(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

REVISED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 October 2020 (29.10.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/219868 A9

(51) International Patent Classification:
C12N 15/86 (2006.01) *C07K 16/18* (2006.01)

(21) International Application Number:
PCT/US2020/029802

(22) International Filing Date:
24 April 2020 (24.04.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/838,165 24 April 2019 (24.04.2019) US
62/967,472 29 January 2020 (29.01.2020) US

(71) Applicant: **REGENXBIO INC.** [US/US]; 9600 Blackwell Road, Suite 210, Rockville, MD 20850 (US).

(72) Inventors: **DANOS, Olivier**; 1349 Lexington Avenue, Apartment 4G, New York, NY 10128 (US). **WU, Zuchun**; 14716 Soft Wind Dr., North Potomac, MD 20878 (US). **LIU, Ye**; 6828 Walnut Creek Ct., Clarksville, MD 21029 (US). **EVEREN, Sherri, Van**; 823 Paulson Cirle, Menlo Park, CA 94025 (US). **GERNER, Franz**; 3546 Brethren Church Road, Myersville, MD 21773 (US). **BRUDER, Joseph**; 567 Chestertown St., Gaithersburg, MD 20878 (US). **QIAO, Chunping**; 4809 Walkingfern Drive, Rockville, MD 20853 (US). **MCDOUGALD, Devin**; 2950 Van Ness Street NW, Apt. 714, Washington, DC 20008 (US). **WANG, Xu**; 2130 Dominion Heights Ct., Falls Church, VA 22043 (US). **GLENN, Justin**; 8010 Gramercy Boulevard, Apt. 166, Rockville, MD 20855 (US).

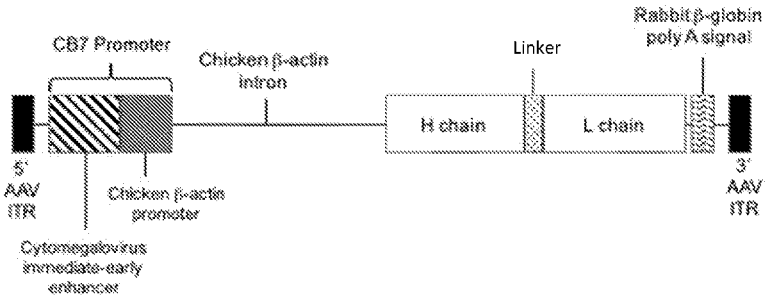
(74) Agent: **BRIVANLOU, Margaret** et al.; Ballard Spahr LLP, 999 Peachtree Street, Suite 1000, Atlanta, GA 30309 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: FULLY-HUMAN POST-TRANSLATIONALLY MODIFIED ANTIBODY THERAPEUTICS

FIG. 1



(57) Abstract: Provided are methods and compositions for the delivery of fully human post-translationally modified therapeutic monoclonal antibodies and antigen-binding fragments thereof. The fully human post-translationally modified therapeutic monoclonal antibodies may be delivered by gene therapy methods, e.g., as a recombinant adeno-associated virus (rAAV) vector to the appropriate tissue. Methods of manufacture of the AAV vectors, pharmaceutical compositions and methods of treatment are also provided. In addition, provided are methods of producing therapeutic antibodies that are "biobetters" as fully human post-translationally modified. These fully human post-translationally modified therapeutic antibodies may be administered to a subject in need of treatment with the therapeutic antibody.

WO 2020/219868 A9

[Continued on next page]

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the revised international search report:
16 September 2021 (16.09.2021)

(15) Information about Correction:
see Notice of 16 September 2021 (16.09.2021)

FULLY-HUMAN POST-TRANSLATIONALLY MODIFIED ANTIBODY THERAPEUTICS

0. SEQUENCE LISTING

[0000] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 24, 2020, is named 38013_0001P1_SL.txt and is 690,185 bytes in size.

1. INTRODUCTION

[0001] Compositions and methods are described for the delivery of a fully human post-translationally modified (HuPTM) therapeutic monoclonal antibody ("mAb") or the HuPTM antigen-binding fragment of a therapeutic mAb—*e.g.*, a fully human-glycosylated (HuGly) Fab of the therapeutic mAb—to a human subject diagnosed with a disease or condition indicated for treatment with the therapeutic mAb.

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.

3. SUMMARY OF THE INVENTION

[0003] Compositions and methods are described for the delivery of a HuPTM mAb or a 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 a disease or condition indicated for treatment with the therapeutic 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 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 that continuously supplies the HuPTM mAb or antigen-binding fragment of the therapeutic

mAb, *e.g.,* a human-glycosylated transgene product, to a target tissue where the mAb or antigen-binding fragment there of exerts its therapeutic effect.

[0004] 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:

- *Nervous system targets,* including Amyloid beta (Aβ or Abeta) peptides derived from the amyloid precursor protein (APP), including but not limited solanezumab, GSK933776, and lecanemab (see **FIGS. 2A-C**), indicated for treating Alzheimer's disease; sortilin, including but not limited to AL-001 (see **FIG. 3**), for treating frontotemporal dementia (FTD); Tau protein implicated in tauopathies, including Alzheimer's disease, progressive supranuclear palsy, FTD, chronic traumatic encephalopathy, Pick's Complex, primary age-related tauopothy, including but not limited to ABBV-8E12, UCB-0107, and NI-105 (BIIB076) (see **FIGS. 4A-C**) for treating tauopathies; SEMA4D, including but not limited to VX15/2503 (see **FIG. 5**), for treating Huntington's disease and juvenile Huntington's disease; alpha-synuclein, including but not limited to prasinezumab, NI-202 (BIIB054) and MED-1341 (see **FIGS. 6A-C**), for treating Parkinson's disease and synucleinopathies; superoxide dismutase-1 (SOD-1), including but not limited NI-204 (see **FIGS. 7A and B**), for treating ALS and Alzheimer's disease; and CGRP receptor, including but not limited to eptinezumab, fremanezumab, and galcanezumab (see **FIGS. 8A-C**), for treating migraines and cluster headaches;
- *Ocular Anti-Angiogenic Targets,* including but not limited to VEGF (vascular endothelial growth factor), including but not limited to sevacizumab (see **FIG. 9A**), for treating retinal disorders including diabetic retinopathy (DR), myopic choroidal neovascularization (mCNV), age-related macular degeneration (AMD), and macular edema; erythropoietin receptor, including but not limited to LKA-651 (see **FIGS. 9B and C**), indicated for treatment of retinal diseases such as retinal vein occlusion (RVO), wet AMD, and macular edema; amyloid beta (Aβ or Abeta) peptides derived from the amyloid precursor protein (APP), including but not limited to solanezumab, GSK933776, or lecanemab (see **FIGS. 2A-C**), for treating dry AMD; activin receptor like kinase 1 (ALK1), including but not

limited to ascrinvacumab (see **FIG. 10A**), indicated for treating neovascular age-related macular degeneration; complement component 5 (C5), including but not limited to tesidolumab and ravulizumab (see **FIG. 10B and 10D**), indicated for treating dry AMD and non-infectious uveitis, endoglin (END or CD105), including but not limited to carotuximab (see **FIG. 10C**), indicated for treating wet AMD and other retinal disorders caused by increased vascularization; complement component 1Q (C1Q), including but not limited to ANX-007 (see **FIG. 11**), indicated for treating glaucoma; and plasma protein targets, such as human complement proteins including but not limited to plasma kallikrein (pKal), including but not limited to lanadelumab (see **FIG. 19**) for treating diabetic retinopathy and diabetic macular edema;

- *Complement component 5*, including but not limited to ravulizumab, indicated for treating myasthenia gravis (see **FIG. 10D**);
- *TNF-alpha,* including but not limited, to adalimumab (HUMIRA®), infliximab (REMICADE®), and golimumab, indicated for treating non-infectious uveitis (see **FIGS. 12A-C**);
- *Repulsive guidance molecule-A*, including but not limited to elezanumab (see **FIG. 13**), for treating multiple sclerosis;
- *Transthyretin (TTR),* including but not limited to NI-301 and PRX-004 (see **FIGS. 14A and B**), indicated for treating amyloidosis;
- *Connective tissue growth factor (CTGF),* including but not limited to pamrevlumab (see **FIG. 15**), indicated for treating fibrotic diseases (e.g. diabetic nephropathy, liver fibrosis, idiopathic pulmonary fibrosis);
- *Neuromyelitis optica (NMO)/Non-Infectious Uveitis targets,* including the TNF-alpha targeted antibodies above, and interleukin 6 (IL6)- and interleukin 6 receptor (IL6R)-targeted antibodies, including but not limited to satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, and tocilizumab (see **FIGS. 16A-H**), indicated for treating NMO, DR, DME, and non-infectious uveitis; and CD19, including but not limited to inebilizumab (see **FIG. 16I**), indicated for treating NMO;

- *Immune response targets*, including interleukin 6 (IL6)- and interleukin 6 receptor (IL6R)-targeted antibodies, including but not limited to satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, and tocilizumab (see **FIGS. 16A-H**), indicated for treating adverse immune responses, such as cytokine release syndrome, such as associated with bacterial or viral infections, and to be administered with immune effecting agents, such as CAR-T and other cell based therapies, and immunooncology agents to counteract, reduce or ameliorate detrimental immune responses associated with such therapies;
- *Integrin beta 7*, including but not limited to etrolizumab (see **FIG. 17**), indicated for treating ulcerative colitis and Crohn's disease;
- *Sclerostin*, including but not limited to romosozumab (EVENITY®) (see **FIG. 18**), indicated for treating osteoporosis and abnormal bone loss or weakness;
- *Plasma Protein targets*, such as human complement proteins including but not limited to plasma kallikrein, including but not limited to lanadelumab (see **FIG. 19**) for treating hereditary angioedema and ocular indications, including diabetic retinopathy and diabetic macular edema; and
- *Anti-IL and IL-Receptor* and other targets for autoimmune, respiratory and allergic diseases, such as interleukin 5 (IL5), including but not limited to benralizumab (see **FIG. 29A**); interleukin 5 receptor (IL5R), including but not limited to reslizumab (see **FIG. 29B**); interleukin 13 (IL13), including but not limited to tralokinumab (see **FIG. 29C**); interleukin 31 receptor alpha (IL-31RA), including but not limited to nemolizumab (see **FIG. 29D**); immunoglobin E (IgE), including but not limited to omalizumab (see **FIG. 29E**); and thymic stromal lymphopoietin (TSLP), including but not limited to tezepelumab (see **FIG. 29F**).or antigen-binding fragments.

[0005] The recombinant vector used for delivering the transgene includes non-replicating recombinant adeno-associated virus vectors ("rAAV"). 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.

[0006] Gene therapy constructs 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 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.

[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.

[0008] 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.

[0009] 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.

[0010] The invention is based, in part, on the following principles:

(i) The mAb therapeutics currently on the market are of the immunoglobulin G (IgG) isotypes, such as IgG1, IgG2, and IgG4, which in general have pharmacokinetic (PK) characteristics, such as slow clearance, long half-life, and limited tissue distribution. After intravenous administration, typical mAb serum PK profiles are biphasic with a rapid distribution phase and a slower elimination phase; thus, repeat administration is required to maintain doses required to treat chronic conditions. Moreover, the distribution of mAbs is generally limited to the vascular and interstitial spaces due to their large size and hydrophilicity. The extent of mAb partitioning from circulation into most tissues generally ranges from about 5–15%, except for brain where it is much lower. (*See*, *e.g.*, Kamath, 2016, Drug Discovery Today: Technologies 21-22: 75-83, which is incorporated by reference herein in its entirety). Continuous production of HuPTMmAbs or HuPTM Fabs *in situ* avoids repeat administrations and allows the use of Fabs, which would otherwise have too short a systemic half-life to achieve efficacy; and the methods of administration described allow direct access to target tissues, such as the brain, where the delivery of higher doses to such tissues can be achieved.

(ii) The Fab region of a number of therapeutic mAbs possesses glycosylation sites. For example, see FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F which identify consensus and non-consensus asparaginal ("N") glycosylation sites as well as glutamine ("Q") residues that are glycosylation sites in the Fab region of certain therapeutic mAbs. (*See, e.g.*, Valliere-Douglass et al., 2009, J. Biol. Chem. 284: 32493-32506, and Valliere-

Douglass et al., 2010, J. Biol. Chem. 285: 16012-16022, each of which is incorporated by reference in its entirety for the identification of N-linked glycosylation sites in antibodies). 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 are modified to contain specific O-glycosylation machinery. *See, e.g.*, Farid-Moayer et al., 2007, J. Bacteriol. 189:8088-8098.) Moreover, the Fab amino acid sequence may be modified to engineer hyperglycosylated variants (*e.g.*, see amino acid substitutions that can be made to engineer hyperglycosylated Fab regions of therapeutic antibodies shown in FIGS. 20A and 20B; and Courtois et al., 2016, mAbs 8: 99-112 which is incorporated by reference herein in its entirety for it description of derivatives of antibodies that are hyperglycosylated on the Fab domain of the full-length antibody).

(iii) In addition to the glycosylation sites, the Fab regions can contain tyrosine ("Y") sulfation sites in or near the CDRs; see FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F which identify tyrosine-O-sulfation sites in the Fab region of certain therapeutic mAbs. (*See, e.g.*, Yang et al., 2015, Molecules 20:2138-2164 (particularly at 2154), which is incorporated by reference in its entirety for the analysis of amino acids surrounding tyrosine residues subjected to protein tyrosine sulfation). The "rules" can be summarized as follows: Y residues with E or 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.*, R, K, or H that abolishes sulfation.

(iv) The glycosylation of Fab regions, such as those shown in FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F and Fc regions (see FIG. 22 and Table 7) by human cells will result in

the addition of glycans that can improve stability, half-life and reduce unwanted aggregation and/or immunogenicity of the transgene product. (*See, e.g.*, Bovenkamp et al., 2016, J. Immunol. 196: 1435-1441 for a review of the emerging importance of Fab glycosylation; and FIG. 22 which identifies glycans that can be attached to HuGlyFab (adapted from Bondt et al., 2014, Mol & Cell Proteomics 13.1: 3029-2029)). The Fab and Fc portions of antibodies have been shown to have 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. (*E.g.*, see 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).

(v) Significantly, glycans that are added to HuPTM mAb and HuGlyFab of the invention are highly processed complex-type N-glycans that contain 2,6-sialic acid. Such glycans are not present in (a) therapeutic mAbs produced in *E. coli* (which are not glycosylated at all); (b) in therapeutic antibodies produced in CHO cells that do not have the 2,6-sialyltransferase required to add 2,6-sialic acid during glycosylation; or (c) in therapeutic antibodies produced in either CHO or murine cell lines that add 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.

(vi) The human glycosylation pattern of the HuPTM mAb and HuGlyFab of the invention should reduce immunogenicity of the transgene product and improve efficacy. Importantly, when the full-length antibodies and antigen-binding fragments, used in accordance with the methods described herein are expressed in human target cells, the need for *in vitro* production in prokaryotic host cells (*e.g.*, *E. coli*) or eukaryotic host cells (*e.g.*, CHO cells or murine NS0 or SP2/0 cells) is circumvented. Instead, as a result of the methods described herein (*e.g.*, use of human target cells to express the antigen-binding

fragments), N-glycosylation sites of the full-length antibodies and antigen-binding fragments are advantageously decorated with glycans relevant to and beneficial to treatment of humans. Such an advantage is unattainable when CHO cells, murine cells, or *E. coli* are utilized in antibody/antigen-binding fragment production, because, *e.g.*, (a) CHO cells lack components needed for addition of certain glycans (*e.g.*, 2,6 sialic acid and bisecting GlcNAc); (b) CHO cells and murine cells (NS0 and SP2/0 cells) add Neu5Gc as sialic acid not typical to humans instead of Neu5Ac; (c) 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); and (d) *E. coli* does not naturally contain components needed for N-glycosylation.

(vii) Tyrosine-sulfation of Fab regions, such as those shown in FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F – a robust post-translational process in many human cells – should result in transgene products with increased avidity for their molecular targets. Indeed, tyrosine-sulfation of the Fab of antibodies 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). Such post-translational modifications are not present on therapeutic antibodies made in *E. coli* (a host that does not possess the enzymes required for tyrosine-sulfation), and at best are under-represented in therapeutic mAbs made in CHO cells. CHO cells are not secretory cells and have a limited capacity for post-translational tyrosine-sulfation. (*See, e.g.,* Mikkelsen & Ezban, 1991, Biochemistry 30: 1533-1537, especially discussion at p. 1537).

[0011] For the foregoing reasons, the production of HuPTM mAb or HuPTM Fab 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.

[0012] As an alternative, or an additional treatment to gene therapy, the full-length HuTPM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and the glycoprotein can be administered to patients.

[0013] Combination therapies involving delivery of the full-length HuPTM mAb or HuPTM 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.

[0014] 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.

[0015] The inventors have also found that full length antibodies can be expressed from AAV based vectors (see Examples 36 and 37). The nucleotide sequence encoding the heavy and light chains of the full-length antibodies may be codon optimized for expression in human cells and may have reduced numbers of CpG dimers in the sequence. Accordingly, provided are compositions comprising AAV vectors that express a transgene encoding a full-length heavy chain (including an Fc domain) and light chain of a therapeutic antibody. Methods of administration and manufacture are also provided.

