaccgt gagcagcgcg 360

agcaccaaag gcccgagcgt gtttccgctg gcgccgagca gcaaaagcac cagcggcggc 420

accgcggcgc tgggctgcct ggtgaaagat tattttccgg aaccggtgac cgtgagctgg 480

aacagcggcg cgctgaccag cggcgtgcat acctttccgg cggtgctgca gagcagcggc 540

ctgtatagcc tgagcagcgt ggtgaccgtg ccgagcagca gcctgggcac ccagacctat 600

atttgcaacg tgaaccataa accgagcaac accaaagtgg ataaaaaagt ggaaccgaaa 660

agctgcgata agacccacac ctgccccccc tgccccgccc ccgagctgct gggcggcccc 720

agcgtgttcc tg 732

<210> 41
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 41
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caggcgccgc gcctgctgat ttatgatatg agcaacctgg cgagcggcat tccggcgcgc 180

tttagcggca gcggcagcgg caccgatttt accctgacca ttagcagcct ggaaccggaa 240

gattttgcgg tgtattattg catgcagtgg agcggctatc cgtatacctt tggcggcggc 300

accaaagtgg aaattaaacg caccgtggcg gcgccgagcg tgtttatttt tccgccgagc 360

gatgaacagc tgaaaagcgg caccgcgagc gtggtgtgcc tgctgaacaa cttttatccg 420

cgcgaagcga aagtgcagtg gaaagtggat aacgcgctgc agagcggcaa cagccaggaa 480

agcgtgaccg aacaggatag caaagatagc acctatagcc tgagcagcac cctgaccctg 540

agcaaagcgg attatgaaaa acataaagtg tatgcgtgcg aagtgaccca tcagggcctg 600

agcagcccgg tgaccaaaag ctttaaccgc ggcgaatgc 639

<210> 42
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (667)..(693)
<223> nucleotides 667 to 693 can be present or absent

<220>
<221> misc
<222> (694)..(726)
<223> nucleotides 694 to 726 can be present or absent

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ccgggcaaag gcctggaatg ggtggcgcag atgcgcaaca aaaactatca gtatggcacc 180

tattatgcgg aaagcctgga aggccgcttt accattagcc gcgatgatag caaaaacagc 240

ctgtatctgc agatgaacag cctgaaaacc gaagataccg cggtgtatta ttgcgcgcgc 300

gaaagctatt atggctttac cagctattgg ggccagggca ccctggtgac cgtgagcagc 360

gcgagcacca aaggcccgag cgtgtttccg ctggcgccgt gcagccgcag caccagcgaa 420

agcaccgcgg cgctgggctg cctggtgaaa gattattttc cggaaccggt gaccgtgagc 480

tggaacagcg gcgcgctgac cagcggcgtg cataccttтc cggcggtgct gcagagcagc 540

ggcctgtata gcctgagcag cgtggtgacc gtgccgagca gcagcctggg caccaaaacc 600

tatacctgca acgtggatca taaaccgagc aacaccaaag tggataaacg cgtggagagc 660

aagtacggcc ccccctgccc cccctgcccc gcccccgagt tcctgggcgg ccccagcgtg 720

ttcctg 726

<210> 43
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 43
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ggcaaagcgc cgaaactgct gatttataac gcgaacaacc tggcggatgg cgtgccgagc 180

cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240

gaagattttg cgacctatta ttgcctgcag cataacagcg cgccgtatac ctttggccag 300

ggcaccaaac tggaaattaa acgcaccgtg gcggcgccga gcgtgtttat ttttccgccg 360

agcgatgaac agctgaaaag cggcaccgcg agcgtggtgt gcctgctgaa caacttttat 420

ccgcgcgaag cgaaagtgca gtggaaagtg gataacgcgc tgcagagcgg caacagccag 480

gaaagcgtga ccgaacagga tagcaaagat agcacctata gcctgagcag caccctgacc 540

ctgagcaaag cggattatga aaaacataaa gtgtatgcgt gcgaagtgac ccatcagggc 600

ctgagcagcc cggtgaccaa aagctttaac cgcggcgaat gc 642

<210> 44
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<220>
<221> misc
<222> (679)..(690)
<223> nucleotides 679 to 690 can be present or absent

<220>
<221> misc
<222> (691)..(708)
<223> nucleotides 691 to 708 can be present or absent

<220>
<221> misc
<222> (709)..(741)
<223> nucleotides 709 to 741 can be present or absent

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cagccgccgg gcaaaggcct ggaatggatt ggcgtgattg attatgatgg cgatacctat 180

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ccggatgtgg tgaccggctt tcattatgat tattggggcc agggcaccat ggtgaccgtg 360

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gtgagctgga acagcggcgc gctgaccagc ggcgtgcata cctttccggc ggtgctgcag 540

agcagcggcc tgtatagcct gagcagcgtg gtgaccgtgc cgagcagcag cctgggcacc 600

cagacctata tttgcaacgt gaaccataaa ccgagcaaca ccaaagtgga taaaaaagtg 660

gaaccgaaaa gctgcgataa gacccacacc tgccccccct gccccgcccc cgagctgctg 720

ggcggcccca gcgtgttcct g 741

<210> 45
<211> 648
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 45
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ctgccgggca ccgcgccgaa actgatgatt tataaagtga ccacccgcgc gagcggcatt 180

ccggatcgct ttagcggcag caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caggcggaag atgaagcgga ttattattgc gcgagctatc gcaactttaa caacgcggtg 300

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gcgggcgtgg aaaccaccac cccgagcaaa cagagcaaca acaaatatgc ggcgagcagc 540

tatctgagcc tgaccccgga acagtggaaa agccatcgca gctatagctg ccaggtgacc 600

catgaaggca gcaccgtgga aaaaaccgtg gcgccgaccg aatgcagc 648

<210> 46
<211> 4513
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 46
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aggggttcct tgtagttaat gattaacccg ccatgctact tatctaccag ggtaatgggg 180

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agcgagcgcg cag 4513

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<211> 4092
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 47
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acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaataggga 180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240

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<211> 2193
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 48
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agatacaaca gagccccata cacctttgga cagggcacaa aggtggaaat caagagaaca 2460

gtggctgccc catctgtgtt catcttccca ccatctgatg aacagctgaa gtctggcact 2520

gcctctgttg tgtgcctgct gaacaacttc taccctagag aagccaaggt gcagtggaag 2580

gttgacaatg ccctgcagtc tggcaatagc caagaatctg tgacagagca ggactccaag 2640

gattccacct acagcctgag cagcaccctg acactgagca aggctgacta tgagaagcac 2700

aaagtgtatg cctgtgaagt gacacaccag ggactgagca gcccagtgac caagagcttc 2760

aacaggggag agtgctgata actcgaggac ggggtgaact acgcctgagg atccgatctt 2820

tttccctctg ccaaaaatta tggggacatc atgaagcccc ttgagcatct gacttctggc 2880

taataaagga aatttatttt cattgcaata gtgtgttgga atttttttgtg tctctcactc 2940

ggaagcaatt cgttgatctg aatttcgacc acccataata cccattaccc tggtagataa 3000

gtagcatggc gggttaatca ttaactacaa ggaacccctа gtgatggagt tggccactcc 3060

ctctctgcgc gctcgctcgc tcactgaggc cgggcgacca aaggtcgccc gacgcccggg 3120

ctttgcccgg gcggcctcag tgagcgagcg agcgcgcag 3159

<210> 53
<211> 2751
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 53
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 agggccaggt 300

gagtatctca gggatccaga catggggata tgggaggtgc ctctgatccc agggctcact 360

gtgggtctct ctgttcacag gttgaattcg ccaccatgta cagaatgcag ctgctgctgc 420

tcattgccct gtctctggcc ctggtcacca attctgaagt gcagctggtg gaaagtggtg 480

gtggactggt gcagcctggc agaagcctga gactgtcttg tgctgcctct ggcttcacct 540

ttgatgacta tgccatgcac tgggtcagac aggcccctgg caaaggactg gaatgggtgt 600

cagccatcac ctggaactct ggccacattg actatgctga ctctgtggaa ggcagattca 660

ccatcagcag agacaatgcc aagaacagcc tgtacctgca gatgaactcc ctgagagctg 720

aggacacagc agtgtactac tgtgccaagg tgtcctacct gagcacagcc agcagcctgg 780

attattgggg ccagggcaca ctggttacag tgtcctctgc cagcacaaag ggcccctctg 840

tttttccact ggctcccagc agcaagagca ccagtggtgg aacagctgcc ctgggctgtc 900

tggtcaagga ttacttccct gagcctgtga cagtgtcttg gaactcaggg gctctgacct 960

ctggggtgca cacatttcca gctgtgctgc agtcctctgg cctgtactct ctgtcctctg 1020

tggtcacagt gcctagctct agcctgggca cccagaccta catctgcaat gtgaaccaca 1080

agcctagcaa caccaaggtg gacaagaagg tggaacccaa gagctgtgac aagacccaca 1140

cctgtcctcc atgtcctgct ccagaactgc ttggaggccc ttctgtgttc ctgtttcctc 1200

caaagcctaa ggacaccctg atgatcagca gaacccctga agtgacctgt gtggtggttg 1260

atgtgtccca tgaggaccca gaagtgaagt tcaattggta tgtggatggg gttgaagtgc 1320

acaatgctaa gaccaagcct agagaggaac agtacaacag cacctacaga gtggtgtctg 1380

tgctgacagt gctgcatcag gactggctga atggcaaaga gtacaagtgc aaagtgtcca 1440

acaaggccct gcctgctcct attgagaaaa ccatctccaa ggccaagggc cagccaagag 1500

aaccccaggt ttacacactg ccacctagca gagatgagct gaccaagaac caggtgtccc 1560

tgacctgcct ggttaagggc ttctaccccct ctgacattgc tgtggaatgg gagagcaatg 1620

gccagcctga gaacaactac aagacaaccc ctcctgtgct ggactctgat ggctcattct 1680

tcctgtacag caagctgact gtggacaagt ccagatggca gcaggggaat gtgttcagct 1740

gctctgtgat gcatgaggcc ctgcacaacc actacaccca gaaaagtctg agtctgagcc 1800

ctggcaagag aaagagaaga ggctctggag aaggcagagg ctccctgctg acatgtgggg 1860

atgttgaaga gaatcctggg cctatgtata ggatgcaact gctcctcctg attgctctga 1920

gcctggctct tgtgaccaac tctgacatcc agatgacaca gagccctagc agcctgtctg 1980

cttctgtggg agacagagtg accatcacat gcagagccag ccagggaatc agaaactacc 2040

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tgaccatttc tagcctgcag cctgaggatg tggccaccta ctactgccag agatacaaca 2220

gagccccata cacctttgga cagggcacaa aggtggaaat caagagaaca gtggctgccc 2280

catctgtgtt catcttccca ccatctgatg aacagctgaa gtctggcact gcctctgttg 2340

tgtgcctgct gaacaacttc taccctagag aagccaaggt gcagtggaag gttgacaatg 2400

ccctgcagtc tggcaatagc caagaatctg tgacagagca ggactccaag gattccacct 2460

acagcctgag cagcaccctg acactgagca aggctgacta tgagaagcac aaagtgtatg 2520

cctgtgaagt gacacaccag ggactgagca gcccagtgac caagagcttc aacaggggag 2580

agtgctgata actcgaggac ggggtgaact acgcctgagg atccgatctt tttccctctg 2640

ccaaaaatta tggggacatc atgaagcccc ttgagcatct gacttctggc taataaagga 2700

aatttatttt cattgcaata gtgtgttgga atttttttgtg tctctcactc g 2751

<210> 54
<211> 1353
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 54
gaagtgcagc tggtggaaag tggtggtgga ctggtgcagc ctggcagaag cctgagactg 60

tcttgtgctg cctctggctt cacctttgat gactatgcca tgcactgggt cagacaggcc 120

cctggcaaag gactggaatg ggtgtcagcc atcacctgga actctggcca cattgactat 180

gctgactctg tggaaggcag attcaccatc agcagagaca atgccaagaa cagcctgtac 240

ctgcagatga actccctgag agctgaggac acagcagtgt actactgtgc caaggtgtcc 300

tacctgagca cagccagcag cctggattat tggggccagg gcacactggt tacagtgtcc 360

tctgccagca caaagggccc ctctgttttt ccactggctc ccagcagcaa gagcaccagt 420

ggtggaacag ctgccctggg ctgtctggtc aaggattact tccctgagcc tgtgacagtg 480

tcttggaact caggggctct gacctctggg gtgcacacat ttccagctgt gctgcagtcc 540

tctggcctgt actctctgtc ctctgtggtc acagtgccta gctctagcct gggcacccag 600

acctacatct gcaatgtgaa ccacaagcct agcaacacca aggtggacaa gaaggtggaa 660

cccaagagct gtgacaagac ccacacctgt cctccatgtc ctgctccaga actgcttgga 720

ggcccttctg tgttcctgtt tcctccaaag cctaaggaca ccctgatgat cagcagaacc 780

cctgaagtga cctgtgtggt ggttgatgtg tcccatgagg acccagaagt gaagttcaat 840

tggtatgtgg atggggttga agtgcacaat gctaagacca agcctagaga ggaacagtac 900

aacagcacct acagagtggt gtctgtgctg acagtgctgc atcaggactg gctgaatggc 960

aaagagtaca agtgcaaagt gtccaacaag gccctgcctg ctcctattga gaaaaccatc 1020

tccaaggcca agggccagcc aagagaaccc caggtttaca cactgccacc tagcagagat 1080

gagctgacca agaaccaggt gtccctgacc tgcctggtta agggcttcta cccctctgac 1140

attgctgtgg aatgggagag caatggccag cctgagaaca actacaagac aacccctcct 1200

gtgctggact ctgatggctc attcttcctg tacagcaagc tgactgtgga caagtccaga 1260

tggcagcagg ggaatgtgtt cagctgctct gtgatgcatg aggccctgca caaccactac 1320

acccagaaaa gtctgagtct gagccctggc aag 1353

<210> 55
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 55
gaagtgcagc tggtggaaag tggtggtgga ctggtgcagc ctggcagaag cctgagactg 60

tcttgtgctg cctctggctt cacctttgat gactatgcca tgcactgggt cagacaggcc 120

cctggcaaag gactggaatg ggtgtcagcc atcacctgga actctggcca cattgactat 180

gctgactctg tggaaggcag attcaccatc agcagagaca atgccaagaa cagcctgtac 240

ctgcagatga actccctgag agctgaggac acagcagtgt actactgtgc caaggtgtcc 300

tacctgagca cagccagcag cctggattat tggggccagg gcacactggt tacagtgtcc 360

tct 363

<210> 56
<211> 294

<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 56
gccagcacaa agggcccctc tgtttttcca ctggctccca gcagcaagag caccagtggt 60

ggaacagctg ccctgggctg tctggtcaag gattacttcc ctgagcctgt gacagtgtct 120

tggaactcag gggctctgac ctctggggtg cacacatttc agctgtgct gcagtcctct 180

ggcctgtact ctctgtcctc tgtggtcaca gtgcctagct ctagcctggg cacccagacc 240

tacatctgca atgtgaacca caagcctagc aacaccaagg tggacaagaa ggtg 294

<210> 57
<211> 651
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 57
gctccagaac tgcttggagg cccttctgtg ttcctgtttc ctccaaagcc taaggacacc 60

ctgatgatca gcagaacccc tgaagtgacc tgtgtggtgg ttgatgtgtc ccatgaggac 120

ccagaagtga agttcaattg gtatgtggat ggggttgaag tgcacaatgc taagaccaag 180

cctagagagg aacagtacaa cagcacctac agagtggtgt ctgtgctgac agtgctgcat 240

caggactggc tgaatggcaa agagtacaag tgcaaagtgt ccaacaaggc cctgcctgct 300

cctattgaga aaaccatctc caaggccaag ggccagccaa gagaacccca ggtttacaca 360

ctgccaccta gcagagatga gctgaccaag aaccaggtgt ccctgacctg cctggttaag 420

ggcttctacc cctctgacat tgctgtggaa tgggagagca atggccagcc tgagaacaac 480

tacaagacaa cccctcctgt gctggactct gatggctcat tcttcctgta cagcaagctg 540

actgtggaca agtccagatg gcagcagggg aatgtgttca gctgctctgt gatgcatgag 600

gccctgcaca accactacac ccagaaaagt ctgagtctga gccctggcaa g 651

<210> 58
<211> 651
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 58
gctccagaac tgcttggagg cccttctgtg ttcctgtttc ctccaaagcc taaggacacc 60

ctgatgatca gcagaacccc tgaagtgacc tgtgtggtgg ttgatgtgtc ccatgaggac 120

ccagaagtga agttcaattg gtatgtggat ggggttgaag tgcacaatgc taagaccaag 180

cctagagagg aacagtacaa cagcacctac agagtggtgt ctgtgctgac agtgctgcat 240

caggactggc tgaatggcaa agagtacaag tgcaaagtgt ccaacaaggc cctgcctgct 300

cctattgaga aaaccatctc caaggccaag ggccagccaa gagaacccca ggtttacaca 360

ctgccaccta gcagagatga gctgaccaag aaccaggtgt ccctgacctg cctggttaag 420

ggcttctacc cctctgacat tgctgtggaa tgggagagca atggccagcc tgagaacaac 480

tacaagacaa cccctcctgt gctggactct gatggctcat tcttcctgta cagcaagctg 540

actgtggaca agtccagatg gcagcagggg aatgtgttca gctgctctgt gatgcatgag 600

gccctgcaca accactacac ccagaaaagt ctgagtctga gccctggcaa g 651

<210> 59
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 59
gacatccaga tgacacagag ccctagcagc ctgtctgctt ctgtgggaga cagagtgacc 60