3.1 ILLUSTRATIVE EMBODIMENTS

Compositions of Matter

1. A pharmaceutical composition for treating Alzheimer's disease (AD), frontotemporal dementia (FD), tauopathies, progressive supranuclear palsy, chronic traumatic encephalopathy, Pick's Complex, and primary age-related tauopathy, Huntington's disease, juvenile Huntington's disease, Parkinson's disease, synucleinopathies, ALS, migraines, or cluster headaches in a human subject in need thereof, comprising an adeno-associated virus (AAV) vector having:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), AAV9 capsid (SEQ ID NO: 144), AAVrh10 capsid (SEQ ID NO: 145), an AAVrh20 capsid, an AAVrh39 capsid or an AAVcy5 capsid; 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 substantially full-length or full-length mAb of an anti-amyloid beta (anti-Aβ), anti-sortilin, anti-Tau protein (anti-Tau), anti-semaphorin 4D (anti-SEMA4D), anti-alpha synuclein (anti-SNCA), anti-superoxide dismutase-1 (anti-SOD1) or anti-calcitonin gene-related peptide receptor (anti-CGRPR) monoclonal antibody (mAb), or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human CNS cells, human liver cells and/or human muscle cells;

wherein said AAV vector is formulated for administration to said subject, optionally wherein administration is intrathecal, intravenous, subcutaneous, intranasal, or intramuscular.

2. The pharmaceutical composition of paragraph 1, wherein the anti-Aβ mAb is solanezumab, lecanemab, or GSK933776; the anti-sortilin mAb is AL-001; the anti-Tau mAb is ABBV-8E12, UCB-0107, or NI-105 (BIIB076); the anti-SEMA4D mAb is VX15/2503; the anti-SNCA mAb is prasinezumab, NI-202 (BIIB054), or MED-1341; the anti-SOD1 mAb is NI-2041.10D12 or NI-204.12G7; and the anti-CGRPR mAb is eptinezumab, fremanezumab, or galcanezumab.

3. The pharmaceutical composition of paragraphs 1 or 2, wherein the antigen binding fragment is a Fab, a $F(ab')_2$, or a single chain variable domain (scFv).

4. The pharmaceutical composition of any of paragraphs 1 to 3, 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: 290 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: 291 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: 360 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 392 and a light chain with an amino acid sequence of SEQ ID NO: 361; or a heavy chain with an amino acid sequence of SEQ ID NO: 5 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 6; or a heavy chain with an amino acid sequence of SEQ ID NO: 7 and optionally an Fc polypeptide of an IgG4 isotype (e.g., an amino acid sequence of SEQ ID NO: 285) and a light chain with an amino acid sequence of SEQ ID NO: 8; or 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: 292 and a light chain with an amino acid sequence of SEQ ID NO: 10; or a heavy chain with an amino acid sequence of SEQ ID NO: 11 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 12; or a heavy chain with an amino acid sequence of SEQ ID NO: 13 and optionally an Fc polypeptide of an IgG4 isotype (e.g., an amino acid sequence of SEQ ID NO: 285) and a light chain with an amino acid sequence of SEQ ID NO: 14; or 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: 293 and a light chain with an amino acid sequence of SEQ ID NO: 16; or a heavy chain with an amino acid sequence of SEQ ID NO: 17 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 18; or a heavy chain with an amino acid sequence of SEQ ID NO: 19 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 294 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: 295 and a light chain with an amino acid sequence of SEQ ID NO: 22; or a heavy chain with an amino acid sequence of SEQ ID NO: 23 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 24; or a heavy chain with an amino acid sequence of SEQ ID NO: 25 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 296 and a light chain with an amino acid sequence of SEQ ID NO: 26; or a heavy chain with an amino acid sequence of SEQ ID NO: 27 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 297 and a light chain with an amino acid sequence of SEQ ID NO: 28; or a heavy chain with an amino acid sequence of SEQ ID NO: 29 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 298 and a light chain with an amino acid sequence of SEQ ID NO: 30.

5. The pharmaceutical composition of paragraph 4, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 71 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 72 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 73 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 74 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 376 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 377 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 75 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 76 encoding the light chain; or a heavy chain with an nucleotide sequence of SEQ ID NO: 77 and a light chain with an nucleotide sequence of SEQ ID NO: 78; a heavy chain with an nucleotide sequence of SEQ ID NO: 79 and a light chain with an nucleotide sequence of SEQ ID NO: 80; or a heavy chain with an nucleotide sequence of SEQ ID NO: 81 and a light chain with an nucleotide sequence of SEQ ID NO: 82; or a heavy chain with an nucleotide sequence of SEQ ID NO: 83 and a light chain with an nucleotide sequence of SEQ ID NO: 84; or a heavy chain with an nucleotide sequence of SEQ ID NO: 85 and a light chain with an nucleotide sequence of SEQ ID NO: 86; or a heavy chain with an nucleotide sequence of SEQ ID NO: 87 and a light chain with an nucleotide sequence of SEQ ID NO: 88; or a heavy chain with an nucleotide sequence of SEQ ID NO: 89 and a light chain with an nucleotide sequence of SEQ ID NO: 90; or a heavy chain with an nucleotide sequence of SEQ ID NO: 91 and a light chain with an nucleotide sequence of SEQ ID NO: 92; or a heavy chain with an nucleotide sequence of SEQ ID NO: 93 and a light chain with an

nucleotide sequence of SEQ ID NO: 94; or a heavy chain with an nucleotide sequence of SEQ ID NO: 95 and a light chain with an nucleotide sequence of SEQ ID NO: 96; or a heavy chain with an nucleotide sequence of SEQ ID NO: 97 and a light chain with an nucleotide sequence of SEQ ID NO: 98; or a heavy chain with an nucleotide sequence of SEQ ID NO: 99 and a light chain with an nucleotide sequence of SEQ ID NO: 100.

6. The pharmaceutical composition of any of paragraphs 1 to 4, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

7. The pharmaceutical composition of any of paragraphs 1 to 6, 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 CNS, muscle, or liver cells.

8. The pharmaceutical composition of paragraph 7, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 2.

9. The pharmaceutical composition of any of paragraphs 1 to 8, wherein the AAV capsid is AAV8 or AAV9.

10. A pharmaceutical composition for treating retinal disorders including diabetic retinopathy, myopic choroidal neovascularization (mCNV), macular degeneration (e.g., neovascular (wet) or dry age-related macular degeneration (nAMD)), macular edema (e.g., macular edema following a retinal vein occlusion (RVO) or diabetic macular edema (DME)), retinal vein occlusion, diabetic retinopathy (DR), non-infectious uveitis, or glaucoma, or abnormal vascularization of the retina in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV2.7m8 capsid (SEQ ID NO: 142), an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144); or an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or

full-length mAB of an anti-vascular endothelial growth factor (anti-VEGF), anti-erythropoietin receptor (anti-EPOR), anti-Aβ, anti-activin receptor like kinase 1 (anti-ALK1), anti-complement component 5 (anti-C5), anti-endoglin (anti-ENG), anti-complement component 1Q (anti-CC1Q), or anti-pKal mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human retina cells;

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

11. The pharmaceutical composition of paragraph 10, wherein the anti-VEGF mAb is sevacizumab; anti-EPOR mAb is LKA-651 (NSV2) or LKA-651 (NSV3); anti- Aβ mAb is solanezumab, lecanemab, or GSK933776; anti-ALK1 mAb is ascrinvacumab; anti-C5 mAb is tesidolumab or ravulizumab; anti-ENG mAb is carotuximab; the anti-CC1Q mAb is ANX-007; and the anti-pKal mAb is lanadelumab.

12. The pharmaceutical composition of paragraphs 10 or 11, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

13. The pharmaceutical composition of any of paragraphs 10 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: 290 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: 360 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 392 and a light chain with an amino acid sequence of SEQ ID NO: 361; or a heavy chain with an amino acid sequence of SEQ ID NO: 31 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 299 and a light chain with an amino acid sequence of SEQ ID NO: 32; or a heavy chain with an amino acid sequence of SEQ ID NO: 33 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 34; or a heavy chain with an amino acid sequence of SEQ ID NO: 35 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 36; 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: 291 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: 37 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 300 and a light chain with an amino acid sequence of SEQ ID NO: 38; or a heavy chain with an amino acid sequence of SEQ ID NO: 39 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 301 and a light chain with an amino acid sequence of SEQ ID NO: 40; or a heavy chain with an amino acid sequence of SEQ ID NO: 362 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 393 and a light chain with an amino acid sequence of SEQ ID NO: 363; or a heavy chain with an amino acid sequence of SEQ ID NO: 41 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 302 and a light chain with an amino acid sequence of SEQ ID NO: 42; or a heavy chain with an amino acid sequence of SEQ ID NO: 43 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 44; or a heavy chain with an amino acid sequence of SEQ ID NO: 69 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 314 and a light chain with an amino acid sequence of SEQ ID NO: 70.

14. The pharmaceutical composition of paragraph 13, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 71 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 72 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 376 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 377 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 101 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 102 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 103 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 104 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 105 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 106 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 73 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 74 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 107 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 108 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 109 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 110 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 378 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 379 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 111

encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 112 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 113 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 114 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 139 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 140 encoding the light chain; or a nucleotide sequence of SEQ ID NO 141, 286, 287, or 435 to 443.

15. The pharmaceutical composition of any of paragraphs 10 to 13, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

16. The pharmaceutical composition of any of paragraphs 10 to 15, 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 retina cells.

17. The pharmaceutical composition of paragraph 16, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 2, Table 3 or Table 4.

18. The pharmaceutical composition of any of paragraphs 10 to 17, wherein the AAV capsid is AAV8.

19. A pharmaceutical composition for treating non-infectious uveitis in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV2.7m8 (SEQ ID NO: 142), an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), or an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or full-length anti-tumor necrosis factor-alpha (anti-TNFα) mAb or an antigen-binding fragment thereof, a substantially full-length or full-length anti-complement component 5 (C5) mAb or an antigen-binding fragment thereof, a substantially full-length or full-length anti-interleukin-6 (IL-6) mAb or an antigen-binding fragment thereof, or a

substantially full-length or full-length anti-interleukin-6 receptor (IL-6R) mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human retina cells;

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

20. The pharmaceutical composition of paragraph 19 wherein the anti-TNFα mAb is adalimumab, infliximab or golimumab; the anti-C5 mAb is tesidolumab or ravulizumab; the anti-IL-6 mAb is siltuximab, clazakimzumab, sirukumab, olokizumab or gerilimzumab; or the anti-IL-6R mAb is satralizumab, sarilumab or tocilizumab.

21. The pharmaceutical composition of paragraphs 19 or 20, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

22. The pharmaceutical composition of any of paragraphs 19 to 21, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 45 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 303 and a light chain with an amino acid sequence of SEQ ID NO: 46, or SEQ ID NO; 451, 452 or 453; or a heavy chain with an amino acid sequence of SEQ ID NO: 47 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 304 and a light chain with an amino acid sequence of SEQ ID NO: 48; or a heavy chain with an amino acid sequence of SEQ ID NO: 49 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 305 and a light chain with an amino acid sequence of SEQ ID NO: 50; a heavy chain with an amino acid sequence of SEQ ID NO: 39 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 301 and a light chain with an amino acid sequence of SEQ ID NO: 40; a heavy chain with an amino acid sequence of SEQ ID NO: 362 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 393 and a light chain with an amino acid sequence of SEQ ID NO: 363; a heavy chain with an amino acid sequence of SEQ ID NO: 331 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 355 and a light chain with an amino acid sequence of SEQ ID NO: 332; a heavy chain with an amino acid sequence of SEQ ID NO: 333 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 356 and a light chain with an amino acid sequence of SEQ ID NO: 334; a

heavy chain with an amino acid sequence of SEQ ID NO: 335 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 357 and a light chain with an amino acid sequence of SEQ ID NO: 336; a heavy chain with an amino acid sequence of SEQ ID NO: 337 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 358 and a light chain with an amino acid sequence of SEQ ID NO: 338; a heavy chain with an amino acid sequence of SEQ ID NO: 339 and a light chain with an amino acid sequence of SEQ ID NO: 340; a heavy chain with an amino acid sequence of SEQ ID NO: 59 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 309 and a light chain with an amino acid sequence of SEQ ID NO: 60; a heavy chain with an amino acid sequence of SEQ ID NO: 61 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 310 and a light chain with an amino acid sequence of SEQ ID NO: 62; and a heavy chain with an amino acid sequence of SEQ ID NO: 341 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 359 and a light chain with an amino acid sequence of SEQ ID NO: 342.

23. The pharmaceutical composition of paragraph 22, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 115 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 116 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 117 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 118 encoding the light chain; a nucleotide sequence of SEQ ID NO: 119 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 120 encoding the light chain; nucleotide sequence of SEQ ID NO: 109 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 110 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 378 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 379 encoding the light chain; a nucleotide sequence of SEQ ID NO: 343 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 344 encoding the light chain; nucleotide sequence of SEQ ID NO: 345 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 346 encoding the light chain; a nucleotide sequence of SEQ ID NO: 347 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 348 encoding the light chain; a nucleotide sequence of SEQ ID NO: 349 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 350 encoding the light chain; nucleotide sequence of SEQ ID NO: 351 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 352 encoding the light chain; a nucleotide sequence of SEQ ID NO: 129 encoding the heavy chain and a nucleotide sequence of SEQ

ID NO: 130 encoding the light chain; a nucleotide sequence of SEQ ID NO: 131 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 132 encoding the light chain; or nucleotide sequence of SEQ ID NO: 341 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 342 encoding the light chain.

24. The pharmaceutical composition of any of paragraphs 19 to 22, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

25. The pharmaceutical composition of any of paragraphs 19 to 24, 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 retina cells.

26. The pharmaceutical composition of paragraph 25, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 2, Table 3 or Table 4.

27. The pharmaceutical composition of any of paragraphs 19 to 26, wherein the AAV capsid is AAV8.

28. A pharmaceutical composition for treating multiple sclerosis in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), AAV9 capsid (SEQ ID NO: 144), AAVrh10 capsid (SEQ ID NO: 145), an AAVrh20 capsid, an AAVrh39 capsid or an AAVcy5 capsid; and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or full-length anti-repulsive guidance molecule-A (anti-RGMa) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human CNS cells, human liver cells, and/or human muscle cells;

wherein said AAV vector is formulated for administration to the subject, optionally wherein administration is intrathecal, intravenous, subcutaneous, intranasal, or intramuscular.

29. The pharmaceutical composition of paragraph 28 wherein the anti-RGMa mAb is elezanumab.

30. The pharmaceutical composition of paragraphs 28 or 29, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

31. The pharmaceutical composition of any of paragraphs 28 to 30, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 51 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 306 and a light chain with an amino acid sequence of SEQ ID NO: 52.

32. The pharmaceutical composition of paragraph 31, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 121 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 122 encoding the light chain.

33. The pharmaceutical composition of any of paragraphs 28 to 31, wherein the antibody or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

34. The pharmaceutical composition of any of paragraphs 28 to 33, 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 CNS cells.

35. The pharmaceutical composition of paragraph 34, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 2, Table 3 or Table 4.

36. The pharmaceutical composition of any of paragraphs 28 to 35, wherein the AAV capsid is AAV9.

37. A pharmaceutical composition for treating amyloidosis (ATTR), familial amyloid cardiomyopathy (FAC), or familial amyloid polyneuropathy (FAP) in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or full-length anti-transthyretin (anti-TTR) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for subcutaneous, intramuscular or intravenous administration to the subject.

38. The pharmaceutical composition of paragraph 37, wherein the anti-TTR mAb is NI-301 or PRX-004.

39. The pharmaceutical composition of paragraphs 37 or 38, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

40. The pharmaceutical composition of any of paragraphs 37 to 39, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 53 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 54; or a heavy chain with an amino acid sequence of SEQ ID NO: 55 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 307 and a light chain with an amino acid sequence of SEQ ID NO: 56.

41. The pharmaceutical composition of paragraph 40, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 123 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 124 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 125 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 126 encoding the light chain.

42. The pharmaceutical composition of any of paragraphs 37 to 41, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

43. The pharmaceutical composition of any of paragraphs 37 to 42, 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 liver cells or human muscle cells.

44. The pharmaceutical composition of paragraph 43, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 3 or Table 4.

45. The pharmaceutical composition of any of paragraphs 37 to 44, wherein the AAV capsid is AAV8.

46. A pharmaceutical composition for treating fibrotic disorders, pulmonary fibrosis, cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), liver cirrhosis, atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, arthrofibrosis, Crohn's disease, ulcerative colitis, mediastinal fibrosis, myelofibrosis (MF), nephrogenic systemic fibrosis (NSF), progressive massive fibrosis (PMF), and retroperitoneal fibrosis (RPF) in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), or AAVrh10 (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or full-length anti-connective tissue growth factor (anti-CTGF) mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for subcutaneous, intramuscular or intravenous administration to the subject.

47. The pharmaceutical composition of paragraph 46, wherein the anti-CTGF mAb is pamrevlumab.

48. The pharmaceutical composition of paragraphs 46 or 47, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

49. The pharmaceutical composition of any of paragraphs 46 to 48, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 57 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 308 and a light chain with an amino acid sequence of SEQ ID NO: 58.

50. The pharmaceutical composition of paragraph 49, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 127 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 128 encoding the light chain.

51. The pharmaceutical composition of any of paragraphs 44 to 50, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

52. The pharmaceutical composition of any of paragraphs 44 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 liver cells or human muscle cells.

53. The pharmaceutical composition of paragraph 52, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 3 or Table 4.

54. The pharmaceutical composition of any of paragraphs 44 to 53, wherein the AAV capsid is AAV8.

55. A pharmaceutical composition for treating non-infectious uveitis, neuromyelitis optica (NMO), diabetic retinopathy (DR), or diabetic macular edema (DME) in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV2.7m8 capsid (SEQ ID NO: 142), an AAV9 capsid (SEQ ID NO: 144), or an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or full-length mAb of an anti-interleukin-6 receptor (anti-IL6R), anti-interleukin-6 (IL6), or anti-cluster of differentiation 19 (anti-CD19) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human retina cells;

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

56. The pharmaceutical composition of paragraph 55, wherein the anti-IL6R mAb is satralizumab, sarilumab, or tocilizumab, or the anti-IL6 mAb is siltuximab, clazakizumab, sirukumab, olokizumab, or gerilimzumab, or the anti-CD19 mAb is inebilizumab.

57. The pharmaceutical composition of paragraphs 55 or 56, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

58. The pharmaceutical composition of any of paragraphs 55 to 57, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 59 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 309 and a light chain with an amino acid sequence of SEQ ID NO: 60; or a heavy chain with an amino acid sequence of SEQ ID NO: 61 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 310 and a light chain with an amino acid sequence of SEQ ID NO: 62; or a heavy chain with an amino acid sequence of SEQ ID NO: 331 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 355 and a light chain with an amino acid sequence of SEQ ID NO: 332; or a heavy chain with an amino acid sequence of SEQ ID NO: 333 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 356 and a light chain with an amino acid sequence of SEQ ID NO: 334; or a heavy chain with an amino acid sequence of SEQ ID NO: 335 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 357 and a light chain with an amino acid sequence of SEQ ID NO: 336; or a heavy chain with an amino acid sequence of SEQ ID NO: 337 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 358 and a light chain with an amino acid sequence of SEQ ID NO: 338; or a heavy chain with an amino acid sequence of SEQ

ID NO: 339 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 283 and a light chain with an amino acid sequence of SEQ ID NO: 340; or a heavy chain with an amino acid sequence of SEQ ID NO: 341 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 359 and a light chain with an amino acid sequence of SEQ ID NO: 342; a heavy chain with an amino acid sequence of SEQ ID NO: 63 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 311 and a light chain with an amino acid sequence of SEQ ID NO: 64.

59. The pharmaceutical composition of paragraph 58, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 129 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 130 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 131 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 132 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 343 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 344 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 345 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 346 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 347 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 348 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 349 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 350 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 351 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 352 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 353 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 354 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 133 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 134 encoding the light chain.

60. The pharmaceutical composition of any of paragraphs 55 to 59, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

61. The pharmaceutical composition of any of paragraphs 55 to 60, 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 retinal cells.

62. The pharmaceutical composition of paragraph 61, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 2, Table 3 or Table 4.

63. The pharmaceutical composition of any of paragraphs 55 to 62, wherein the AAV capsid is AAV8.

64. A pharmaceutical composition for treating inflammatory bowel disease (IBD) including UC and CD in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143); AAV9 capsid (SEQ ID NO: 144); or AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a substantially full-length or full-length anti-integrin β7 subunit (anti-ITGB7) mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for subcutaneous, intramuscular, or intravenous administration to the subject.

65. The pharmaceutical composition of paragraph 64, wherein the anti-ITGB7 mAb is etrolizumab.

66. The pharmaceutical composition of paragraphs 64 or 65, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

67. The pharmaceutical composition of any of paragraphs 64 to 66, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 65 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 312 and a light chain with an amino acid sequence of SEQ ID NO: 66.

68. The pharmaceutical composition of paragraph 67, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 135 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 136 encoding the light chain.

69. The pharmaceutical composition of any of paragraphs 64 to 68, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

70. The pharmaceutical composition of any of paragraphs 64 to 69, 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 liver cells or human muscle cells.

71. The pharmaceutical composition of paragraph 70, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 3 or Table 4.

72. The pharmaceutical composition of any of paragraphs 64 to 71, wherein the AAV capsid is AAV8.

73. A pharmaceutical composition for treating osteoporosis or abnormal bone loss or weakness (e.g., treating giant cell tumor of bone, treating treatment-induced bone loss, slowing the loss of (or increasing) bone mass in breast and prostate cancer patients, preventing skeletal-related events due to bone metastasis, or for decreasing bone resorption and turnover in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143); AAVrh10 capsid (SEQ ID NO: 145); or an AAV9 capsid (SEQ ID NO: 144); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or full-length anti-sclerostin (anti-SOST) mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous, intramuscular, or subcutaneous administration to the subject.

74. The pharmaceutical composition of paragraph 73, wherein the anti-SOST mAb is romosozumab.

75. The pharmaceutical composition of paragraphs 73 or 74, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

76. The pharmaceutical composition of any of paragraphs 73 to 75, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 67 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 313 and a light chain with an amino acid sequence of SEQ ID NO: 68.

77. The pharmaceutical composition of paragraph 76, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 137 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 138 encoding the light chain.

78. The pharmaceutical composition of any of paragraphs 73 to 77, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

79. The pharmaceutical composition of any of paragraphs 73 to 78, 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 liver cells or human muscle cells.

80. The pharmaceutical composition of paragraph 79, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 3 or Table 4.

81. The pharmaceutical composition of any of paragraphs 73 to 80, wherein the AAV capsid is AAV8.

82. A pharmaceutical composition for treating angioedema including hereditary angioedema in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143); AAVrh10 capsid (SEQ ID NO: 145); or AAV9 capsid (SEQ ID NO: 144); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or full-length anti-kallikrein (anti-pKal) mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous, intramuscular, or subcutaneous administration to the subject.

83. The pharmaceutical composition of paragraph 82, wherein the anti-pKal mAb is lanadelumab.

84. The pharmaceutical composition of paragraphs 82 or 83, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

85. The pharmaceutical composition of any of paragraphs 82 to 84, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 69 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 314 and a light chain with an amino acid sequence of SEQ ID NO: 70.

86. The pharmaceutical composition of paragraph 85, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 139 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 140 encoding the light chain; or a nucleotide sequence of SEQ ID NO 141, 286, 287, or 435 to 443.

87. The pharmaceutical composition of any of paragraphs 82 to 85, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

88. The pharmaceutical composition of any of paragraphs 82 to 87, 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 retinal cells.

89. The pharmaceutical composition of paragraph 88, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 3 or Table 4.

90. The pharmaceutical composition of any of paragraphs 82 to 89, wherein the AAV capsid is AAV8.

Method of Treatment

91. A method of treating Alzheimer's disease (AD), frontotemporal dementia (FD), tauopathies, progressive supranuclear palsy, chronic traumatic encephalopathy, Pick's Complex, and primary age-related tauopathy, Huntington's disease, juvenile Huntington's disease, Parkinson's disease, synucleinopathies, ALS, migraines or cluster headaches in a human subject in need thereof, comprising delivering to the cerebrospinal fluid (CSF) of said human subject, a therapeutically effective amount of a substantially full-length or full-length mAb of an anti-amyloid beta (anti-Aβ), anti-sortilin, anti-Tau protein (anti-Tau), anti-semaphorin 4D (anti-SEMA4D), anti-alpha synuclein (anti-SNCA), anti-superoxide dismutase-1 (anti-SOD1) or anti-calcitonin gene-related peptide receptor (anti-CGRPR) mAb, or antigen-binding fragment thereof, expressed from a transgene and produced by human CNS cells.

92. A method of treating Alzheimer's disease, frontotemporal dementia (FD), tauopathies, progressive supranuclear palsy, chronic traumatic encephalopathy, Pick's Complex, and primary age-related tauopathy, Huntington's disease, juvenile Huntington's disease, Parkinson's disease, synucleinopathies, ALS, migraines or cluster headaches in a human subject in need thereof, comprising:

administering to said subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding a substantially full-length or full-length mAb of an anti-amyloid beta (anti-Aβ), anti-sortilin, anti-Tau protein (anti-Tau), anti-semaphorin 4D (anti-SEMA4D), anti-alpha synuclein (anti-SNCA), anti-superoxide dismutase-1 (anti-SOD1) or anti-calcitonin gene-related peptide receptor (anti-CGRPR) mAb, or an antigen-binding fragment

thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human CNS cells, so that a depot is formed that releases a human post-translationally modified (HuPTM) form of said mAb or antigen-binding fragment thereof.

93. The method of paragraphs 91 or 92 wherein the anti-Aβ mAb is solanezumab, lecanemab, or GSK933776; the anti-sortilin mAb is AL-001; the anti-Tau mAb is ABBV-8E12, UCB-0107, or NI-105 (BIIB076); the anti-SEMA4D mAb is VX15/2503; the anti-SNCA mAb is prasinezumab, NI-202 (BIIB054), or MED-1341; the anti-SOD1 mAb is NI-2041.10D12 or NI-204.12G7; and the anti-CGRPR mAb is eptinezumab, fremanezumab, or galcanezumab.

94. The method of any of paragraphs 91 to 93 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

95. The method of any of paragraphs 91 to 94, 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: 290 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: 292 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: 360 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 392 and a light chain with an amino acid sequence of SEQ ID NO: 361; or a heavy chain with an amino acid sequence of SEQ ID NO: 5 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 6; or a heavy chain with an amino acid sequence of SEQ ID NO: 7 and optionally an Fc polypeptide of an IgG4 isotype (e.g., an amino acid sequence of SEQ ID NO: 285) and a light chain with an amino acid sequence of SEQ ID NO: 8; or 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: 292 and a light chain with an amino acid sequence of SEQ ID NO: 10; or a heavy chain with an amino acid sequence of SEQ ID NO: 11 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 12; or a heavy chain with an amino acid sequence of SEQ ID NO: 13 and optionally an Fc polypeptide of an

IgG4 isotype (e.g., an amino acid sequence of SEQ ID NO: 285) and a light chain with an amino acid sequence of SEQ ID NO: 14; or 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: 293 and a light chain with an amino acid sequence of SEQ ID NO: 16; or a heavy chain with an amino acid sequence of SEQ ID NO: 17 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 18; or a heavy chain with an amino acid sequence of SEQ ID NO: 19 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 294 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: 295 and a light chain with an amino acid sequence of SEQ ID NO: 22; or a heavy chain with an amino acid sequence of SEQ ID NO: 23 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 24; or a heavy chain with an amino acid sequence of SEQ ID NO: 25 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 296 and a light chain with an amino acid sequence of SEQ ID NO: 26; or a heavy chain with an amino acid sequence of SEQ ID NO: 27 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 297 and a light chain with an amino acid sequence of SEQ ID NO: 28; or a heavy chain with an amino acid sequence of SEQ ID NO: 29 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 298 and a light chain with an amino acid sequence of SEQ ID NO: 30.

96. The method of paragraph 95, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 71 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 72 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 73 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 74 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 376 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 377 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 75 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 76 encoding the light chain; or a heavy chain with an nucleotide sequence of SEQ ID NO: 77 and a light chain with an nucleotide sequence of SEQ ID NO: 78; a heavy chain with an nucleotide sequence of SEQ ID NO: 79 and a light chain with an nucleotide sequence of SEQ ID NO: 80; or a heavy chain with an nucleotide sequence of SEQ ID NO: 81 and a light chain with an nucleotide

sequence of SEQ ID NO: 82; or a heavy chain with an nucleotide sequence of SEQ ID NO: 83 and a light chain with an nucleotide sequence of SEQ ID NO: 84; or a heavy chain with an nucleotide sequence of SEQ ID NO: 85 and a light chain with an nucleotide sequence of SEQ ID NO: 86; or a heavy chain with an nucleotide sequence of SEQ ID NO: 87 and a light chain with an nucleotide sequence of SEQ ID NO: 88; or a heavy chain with an nucleotide sequence of SEQ ID NO: 89 and a light chain with an nucleotide sequence of SEQ ID NO: 90; or a heavy chain with an nucleotide sequence of SEQ ID NO: 91 and a light chain with an nucleotide sequence of SEQ ID NO: 92; or a heavy chain with an nucleotide sequence of SEQ ID NO: 93 and a light chain with an nucleotide sequence of SEQ ID NO: 94; or a heavy chain with an nucleotide sequence of SEQ ID NO: 95 and a light chain with an nucleotide sequence of SEQ ID NO: 96; or a heavy chain with an nucleotide sequence of SEQ ID NO: 97 and a light chain with an nucleotide sequence of SEQ ID NO: 98; or a heavy chain with an nucleotide sequence of SEQ ID NO: 99 and a light chain with an nucleotide sequence of SEQ ID NO: 100.

97. The method of any of paragraphs 91 to 95, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

98. The method of any of paragraphs 91 to 97 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

99. The method of any of paragraphs 91 to 98 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc and/or α-Gal.

100. The method of any of paragraphs 91 to 99 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

101. The method of any of paragraphs 92 to 100 wherein the recombinant expression vector is AAV9.

102. The method of any of paragraphs 92 to 101 in which production of said HuPTM form of said mAb or antigen-binding fragment thereof is confirmed by transducing human CNS cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

103. A method of treating diabetic retinopathy, myopic choroidal neovascularization (mCNV), macular degeneration (e.g., neovascular (wet) or dry age-related macular degeneration (nAMD)), macular edema (e.g., macular edema following a retinal vein occlusion (RVO) or diabetic macular edema (DME)), RVO, diabetic retinopathy (DR), non-infectious uveitis, glaucoma, or abnormal vascularization of the retina in a human subject in need thereof, comprising delivering to the retina of said human subject, a therapeutically effective amount of a substantially full-length or full-length mAb of an anti-vascular endothelial growth factor (anti-VEGF), anti-erythropoietin receptor (anti-EPOR), anti-Aβ, anti-activin receptor like kinase 1 (anti-ALK1), anti-complement component 5 (anti-C5), anti-endoglin (anti-ENG), anti-complement component 1Q (anti-CC1Q)), or anti-pKal mAb, or antigen-binding fragment thereof, expressed from a transgene and produced by human retina cells.

104. A method of treating diabetic retinopathy, myopic choroidal neovascularization (mCNV), macular degeneration (e.g., neovascular (wet) or dry age-related macular degeneration (nAMD)), macular edema (e.g., macular edema following a retinal vein occlusion (RVO) or diabetic macular edema (DME)), RVO, diabetic retinopathy (DR), non-infectious uveitis, glaucoma or abnormal vascularization of the retina in a human subject in need thereof, comprising:

administering to the retina of said subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding a substantially full-length or full-length mAb of an anti-vascular endothelial growth factor (anti-VEGF), anti-erythropoietin receptor (anti-EPOR), anti-Aβ, anti-activin receptor like kinase 1 (anti-ALK1), anti-complement component 5 (anti-C5), anti-endoglin (anti-ENG), anti-complement component 1Q (anti-CC1Q), or anti-pKal mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human retina cells, so that a depot is formed that releases a HuPTM form of mAb or antigen-binding fragment thereof.

105. The method of paragraph 103 or 104 wherein the anti-VEGF mAb is sevacizumab; anti-EPOR mAb is LKA-651 (NSV2) or LKA-651 (NSV3); anti- Aβ mAb is solanezumab, lecanemab, or GSK933776; anti-ALK1 mAb is ascrinvacumab; anti-C5 mAb is tesidolumab or ravulizumab; anti-ENG mAb is carotuximab; the anti-CC1Q mAb is ANX-007; and the anti-pKal mAb is lanadelumab.

106. The method of any of paragraphs 103 to 105 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

107. The method of any of paragraphs 103 to 106, 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: 290 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: 360 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 392 and a light chain with an amino acid sequence of SEQ ID NO: 361; or a heavy chain with an amino acid sequence of SEQ ID NO: 31 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 299 and a light chain with an amino acid sequence of SEQ ID NO: 32; or a heavy chain with an amino acid sequence of SEQ ID NO: 33 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 34; or a heavy chain with an amino acid sequence of SEQ ID NO: 35 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 36; 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: 291 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: 37 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 300 and a light chain with an amino acid sequence of SEQ ID NO: 38; or a heavy chain with an amino acid sequence of SEQ ID NO: 39 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 301 and a light chain with an amino acid sequence of SEQ ID NO: 40; or a heavy chain with an amino acid sequence of SEQ ID NO: 362 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 393 and a light chain with an amino acid sequence of SEQ ID NO: 363; or a heavy chain with an amino acid sequence of SEQ ID NO: 41 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 302 and a light chain with an amino acid sequence of SEQ ID NO: 42; or a heavy chain with an amino acid sequence of SEQ ID NO: 43 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 44; or a heavy chain with an amino

acid sequence of SEQ ID NO: 69 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 314 and a light chain with an amino acid sequence of SEQ ID NO: 70.