atcacatgca gagccagcca gggaatcaga aactacctgg cctggtatca gcaaaagcct 120

ggcaaggccc ctaagctgct gatctatgca gccagcacac tgcagtcagg ggtgccaagc 180

agattttcag gctctggctc tggcacagac ttcaccctga ccatttctag cctgcagcct 240

gaggatgtgg ccacctacta ctgccagaga tacaacagag ccccatacac ctttggacag 300

ggcacaaagg tggaaatcaa g 321

<210> 60
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 60
agaacagttg cagcaccctc agttttcatc ttccccccct cagatgaaca gctgaagtct 60

ggcactgcct ctgttgtgtg cctgctgaac aacttctacc ccagagaagc caaggtgcag 120

tggaaggttg acaatgccct gcagtcaggc aacagccaag aatctgtgac tgaacaggat 180

tccaaggata gcacctacag cctgagcagc accctgacac tgagcaaggc tgactatgag 240

aagcacaaag tgtatgcctg tgaagtgacc caccagggac tgagcagccc agtgaccaag 300

agcttcaaca ggggagagtg ctga 324

<210> 61
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 61

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

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

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

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

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

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

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

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

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

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

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
165 170 175

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

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

<210> 62
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 62

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

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

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

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
50 55 60

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

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


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


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


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


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


Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                165                 170                 175


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


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


<210>  63
<211>  205
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic construct; antibody fragment

<400>  63

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


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


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

```
Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
    50                  55                  60

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

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

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

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

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

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

Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
                165                 170                 175

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

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

<210> 64
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 64

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

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

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

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

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

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

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

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

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

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

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                165                 170                 175

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

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

<210> 65
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 65

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


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


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


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


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


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


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


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


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


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


Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                165                 170                 175


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

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

<210> 66
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 66

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

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

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

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

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

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

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

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

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

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

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                165   170   175

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

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

<210> 67
<211> 203
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 67

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

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

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

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
    50   55   60

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

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

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

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

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

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

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                165                 170                 175

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

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200
```

<210> 68
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 68

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

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

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

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

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

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

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

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

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

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

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                165                 170                 175

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

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

<210> 69
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 69

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

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

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

Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu
    50                  55                  60
```

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


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


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


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


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


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


Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                165                 170                 175


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


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


<210>  70
<211>  205
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic construct; antibody fragment

<400>  70

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


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

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

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

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

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

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

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

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

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

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                165                 170                 175

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

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

<210> 71
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 71

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

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

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

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

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

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

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

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

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

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

Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
                165                 170                 175

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

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

<210> 72
<211> 204

<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody fragment

<400> 72

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

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

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

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

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

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

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

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

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

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

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
165 170 175

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

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
195 200

<210> 73
<211> 1725
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 73

Gly Ala Cys Ala Thr Thr Gly Ala Thr Thr Ala Thr Thr Gly Ala Cys
1 5 10 15

Thr Ala Gly Thr Thr Ala Thr Thr Ala Ala Thr Ala Gly Thr Ala Ala
20 25 30

Thr Cys Ala Ala Thr Thr Ala Cys Gly Gly Gly Gly Thr Cys Ala Thr
35 40 45

Thr Ala Gly Thr Thr Cys Ala Thr Ala Gly Cys Cys Cys Ala Thr Ala
50 55 60

Thr Ala Thr Gly Gly Ala Gly Thr Thr Cys Cys Gly Cys Gly Thr Thr
65 70 75 80

Ala Cys Ala Thr Ala Ala Cys Thr Thr Ala Cys Gly Gly Thr Ala Ala
85 90 95

Ala Thr Gly Gly Cys Cys Cys Gly Cys Cys Thr Gly Gly Cys Thr Gly
100 105 110

Ala Cys Cys Gly Cys Cys Cys Ala Ala Cys Gly Ala Cys Cys Cys Cys
115 120 125

Cys Gly Cys Cys Cys Ala Thr Thr Gly Ala Cys Gly Thr Cys Ala Ala
130 135 140

Thr Ala Ala Thr Gly Ala Cys Gly Thr Ala Thr Gly Thr Thr Cys Cys
145 150 155 160

```
Cys Ala Thr Ala Gly Thr Ala Ala Cys Gly Cys Cys Ala Ala Thr Ala
                165                 170                 175

Gly Gly Gly Ala Cys Thr Thr Thr Cys Cys Ala Thr Thr Gly Ala Cys
            180                 185                 190

Gly Thr Cys Ala Ala Thr Gly Gly Gly Thr Gly Gly Ala Gly Thr Ala
        195                 200                 205

Thr Thr Thr Ala Cys Gly Gly Thr Ala Ala Ala Cys Thr Gly Cys Cys
    210                 215                 220

Cys Ala Cys Thr Thr Gly Gly Cys Ala Gly Thr Ala Cys Ala Thr Cys
225                 230                 235                 240

Ala Ala Gly Thr Gly Thr Ala Thr Cys Ala Thr Ala Thr Gly Cys Cys
                245                 250                 255

Ala Ala Gly Thr Ala Cys Gly Cys Cys Cys Cys Cys Thr Ala Thr Thr
            260                 265                 270

Gly Ala Cys Gly Thr Cys Ala Ala Thr Gly Ala Cys Gly Gly Thr Ala
        275                 280                 285

Ala Ala Thr Gly Gly Cys Cys Cys Gly Cys Cys Thr Gly Gly Cys Ala
    290                 295                 300

Thr Thr Ala Thr Gly Cys Cys Cys Ala Gly Thr Ala Cys Ala Thr Gly
305                 310                 315                 320

Ala Cys Cys Thr Thr Ala Thr Gly Gly Gly Ala Cys Thr Thr Thr Cys
                325                 330                 335

Cys Thr Ala Cys Thr Thr Gly Gly Cys Ala Gly Thr Ala Cys Ala Thr
            340                 345                 350

Cys Thr Ala Cys Gly Thr Ala Thr Thr Ala Gly Thr Cys Ala Thr Cys
        355                 360                 365
```

```
Gly Cys Thr Ala Thr Thr Ala Cys Cys Ala Thr Gly Gly Thr Cys Gly
    370                 375                 380

Ala Gly Gly Thr Gly Ala Gly Cys Cys Cys Cys Ala Cys Gly Thr Thr
385                 390                 395                 400

Cys Thr Gly Cys Thr Thr Cys Ala Cys Thr Cys Thr Cys Cys Cys Cys
                405                 410                 415

Ala Thr Cys Thr Cys Cys Cys Cys Cys Cys Cys Cys Thr Cys Cys Cys
            420                 425                 430

Cys Ala Cys Cys Cys Cys Cys Ala Ala Thr Thr Thr Thr Gly Thr Ala
        435                 440                 445

Thr Thr Thr Ala Thr Thr Thr Ala Thr Thr Thr Thr Thr Thr Ala Ala
    450                 455                 460

Thr Thr Ala Thr Thr Thr Thr Gly Thr Gly Cys Ala Gly Cys Gly Ala
465                 470                 475                 480

Thr Gly Gly Gly Gly Gly Cys Gly Gly Gly Gly Gly Gly Gly Gly Gly
                485                 490                 495

Gly Gly Gly Gly Gly Gly Gly Cys Gly Cys Gly Cys Gly Cys Cys Ala
            500                 505                 510

Gly Gly Cys Gly Gly Gly Gly Cys Gly Gly Gly Gly Cys Gly Gly Gly
        515                 520                 525

Gly Cys Gly Ala Gly Gly Gly Gly Cys Gly Gly Gly Gly Cys Gly Gly
    530                 535                 540

Gly Gly Cys Gly Ala Gly Gly Cys Gly Gly Ala Gly Ala Gly Gly Thr
545                 550                 555                 560

Gly Cys Gly Gly Cys Gly Gly Cys Ala Gly Cys Cys Ala Ala Thr Cys
                565                 570                 575

Ala Gly Ala Gly Cys Gly Gly Cys Gly Cys Gly Cys Thr Cys Cys Gly
            580                 585                 590
```

```
Ala Ala Ala Gly Thr Thr Thr Cys Cys Thr Thr Thr Thr Ala Thr Gly
        595                 600                 605