108. The method of paragraph 107, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 71 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 72 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 376 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 377 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 101 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 102 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 103 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 104 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 105 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 106 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 73 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 74 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 107 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 108 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 109 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 110 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 378 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 379 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 111 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 112 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 113 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 114 encoding the light chain, or a nucleotide sequence of SEQ ID NO 141, 286, 287, or 435 to 443.

109. The method of any of paragraphs 103 to 105, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

110. The method of any of paragraphs 103 to 109 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

111. The method of any of paragraphs 103 to 110 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

112. The method of any of paragraphs 103 to 111 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

113. The method of any of paragraphs 104 to 112 wherein the recombinant expression vector is AAV2.7m8, AAV8, or AAV9.

114. The method of any of paragraphs 104 to 113 in which production of said HuPTM form of the mAb or antigen-binding fragment thereof is confirmed by transducing human retinal cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

115. A method of treating non-infectious uveitis in a human subject in need thereof, comprising delivering to the retina of said human subject, a therapeutically effective amount of a substantially full-length or full-length anti-tumor necrosis factor-alpha (anti-TNFα) mAb or antigen-binding fragment thereof, expressed from a transgene and produced by human retina cells.

116. A method of treating non-infectious uveitis in a human subject in need thereof, comprising:

administering to the retina of said human subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding a substantially full-length or full-length anti-tumor necrosis factor-alpha (anti-TNFα) mAb, or an antigen-binding fragment thereof, a substantially full-length or full-length anti-complement component 5 (C5) mAb or an antigen-binding fragment thereof, a substantially full-length or full-length anti-interleukin-6 (IL-6) mAb or an antigen-binding fragment thereof, a substantially full-length or full-length anti-interleukin-6 receptor (IL-6R) mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human retina cells, so that a depot is formed that releases a HuPTM form of said mAb or antigen-binding fragment.

117. The method of paragraphs 115 or 116 wherein the anti-TNFα mAb is adalimumab, infliximab or golimumab the anti-C5 mAb is tesidolumab or ravulizumab; the anti-IL-6 mAb is siltuximab, clazakimzumab, sirukumab, olokizumab or gerilimzumab; or the anti-IL-6R mAb is satralizumab, sarilumab or tocilizumab.

118. The method of any of paragraphs 115 to 117 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

119. The method of any of paragraphs 115 to 118, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 45 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 303 and a light chain with an amino acid sequence of SEQ ID NO: 46; or a heavy chain with an amino acid sequence of SEQ ID NO: 47 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 304 and a light chain with an amino acid sequence of SEQ ID NO: 48; or a heavy chain with an amino acid sequence of SEQ ID NO: 49 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 305; and a light chain with an amino acid sequence of SEQ ID NO: 50; a heavy chain with an amino acid sequence of SEQ ID NO: 39 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 301 and a light chain with an amino acid sequence of SEQ ID NO: 40; a heavy chain with an amino acid sequence of SEQ ID NO: 362 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 393 and a light chain with an amino acid sequence of SEQ ID NO: 363; a heavy chain with an amino acid sequence of SEQ ID NO: 331 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 355 and a light chain with an amino acid sequence of SEQ ID NO: 332; a heavy chain with an amino acid sequence of SEQ ID NO: 333 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 356 and a light chain with an amino acid sequence of SEQ ID NO: 334; a heavy chain with an amino acid sequence of SEQ ID NO: 335 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 357 and a light chain with an amino acid sequence of SEQ ID NO: 336; a heavy chain with an amino acid sequence of SEQ ID NO: 337 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 358 and a light chain with an amino acid sequence of SEQ ID NO: 338; a heavy chain with an amino acid sequence of SEQ ID NO: 339 and a light chain with an amino acid sequence of SEQ ID NO: 340; a heavy chain with an amino acid sequence of SEQ ID NO: 59 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 309 and a light chain with an amino acid sequence of SEQ ID NO: 60; a heavy chain with an amino acid sequence of SEQ ID NO: 61 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 310 and a light chain with an amino acid sequence of SEQ ID NO: 62; and a heavy chain with an amino acid sequence of SEQ ID NO: 341 and

optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 359 and a light chain with an amino acid sequence of SEQ ID NO: 342.

120. The method of paragraph 119, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 115 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 116 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 117 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 118 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 119 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 120 encoding the light chain; nucleotide sequence of SEQ ID NO: 109 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 110 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 378 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 379 encoding the light chain; a nucleotide sequence of SEQ ID NO: 343 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 344 encoding the light chain; nucleotide sequence of SEQ ID NO: 345 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 346 encoding the light chain; a nucleotide sequence of SEQ ID NO: 347 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 348 encoding the light chain; a nucleotide sequence of SEQ ID NO: 349 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 350 encoding the light chain; nucleotide sequence of SEQ ID NO: 351 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 352 encoding the light chain; a nucleotide sequence of SEQ ID NO: 129 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 130 encoding the light chain; a nucleotide sequence of SEQ ID NO: 131 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 132 encoding the light chain; or nucleotide sequence of SEQ ID NO: 341 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 342 encoding the light chain.

121. The method of any of paragraphs 115 to 118, wherein the antibody or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

122. The method of any of paragraphs 115 to 121 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

123. The method of any of paragraphs 115 to 122 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

124. The method of any of paragraphs 115 to 123 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

125. The method of any of paragraphs 116 to 124 wherein the recombinant expression vector is AAV2.7m8, AAV8, or AAV9.

126. The method of any of paragraphs 116 to 125 in which production of the HuPTM form of the mAb or antigen-binding fragment thereof is confirmed by transducing human retina cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

127. A method of treating multiple sclerosis in a human subject in need thereof, comprising delivering to the cerebrospinal fluid (CSF) of said human subject, a therapeutically effective amount of a substantially full-length or full-length anti-repulsive guidance molecule-A (anti-RGMa) mAb or antigen-binding fragment thereof, expressed from a transgene and produced by human CNS cells.

128. A method of treating multiple sclerosis in a human subject in need thereof, comprising:

administering to the CNS of said human subject, a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding a substantially full-length or full-length anti-repulsive guidance molecule-A (anti-RGMa) mAb or antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human CNS cells, so that a depot is formed that released a HuPTM form of said mAb or antigen-binding fragment thereof.

129. The method of paragraphs 127 or 128 wherein the anti-RGMa mAb is elezanumab.

130. The method of any of paragraphs 127 to 129 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

131. The method of any of paragraphs 127 to 130, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 51 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 306 and a light chain with an amino acid sequence of SEQ ID NO: 52.

132. The method of paragraph 131, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 121 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 122 encoding the light chain.

133. The method of any of paragraphs 127 to 131, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

134. The method of any of paragraphs 127 to 133 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

135. The method of any of paragraphs 127 to 134 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

136. The method of any of paragraphs 127 to 135 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

137. The method of any of paragraphs 128 to 136 wherein the recombinant expression vector is AAV9.

138. The method of any of paragraphs 128 to 136 in which production of the HuPTM form of said mAb or antigen-binding fragment thereof is confirmed by transducing human CNS cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

139. A method of treating amyloidosis (ATTR), familial amyloid cardiomyopathy (FAC), or familial amyloid polyneuropathy (FAP) in a human subject in need thereof, comprising delivering to circulation of said human subject, a therapeutically effective amount of a substantially full-length or full-length anti-transthyretin (anti-TTR) mAb or antigen-binding fragment thereof, expressed from a transgene and produced by human liver cells or human muscle cells.

140. A method of treating asthma in a human subject in need thereof, comprising:

administering to the liver or muscle of said human subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding a substantially full-length or full-length anti-transthyretin (anti-TTR) mAb or an antigen-binding fragment thereof,

operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells, so that a depot is formed that releases a HuPTM form of said mAb or antigen-binding fragment thereof.

141. The method of paragraphs 139 or 140 wherein the anti-TTR mAb is NI-301 or PRX-004.

142. The method of any of paragraphs 139 to 141 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

143. The method of any of paragraphs 139 to 142, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 53 and optionally an Fc polypeptide of an IgG1 isotype (e.g., an amino acid sequence of SEQ ID NO: 283) and a light chain with an amino acid sequence of SEQ ID NO: 54; or a heavy chain with an amino acid sequence of SEQ ID NO: 55 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 307 and a light chain with an amino acid sequence of SEQ ID NO: 56.

144. The method of paragraph 143, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 123 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 124 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 125 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 126 encoding the light chain.

145. The method of any of paragraphs 139 to 143, wherein the antibody or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

146. The method of any of paragraphs 139 to 145 wherein the mAb or antigen-binding fragment thereof contains an alpha2,6-sialylated glycan.

147. The method of any of paragraphs 139 to 146 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

148. The method of any of paragraphs 139 to 147 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

149. The method of any of paragraphs 140 to 148 wherein the recombinant expression vector is AAV8 or AAV9.

150. The method of any of paragraphs 140 to 149 in which production of said HuPTM form of said mAb or antigen-binding fragment thereof is confirmed by transducing human liver cells or human muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

151. A method of treating fibrotic disorders including pulmonary fibrosis, cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), liver cirrhosis, atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, arthrofibrosis, Crohn's disease, mediastinal fibrosis, myelofibrosis (MF), nephrogenic systemic fibrosis (NSF), progressive massive fibrosis (PMF), and retroperitoneal fibrosis (RPF) in a human subject in need thereof, comprising delivering to the circulation of said human subject, a therapeutically effective amount of a substantially full-length or full-length anti-connective tissue growth factor (anti-CTGF) mAb or antigen-binding fragment thereof, expressed from a transgene and produced by human liver cells or human muscle cells.

152. A method of treating fibrotic disorders including pulmonary fibrosis, cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), liver cirrhosis, atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, arthrofibrosis, Crohn's disease, mediastinal fibrosis, myelofibrosis (MF), nephrogenic systemic fibrosis (NSF), progressive massive fibrosis (PMF), and retroperitoneal fibrosis (RPF) in a human subject in need thereof, comprising:

administering to the liver or muscle of said human subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding a substantially full-length or full-length anti-connective tissue growth factor (anti-CTGF) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells, so that a depot is formed that releases a HuPTM form of the mAb or antigen-binding fragment thereof.

153. The method of paragraph 151 or 152 wherein the anti-CTGF mAb is pamrevlumab.

154. The method of any of paragraphs 151 to 153 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

155. The method of any of paragraphs 151 to 154, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 57 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 308 and a light chain with an amino acid sequence of SEQ ID NO: 58.

156. The method of paragraph 155, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 127 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 128 encoding the light chain.

157. The method of any of paragraphs 151 to 155, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

158. The method of any of paragraphs 151 to 157 wherein the mAb or antigen-binding fragment thereof contains an alpha2,6-sialylated glycan.

159. The method of any of paragraphs 151 to 158 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

160. The method of any of paragraphs 151 to 159 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

161. The method of any of paragraphs 152 to 160 wherein the recombinant expression vector is AAV8 or AAV9.

162. The method of any of paragraphs 152 to 161 in which production of said HuPTM form of the mAb or antigen-binding fragment thereof is confirmed by transducing human liver cells or human muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

163. A method of treating non-infectious uveitis, neuromyelitis optica (NMO), diabetic retinopathy (DR) or diabetic macular edema (DME) in a human subject in need thereof, comprising delivering to the retina of said human subject, a therapeutically effective amount of a substantially full-length or full-length mAb of an anti-interleukin-6 receptor (anti-IL6R) mAb, anti-interleukin-6

(IL6) mAb, or anti-cluster of differentiation 19 (anti-CD19) mAb, or antigen-binding fragment thereof, expressed from a transgene and produced by human retina cells.

164. A method of treating non-infectious uveitis, neuromyelitis optica (NMO), diabetic retinopathy (DR) or diabetic macular edema (DME) in a human subject in need thereof, comprising:

administering to the retina of said human subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding a substantially full-length or full-length mAb of an anti-interleukin-6 receptor (anti-IL6R) mAb, anti-interleukin-6 (IL6) mAb, or anti-cluster of differentiation 19 (anti-CD19) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human retina cells, so that a depot is formed that releases a HuPTM form of the mAb or antigen-binding fragment thereof.

165. The method of paragraph 163 or 164 wherein the anti-IL6R is satralizumab, sarilumab, or tocilizumab, or the anti-IL6 mAb is siltuximab, clazakizumab, sirukumab, olokizumab, or gerilimzumab, or the anti-CD19 mAb is inebilizumab.

166. The method of any of paragraphs 163 to 165 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

167. The method of any of paragraphs 163 to 166, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 59 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 309 and a light chain with an amino acid sequence of SEQ ID NO: 60; or a heavy chain with an amino acid sequence of SEQ ID NO: 61 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 310 and a light chain with an amino acid sequence of SEQ ID NO: 62; or a heavy chain with an amino acid sequence of SEQ ID NO: 341 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 359 and a light chain with an amino acid sequence of SEQ ID NO: 342; or a heavy chain with an amino acid sequence of SEQ ID NO: 331 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 355 and a light chain with an amino acid sequence of SEQ ID NO: 332; or a heavy chain with an amino acid sequence of SEQ ID NO: 333 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 356 and a light chain with an amino acid sequence of SEQ

ID NO: 334; or a heavy chain with an amino acid sequence of SEQ ID NO: 335 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 357 and a light chain with an amino acid sequence of SEQ ID NO: 336; or a heavy chain with an amino acid sequence of SEQ ID NO: 337 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 358 and a light chain with an amino acid sequence of SEQ ID NO: 338; or a heavy chain with an amino acid sequence of SEQ ID NO: 339 and optionally an Fc polypeptide with an IgG1 amino acid sequence of SEQ ID NO: 283 and a light chain with an amino acid sequence of SEQ ID NO: 340; or a heavy chain with an amino acid sequence of SEQ ID NO: 341 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 359 and a light chain with an amino acid sequence of SEQ ID NO: 342; a heavy chain with an amino acid sequence of SEQ ID NO: 63 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 311 and a light chain with an amino acid sequence of SEQ ID NO: 64.

168. The method of paragraph 167, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 129 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 130 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 131 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 132 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 343 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 344 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 345 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 346 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 347 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 348 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 349 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 350 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 351 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 352 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 353 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 354 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 133 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 134 encoding the light chain.

169. The method of any of paragraphs 163 to 167, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

170. The method of any of paragraphs 163 to 168 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

171. The method of any of paragraphs 163 to 169 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

172. The method of any of paragraphs 163 to 170 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

173. The method of any of paragraphs 164 to 171 wherein the recombinant expression vector is AAV8, AAV2.7m8 or AAV9.

174. The method of any of paragraphs 164 to 172 in which production of said HuPTM form of said mAb or antigen-binding fragment thereof is confirmed by transducing human retina cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

175. A method of treating inflammatory bowel disease (IBD) including UC and CD in a human subject in need thereof, comprising delivering to the circulation of said human subject, a therapeutically effective amount of a substantially full-length or full-length anti-integrin β7 subunit (anti-ITGB7) mAb or antigen-binding fragment thereof, expressed from a transgene and produced by human liver cells or human muscle cells.

176. A method of treating inflammatory bowel disease (IBD) including UC and CD in a human subject in need thereof, comprising:

administering to the liver or muscle of said human subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding a substantially full-length or full-length anti-integrin β7 subunit (anti-ITGB7) mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells, so that a depot is formed that releases a HuPTM form of said mAb or antigen-binding fragment thereof.

177. The method of paragraph 175 or 176 wherein the anti-ITGB7 mAb is etrolizumab.

178. The method of any of paragraphs 175 to 177 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

179. The method of any of paragraphs 175 to 178, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 65 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 312 and a light chain with an amino acid sequence of SEQ ID NO: 66.

180. The method of paragraph 179, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 135 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 136 encoding the light chain.

181. The method of any of paragraphs 175 to 179, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

182. The method of any of paragraphs 175 to 181 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

183. The method of any of paragraphs 175 to 182 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

184. The method of any of paragraphs 175 to 183 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

185. The method of any of paragraphs 176 to 184 wherein the recombinant expression vector is AAV8 or AAV9.

186. The method of any of paragraphs 176 to 185 in which production of said HuPTM form of said mAb or antigen-binding fragment thereof is confirmed by transducing human liver cells or human muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

187. A method of treating systemic osteoporosis or abnormal bone loss or weakness (e.g., treating giant cell tumor of bone, treating treatment-induced bone loss, slowing the loss of (or increasing) bone mass in breast and prostate cancer patients, preventing skeletal-related events due to

bone metastasis or for decreasing bone resorption and turnover in a human subject in need thereof, comprising delivering to the circulation of said human subject, a therapeutically effective amount of a substantially full-length or full-length anti-sclerostin (anti-SOST) mAb or antigen-binding fragment thereof, expressed from a transgene and produced by human liver cells or human muscle cells.

188. A method of treating osteoporosis or abnormal bone loss or weakness (e.g., treating giant cell tumor of bone, treating treatment-induced bone loss, slowing the loss of (or increasing) bone mass in breast and prostate cancer patients, preventing skeletal-related events due to bone metastasis or for decreasing bone resorption and turnover in a human subject in need thereof, comprising:

administering to the liver 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-sclerostin (anti-SOST) mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or in human muscle cells, so that a depot is formed that releases a HuPTM form of said mAb or antigen-binding fragment thereof.

189. The method of paragraph 187 or 188 wherein the anti-SOST mAb is romosozumab.

190. The method of any of paragraphs 187 to 189 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

191. The method of any of paragraphs 187 to 190, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 67 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 313 and a light chain with an amino acid sequence of SEQ ID NO: 68.

192. The method of paragraph 191, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 137 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 138 encoding the light chain.

193. The method of any of paragraphs 187 to 191, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

194. The method of any of paragraphs 187 to 193 wherein the mAb or antigen-binding fragment thereof contains an alpha2,6-sialylated glycan.

195. The method of any of paragraphs 187 to 194 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

196. The method of any of paragraphs 187 to 195 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

197. The method of any of paragraphs 188 to 196 wherein the recombinant expression vector is AAV8 or AAV9.

198. The method of any of paragraphs 188 to 196 in which production of said HuPTM form of said mAb or antigen-binding fragment thereof is confirmed by transducing human liver cells or human muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

199. A method of treating angioedema in a human subject in need thereof, comprising delivering to the circulation of said human subject, a therapeutically effective amount of a substantially full-length or full-length anti-kallikrein (anti-pKal) mAb or antigen-binding fragment thereof, expressed from a transgene and produced by human muscle cells or human liver cells.

200. A method of treating angioedema in a human subject in need thereof, comprising:

administering to the muscle or liver 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-kallikrein (anti-pKal) mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human muscle cells or human liver cells, so that a depot is formed that releases a HuPTM form of said mAb or antigen-binding fragment thereof.

201. The method of paragraph 199 or 200 wherein the anti-pKal mAb is lanadelumab.

202. The method of any of paragraphs 199 to 201 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

203. The method of any of paragraphs 199 to 202, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 69 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 314 and a light chain with an amino acid sequence of SEQ ID NO: 70.

204. The method of paragraph 203, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 139 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 140 encoding the light chain.

205. The method of any of paragraphs 199 to 203, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

206. The method of any of paragraphs 199 to 205 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

207. The method of any of paragraphs 199 to 206 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

208. The method of any of paragraphs 199 to 207 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

209. The method of any of paragraphs 200 to 208 wherein the recombinant expression vector is AAV8 or AAV9.

210. The method of any of paragraphs 200 to 209 in which production of said HuPTM form of said mAb or antigen-binding fragment thereof is confirmed by transducing human liver cells or human muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

Method of Manufacture

211. A method of producing recombinant AAVs comprising:

(a) culturing a host cell containing:

(i) an artificial genome comprising a *cis* expression cassette flanked by AAV ITRs, wherein the *cis* expression cassette comprises a transgene encoding a therapeutic antibody operably linked to expression control elements that will control expression of the transgene in human 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*;

(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.

212. The method of paragraph 211, 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 solanezumab, lecanemab, GSK933776, AL-001, ABBV-8E12, UCB-0107, NI-105 (BIIB076), VX15/2503, prasinezumab, NI-202 (BIIB054), MED-1341, NI-2041.10D12, NI-204.12G7, eptinezumab, fremanezumab, galcanezumab, or elezanumab.

213. The method of paragraph 212, wherein the AAV capsid protein is an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid protein.

214. The method of paragraph 211, 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 sevacizumab, LKA-651 (NSV2), LKA-651 (NSV3), GSK933776, solanezumab, lecanemab, ascrinvacumab, tesidolumab, ravulizumab, carotuximab, ANX-007, lanadelumab, adalimumab, infliximab, golimumab, satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, or inebilizumab.

215. The method of paragraph 214, wherein the AAV capsid protein is an AAV2.7m8, AAV8, or AAV9 capsid protein.

216. The method of paragraph 211, 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 NI-301, PRX-004, pamrevlumab, etrolizumab, romosozumab, or lanadelumab.

217. The method of paragraph 216, wherein the AAV capsid protein is an AAV8, AAV9, or AAVrh10 capsid protein.

218. The method of paragraph 211, wherein the transgene encodes a substantially full-length or full-length mAb.

Autoimmune, Respiratory, and Allergic Disease

Compositions of Matter

219. A pharmaceutical composition for treating atopic dermatitis in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), or an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding an anti-IL13 mAb or anti-IL31RA, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous administration to the liver or muscle of said subject.

220. The pharmaceutical composition of paragraph 219 wherein the anti-IL13 or the IL31RA is tralokinumab or nemolizumab.

221. The pharmaceutical composition of paragraphs 219 or 220, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

222. The pharmaceutical composition of any of paragraphs 219 to 221, wherein the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 368 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 396 and a light chain with an amino acid sequence of SEQ ID NO: 369; or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 370 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 397 and a light chain with an amino acid sequence of SEQ ID NO: 371.

223. The pharmaceutical composition of paragraph 222, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 384 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 385 encoding the light chain; or the transgene comprises a nucleotide sequence of SEQ ID NO: 386 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 387 encoding the light chain.

224. The pharmaceutical composition of any of paragraphs 219 to 221, wherein the antibody or antigen-binding fragment thereof is a hyperglycosylated mutant.

225. The pharmaceutical composition of any of paragraphs 219 to 224, 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 liver cells or human muscle cells.

226. The pharmaceutical composition of paragraph 225, wherein said signal sequence is selected from the signal sequences in Table 2 or 3.

227. The pharmaceutical composition of any of paragraphs 219 to 226, wherein the AAV capsid is AAV8.

228. A pharmaceutical composition for treating eosinophilic asthma in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), or an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding an anti-IL5R mAb or anti-IgE mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous administration to the liver or muscle of said subject.

229. The pharmaceutical composition of paragraph 228 wherein the anti-IL5R or anti-IgE mAb is reslizumab or omalizumab.

230. The pharmaceutical composition of paragraphs 228 or 229, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

231. The pharmaceutical composition of any of paragraphs 228 to 230, wherein the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 364 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 394 and a light chain with an amino acid sequence of SEQ ID NO: 365; or a heavy chain with an amino acid sequence of SEQ ID NO: 372 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 398 and a light chain with an amino acid sequence of SEQ ID NO: 373.

232. The pharmaceutical composition of paragraph 231, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 380 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 381 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 388 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 389 encoding the light chain.

233. The pharmaceutical composition of any of paragraphs 228 to 231, wherein the antibody or antigen-binding fragment thereof is a hyperglycosylated mutant.

234. The pharmaceutical composition of any of paragraphs 228 to 233, 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 liver cells or human muscle cells.

235. The pharmaceutical composition of paragraph 234, wherein said signal sequence is selected from the signal sequences in Table 2 or 3.

236. The pharmaceutical composition of any of paragraphs 228 to 235, wherein the AAV capsid is AAV8.

237. A pharmaceutical composition for treating asthma or chronic obstructive pulmonary disease (COPD) in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), or an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding an anti-IL5, anti-IL-5R, anti-IgE, or anti-TSLP mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous administration to the liver or muscle of said subject.

238. The pharmaceutical composition of paragraph 237 wherein the anti-IL-5, anit-IL5R, anti-IgE, or anti-TSLP mAb is benralizumab, reslizumab, omalizumab, or tezepelumab. .

239. The pharmaceutical composition of paragraphs 237 or 238, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

240. The pharmaceutical composition of any of paragraphs 237 to 239, wherein the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 364 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 394 and a light chain with an amino acid sequence of SEQ ID NO: 365; a heavy chain with an amino acid sequence of SEQ ID NO: 366 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 395 and a light chain with an amino acid sequence of SEQ ID NO: 367; a heavy chain with an amino acid sequence of SEQ ID NO: 372 and a light chain with an amino acid sequence of SEQ ID NO: 373; or a heavy chain with

an amino acid sequence of SEQ ID NO: 374 and optionally an IgG2 Fc polypeptide of an amino acid sequence of SEQ ID NO: 284 and a light chain with an amino acid sequence of SEQ ID NO: 375

241. The pharmaceutical composition of paragraph 240, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 380 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 381 encoding the light chain; a nucleotide sequence of SEQ ID NO: 382 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 383 encoding the light chain; a nucleotide sequence of SEQ ID NO: 388 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 389 encoding the light chain; a nucleotide sequence of SEQ ID NO: 390 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 391 encoding the light chain.

242. The pharmaceutical composition of any of paragraphs 237 to 240, wherein the antibody or antigen-binding fragment thereof is a hyperglycosylated mutant.

243. The pharmaceutical composition of any of paragraphs 237 to 242, 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 liver cells or human muscle cells.

244. The pharmaceutical composition of paragraph 243, wherein said signal sequence is selected from the signal sequences in Table 2 or 3.

245. The pharmaceutical composition of any of paragraphs 237 to 244, wherein the AAV capsid is AAV8.

246. A pharmaceutical composition for treating chronic idiopathic urticaria in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO:143), an AAV9 capsid (SEQ ID NO: 144), or an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding an anti-IgE mAb, or an antigen-

binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous administration to the liver or muscle of said subject.

247. The pharmaceutical composition of paragraph 246, wherein the anti-IgE mAb is omalizumab.

248. The pharmaceutical composition of paragraphs 246 or 247, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

249. The pharmaceutical composition of any of paragraphs 246 to 248, wherein the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 372 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 398 and a light chain with an amino acid sequence of SEQ ID NO: 373.

250. The pharmaceutical composition of paragraph 249, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 388 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 389 encoding the light chain.

251. The pharmaceutical composition of any of paragraphs 246 to 249, wherein the antibody or antigen-binding fragment thereof is a hyperglycosylated mutant.

252. The pharmaceutical composition of any of paragraphs 246 to 251, 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 liver cells or human muscle cells.

253. The pharmaceutical composition of paragraph 252, wherein said signal sequence is selected from the signal sequences in Table 2 or 3.

The pharmaceutical composition of any of paragraphs 246 to 253, wherein the AAV capsid is AAV8.

Method of Treatment

254. A method of treating atopic dermatitis in a human subject in need thereof, comprising delivering to the circulation of said human subject, a therapeutically effective amount of an anti-IL13 or anti-IL31RA mAb or antigen-binding fragment thereof, produced by human liver cells or human muscle cells.

255. A method of treating atopic dermatitis in a human subject in need thereof, comprising:

administering to the liver or muscle of said subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding an anti-IL13 or anti-IL31RA mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells, so that a depot is formed that releases a HuPTM form of said mAb or antigen-binding fragment thereof.

256. The method of paragraph 254 or 255 wherein the anti-IL13 or anti-IL31RA mAb is tralokinumab or nemolizumab.

257. The method of any of paragraphs 254 to 256 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

258. The method of any of paragraphs 254 to 257, wherein the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 368 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 396 and a light chain with an amino acid sequence of SEQ ID NO: 369; or a heavy chain with an amino acid sequence of SEQ ID NO: 370 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 397 and a light chain with an amino acid sequence of SEQ ID NO: 371.

259. The method of claim 258, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 384 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 385 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 386 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 387 encoding the light chain.

260. The method of any of paragraphs 254 to 258, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant.

261. The method of any of paragraphs 254 to 260 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

262. The method of any of paragraphs 254 to 261 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

263. The method of any of paragraphs 254 to 262 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

264. The method of any of paragraphs 254 to 263 wherein the recombinant expression vector is AAV8 or AAV9.

265. The method of any of paragraphs 254 to 264 in which production of said HuPTM form of the mAb or antigen-binding fragment thereof is confirmed by transducing human liver cells or muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

266. A method of treating eosinophilic asthma in a human subject in need thereof, comprising delivering to the circulation of said human subject, a therapeutically effective amount of an anti-IL5R or anti-IgE mAb or antigen-binding fragment thereof, produced by human liver cells or human muscle cells.

267. A method of treating eosinophilic asthma in a human subject in need thereof, comprising:

administering to the liver or muscle of said subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding an anti-IL5R or anti-IgE mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells, so that a depot is formed that releases a HuPTM form of said mAb or antigen-binding fragment thereof.

268. The method of paragraph 266 or 267 wherein the anti-IL5R or anti-IgE mAb is reslizumab or omalizumab.

269. The method of any of paragraphs 266 to 268 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

270. The method of any of paragraphs 266 to 269, wherein the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 366 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 395 and a light chain with an amino acid sequence of SEQ ID NO: 367; or a heavy chain with an amino acid sequence of SEQ ID NO: 372 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 398 and a light chain with an amino acid sequence of SEQ ID NO: 373.

271. The method of claim 270, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 382 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 383 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 388 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 389 encoding the light chain.

272. The method of any of paragraphs 266 to 270, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant.

273. The method of any of paragraphs 266 to 272 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

274. The method of any of paragraphs 266 to 273 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

275. The method of any of paragraphs 266 to 274 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

276. The method of any of paragraphs 266 to 275 wherein the recombinant expression vector is AAV8 or AAV9.

277. The method of any of paragraphs 266 to 276 in which production of said HuPTM form of the mAb or antigen-binding fragment thereof is confirmed by transducing human liver cells or muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

278. A method of treating asthma or COPD in a human subject in need thereof, comprising delivering to the circulation of said human subject, a therapeutically effective amount of an anti-IL5, anti-IL5R, anti-IgE, or anti-TSLP mAb or antigen-binding fragment thereof, produced by human liver cells or human muscle cells.

279. A method of treating eosinophilic asthma in a human subject in need thereof, comprising:

administering to the liver or muscle of said subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding an anti-IL5R, anti-IL5, anti-IgE, or anti-TSLP mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells, so that a depot is formed that releases a HuPTM form of said mAb or antigen-binding fragment thereof.

280. The method of paragraph 278 or 279 wherein the anti-IL5R, anti-IL5, anti-IgE, or anti-TSLP mAb is benralizumab, reslizumab, omalizumab, or tezepelumab.

281. The method of any of paragraphs 278 to 280 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

282. The method of any of paragraphs 278 to 281, wherein the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 364 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 394 and a light chain with an amino acid sequence of SEQ ID NO: 365; or a heavy chain with an amino acid sequence of SEQ ID NO: 366 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 395 and a light chain with an amino acid sequence of SEQ ID NO: 367; or a heavy chain with an amino acid sequence of SEQ ID NO: 372 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 398 and a light chain with an amino acid sequence of SEQ ID NO: 373; or a heavy chain with an amino acid sequence of SEQ ID NO: 374 and optionally an IgG2 Fc polypeptide of an amino acid sequence of SEQ ID NO: 284 and a light chain with an amino acid sequence of SEQ ID NO: 375.

283. The method of paragraph 282, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 380 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 381 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 383 encoding the heavy chain and a nucleotide

sequence of SEQ ID NO: 383 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 388 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 389 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 390 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 391 encoding the light chain.

284. The method of any of paragraphs 278 to 283, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant.

285. The method of any of paragraphs 278 to 284 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

286. The method of any of paragraphs 278 to 285 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

287. The method of any of paragraphs 278 to 286 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

288. The method of any of paragraphs 278 to 287 wherein the recombinant expression vector is AAV8 or AAV9.

289. The method of any of paragraphs 278 to 288 in which production of said HuPTM form of the mAb or antigen-binding fragment thereof is confirmed by transducing human liver cells or muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

290. A method of treating chronic idiopathic urticaria in a human subject in need thereof, comprising delivering to the circulation of said human subject, a therapeutically effective amount of an anti-IgE mAb or antigen-binding fragment thereof, produced by human liver cells or human muscle cells.

291. A method of treating eosinophilic asthma in a human subject in need thereof, comprising:

administering to the liver or muscle of said subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding an anti-IgE mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that

control expression of the transgene in human liver cells or human muscle cells, so that a depot is formed that releases a HuPTM form of said mAb or antigen-binding fragment thereof.

292. The method of paragraph 290 or 291 wherein the anti-IgE mAb is omalizumab.

293. The method of any of paragraphs 290 to 292 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

294. The method of any of paragraphs 290 to 293, wherein the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 372 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 398 and a light chain with an amino acid sequence of SEQ ID NO: 373.

295. The method of paragraph 294, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 388 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 389 encoding the light chain.

296. The method of any of paragraphs 290 to 295, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant.

297. The method of any of paragraphs 290 to 296 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

298. The method of any of paragraphs 290 to 297 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

299. The method of any of paragraphs 290 to 298 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

300. The method of any of paragraphs 290 to 299 wherein the recombinant expression vector is AAV8 or AAV9.

301. The method of any of paragraphs 290 to 300 in which production of said HuPTM form of the mAb or antigen-binding fragment thereof is confirmed by transducing human liver cells or muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

Method of Manufacture

302. The method of paragraph 211, 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 benralizumab, reslizumab, tralokinumab, nemolizumab, omalizumab, or tezepelumab.

303. The method of paragraph 302, wherein the AAV capsid protein is an AAV8, AAV9, or AAVrh10 capsid protein.

Myasthenia Gravis

Compositions of Matter

304. A pharmaceutical composition for treating myasthenia gravis in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), or an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding an anti-C5 mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous administration to the liver or muscle of said subject.

305. The pharmaceutical composition of paragraph 304 wherein the anti-C5 is ravulizumab.

306. The pharmaceutical composition of paragraphs304 or 305, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

307. The pharmaceutical composition of any of paragraphs 304 to 306, wherein the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 362 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 393 and a light chain with an amino acid sequence of SEQ ID NO: 363.