Gly Cys Gly Ala Gly Gly Cys Gly Gly Cys Gly Gly Cys Gly Gly Cys
    610                 615                 620

Gly Gly Cys Gly Gly Cys Cys Cys Thr Ala Thr Ala Ala Ala Ala Ala
625                 630                 635                 640

Gly Cys Gly Ala Ala Gly Cys Gly Cys Gly Cys Gly Gly Cys Gly Gly
                645                 650                 655

Gly Cys Gly Gly Gly Ala Gly Thr Cys Gly Cys Thr Gly Cys Gly Cys
            660                 665                 670

Gly Cys Thr Gly Cys Cys Thr Thr Cys Gly Cys Cys Cys Cys Gly Thr
        675                 680                 685

Gly Cys Cys Cys Cys Gly Cys Thr Cys Cys Gly Cys Cys Gly Cys Cys
    690                 695                 700

Gly Cys Cys Thr Cys Gly Cys Gly Cys Cys Gly Cys Cys Cys Gly Cys
705                 710                 715                 720

Cys Cys Cys Gly Gly Cys Thr Cys Thr Gly Ala Cys Thr Gly Ala Cys
                725                 730                 735

Cys Gly Cys Gly Thr Thr Ala Cys Thr Cys Cys Cys Ala Cys Ala Gly
            740                 745                 750

Gly Thr Gly Ala Gly Cys Gly Gly Gly Cys Gly Gly Gly Ala Cys Gly
        755                 760                 765

Gly Cys Cys Cys Thr Thr Cys Thr Cys Cys Thr Cys Cys Gly Gly Gly
    770                 775                 780

Cys Thr Gly Thr Ala Ala Thr Thr Ala Gly Cys Gly Cys Thr Thr Gly
785                 790                 795                 800
```

```
Gly Thr Thr Thr Ala Ala Thr Gly Ala Cys Gly Gly Cys Thr Thr Gly
                805                 810                 815

Thr Thr Thr Cys Thr Thr Thr Thr Cys Thr Gly Thr Gly Gly Cys Thr
            820                 825                 830

Gly Cys Gly Thr Gly Ala Ala Ala Gly Cys Cys Thr Thr Gly Ala Gly
        835                 840                 845

Gly Gly Gly Cys Thr Cys Cys Gly Gly Gly Ala Gly Gly Gly Cys Cys
    850                 855                 860

Cys Thr Thr Thr Gly Thr Gly Cys Gly Gly Gly Gly Gly Gly Ala Gly
865                 870                 875                 880

Cys Gly Gly Cys Thr Cys Gly Gly Gly Gly Gly Gly Thr Gly Cys Gly
                885                 890                 895

Thr Gly Cys Gly Thr Gly Thr Gly Thr Gly Thr Gly Thr Gly Cys Gly
            900                 905                 910

Thr Gly Gly Gly Gly Ala Gly Cys Gly Cys Cys Gly Cys Gly Thr Gly
        915                 920                 925

Cys Gly Gly Cys Thr Cys Cys Gly Cys Gly Cys Thr Gly Cys Cys Cys
    930                 935                 940

Gly Gly Cys Gly Gly Cys Thr Gly Thr Gly Ala Gly Cys Gly Cys Thr
945                 950                 955                 960

Gly Cys Gly Gly Gly Cys Gly Cys Gly Gly Cys Gly Cys Gly Gly Gly
                965                 970                 975

Gly Cys Thr Thr Thr Gly Thr Gly Cys Gly Cys Thr Cys Cys Gly Cys
            980                 985                 990

Ala Gly Thr Gly Thr Gly Cys Gly  Cys Gly Ala Gly Gly  Gly Gly Ala
        995                 1000                1005

Gly Cys  Gly Cys Gly Gly Cys  Cys Gly Gly Gly Gly  Gly Cys Gly
    1010                1015                1020
```

```
Gly Thr  Gly Cys Cys Cys Cys  Gly Cys Gly Gly Thr  Gly Cys Gly
    1025                1030                1035

Gly Gly  Gly Gly Gly Gly Gly  Cys Thr Gly Cys Gly  Ala Gly Gly
    1040                1045                1050

Gly Gly  Ala Ala Cys Ala Ala  Ala Gly Gly Cys Thr  Gly Cys Gly
    1055                1060                1065

Thr Gly  Cys Gly Gly Gly Gly  Thr Gly Thr Gly Thr  Gly Cys Gly
    1070                1075                1080

Thr Gly  Gly Gly Gly Gly Gly  Gly Thr Gly Ala Gly  Cys Ala Gly
    1085                1090                1095

Gly Gly  Gly Gly Thr Gly Thr  Gly Gly Gly Cys Gly  Cys Gly Thr
    1100                1105                1110

Cys Gly  Gly Thr Cys Gly Gly  Gly Cys Thr Gly Cys  Ala Ala Cys
    1115                1120                1125

Cys Cys  Cys Cys Cys Cys Thr  Gly Cys Ala Cys Cys  Cys Cys Cys
    1130                1135                1140

Cys Thr  Cys Cys Cys Cys Gly  Ala Gly Thr Thr Gly  Cys Thr Gly
    1145                1150                1155

Ala Gly  Cys Ala Cys Gly Gly  Cys Cys Cys Gly Gly  Cys Thr Thr
    1160                1165                1170

Cys Gly  Gly Gly Thr Gly Cys  Gly Gly Gly Gly Cys  Thr Cys Cys
    1175                1180                1185

Gly Thr  Ala Cys Gly Gly Gly  Gly Cys Gly Thr Gly  Gly Cys Gly
    1190                1195                1200

Cys Gly  Gly Gly Gly Cys Thr  Cys Gly Cys Cys Gly  Thr Gly Cys
    1205                1210                1215
```

```
Cys Gly  Gly Gly Cys Gly Gly  Gly Gly Gly Gly Thr  Gly Gly Cys
    1220                 1225                 1230

Gly Gly  Cys Ala Gly Gly Thr  Gly Gly Gly Gly Gly  Thr Gly Cys
    1235                 1240                 1245

Cys Gly  Gly Gly Cys Gly Gly  Gly Gly Cys Gly Gly  Gly Gly Cys
    1250                 1255                 1260

Cys Gly  Cys Cys Thr Cys Gly  Gly Gly Cys Cys Gly  Gly Gly Gly
    1265                 1270                 1275

Ala Gly  Gly Gly Cys Thr Cys  Gly Gly Gly Gly Gly  Ala Gly Gly
    1280                 1285                 1290

Gly Gly  Cys Gly Cys Gly Gly  Cys Gly Gly Cys Cys  Cys Cys Cys
    1295                 1300                 1305

Gly Gly  Ala Gly Cys Gly Cys  Cys Gly Gly Cys Gly  Gly Cys Thr
    1310                 1315                 1320

Gly Thr  Cys Gly Ala Gly Gly  Cys Gly Cys Gly Gly  Cys Gly Ala
    1325                 1330                 1335

Gly Cys  Cys Gly Cys Ala Gly  Cys Cys Ala Thr Thr  Gly Cys Cys
    1340                 1345                 1350

Thr Thr  Thr Thr Ala Thr Gly  Gly Thr Ala Ala Thr  Cys Gly Thr
    1355                 1360                 1365

Gly Cys  Gly Ala Gly Ala Gly  Gly Gly Cys Gly Cys  Ala Gly Gly
    1370                 1375                 1380

Gly Ala  Cys Thr Thr Cys Cys  Thr Thr Thr Gly Thr  Cys Cys Cys
    1385                 1390                 1395

Ala Ala  Ala Thr Cys Thr Gly  Thr Gly Cys Gly Gly  Ala Gly Cys
    1400                 1405                 1410

Cys Gly  Ala Ala Ala Thr Cys  Thr Gly Gly Gly Ala  Gly Gly Cys
    1415                 1420                 1425
```

```
Gly Cys  Cys Gly Cys Cys Gly  Cys Ala Cys Cys Cys  Cys Cys Thr
    1430                1435                1440


Cys Thr  Ala Gly Cys Gly Gly  Gly Cys Gly Cys Gly  Gly Gly Gly
    1445                1450                1455


Cys Gly  Ala Ala Gly Cys Gly  Gly Thr Gly Cys Gly  Gly Cys Gly
    1460                1465                1470


Cys Cys  Gly Gly Cys Ala Gly  Gly Ala Ala Gly Gly  Ala Ala Ala
    1475                1480                1485


Thr Gly  Gly Gly Cys Gly Gly  Gly Gly Ala Gly Gly  Gly Cys Cys
    1490                1495                1500


Thr Thr  Cys Gly Thr Gly Cys  Gly Thr Cys Gly Cys  Cys Gly Cys
    1505                1510                1515


Gly Cys  Cys Gly Cys Cys Gly  Thr Cys Cys Cys Cys  Thr Thr Cys
    1520                1525                1530