308. The pharmaceutical composition of paragraph 307, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 378 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 379 encoding the light chain.

309. The pharmaceutical composition of any of paragraphs 304 to 308, wherein the antibody or antigen-binding fragment thereof is a hyperglycosylated mutant.

310. The pharmaceutical composition of any of paragraphs 304 to 310, 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 liver cells or human muscle cells.

311. The pharmaceutical composition of paragraph 310, wherein said signal sequence is selected from the signal sequences in Table 2 or 3.

312. The pharmaceutical composition of any of paragraphs 304 to 311, wherein the AAV capsid is AAV8.

Method of Treatment

313. A method of treating myasthenia gravis in a human subject in need thereof, comprising delivering to the circulation of said human subject, a therapeutically effective amount of an anti-C5 mAb or antigen-binding fragment thereof, produced by human liver cells or human muscle cells.

314. A method of treating myasthenia gravis in a human subject in need thereof, comprising:

administering to the liver or muscle of said subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding an anti-C5 mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells, so that a depot is formed that releases a HuPTM form of said mAb or antigen-binding fragment thereof.

315. The method of paragraph 313 or314 wherein the anti-C5 is ravulizumab.

316. The method of any of paragraphs 313 to 315 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

317. The method of any of paragraphs 313 to 316, wherein the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 362 and optionally an Fc polypeptide of an amino acid sequence of SEQ ID NO: 393 and a light chain with an amino acid sequence of SEQ ID NO: 363.

318. The method of claim 260, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 378 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 379 encoding the light chain.

319. The method of any of paragraphs 313 to 318, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant.

320. The method of any of paragraphs 313 to 319 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

321. The method of any of paragraphs 313 to 320 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

322. The method of any of paragraphs 313 to 321 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

323. The method of any of paragraphs 313 to 322 wherein the recombinant expression vector is AAV8 or AAV9.

324. The method of any of paragraphs 313 to 323 in which production of said HuPTM form of the mAb or antigen-binding fragment thereof is confirmed by transducing human liver cells or muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

Method of Manufacture

325. The method of paragraph 211, 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 ravulizumab.

326. The method of paragraph 304, wherein the AAV capsid protein is an AAV8, AAV9, or AAVrh10 capsid protein.

Compositions and Methods for Inhibiting Immune Response

327. A pharmaceutical composition for reducing, inhibiting or ameliorating a detrimental immune response in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or full-length mAb of an anti-interleukin-6 receptor (anti-IL6R) or anti-interleukin-6 (IL6), or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or muscle cells;

wherein said AAV vector is formulated for subcutaneous, intramuscular, intravenous or pulmonary administration to the subject.

328. The pharmaceutical composition of paragraph 327, wherein the anti-IL6R mAb is satralizumab, sarilumab, or tocilizumab, or the anti-IL6 mAb is siltuximab, clazakizumab, sirukumab, olokizumab, or gerilimzumab.

329. The pharmaceutical composition of paragraphs 327 or 328, wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

330. The pharmaceutical composition of any of paragraphs 327 to 329, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 59 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 309 and a light chain with an amino acid sequence of SEQ ID NO: 60; or a heavy chain with an amino acid sequence of SEQ ID NO: 61 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 310 and a light chain with an amino acid sequence of SEQ ID NO: 62; or a heavy chain with an amino acid sequence of SEQ ID NO: 331 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 355 and a light chain with an amino acid sequence of SEQ ID NO: 332; or a heavy chain with an amino acid sequence of SEQ ID NO: 333 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 356 and a light chain with an amino acid sequence of SEQ ID NO: 334; or a heavy chain with an amino acid sequence of SEQ ID NO: 335 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 357 and a light chain with an amino acid sequence of SEQ ID NO: 336; or a heavy chain with an amino acid sequence of SEQ ID NO: 337 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 358 and a light chain with an amino acid sequence of SEQ ID NO: 338; or a heavy chain with an amino acid sequence of SEQ ID NO: 339 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 283 and a light chain with an amino acid sequence of SEQ ID NO: 340; or a heavy chain with an amino acid sequence of SEQ ID NO: 341 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 359 and a light chain with an amino acid sequence of SEQ ID NO: 342.

331. The pharmaceutical composition of paragraph 330, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 129 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 130 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 131 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 132 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 343 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 344 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 345 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 346 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 347 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 348 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 349 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 350 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 351 encoding the

heavy chain and a nucleotide sequence of SEQ ID NO: 352 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 353 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 354 encoding the light chain.

332. The pharmaceutical composition of any of paragraphs 327 to 331, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

333. The pharmaceutical composition of any of paragraphs 327 to 331, 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 liver cells or human muscle cells.

334. The pharmaceutical composition of paragraph 333, wherein said signal sequence is MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence from Table 3 or Table 4.

335. The pharmaceutical composition of any of paragraphs 327 to 334, wherein the AAV capsid is AAV8.

336. A method of reducing, inhibiting or ameliorating a detrimental immune response in a human subject in need thereof, comprising delivering to the circulation or tissue that is the target of the immune response of said human subject, a therapeutically effective amount of a substantially full-length or full-length mAb of an anti-interleukin-6 receptor (anti-IL6R) mAb, anti-interleukin-6 (IL6) mAb, or antigen-binding fragment thereof, expressed from a transgene and produced by human muscle or liver cells.

337. A method reducing, inhibiting or ameliorating a detrimental immune response in a human subject in need thereof, comprising:

administering to the muscle or liver of said human subject a therapeutically effective amount of a recombinant nucleotide expression vector comprising a transgene encoding a substantially full-length or full-length mAb of an anti-interleukin-6 receptor (anti-IL6R) mAb, anti-interleukin-6 (IL6) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory

sequences that control expression of the transgene in human muscle or liver cells, so that a depot is formed that releases a HuPTM form of the mAb or antigen-binding fragment thereof.

338. The method of paragraph 336 or 337 wherein the anti-IL6R is satralizumab, sarilumab, or tocilizumab, or the anti-IL6 mAb is siltuximab, clazakizumab, sirukumab, olokizumab, or gerilimzumab.

339. The method of any of paragraphs 336 to 338 wherein the antigen-binding fragment is a Fab, a $F(ab')_2$, or an scFv.

340. The method of any of paragraphs 336 to 339, wherein the full-length mAb or the antigen-binding fragment comprises a heavy chain with an amino acid sequence of SEQ ID NO: 59 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 309 and a light chain with an amino acid sequence of SEQ ID NO: 60; or a heavy chain with an amino acid sequence of SEQ ID NO: 61 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 310 and a light chain with an amino acid sequence of SEQ ID NO: 62; or a heavy chain with an amino acid sequence of SEQ ID NO: 341 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 359 and a light chain with an amino acid sequence of SEQ ID NO: 342; or a heavy chain with an amino acid sequence of SEQ ID NO: 331 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 355 and a light chain with an amino acid sequence of SEQ ID NO: 332; or a heavy chain with an amino acid sequence of SEQ ID NO: 333 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 356 and a light chain with an amino acid sequence of SEQ ID NO: 334; or a heavy chain with an amino acid sequence of SEQ ID NO: 335 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 357 and a light chain with an amino acid sequence of SEQ ID NO: 336; or a heavy chain with an amino acid sequence of SEQ ID NO: 337 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 358 and a light chain with an amino acid sequence of SEQ ID NO: 338; or a heavy chain with an amino acid sequence of SEQ ID NO: 339 and optionally an Fc polypeptide with an IgG1 amino acid sequence of SEQ ID NO: 283 and a light chain with an amino acid sequence of SEQ ID NO: 340; or a heavy chain with an amino acid sequence of SEQ ID NO: 341 and optionally an Fc polypeptide with an amino acid sequence of SEQ ID NO: 359 and a light chain with an amino acid sequence of SEQ ID NO: 342.

341. The method of paragraph 340, wherein the transgene comprises a nucleotide sequence of SEQ ID NO: 129 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 130 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 131 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 132 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 343 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 344 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 345 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 346 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 347 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 348 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 349 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 350 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 351 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 352 encoding the light chain; or a nucleotide sequence of SEQ ID NO: 353 encoding the heavy chain and a nucleotide sequence of SEQ ID NO: 354 encoding the light chain.

342. The method of any of paragraphs 336 to 339, wherein the mAb or antigen-binding fragment thereof is a hyperglycosylated mutant or wherein the Fc polypeptide of the mAb is glycosylated or aglycosylated.

343. The method of any of paragraphs 336 to 342 wherein the mAb or antigen-binding fragment thereof contains an alpha 2,6-sialylated glycan.

344. The method of any of paragraphs 336 to 343 wherein the mAb or antigen-binding fragment thereof is glycosylated but does not contain detectable NeuGc or α-Gal.

345. The method of any of paragraphs 336 to 344 wherein the mAb or antigen-binding fragment thereof contains a tyrosine sulfation.

346. The method of any of paragraphs 336 to 345 wherein the recombinant expression vector is AAV8 or AAV9.

347. The method of any of paragraphs 336 to 346 in which production of said HuPTM form of said mAb or antigen-binding fragment thereof is confirmed by transducing human liver or muscle cells in culture with said recombinant nucleotide expression vector and expressing said mAb or antigen-binding fragment thereof.

AAV encoding Full Length mAb Composition Embodiments

348. 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 an AAV8 capsid (SEQ ID NO: 143), AAV9 capsid (SEQ ID NO: 144), AAVrh10 capsid (SEQ ID NO: 145), an AAVrh20 capsid, an AAVrh39 capsid or an AAVcy5 capsid; 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 substantially full-length or full-length mAb operably linked to one or more regulatory sequences that control expression of the transgene in human 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.

349. The composition of paragraph 348, wherein said mAb comprises a heavy chain with a Fc polypeptide and a light chain having any one of the sequence combinations specified in paragraphs 4, 13, 22, 31, 40, 49, 58, 67, 76, 85, 95, 107, 119, 131, 143, 155, 167, 179, 191, 203, 222, 231, 240, 249, 258, 270, 282, 294, 307, and 317.

350. The composition of paragraph 348-349, wherein said mAb is a full length lanadelumab.

351. The composition of paragraph 350, wherein the transgene comprises a Furin/T2A linker between the nucleotide sequences coding for the heavy and light chains of said mAb.

352. The composition of paragraphs 350 to 351, wherein the regulatory sequence includes a regulatory sequence from Table 1.

353. The composition of paragraph 352, wherein the regulator sequence is a LMTP6 promoter, an ApoE.hAAT regulatory sequence, a CAG promoter, a CK8 regulatory sequence, or a TBG promoter.

354. The composition of paragraphs 350 to 353, wherein the transgene comprises a nucleotide sequence of SEQ ID NO. 141, 286, 287, or 435 to 444.

355. The composition of paragraphs 350 to 354, wherein the viral capsid is and AAV8 viral capsid.

356. A pharmaceutical composition for delivering lanadelumab to the bloodstream to treat hereditary angioedema in a human subject in need thereof, said composition comprising a recombinant AAV comprising a transgene encoding lanadelumab operably linked to one or more regulatory sequences that control expression of the transgene in muscle and/or liver cells, wherein said recombinant AAV is administered to said human subject at a dose sufficient to result in expression from the transgene and secretion of lanadelumab into the bloodstream of the human subject to produce lanadelumab plasma levels of at least 5 μg/ml to at least 35 μg/ml lanadelumab in said subject.

357. A method of treating hereditary angioedema in a human subject in need thereof, comprising administering to the subject a dose of a composition comprising a recombinant AAV comprising a transgene encoding lanadelumab operably linked to one or more regulatory sequences that control expression of the transgene in muscle and/or liver cells, in an amount sufficient to result in expression from the transgene and secretion of lanadelumab into the bloodstream of the human subject to produce lanadelumab plasma levels of at least 5 μg/ml to at least 35 μg/ml lanadelumab in said subject.

358. The method or composition of paragraphs 356 or 357 wherein the transgene comprises the nucleotide sequence of SEQ ID NO: 141, 286, 287, or 435 to 444

359. The meothd or composition of paragraphs 356 to 358, wherein the lanadelumab plasma levels are 20 μg/ml to 35 μg/ml.

360. The method or composition of paragraphs 356 to 359, wherein the lanadelumab plasma levels are maintained for at least three months.

361. The method or composition of paragraphs 356 to 360 wherein the lanadelumab antibody secreted into the plasma exhibits greater a greater than at least 40%, 45%, 50%, 55%, 60%, 65% or 70 reduction in pKal activity as measured by a kinetic enzymatic functional assay.

362. The method or composition of paragraph 361 wherein the activity of the lanadelumab antibody is measured at 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks or 12 weeks after said administration.

363. A method of determining human anti-pKal antibody activity in a sample, said method comprising

a. Incubating the sample with activated human pKal;

b. Subsequently incubating the sample having been incubated with the activated human pKal with the synthetic substrate Pro-Phe-Arg-AMC

c. Measure the relase of AMC over three hours as compared to a control sample.

Additional Embodiments

364. A pharmaceutical composition for delivery of an antibody or antigen binding fragment thereof to the bloodstream of a human subject in need thereof, comprising an AAV vector comprising:

(a) An AAV viral capsid that infects liver and/or muscle cells; and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a full-length antibody or an antigen-binding fragment thereof, operably linked to a chimeric promoter that directs expression in muscle and liver cells;

wherein said AAV vector is formulated for intramuscular administration.

365. The pharmaceutical composition of paragraph 364 wherein the chimeric promoter is LMTP6 (SEQ ID NO: 320), LMTP13 (SEQ ID NO: 321), LMTP14 (SEQ ID NO: 322), LMTP15 (SEQ ID NO: 323), LMTP18 (SEQ ID NO: 324), LMTP19 (SEQ ID NO: 325), or LMTP20 (SEQ ID NO: 326).

366. The pharmaceutical composition of paragraph 365 wherein the chimeric promoter is LMPT6 (SEQ ID NO: 320).

367. The pharmaceutical composition of any one of paragraphs 364 to 366, wherein the AAV viral capsid is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), an AAVrh10 capsid (SEQ ID NO: 145).

368. The pharmaceutical composition of any of paragraphs 364 to 3673, wherein the antibody is sevacizumab, LKA-651, ravulizumab, adalimumab, infliximab, golimumab, elezanumab, NI-301, PRX-004, pamrevlumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, satralizumab, sarilumab, tocilizumab, inebilizumab, etrolizumab, romosozumab, lanadelumab, benralizumab, reslizumab, tralokinumab, nemolizumab, omalizumab, or tezepelumab.

369. The pharmaceutical composition of any of paragraphs 364 to 366, wherein the transgene comprises nucleotide sequence SEQ ID NO; 443.

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0016] **FIG. 1**. A schematic of an rAAV vector genome construct containing an expression cassette encoding the heavy and light chains of the Fab region of a therapeutic mAb controlled by expression elements, flanked by the AAV ITRs.

[0017] **FIGS. 2A-C**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibodies to amyloid β peptides: solanezumab Fab (**FIG. 2A**), GSK933776 (**FIG. 2B**) and lecanemab (**FIG. 2C**). 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 heavy chain hinge regions are highlighted in grey.

[0018] **FIG. 3**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibodies to sortilin: AL-001 (**FIG. 3**). 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 heavy chain hinge regions are highlighted in grey.

[0019] **FIGS. 4A-4C**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibodies to tau: ABBV-8E12 (**FIG. 4A**), UCB-0107 (**FIG. 4B**), and NI-105 (**FIG. 4C**).

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 heavy chain hinge regions are highlighted in grey.

[0020] **FIG. 5**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibodies to SEMA4D: VX15/2503 (**FIG. 5**). 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 regions are highlighted in grey.

[0021] **FIGS. 6A-C**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibodies to alpha-synuclein: prasinezumab (**FIG. 6A**), NI-202 (**FIG. 6B**), and MEDI-1341 (**FIG. 6C**). 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] **FIGS. 7A and B**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibodies to superoxide dismutase 1 (SOD1): NI-205.10D12 (**FIG.7A**); and NI-205.12G7 (**FIG. 7B**). 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 regions are highlighted in grey.

[0023] **FIGS. 8A-C**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibodies directed at CGRPR: eptinezumab (**FIG. 8A**), fremanezumab (**FIG. 8B**), and galcanezumab (**FIG. 8C**). 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 regions are highlighted in grey.

[0024] **FIGS. 9A-C**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibody directed at biological factors: anti-VEGF, sevacizumab (**FIG. 9A**); anti-EpoR, LKA-651.NVS2 (**FIG. 9B**), and LKA-651.NVS3 (**FIG. 9C**). 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 regions are highlighted in grey.

[0025] **FIGS. 10A-D**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibody directed at biological factors: anti-ALK1, ascrinvacumab (**FIG. 10A**); anti-C5, tesidolumab (**FIG. 10B**) and ravulizumab (**FIG. 10D**), and anti-endoglin, carotuximab (**FIG. 10C**). 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 heavy chain hinge regions are highlighted in grey.

[0026] **FIG. 11**. The amino acid sequence of a transgene construct for the Fab region of ANX-007, a therapeutic antibody to CC1Q. 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. The hinge region is highlighted in grey.