Thr Cys  Cys Cys Thr Cys Thr  Cys Cys Ala Gly Cys  Cys Thr Cys
    1535                1540                1545


Gly Gly  Gly Gly Cys Thr Gly  Thr Cys Cys Gly Cys  Gly Gly Gly
    1550                1555                1560


Gly Gly  Gly Ala Cys Gly Gly  Cys Thr Gly Cys Cys  Thr Thr Cys
    1565                1570                1575


Gly Gly  Gly Gly Gly Gly Gly  Ala Cys Gly Gly Gly  Gly Cys Ala
    1580                1585                1590


Gly Gly  Gly Cys Gly Gly Gly  Gly Thr Thr Cys Gly  Gly Cys Thr
    1595                1600                1605


Thr Cys  Thr Gly Gly Cys Gly  Thr Gly Thr Gly Ala  Cys Cys Gly
    1610                1615                1620
```

```
Gly Cys  Gly Gly Cys Thr Cys  Thr Ala Gly Ala Gly  Cys Cys Thr
    1625                1630                1635


Cys Thr  Gly Cys Thr Ala Ala  Cys Cys Ala Thr Gly  Thr Thr Cys
    1640                1645                1650


Ala Thr  Gly Cys Cys Thr Thr  Cys Thr Thr Cys Thr  Thr Thr Thr
    1655                1660                1665


Thr Cys  Cys Thr Ala Cys Ala  Gly Cys Thr Cys Cys  Thr Gly Gly
    1670                1675                1680


Gly Cys  Ala Ala Cys Gly Thr  Gly Cys Thr Gly Gly  Thr Thr Ala
    1685                1690                1695


Thr Thr  Gly Thr Gly Cys Thr  Gly Thr Cys Thr Cys  Ala Thr Cys
    1700                1705                1710


Ala Thr  Thr Thr Thr Gly Gly  Cys Ala Ala Ala Gly
    1715                1720                1725
```

<210> 74
<211> 1676
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 74

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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 cccacccccа 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 ctacag 1676

<210> 75
<211> 251
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 75
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> 76
<211> 212
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 76
gggcagagcg cacatcgccc acagtccccg agaagttggg gggaggggtc ggcaattgaa 60

cgggtgccta gagaaggtgg cgcggggtaa actgggaaag tgatgtcgtg tactggctcc 120

gccttttttcc cgagggtggg ggagaaccgt atataagtgc agtagtcgcc gtgaacgttc 180

tttttcgcaa cgggtttgcc gccagaacac ag 212

<210> 77
<211> 295
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 77
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> 78
<211> 127
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; polyA

<400> 78
gatctttttc cctctgccaa aaattatggg gacatcatga agccccttga gcatctgact 60

tctggctaat aaaggaaatt tattttcatt gcaatagtgt gttggaattt tttgtgtctc 120

tcactcg 127

<210> 79
<211> 133
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; chimeric intron

<400> 79
gtaagtatca aggttacaag acaggtttaa ggagaccaat agaaactggg cttgtcgaga 60

cagagaagac tcttgcgttt ctgataggca cctattggtc ttactgacat ccactttgcc 120

tttctctcca cag 133

<210> 80
<211> 82
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; intron

<400> 80
gtgagtatct cagggatcca gacatgggga tatgggaggt gcctctgatc ccagggctca 60

ctgtgggtct ctctgttcac ag 82

<210> 81
<211> 130
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; ITR

<400> 81
ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgaccttt 60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtggccaa ctccatcact 120

aggggttcct 130

<210> 82
<211> 106

<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; ITR

<400> 82
ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgaccttt 60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtgg 106

<210> 83
<211> 143
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; ITR

<400> 83
gaacccctag tgatggagtt ggccactccc tctctgcgcg ctcgctcgct cactgaggcc 60

gcccgggcaa agcccgggcg tcgggcgacc tttggtcgcc cggcctcagt gagcgagcga 120

gcgcgcagag agggagtggc caa 143

<210> 84
<211> 110
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; ITR

<400> 84
ttggccactc cctctctgcg cgctcgctcg ctcactgagg ccgggcgacc aaaggtcgcc 60

cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc gagcgcgcag 110

<210> 85
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 85

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> 86
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; signal sequence

<400> 86
atgtatagga tgcaactgct cctcctgatt gctctgagcc tggctcttgt gaccaactct   60

<210> 87
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 87

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> 88
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 88

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> 89
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 89

Met Ala Pro Leu Arg Pro Leu Leu Ile Leu Ala Leu Leu Ala Trp Val
1 5 10 15

Ala Leu Ala

<210> 90
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 90

Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1 5 10 15

Val Ala

<210> 91
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 91

Met Arg Leu Leu Ala Phe Leu Ser Leu Leu Ala Leu Val Leu Gln Glu
1 5 10 15

Thr Gly Thr

<210> 92
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 92

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser

<210> 93
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 93

Met Ala Phe Leu Trp Leu Leu Ser Cys Trp Ala Leu Leu Gly Thr Thr
1 5 10 15

Phe Gly

<210> 94
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 94

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> 95
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 95

Met Asn Leu Leu Leu Ile Leu Thr Phe Val Ala Ala Ala Val Ala
1 5 10 15

<210> 96
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 96

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser

<210> 97
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 97

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> 98
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 98

Met Lys Ala Ala Val Leu Thr Leu Ala Val Leu Phe Leu Thr Gly Ser
1   5   10   15

Gln Ala

<210> 99
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 99

Met Lys Leu Leu Ala Ala Thr Val Leu Leu Leu Thr Ile Cys Ser Leu
1   5   10   15

Glu Gly

<210> 100
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 100

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> 101
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 101

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> 102
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 102

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> 103
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 103

Met Trp Leu Leu Val Ser Val Ile Leu Ile Ser Arg Ile Ser Ser Val
1   5   10   15

Gly Gly

<210> 104
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 104

Met Leu Leu Leu Phe Ser Val Ile Leu Ile Ser Trp Val Ser Thr Val
1   5   10   15

Gly Gly

<210> 105
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 105

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

Ala Trp Thr

<210> 106
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 106

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> 107
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 107

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> 108
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 108

Met Lys Ser Leu Val Leu Leu Leu Cys Leu Ala Gln Leu Trp Gly Cys
1   5   10   15

His Ser

<210> 109
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 109

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> 110
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 110

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

Leu Thr

<210> 111
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 111

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> 112
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 112

Met Glu His Lys Glu Val Val Leu Leu Leu Leu Leu Leu Phe Leu Lys Ser
1   5   10   15

Gly Gln Gly

<210> 113
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 113

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> 114
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 114

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> 115
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 115

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> 116
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 116

Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu
1   5   10   15

Cys Leu Ala

<210> 117
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 117

Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu
1   5   10   15

Ala

<210> 118
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 118

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> 119
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 119

Met Lys Leu Val Phe Leu Val Leu Leu Phe Leu Gly Ala Leu Gly Leu
1   5   10   15

Cys Leu Ala

<210> 120
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 120

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> 121
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 121

Met Ser Leu Ser Ala Phe Thr Leu Phe Leu Ala Leu Ile Gly Gly Thr
1   5   10   15

Ser Gly

<210> 122
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 122

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> 123
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 123

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> 124
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 124

Met Gln Ala Leu Val Leu Leu Leu Cys Ile Gly Ala Leu Leu Gly His
1   5   10   15

Ser Ser Cys

<210> 125
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 125

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> 126
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 126

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> 127
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 127

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> 128
<211> 3
<212> PRT
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<220>
<223> synthetic construct; linker

<400> 128

Gly Ser Gly
1

<210> 129
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 129

Arg Lys Arg Arg
1

<210> 130
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 130

Arg Arg Arg Arg
1

<210> 131
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 131

Arg Arg Lys Arg
1

<210> 132
<211> 4

<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 132

Arg Lys Lys Arg
1

<210> 133
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 133

Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro
1   5   10   15

Gly Pro

<210> 134
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 134

Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu
1   5   10   15

Glu Asn Pro Gly Pro
            20

<210> 135
<211> 19
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; linker

<400> 135

Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn
1 5 10 15

Pro Gly Pro

<210> 136
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 136

Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val
1 5 10 15

Glu Glu Asn Pro Gly Pro
20

<210> 137
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 137

Gln Cys Thr Asn Tyr Ala Leu Leu Lys Leu Ala Gly Asp Val Glu Ser
1 5 10 15

Asn Pro Gly Pro
20

<210> 138
<211> 23
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; linker

<400> 138

Gly Ser Gly Gln Cys Thr Asn Tyr Ala Leu Leu Lys Leu Ala Gly Asp
1 5 10 15

Val Glu Ser Asn Pro Gly Pro
20

<210> 139
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 139

Ala Pro Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu Ala Gly
1 5 10 15

Asp Val Glu Ser Asn Pro Gly Pro
20

<210> 140
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 140

Gly Ser Gly Ala Pro Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys
1 5 10 15

Leu Ala Gly Asp Val Glu Ser Asn Pro Gly Pro
20 25

<210> 141
<211> 22
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; linker

<400> 141

Arg Lys Arg Arg Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val
1 5 10 15

Glu Glu Asn Pro Gly Pro
20

<210> 142
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 142

Arg Lys Arg Arg Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys
1 5 10 15

Gly Asp Val Glu Glu Asn Pro Gly Pro
20 25

<210> 143
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 143

Arg Lys Arg Arg Ala Pro Val Lys Gln Thr Leu Asn Phe Asp Leu Leu
1 5 10 15

Lys Leu Ala Gly Asp Val Glu Ser Asn Pro Gly Pro
20 25

<210> 144
<211> 31
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; linker

<400> 144

Arg Lys Arg Arg Gly Ser Gly Ala Pro Val Lys Gln Thr Leu Asn Phe
1 5 10 15

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

<210> 145
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 145
agaaagagaa gaggctctgg agaaggcaga ggctccctgc tgacatgtgg ggatgttgaa 60

gagaatcctg ggcct 75

<210> 146
<211> 12
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 146
agaaagagaa ga 12

<210> 147
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 147
agaaagagaa gaggctctgg a 21

<210> 148
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 148
ggctctgga 9

<210> 149
<211> 54
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; linker

<400> 149
gaaggcagag gctccctgct gacatgtggg gatgttgaag agaatcctgg gcct 54

<210> 150
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 150

Cys Pro Pro Cys Pro Ala
1 5

<210> 151
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 151

Cys Pro Pro Cys Pro
1 5

<210> 152
<211> 5
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; hinge region

<400> 152

Cys Pro Pro Cys Ala
1   5

<210> 153
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 153

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> 154
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 154

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
            20

<210> 155
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 155

Glu Pro Lys Ser Cys Asp Lys Thr His Leu
1 5 10

<210> 156
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 156

Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10

<210> 157
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 157

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

<210> 158
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<400> 158

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

<210> 159
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 159

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> 160
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
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<400> 160

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> 161
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 161

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

Pro Glu Ala Ala Gly Gly
20

<210> 162
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 162

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

Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
20 25

<210> 163
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 163

Glu Arg Lys Ser Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
1 5 10 15

Ala Gly

<210> 164
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 164

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

<210> 165
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 165

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly

<210> 166
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 166

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10

<210> 167
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 167

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala
1 5 10

<210> 168
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
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<400> 168

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
20

<210> 169
<211> 24

<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 169

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu
20

<210> 170
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 170

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
1 5 10 15

Ala Gly

<210> 171
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 171

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

<210> 172
<211> 22
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; hinge region

<400> 172

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

Pro Glu Leu Ala Gly Ala
20

<210> 173
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 173

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

Pro Glu Leu Ala Gly Ala Pro Ser Val Phe Leu
20 25

<210> 174
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 174

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

Pro Glu Leu Ala Gly Ala Pro Ser Val Phe Leu
20 25

<210> 175
<211> 22
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; hinge region

<400> 175

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

Pro Glu Phe Glu Gly Gly
            20

<210> 176
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 176

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

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

<210> 177
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge region

<400> 177

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

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

<210> 178
<211> 15
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; signal peptide

<400> 178

Met Trp Cys Ile Val Leu Phe Ser Leu Leu Ala Trp Val Tyr Ala
1 5 10 15

<210> 179
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 179

Met Asn Pro Thr Leu Ile Leu Ala Ala Phe Cys Leu Gly Ile Ala Ser
1 5 10 15

Ala

<210> 180
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 180

Met Trp Gln Leu Trp Ala Ser Leu Cys Cys Leu Leu Val Leu Ala Asn
1 5 10 15

Ala

<210> 181
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 181

Met Leu Leu Ile Leu Leu Ser Val Ala Leu Leu Ala Phe Ser Ser Ala
1   5   10   15

<210> 182
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 182

Met Trp Lys Arg Trp Leu Ala Leu Ala Leu Ala Leu Val Ala Val Ala
1   5   10   15

Trp Val Arg Ala
            20

<210> 183
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody heavy chain

<220>
<221> misc
<222> (670)..(681)
<223> nucleotides 670-681 can be present or absent

<220>
<221> misc
<222> (682)..(699)
<223> nucleotides 682-699 can be present or absent

<220>
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<222> (700)..(732)
<223> nucleotides 700-732 can be present or absent

<400> 183
caggtgcagc tgcaggaaag cggcccgggc ctggtgcgcc cgagccagac cctgagcctg   60

acctgcaccg tgagcggcta tagcattacc agcgatcatg cgtggagctg ggtgcgccag   120

ccgccgggcc gcggcctgga atggattggc tatattagct atagcggcat taccacctat   180

aacccgagcc tgaaaagccg cgtgaccatg ctgcgcgata ccagcaaaaa ccagtttagc   240

ctgcgcctga gcagcgtgac cgcggcggat accgcggtgt attattgcgc gcgcagcctg 300

gcgcgcacca ccgcgatgga ttattggggc cagggcagcc tggtgaccgt gagcagcgcg 360

agcaccaaag gcccgagcgt gtttccgctg gcgccgagca gcaaaagcac cagcggcggc 420

accgcggcgc tgggctgcct ggtgaaagat tattttccgg aaccggtgac cgtgagctgg 480

aacagcggcg cgctgaccag cggcgtgcat acctttccgg cggtgctgca gagcagcggc 540

ctgtatagcc tgagcagcgt ggtgaccgtg ccgagcagca gcctgggcac ccagacctat 600

atttgcaacg tgaaccataa accgagcaac accaaagtgg ataaaaaagt ggaaccgaaa 660

agctgcgata agacccacac ctgccccccc tgccccgccc ccgagctgct gggcggcccc 720

agcgtgttcc tg 732

<210> 184
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody light chain

<400> 184
gatattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgcc gcgcgagcca ggatattagc agctatctga actggtatca gcagaaaccg 120

ggcaaagcgc cgaaactgct gatttattat accagccgcc tgcatagcgg cgtgccgagc 180

cgctttagcg gcagcggcag cggcaccgat tttaccttta ccattagcag cctgcagccg 240

gaagatattg cgacctatta ttgccagcag ggcaacaccc tgccgtatac ctttggccag 300

ggcaccaaag tggaaattaa acgcaccgtg gcggcgccga gcgtgtttat ttttccgccg 360

agcgatgaac agctgaaaag cggcaccgcg agcgtggtgt gcctgctgaa caacttttat 420

ccgcgcgaag cgaaagtgca gtggaaagtg gataacgcgc tgcagagcgg caacagccag 480

gaaagcgtga ccgaacagga tagcaaagat agcacctata gcctgagcag caccctgacc 540

ctgagcaaag cggattatga aaaacataaa gtgtatgcgt gcgaagtgac ccatcagggc 600

ctgagcagcc cggtgaccaa aagctttaac cgcggcgaat gc 642

<210> 185
<211> 205

<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; Fc domain

<400> 185

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

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

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

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

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

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

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

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

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

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

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
165 170 175

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

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

<210> 186
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 186

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> 187
<211> 735
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 187

```
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> 188
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 188

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> 189
<211> 736
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic constructs; AAV vector

<400> 189

```
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> 190
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 190

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> 191
<211> 734
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 191

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> 192
<211> 734
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 192

```
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> 193
<211> 724
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 193

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> 194
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 194

```
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> 195
<211> 737
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 195

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> 196
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 196

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> 197
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 197

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> 198
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 198

```
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> 199
<211> 738

<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 199

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> 200
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 200

```
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> 201
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 201

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> 202
<211> 738

<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 202

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> 203
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 203

```
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> 204
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 204

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> 205
<211> 735

<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 205

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>  206
<211>  735
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic constructs; AAV vector

<400>  206

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> 207
<211> 735
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 207