[0027] **FIGS. 12A-C**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibody directed at TNF-alpha: adalimumab (**FIG. 12A**), infliximab (**FIG. 12B**), and golimumab (**FIG. 12C**). 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 heavy chain hinge regions are highlighted in grey.

[0028] **FIG. 13**. The amino acid sequence of a transgene construct for the Fab region of elezanumab, a therapeutic antibody to RGMa. 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.

[0029] **FIGS. 14A and B**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibody directed at transthyretin (TTR): NI-301 (**FIG. 14A**) and PRX-004 (**FIG. 14B**). 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.

[0030] **FIG. 15**. The amino acid sequence of a transgene construct for the Fab region of pamrevlumab, a therapeutic antibody to CTGF. 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.

[0031] **FIGS. 16A-I**. The amino acid sequence of a transgene construct for the Fab region of therapeutic antibody directed at biological factors: anti-IL6R, satralizumab (**FIG. 16A**), sarilumab (**FIG. 16B**), tocilizumab (**FIG. 16H**); anti-IL6, siltuximab (**FIG. 16C**), clazakizumab (**FIG. 16D**), sirukumab (**FIG. 16E**), olokizumab (**FIG. 16F**), gerilimzumab (**FIG. 16G**), and anti-CD19, inebilizumab (**FIG. 16I**). 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.

[0032] **FIG. 17**. The amino acid sequence of a transgene construct for the Fab region of etrolizumab, a therapeutic antibody to ITGB7. 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.

[0033] **FIG. 18**. The amino acid sequence of a transgene construct for the Fab region of romosozumab, a therapeutic antibody to sclerostin. 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.

[0034] **FIG. 19**. The amino acid sequence of a transgene construct for the Fab region of lanadelumab, a therapeutic antibody to plasma kallikrein (pKal). 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.

[0035] **FIGS. 20A and B**. Amino acid sequence alignment of the amino acid sequences of the heavy (**FIG. 20A**) (residues 1-220 of SEQ ID NO: 1, residues 1-223 of SEQ ID NO: 3, residues 1-237 of SEQ ID NO: 5, residues 1-220 of SEQ ID NO: 7, residues 1-223 of SEQ ID NO: 9, residues 1-232 of SEQ ID NO: 11, residues 1-228 of SEQ ID NO: 13, residues 1-224 of SEQ ID NO: 15, residues 1-232 of SEQ ID NO: 17, residues 1-230 of SEQ ID NO: 19, residues 1-234 of SEQ ID NO: 21, residues 1-231 of SEQ ID NO: 23, residues 1-219 of SEQ ID NO: 25, residues 1-227 of SEQ ID NO: 27, residues 1-224 of SEQ ID NO: 29, residues 1-230 of SEQ ID NO: 31, residues 1-225 of SEQ ID NO: 33, residues 1-235 of SEQ ID NO: 35, residues 1-223 of SEQ ID NO: 37, residues 1-224 of SEQ ID NO: 39, residues 1-226 of SEQ ID NO: 41, residues 1-229 of SEQ ID NO: 43, residues 1-229 of SEQ ID NO: 45, residues 1-228 of SEQ ID NO: 47, residues 1-237 of SEQ ID NO: 49, residues 1-228 of SEQ ID NO: 51, residues 1-228 of SEQ ID NO: 53, residues 1-225 of SEQ ID NO: 55, residues 1-224 of SEQ ID NO: 57, residues 1-224 of SEQ ID NO: 59, residues 1-224 of SEQ ID NO: 61, residues 1-229 of SEQ ID NO: 63, residues 1-225 of SEQ ID NO: 65, residues 1-228 of SEQ ID NO: 67, residues 1-230 of SEQ ID NO: 69, residues 1-227 of SEQ ID NO: 331, residues 1-228 of SEQ ID NO: 333, residues 1-227 of SEQ ID NO: 335, residues 1-224 of SEQ ID NO: 337, residues 1-230 of SEQ ID NO: 339, residues 1-228 of SEQ ID NO: 341, residues 1-232 of SEQ ID NO: 360, residues 1-227 of SEQ ID NO: 362, residues 1-229 of SEQ ID NO: 364, residues 1-221 of SEQ ID NO: 366, residues 1-226 of SEQ ID NO: 368, residues 1-226 of SEQ ID NO: 370, residues 1-225 of SEQ ID NO: 372, and residues 1-227 of SEQ ID NO: 374, respectively, in order of appearance) and light (**FIG. 20B**) (SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48,

50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 332, 334, 336, 338, 340, 342, 361, 363, 365, 367, 369, 371, 373, and 375, respectively, in order of appearance) chain Fab portions of the therapeutic antibodies disclosed herein. Positions that may be substituted to produce hyperglycosylated variants of the Fab regions are highlighted. Four substitutions (one in the heavy chain and three in the light chain) that should result in hyperglycosylation of the Fab region by human cells are annotated above the amino acid residue positions. (For engineering mAbs or antigen-binding fragments to contain additional glycosylation sites on the Fab domain, see *e.g.,* Courtois et al., 2016, mAbs 8: 99-112 for a description of derivatives of antibodies that are hyperglycosylated on the Fab domain of the full-length antibody).

[0036] **FIG. 21**. Clustal Multiple Sequence Alignment of AAV capsids 1-9. Amino acid substitutions (shown in bold in the bottom rows) can be made to AAV9 and 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 SEQ ID NOs as follows: AAV1 is SEQ ID NO: 274; AAV2 is SEQ ID NO: 275; AAV3-3 is SEQ ID NO: 276; AAV4-4 is SEQ ID NO: 277; AAV5 is SEQ ID NO: 278; AAV6 is SEQ ID NO: 279; AAV7 is SEQ ID NO: 280; AAV8 is SEQ ID NO: 143; AAV9 is SEQ ID NO: 144; AAVrh10 is SEQ ID NO: 145; hu31 is SEQ ID NO: 281; and hu32 is SEQ ID NO: 282.

[0037] **FIG. 22**. 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).

[0038] **FIG. 23**. Clustal Multiple Sequence Alignment of constant heavy chain regions (CH2 and CH3) of IgG1 (SEQ ID NO: 283), IgG2 (SEQ ID NO: 284), and IgG4 (SEQ ID NO: 285). 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.

[0039] **FIGS. 24A-D**. **A**. Schematic showing the genome configuration of AAV8 and AAV9. The expression cassette utilizes the CAG promoter (SEQ ID NO: 411) to drive expression of a human antibody that binds to and inhibits for example, plasma kallikrein (pKal) or TNFα. A mutant IL2 leader (mIL2, SEQ ID NO: 146) targets the heavy and light chains for secretion and the furin–F2A sequence (SEQ ID NO: 231) drives the cleavage of the polyprotein into heavy and light chain components. **B**.

Transfection titration comparing CAG.L01 (SEQ ID NO: 435; containing lanadelumab sequence L01 (SEQ ID NO: 141)) and CAG.L02 (SEQ ID NO: 437; containing lanadelumab sequence L02 (SEQ ID NO: 286)) proviral plasmid constructions. Top panels demonstrate reporter transgene (eGFP) expression following transfection of different plasmid quantities (4 µg-nontransfected). Bottom left panel depicts lanadelumab expression in the cell lysate while the bottom right panel detects plasmid expressed lanadelumab secreted into the cell supernatant. **C**. Transfection titration comparing CAG.L02 and CAG.L03 proviral plasmid constructions. Panels depict different exposure lengths (30 seconds or 60 seconds) of expressed lanadelumab from CAG.L02 or CAG.L03 constructs secreted into the cell supernatant. **D**. Transfection titration comparing Lanadelumab Fab proviral plasmid constructions. Figure depicts levels of Lanadelumab Fab following transfection of different plasmid quantities. L01 construct (CAG.L01: SEQ ID NO: 435) is driven by the CB promoter, while L02 (CAG. L02: SEQ ID NO: 437) is driven by the CAG promoter (SEQ ID NO: 411).

[0040] **FIG. 25**. The indicated AAV9 and AAV8 vectors (n=5 per group) were administered to NGS mice via either intravenous (IV) or intramuscular (IM) routes. IV administrations were into the tail vein and IM administrations were bilateral into the gastrocnemius muscles. Mice treated with vehicle were included as controls. Seven weeks post administration mice were sacrificed, and serum human antibody levels were determined by ELISA.

[0041] **FIG. 26**. A time course of antibody expression (lanadelumab serum levels) in NGS mice post-AAV9 administration (n=5 per group) is shown. AAV9 vectors (2e11 gc) were injected either IV or IM and serum antibody levels were determined by ELISA at day 7 (D7), day 21 (D21), day 35 (D35), and day 49 (D49).

[0042] **FIG. 27** depicts the expression of the monoclonal antibody lanadelumab (Mab1) in C2C12 muscle cells upon transduction of the cells with different cis plasmids expressing lanadelumab under the control of different regulatory elements: CAG (SEQ ID NO: 411), LMTP6 (SEQ ID NO: 320), and ApoE.hAAT (SEQ ID NO: 412). For detection of antibody protein, following transduction, the cells were treated with FITC conjugated anti-Fc (IgG) antibody. DAPI staining is shown to confirm confluency and viability of the cells under all conditions tested.

[0043] **FIGS. 28A and B. A** Serum expression levels (μg/ml) of lanadelumab upon intravenous injection of C/57BL6 mice with $2.5x10^{12}$ vg/kg of AAV8 vectors encoding a lanadelumab regulated by different liver-specific, liver-tandem and liver-muscle regulatory elements (see Table 1). CAG (SEQ ID NO: 411) and TBG (SEQ ID NO: 423) promoters were used as controls. Data from the blood draw at 1, 3, 5 and 7 weeks post injection are shown. LSPX1, liver-specific promoter 1 (SEQ ID NO: 315); LSXP2, liver-specific promoter 2 (SEQ ID NO: 316); LTP1, liver-specific tandem promoter 1 (SEQ ID NO: 317); LMTP6, liver and muscle dual-specific tandem promoter 6 (SEQ ID NO: 320). Protein expression levels were quantified by ELISA from biweekly serum collections. N=5 mice per vector. Numbers on x-axis represent the weeks post vector administration. Data represent mean + SEM. **8B**. Quantification of viral genomes in liver. C57Bl/6 mice were administrated intravenously with AAV8 vectors driven by different liver-specific promoters at equivalent doses ($2.5x10^{12}$ vg/kg). N=5 mice per group. Vector DNA was analyzed by ddPCR in mouse liver samples collected at 49 days post vector administration. Data represent mean + SEM.

[0044] **FIGS. 29A-F.** The amino acid sequence of a transgene construct for the Fab region of therapeutic antibody directed at biological factors: anti-IL5, benralizumab (**A**); anti-IL5R, reslizumab (**B**); anti-IL13, tralokinumab (**C**); anti-IL31R, nemolizumab (**D**), anti-IgE, omalizumab (**E**), and anti-TSLP, tezepelumab (**F**). 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.

[0045] **FIGS. 30A and 30B. A.** Route of administration and dose selection in Wistar rats. AAV8 vectors encoding vectorized lanadelumab driven by CAG promoters were injected intramuscularly at $1x\ 10^{13}$ vg/kg (body weight) or intravenously at $1x10^{13}$ vg/kg and $1x10^{14}$ vg/kg into SD rats. Protein expression was quantified by ELISA from serum collected every three to seven days. N=3 rats per vector. Data represent mean + SEM. * indicates $p < 0.05$, ** indicates $p < 0.01$ with Welch's t test. **B**. AAV8 vectors encoding vectorized lanadelumab driven by CAG (SEQ ID NO: 411) or ApoE.hAAT (SEQ ID NO: 412) promoters were injected intravenously at $5x10^{13}$ vg/kg into Wistar and SD rats. Protein expression was quantified by ELISA from weekly serum collection. N=3 rats per

vector. Data represent mean + SEM. P value: *, $p < 0.05$; **, $p < 0.01$. Serum antibody concentrations (mean and SEM) in animals of each group at each time point are presented in the table.

[0046] **FIGS. 31A-31D**. **A**. Serum anti-kallikrein (pKal) (lanadelumab) antibody concentration following AAV8 delivery. Animals received bilateral injections of $5x10^{10}$ vg/kg into the GA muscle. Serum was collected biweekly and vectorized antibody concentration was quantified with ELISA. **B.** Vector genome quantification from relevant tissues with digital droplet PCR (ddPCR). **C.** Comparison of vector gene expression from liver. Data represent relative fold gene expression as quantified by the ΔΔCT method. **D.** Comparison of AAV transgene expression from tissues using digital droplet PCR (ddPCR). Anti-pKal antibody mRNA copies were normalized to *GAPDH* mRNA copies across tissues. Data are represented as mean ± SEM. Statistical significance was determined using a one-way ANOVA followed by Tukey's HSD post-test. *P<0.05, **P<0.01.

[0047] **FIG. 32**: Antibody concentrations in the serum of wild type mice treated with AAV8.Lanadelumab vectors produced with different BV/Sf9 production systems compared to an HEK system. C57BL/6 mice were intravenously injected with vectors at a dose of $2.5x10^{12}$ vg/kg.

[0048] **FIGS. 33A-33F. A** and **B** show the pKal titration curve and signal-to-noise ratios for indicated pKal concentrations. **C**. Two pKal concentrations (6.25nM and 12.5nM) were used to measure the suppressive range of lanadelumab (compared to non-specific human IgG control antibody) in an antibody-dose response. C57BL/6 mice (n=5) were administered $5x10^{10}$ vector genomes (vg) ($2.5x10^{12}$ vg/kg) of ApoE.hAAT.L02.AAV8 per mouse intravenously. Shown are the compiled enzyme activities and percent reductions in pKal activity for both mouse groups **D** and **E**. The slopes of enzymatic progressive activity curves and an AMC standard were used to calculate specific pKal enzymatic activity, where significantly less activity was recorded at day 49 compared to day -7. **F.** The percent reduction in enzymatic activity was calculated as day 49 activity divided by that of day -7. Vectorized anti-pKal antibody-containing IgG significantly reduced pKal activity. All results are a compilation of 2-5 mice per group. To determine significance of differences, Student's t-tests were used (paired, two-tailed), where *p<0.05, **p<0.01, ***p<0.001.

[0049] **FIGS. 34A-34L**. Quantification of mouse paw volumes and paw swellings in carrageenan-induced paw edema mice treated with test articles. Bar charts show the paw volumes (**A**,

C, **E**, **G**, **I**, and **K**) measured at 2 (**A**), 4 (**C**), 6 (**E**), 8 (**G**), 24 (**I**) and 48 (**K**) hours after carrageenan injection in C57BL/6 mice. Paw swelling difference (**B**, **D**, **F**, **H**, **J**, and **L**) was evaluated by calculating the difference of paw volumes measured at each time point and the baseline. N=10 mice per group. Data analysis was done with One-way ANOVA with Dunnett's post-hoc test for multiple comparisons. Data represent mean + S.DEM. P values: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$; ****, $p<0.0001$.

[0050] **FIGS. 35A and 35B**: Time course of mouse paw volumes measured in carrageenan-induced paw edema mice treated with test articles. Mouse paw volumes were measured before (baseline) and at different time points after 0.7% (**A**) or 1% (**B**) carrageenan injection. N=10 mice per group. Data represent mean ± SEM.

[0051] **FIGS. 36A and 36B**: Characterization of vectorized adalimumab IgG and Fab cis plasmid expression. (**A**) Western blot depicting expression of adalimumab IgG and Fab derived from cell supernatant of 293T cells transfected with the respective cis plasmids. (**B**) Human TNFα binding ELISA derived from cells transfected with the cis plasmid. pAAV.CAG.Lanadelumab.IgG was used as a non-specific antibody (mAb) control. Data represented as mean±SEM.

[0052] **FIGS. 37A-37C. Characterization of AAV8 expressed adalimumab IgG expression and activity.** (**A**) Quantification of AAV8 expressed adalimumab at two multiplicity of infection (MOI) following transduction of 293T.AAVR cells. (**B**) Western blot depicting expression of adalimumab IgG heavy and light chain components at two different MOIs. (**C**) Human TNFα binding ELISA of adalimumab IgG derived from cell culture supernatant. Data represented as mean±SEM.

[0053] **FIG. 38**. Comparison of self-complementary AAV cis plasmids encoding vectorized adalimumab Fab. Negative control includes cell supernatant from non-transfected cells. Data represented as mean±SEM.

[0054] **FIG. 39**. Binding of TNFα across model species (mouse, rat, and human) by vectorized adalimumab IgG and Fab. Negative control included supernatant derived from non-transfected cells. Vectorized lanadelumab (pAAV.CAG.lanadelumab.IgG) functioned as a non-specific antibody control. Data represented as mean±SEM.

5. DETAILED DESCRIPTION OF THE INVENTION

[0055] Compositions and methods are described for the delivery of a fully human post-translationally modified (HuPTM) therapeutic monoclonal antibody (mAb) or a 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 a disease or condition 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 that continuously supplies the HuPTM mAb or antigen-binding fragment of the therapeutic mAb, *e.g.*, a human-glycosylated transgene product, to a target tissue where the mAb or antigen-binding fragment there of exerts its therapeutic effect.