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> 208
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 208

```
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> 209
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic constructs; AAV vector

<400> 209

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

<220>
<223> synthetic constructs; AAV vector

<400> 210

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> 211
<211> 1212
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 211
gtctaacaaa aaagccaaaa acggccagaa tttagcggac aatttactag tctaacactg 60

aaaattacat attgacccaa atgattacat ttcaaaaggt gcctaaaaaa cttcacaaaa 120

cacactcgcc aaccccgagc gcatagttca aaaccggagc ttcagctact taagaagata 180

ggtacataaa accgaccaaa gaaactgacg cctcacttat ccctcccctc accagaggtc 240

cggcgcctgt cgattcagga gagcctaccc taggcccgaa ccctgcgtcc tgcgacggag 300

aaaagcctac cgcacaccta ccggcaggtg gccccaccct gcattataag ccaacagaac 360

gggtgacgtc acgacacgac gagggcgcgc gctcccaaag gtacgggtgc actgcccaac 420

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

aaagccccgg ccagcccagc agcccgctac tcaccaagtg acgatcacag cgatccacaa 840

acaagaaccg cgacccaaat cccggctgcg acggaactag ctgtgccaca cccggcgcgt 900

ccttatataa tcatcggcgt tcaccgcccc acggagatcc ctccgcagaa tcgccgagaa 960

gggactactt ttcctcgcct gttccgctct ctggaaagaa aaccagtgcc ctagagtcac 1020

ccaagtcccg tcctaaaatg tccttctgct gatactgggg ttctaaggcc gagtcttatg 1080

agcagcgggc cgctgtcctg agcgtccggg cggaaggatc aggacgctcg ctgcgccctt 1140

cgtctgacgt ggcagcgctc gccgtgagga ggggggcgcc cgcgggaggc gccaaaaccc 1200

ggcgcggagg cc 1212

<210> 212
<211> 1724
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 212
ggaggctgag gggtggggaa agggcatggg tgtttcatga ggacagagct tccgtttcat 60

gcaatgaaaa gagtttggag acggatggtg gtgactggac tatacactta cacacggtag 120

cgatggtaca ctttgtatta tgtatatttt accacgatct ttttaaagtg tcaaaggcaa 180

atggccaaat ggttccttgt cctatagctg tagcagccat cggctgttag tgacaaagcc 240

cctgagtcaa gatgacagca gcccccataa ctcctaatcg gctctcccgc gtggagtcat 300

ttaggagtag tcgcattaga gacaagtcca acatctaatc ttccaccctg gccagggccc 360

cagctggcag cgagggtggg agactccggg cagagcagag ggcgctgaca ttggggcccg 420

gcctggcttg ggtccctctg gcctttcccc aggggccctc tttccttggg gctttcttgg 480

gccgccactg ctcccgctcc tctcccccca tcccaccccc tcacccccctc gttcttcata 540

tccttctcta gtgctccctc cactttcatc cacccttctg caagagtgtg ggaccacaaa 600

tgagttttca cctggcctgg ggacacacgt gcccccacag gtgctgagtg actttctagg 660

acagtaatct gctttaggct aaaatgggac ttgatcttct gttagcccta atcatcaatt 720

agcagagccg gtgaaggtgc agaacctacc gcctttccag gcctcctccc acctctgcca 780

cctccactct ccttcctggg atgtgggggc tggcacacgt gtggcccagg gcattggtgg 840

gattgcactg agctgggtca ttagcgtaat cctggacaag ggcagacagg gcgagcggag 900

ggccagctcc ggggctcagg caaggctggg ggcttccccc agacacccca ctcctcctct 960

gctggacccc cacttcatag ggcacttcgt gttctcaaag ggcttccaaa tagcatggtg 1020

gccttggatg cccagggaag cctcagagtt gcttatctcc ctctagacag aaggggaatc 1080

tcggtcaaga gggagaggtc gccctgttca aggccaccca gccagctcat ggcggtaatg 1140

ggacaaggct ggccagccat cccaccctca gaagggaccc ggtggggcag gtgatctcag 1200

aggaggctca cttctgggtc tcacattctt ggatccggtt ccaggcctcg gccctaaata 1260

gtctccctgg gctttcaaga gaaccacatg agaaaggagg attcgggctc tgagcagttt 1320

caccacccac cccccagtct gcaaatcctg acccgtgggt ccacctgccc caaaggcgga 1380

cgcaggacag tagaagggaa cagagaacac ataaacacag agagggccac agcggctccc 1440

acagtcaccg ccaccttcct ggcggggatg ggtggggcgt ctgagtttgg ttcccagcaa 1500

atccctctga gccgcccttg cgggctcgcc tcaggagcag gggagcaaga ggtgggagga 1560

ggaggtctaa gtcccaggcc caattaagag atcaggtagt gtagggtttg ggagctttta 1620

aggtgaagag gcccgggctg atcccacagg ccagtataaa gcgccgtgac cctcaggtga 1680

tgcgccaggg ccggctgccg tcggggacag ggctttccat agcc 1724

<210> 213
<211> 806
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 213
agatcttccc cacctagcca cctggcaaac tgctccttct ctcaaaggcc caaacatggc 60

ctcccagact gcaaccccca ggcagtcagg ccctgtctcc acaacctcac agccaccctg 120

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

tcagaggagt gtggggactg gatgactcca gaggtaactt gtgggggaac gaacaggtaa 420

ggggctgtgt gacgagatga gagactggga gaataaacca gaaagtctct agctgtccag 480

aggacatagc acagaggccc atggtcccta tttcaaaccc aggccaccag actgagctgg 540

gaccttggga cagacaagtc atgcagaagt taggggacct tctcctccct tttcctggat 600

ggatcctgag taccttctcc tccctgacct caggcttcct cctagtgtca ccttggcccc 660

tcttagaagc caattaggcc ctcagtttct gcagcgggga ttaatatgat tatgaacacc 720

cccaatctcc cagatgctga ttcagccagg agcttaggag ggggaggtca ctttataagg 780

gtctgggggg gtcagaaccc agagtc 806

<210> 214
<211> 1003
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 214
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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

cctgtcctca ggttaaccca gtcactccct gtacctcagt ccctacccat cacaattctc 420

cagcccatga gcttcgggct gtacttcccc aacgggttct cccattttgg gtacatggcc 480

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atcccccca acccctccca tacacataca catgtgcact cgtgcactca acccagcaca 600

ggataatgtt cattcttgac ctttccacat acatctggct atgttctctc tcttatctac 660

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

gcaaccagag ctcgaggctg atgcgagctt catctcttcc ctc 1003

<210> 215
<211> 523
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 215
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atcccccca acccctccca tacacataca catgtgcact cgtgcactca acccagcaca 120

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> 216
<211> 215
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 216
tgatccctgg ccactaatct gtactcacta atctgttttc caaactcttg gcccctgagc 60

taattatagc agtgcttcat gccacccacc ccaaccctat ccttgttctc tgactcccac 120

taatctacac attcagagga ttgtggatat aagaggctgg gaggccagct tagcaaccag 180

agctcgaggc tgatgcgagc ttcatctctt ccctc 215

<210> 217
<211> 198
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 217
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gaggaagggg ccgggcagaa tgatctaatc ggattccaag cagctcaggg gattgtcttt 120

ttctagcacc ttcttgccac tcctaagcgt cctccgtgac cccggctggg atttagcctg 180

gtgctgtgtc agccccgg 198

<210> 218
<211> 142
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 218
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gtgggcagtg ccagcctcta agagtgggca ggggcactgg ccacagagtc ccagggagtc 120

ccaccagcct agtcgccaga cc 142

<210> 219
<211> 109
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 219
gtcaagtgac ggcggctcag cactcacgtg ggcagtgcca gcctctaaga gtgggcaggg 60

gcactggcca cagagtccca gggagtccca ccagcctagt cgccagacc 109

<210> 220
<211> 93
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 220
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tcccagggag tcccaccagc ctagtcgcca gac 93

<210> 221
<211> 1080
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 221
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gctctgctct cttcattgaa caatacaaga ggagtgtgta ggtagacacc caccacttcc 120

aacagcttag gagagccctt gagtatggat tgatgtatta aaatttattg aatcacatgc 180

tgagattttc accagctgcc cgtggggatc tgggcattta ttcccatatt gcactggctg 240

gctggaagcc agcagcataa actccagggc tgttctgtca acccccacca gactcacccc 300

gctccaccag ccccggcagg cttctccttc catctctctg aagcaactta ctgatgggcc 360

ctgccagcca atcacagcca gaataacgta tgatgtcacc agcagccaat cagagctcct 420

cgtcagcata tgcagaattc tgtcatttta ctagggtgat gaaattccca agcaacacca 480

tccttttcag ataagggcac tgaggctgag agaggagctg aaacctaccc ggcgtcacca 540

cacacaggtg gcaaggctgg gaccagaaac caggactgtt gactgcagcc cggtattcat 600

tctttccata gcccacaggg ctgtcaaaga ccccagggcc tagtcagagg ctcctccttc 660

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gcggctcagc actcacgtgg gcagtgccag cctctaagag tgggcagggg cactggccac 1020

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<210> 222
<211> 2280
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV-antibody construct

<400> 222
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cagagcgcac atcgcccaca gtccccgaga agttgggggg aggggtcggc aattgaacgg 180

gtgcctagag aaggtggcgc ggggtaaact gggaaagtga tgtcgtgtac tggctccgcc 240

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<210> 223
<211> 1972
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV-antibody construct

<400> 223
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gccttttcc cgagggtggg ggagaaccgt atataagtgc agtagtcgcc gtgaacgttc 180

ttttcgcaa cgggtttgcc gccagaacac agcaggtgag tatctcaggg atccagacat 240

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<210> 224
<211> 2319
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV-antibody construct

<400> 224
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<210> 225
<211> 2011
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; AAV-antibody construct

<400> 225
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<210> 226
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; signal peptide

<400> 226

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1 5 10 15

Leu Gly Thr Ala Val Pro Ser Thr Gly Ala Ser Lys Ser Lys Arg
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<210> 227
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; HIF1alpha site

<400> 227

Arg Cys Gly Thr Gly
1 5

<210> 228
<211> 969
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 228
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<220>
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<220>
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<220>
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caggggcaca ggggctgccc tcattctacc accacctcca cagcacagac agacactcag 1080

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caccttggac acaggacgct gtggtttctg agccaggtac agtgactcct ttcggtaagt 1260

gcagtggaag ctgtacactg cccaggcaaa gcgtccgggc agcgtaggcg ggcgactcag 1320

atcccagcca gtggacttag cccctgtttg ctcctccgat aactggggtg accttggtta 1380

atattcacca gcagcctccc ccgttgcccc tctggatcca ctgcttaaat acggacgagg 1440

acagggccct gtctcctcag cttcaggcac caccactgac ctgggacagt 1490

<210> 240
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 240
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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 ggtacccggg gatcttgcta ccagtggaac agccactaag 360

gattctgcag tgagagcaga gggccagcta agtggtactc tcccagagac tgtctgactc 420

acgccacccc ctccaccttg gacacaggac gctgtggttt ctgagccagg tacaatgact 480

cctttcggta agtgcagtgg aagctgtaca ctgcccaggc aaagcgtccg ggcagcgtag 540

gcgggcgact cagatcccag ccagtggact tagcccctgt ttgctcctcc gataactggg 600

gtgaccttgg ttaatattca ccagcagcct cccccgttgc ccctctggat ccactgctta 660

aatacggacg aggacagggc cctgtctcct cagcttcagg caccaccact gacctgggac 720

agt 723

<210> 241
<211> 100
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 241
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tgtttgctct ggttaataat ctcaggagca caaacattcc 100

<210> 242
<211> 200
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 242
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tgtttgctct ggttaataat ctcaggagca caaacattcc aggttaattt ttaaaaagca 120

gtcaaaagtc caagtggccc ttggcagcat ttactctctc tgtttgctct ggttaataat 180

ctcaggagca caaacattcc 200

<210> 243
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 243
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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 g 321

<210> 244
<211> 554
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 244
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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> 245
<211> 393
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 245
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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> 246
<211> 393
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 246
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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> 247
<211> 144

<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 247
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ggttataatt aacccagaca tgtggctgcc ccccccccc ccaacacctg ctgcctctaa 120

aaataaccct gtccctggtg gatc 144

<210> 248
<211> 288
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 248
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> 249
<211> 432
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 249
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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 ccccccccccc aacacctgct gcctctaaaa ataaccctgt 420

ccctggtgga tc 432

<210> 250
<211> 199
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; regulatory element

<400> 250
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cctgtctctc ctctatctgc ccatcggccc tttggggagg aggaatgtgc ccaaggacta 120

aaaaaaggcc atggagccag aggggcgagg gcaacagacc tttcatgggc aaaccttggg 180

gccctgctga agctttggc 199

<210> 251
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; cleavage site

<220>
<221> misc
<222> (2)..(2)
<223> Xaa can be any amino acid

<400> 251

Arg Xaa Lys Arg
1

<210> 252
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; cleavage site

<220>

<221> misc
<222> (2)..(2)
<223> Xaa can be any amino acid

<400> 252

Arg Xaa Arg Arg
1

<210> 253
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 253

Asp Thr Ala Val Tyr Tyr
1 5

<210> 254
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 254

Glu Asp Ile Ala Thr Tyr Tyr
1 5

<210> 255
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 255

Glu Asp Glu Ala Asp Tyr Tyr
1 5

<210> 256
<211> 7

<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 256

Glu Asp Thr Ala Val Tyr Tyr
1 5

<210> 257
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; hinge

<400> 257

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly

<210> 258
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 258

Glu Asp Phe Ala Thr Tyr Tyr
1 5

<210> 259
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 259

Glu Asp Phe Ala Val Tyr Tyr
1   5

<210> 260
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 260

Asp Asp Phe Ala Thr Tyr Tyr
1   5

<210> 261
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 261

Glu Asp Thr Ala Met Tyr Tyr
1   5

<210> 262
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 262

Glu Asp Ala Ala Thr Tyr Tyr
1   5

<210> 263
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 263

Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> 264
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 264

Glu Asp Thr Ala Leu Tyr Tyr
1 5

<210> 265
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 265

Glu Asp Phe Ala Ser Tyr Tyr
1 5

<210> 266
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 266

Tyr Thr Cys Asn Val Asp
1 5

<210> 267
<211> 6
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic construct; sulfation site

<400> 267

Glu Leu Leu Ile Tyr Tyr
1   5

<210> 268
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 268

Tyr Tyr Tyr Gly Met Asp
1   5

<210> 269
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 269

Glu Asp Thr Gly Val Tyr Tyr
1   5

<210> 270
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 270

Glu Asp Ile Ala Asp Tyr Tyr
1   5

<210> 271
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; sulfation site

<400> 271

Glu Asp Val Ala Thr Tyr Tyr
1   5

<210> 272
<211> 97
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic construct; intron

<400> 272

Gly Thr Ala Ala Gly Thr Thr Thr Ala Gly Thr Cys Thr Thr Thr Thr
1   5   10   15

Thr Gly Thr Cys Thr Thr Thr Thr Ala Thr Thr Thr Cys Ala Gly Gly
            20   25   30

Thr Cys Cys Cys Gly Gly Ala Thr Cys Cys Gly Gly Thr Gly Gly Thr
        35   40   45

Gly Gly Thr Gly Cys Ala Ala Ala Thr Cys Ala Ala Ala Gly Ala Ala
    50   55   60

Cys Thr Gly Cys Thr Cys Cys Thr Cys Ala Gly Thr Gly Gly Ala Thr
65   70   75   80

Gly Thr Thr Gly Cys Cys Thr Thr Thr Ala Cys Thr Thr Cys Thr Ala
                85   90   95

Gly

<210> 273
<211> 663
<212> DNA
<213> Artificial Sequence

<220>

<223> synthetic construct; promoter

<400> 273
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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

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cgg 663

<210> 274
<211> 762
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 274
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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

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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> 275
<211> 935
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; promoter

<400> 275
gtcgacaaat tctgtcattt tactagggtg atgaaattcc caagcaacac catccttttc 60

agataagggc actgaggctg agagaggagc tgaaacctac ccggggtcac cacacacagg 120

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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

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gggcagggac gggccacagg ccaagggcct taagc 935

<210> 276
<211> 3133

<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody construct

<400> 276
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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

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cggacgcgtc aggtgagtat ctcagggatc cagacatggg gatatgggag gtgcctctga 720

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ctgagcacag ccagcagcct ggattattgg ggccagggca cactggttac agtgtcctct 1200

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ggcctgtact ctctgtcctc tgtggtcaca gtgcctagct ctagcctggg cacccagacc 1440

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aagagctgtg acaagaccca cacctgtcct ccatgtcctg ctccagaact gcttggaggc 1560

ccttctgtgt tcctgtttcc tccaaagcct aaggacaccc tgatgatcag cagaacccct 1620

gaagtgacct gtgtggtggt tgatgtgtcc catgaggacc cagaagtgaa gttcaattgg 1680

tatgtggatg gggttgaagt gcacaatgct aagaccaagc ctagagagga acagtacaac 1740

agcacctaca gagtggtgtc tgtgctgaca gtgctgcatc aggactggct gaatggcaaa 1800

gagtacaagt gcaaagtgtc caacaaggcc ctgcctgctc ctattgagaa aaccatctcc 1860

aaggccaagg gccagccaag agaaccccag gtttacacac tgccacctag cagagatgag 1920

ctgaccaaga accaggtgtc cctgacctgc ctggttaagg gcttctaccc ctctgacatt 1980

gctgtggaat gggagagcaa tggccagcct gagaacaact acaagacaac ccctcctgtg 2040

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cagcagggga atgtgttcag ctgctctgtg atgcatgagg ccctgcacaa ccactacacc 2160

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tgtctctcac tcg 3133

<210> 277
<211> 3554
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct; antibody construct

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