[0056] 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:

- *Nervous system targets, including amyloid beta (Aβ or Abeta) peptides, sortilin, tau protein, SEMA4D, alpha-synuclein, and CGRP receptor*,
- *Ocular Targets including VEGF, EpoR, ALK1, endoglin, complement component 5, and complement component 1Q,*
- *Repulsive guidance molecule-A*
- *Transthyretin*
- *Connective Tissue Growth Factor*
- *Neuromyelitis optica (NMO)/ non-infectious uveitis targets and immune response targets, including interleukin 6 receptor, interleukin 6, and CD19*
- *Integrin beta 7*
- *Sclerostin*
- *TNF-alpha*, and

- *Plasma Protein Targets, such as human complement proteins, including plasma kallikrein,*
- *Autoimmune, respiratory, and allergic disease targets, such as interleukin and interleukin receptors, including IL5, IL5R, IL13, and IL31RA, immunoglobulin E, and thymic stromal lymphopoietin*

or such mAbs 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). The amino acid sequences of the heavy and light chains of antigen binding fragments of the foregoing are provided in Table 5, *infra*, and nucleotide sequences, including codon optimized versions, encoding the heavy and light chains of these antigen binding fragments are provided in Table 6

[0057] The recombinant vector used for delivering the transgene includes non-replicating recombinant adeno-associated virus vectors ("rAAV"). rAAVs are particularly attractive vectors for a number of reasons – they can transduce non-replicating cells, and therefore, can be used to deliver the transgene to tissues where cell division occurs at low levels, such as the CNS; they can be modified to preferentially target a specific organ of choice; and there are hundreds of capsid serotypes to choose from to obtain the desired tissue specificity, and/or to avoid neutralization by pre-existing patient antibodies to some AAVs. Such rAAVs include but are not limited to AAV based vectors comprising capsid components from one or more of AAV1, AAV2, AAV2.m78, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAVrh10 or AAVrh20. In certain embodiments, AAV based vectors provided herein comprise capsids from one or more of AAV8, AAV9, AAV10, AAV11, AAVrh10 or AAVrh20 serotypes.

[0058] 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.

[0059] Gene therapy constructs are designed such that both the heavy and light chains are expressed. More specifically, 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 certain embodiments, the coding sequences encode for a Fab or $F(ab')_2$ or an scFv.

[0060] In certain embodiments, nucleic acids (e.g., polynucleotides) and nucleic acid sequences disclosed herein may be codon-optimized, for example, via any codon-optimization technique known to one of skill in the art (see, e.g., review by Quax et al., 2015, Mol Cell 59:149-161) and may also be optimized to reduce CpG dimers. Nucleotide sequences of the heavy and light chain variable domains of the therapeutic antibodies, which may be codon optimized, are disclosed in Table 6. Each heavy and light chain requires a leader to ensure proper post-translation processing and secretion (unless expressed as an scFv, in which only the N-terminal chain requires a leader sequence). Useful leader sequences for the expression of the heavy and light chains of the therapeutic antibodies in human cells are disclosed herein. An exemplary recombinant expression construct is shown in FIG. 1 and in FIG. 24A.

[0061] 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 HuPTMmAb 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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

[0067] Viral vectors or other DNA expression constructs encoding an 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 to retinal pigment epithelial cells, CNS cells, muscle cells, or liver cells.

[0068] 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 a promoter selected for expression in tissue targeted for expression of the transgene, for example, but not limited to the CB7/CAG promoter (SEQ ID NO: 411, FIG. 24A) and associated upstream regulatory sequences (see FIG. 1), cytomegalovirus (CMV) promoter, Rous sarcoma virus (RSV) promoter, GFAP promoter (glial fibrillary acidic protein), MBP promoter (myelin basic protein), MMT promoter, EF-1 alpha promoter (SEQ ID NO: 415), mU1a (SEQ ID NO: 414), UB6 promoter, chicken beta-actin (CBA) promoter, RPE65 promoter and opsin promoter, liver-specific promoters, such as TBG (Thyroxine-binding Globulin) promoter (SEQ ID NO: 423), APOA2 promoter, SERPINA1 (hAAT) promoter, ApoE.hAAT (SEQ ID NO: 412) or mIR122 promoter, or muscle-specific promoters, such as a human

desmin promoter, CK8 promoter (SEQ ID NO: 413) or Pitx3 promoter, inducible promoters, such as a hypoxia-inducible promoter or a rapamycin-inducible promoter.

[0069] In some aspects herein, transgene expression is controlled by engineered nucleic acid regulatory elements that have more than one regulatory element (promoter or enhancer), including regulatory elements that are arranged in tandem (two or three copies) that promote liver-specific expression, or both liver-specific expression and muscle-specific expression, or both liver-specific and expression and bone-specific expression. These regulatory elements include for the liver-specific expression, LSPX1 (SEQ ID NO: 315), LSPX2 (SEQ ID NO: 316), LTP1 (SEQ ID NO: 317), LTP2 (SEQ ID NO: 318), or LTP3 (SEQ ID NO: 319), liver and muscle expression, LMTP6 (SEQ ID NO: 320), LMTP13 (SEQ ID NO: 321), LMTP14 (SEQ ID NO: 322), LMTP15 (SEQ ID NO: 323), LMTP18 (SEQ ID NO: 324), LMTP19 (SEQ ID NO: 325), or LMTP20 (SEQ ID NO: 326), or liver and bone expression, LBTP1 (SEQ ID NO: 327) or LBTP2 (SEQ ID NO: 328), the sequences of which are provided in Table 1.

[0070] 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.

[0071] In certain embodiments, nucleic acids (*e.g.*, polynucleotides) and nucleic acid sequences disclosed herein may be codon-optimized, for example, via any codon-optimization technique known to one of skill in the art (*see, e.g.*, review by Quax et al., 2015, Mol Cell 59:149-161). Nucleotide sequences for expression in human cells are provided herein for the heavy and light chains of the HuGlyFabs in Table 6.

[0072] 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) a chicken β-actin 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: 231 or 429), ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is shown in FIG. 1.

[0073] 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) a chicken β-actin intron and c) a rabbit β-globin poly A signal; 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: 231 or 429), ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is shown in FIG. 24A.

5.1.1 mRNA Vectors

[0074] 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

[0075] Viral vectors include adenovirus, adeno-associated virus (AAV, *e.g.*, AAV8, AAV9, AAVrh10, AAV2.7m8), 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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 certain embodiments, AAV based vectors provided herein comprise capsid components from one or more of AAV1 (SEQ ID NO: 274), AAV2 (SEQ ID NO: 275), AAV2.7m8 (SEQ ID NO: 142), AAV3 (SEQ ID NO: 276), AAV4 (SEQ ID NO: 277), AAV5, AAV6 (SEQ ID NO: 279), AAV7 (SEQ ID NO: 280), AAV8 (SEQ ID NO: 143), AAV9 (SEQ ID NO: 144), AAV10, AAV11, or AAVrh10 (SEQ ID NO: 145). In certain embodiments, AAV based vectors provided herein comprise components from one or more of AAV8, AAV9, AAV10, AAV11, or AAVrh10 serotypes. Provided are viral vectors in which the capsid protein is a variant of the AAV8 capsid protein (SEQ ID NO: 143), AAV9 capsid protein (SEQ ID NO: 144), or AAVrh10 capsid protein (SEQ ID NO: 145), 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: 143), AAV9 capsid protein (SEQ ID NO: 144), or AAVrh10 capsid protein (SEQ ID NO: 145), while retaining the biological function of the native capsid. In certain embodiments, the encoded AAV capsid has the sequence of SEQ ID NO: 143, 144, or 145 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 AAV9 or AAVrh10 capsid. FIG. 21 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, AAV9 or AAVrh10 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. 21. Amino acid sequence for AAV8, AAV9, and AAVrh10 capsids are provided in FIG. 21.

[0082] In some embodiments, AAV-based vectors comprise components from one or more serotypes of AAV. In some embodiments, AAV based vectors provided herein comprise capsid

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

[0083] In particular embodiments, the recombinant AAV for use in compositions and methods herein is Anc80 or Anc80L65 (see, e.g., Zinn et al., 2015, Cell Rep. 12(6): 1056-1068, which is incorporated by reference in its entirety). In particular embodiments, the recombinant AAV for use in compositions and methods herein is AAV.7m8 (including variants thereof) (see, e.g., US 9,193,956; US 9,458,517; US 9,587,282; US 2016/0376323, and WO 2018/075798, each of which is incorporated herein by reference in its entirety). In particular embodiments, the AAV for use in compositions and

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

[0084] In some embodiments, rAAV particles comprise any AAV capsid disclosed in United States Patent No. 9,840,719 and WO 2015/013313, such as AAV.Rh74 and RHM4-1, each of which is incorporated herein by reference in its entirety. In some embodiments, rAAV particles comprise any AAV capsid disclosed in WO 2014/172669, such as AAV rh.74, which is incorporated herein by reference in its entirety. In some embodiments, rAAV particles comprise the capsid of AAV2/5, as described in Georgiadis et al., 2016, Gene Therapy 23: 857-862 and Georgiadis et al., 2018, Gene Therapy 25: 450, each of which is incorporated by reference in its entirety. In some embodiments, rAAV particles comprise any AAV capsid disclosed in WO 2017/070491, such as AAV2tYF, which is incorporated herein by reference in its entirety. In some embodiments, rAAV particles comprise the capsids of AAVLK03 or AAV3B, as described in Puzzo et al., 2017, Sci. Transl. Med. 29(9): 418, which is incorporated by reference in its entirety. In some embodiments, rAAV particles comprise any

AAV capsid disclosed in US Pat Nos. 8,628,966; US 8,927,514; US 9,923,120 and WO 2016/049230, such as HSC1, HSC2, HSC3, HSC4, HSC5, HSC6, HSC7, HSC8, HSC9, HSC10, HSC11, HSC12, HSC13, HSC14, HSC15, or HSC16, each of which is incorporated by reference in its entirety.

[0085] 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).

[0086] 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).

[0087] AAV8-based, AAV9-based, and AAVrh10-based viral vectors are used in certain of the methods described herein. Nucleotide sequences of AAV based viral vectors and methods of making recombinant AAV and AAV capsids are taught, for example, in United States Patent No. 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, AAV9 or AAVrh10)-based viral vectors encoding a transgene (*e.g.*, an HuPTM Fab). The amino acid sequences of AAV capsids, including AAV8, AAV9 and AAVrh10 are provided in Figure 21.

[0088] 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).

[0089] 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.

[0090] 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-VEGF antigen-binding fragment gene.

[0091] 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.

[0092] In a specific embodiment, a vector for use in the methods described herein is one that encodes an HuPTM mAb antigen binding fragment, such as an HuGlyFab, such that, upon introduction of the vector into a relevant cell, a glycosylated and/or tyrosine sulfated variant of the HuPTM mAb antigen binding fragment or HuGlyFab is expressed by the cell.

5.1.3 Promoters and Modifiers of Gene Expression

[0093] 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.

[0094] In certain embodiments, the viral vectors provided herein comprise one or more promoters that control expression of the transgene. In certain embodiments, the promoter is a constitutive promoter. 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 or CB7 promoter (SEQ ID NO: 411) 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. 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. In certain embodiments, the vectors provided herein comprise one or more tissue specific promoters (e.g., a retinal pigment epithelial cell-specific promoter, a CNS-specific promoter, a liver-specific promoter or muscle specific). In certain embodiments, the viral vectors provided herein comprise a RPE65 promoter or an opsin promoter (a retinal cell/CNS specific promoter). In certain embodiments, the viral vectors provided herein comprises a liver cell specific promoter, such as, a TBG (Thyroxine-binding Globulin) promoter (SEQ ID NO: 423), an APOA2 promoter, a SERPINA1 (hAAT) promoter, an ApoE.hAAT promoter (SEQ ID NO: 412), or a MIR122 promoter. In certain embodiments, the viral vector provided herein comprises a muscle specific promoter, such as a human desmin promoter (Jonuschies et al., 2014, Curr. Gene Ther. 14:276-288), a CK8 promoter (SEQ ID NO: 413; Himeda et al., 2011 Muscle Gene Therapy: Methods and Protocols, Methods in Molecular Biology, Dongsheng Duan (ed.), 709:3-19; SEQ ID NO: 413), or a Pitx3 promoter (Coulon et al., 2007, JBC 282:33192). In other embodiments,

the viral vector comprises a VMD2 promoter. In certain embodiments, the viral vector herein comprises synthetic and tandem promoters, e.g. the promoters listed in **Table 1** below.

[0095] In certain embodiments, the promoter is an inducible promoter. In certain embodiments the promoter is a hypoxia-inducible promoter. In certain embodiments, the promoter comprises a hypoxia-inducible factor (HIF) binding site. In certain embodiments, the promoter comprises a HIF-1α binding site. In certain embodiments, the promoter comprises a HIF-2α binding site. In certain embodiments, the HIF binding site comprises an RCGTG motif. For details regarding the location and sequence of HIF binding sites, *see, e.g.*, Schödel, et al., Blood, 2011, 117(23):e207-e217, which is incorporated by reference herein in its entirety. In certain embodiments, the promoter comprises a binding site for a hypoxia induced transcription factor other than a HIF transcription factor. In certain embodiments, the viral vectors provided herein comprise one or more IRES sites that is preferentially translated in hypoxia. For teachings regarding hypoxia-inducible gene expression and the factors involved therein, *see, e.g.*, Kenneth and Rocha, Biochem J., 2008, 414:19-29, which is incorporated by reference herein in its entirety. In specific embodiments, the hypoxia-inducible promoter is the human N-WASP promoter, *see, e.g.*, Salvi, 2017, Biochemistry and Biophysics Reports 9:13-21 (incorporated by reference for the teaching of the N-WASP promoter) or is the hypoxia-induced promoter of human Epo, *see, e.g.*, Tsuchiya et al., 1993, J. Biochem. 113:395-400 (incorporated by reference for the disclosure of the Epo hypoxia-inducible promoter). In other embodiments, the promoter is a drug inducible promoter, for example, a promoter that is induced by administration of rapamycin or analogs thereof. See, *e.g.*, the disclosure of rapamycin inducible promoters in PCT publications WO94/18317, WO 96/20951, WO 96/41865, WO 99/10508, WO 99/10510, WO 99/36553, and WO 99/41258, and US 7,067,526, which are hereby incorporated by reference in their entireties for the disclosure of drug inducible promoters.

[0096] 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 Table 1 below.

Table 1. Promoter and Other Regulatory Element Sequences

Name/ SEQ ID NO.	Sequence
LSPX1 SEQ ID NO: 315	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactctctctgt ttgctctggttaataatctcaggagcacaaacattccagatccaggttaatttttaaaaagca gtcaaaagtccaagtggcccttggcagcatttactctctctgtttgctctggttaataatctc aggagcacaaacattccagatccggcgcgccagggctggaagctacctttgtctagaaggctc agaggcacacaggagtttctgggctcaccctgccccctccaaccctcagttcccatcctcc agcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactcatgtccc taaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgctgacct tggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccactcgacc ccttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtgagaggg gtacccggggatcttgctaccagtggaacagccactaaggattctgcagtgagagcagagggc cagctaagtggtactctcccagagactgtctgactcacgccacccccctccaccttggacacag gacgctgtggtttctgagccaggtacaatgactcctttcggtaagtgcagtggaagctgtaca ctgcccaggcaaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttag cccctgtttgctcctccgataactggggtgaccttggttaatattcaccagcagcctcccccg ttgcccctctggatccactgcttaaatacggacgaggacagggccctgtctcctcagcttcag gcaccaccactgacctgggacagt
LSXP2 SEQ ID NO: 316	aggctcagaggcacacaggagtttctgggctcaccctgcccccttccaaccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agagggtctagaaggctcagaggcacacaggagtttctgggctcaccctgcccccttccaacc cctcagttcccatcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaact tcagcctactcatgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagcc ctccctgcctgctgaccttggagctggggcagaggtcagagacctctctgggcccatgccacc tccaacatccactcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggt ttaggtagtgtgagaggggtacccggggatcttgctaccagtggaacagccactaaggattct gcagtgagagcagagggccagctaagtggtactctcccagagactgtctgactcacgccaccc cctccaccttggacacaggacgctgtggtttctgagccaggtacaatgactcctttcggtaag tgcagtggaagctgtacactgcccaggcaaagcgtccgggcagcgtaggcgggcgactcagat cccagccagtggacttagcccctgtttgctcctccgataactggggtgaccttggttaatatt caccagcagcctccccgttgcccctctggatccactgcttaaatacggacgaggacagggcc ctgtctcctcagcttcaggcaccaccactgacctgggacagt
LTP1 SEQ ID NO: 317	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactctctctgt ttgctctggttaataatctcaggagcacaaacattccagatccaggttaatttttaaaaagca gtcaaaagtccaagtggcccttggcagcatttactctctctgtttgctctggttaataatctc aggagcacaaacattccagatccggcgcgccagggctggaagctacctttgacatcatttcct ctgcgaatgcatgtataatttctacagaacctattagaaaggatcacccagcctctgcttttg tacaactttcccttaaaaaactgccaattccactgctgtttggcccaatagtgagaacttttt cctgctgcctcttggtgcttttgcctatggcccctattctgcctgctgaagacactcttgcca gcatggacttaaacccctccagctctgacaatcctctttctcttttgttttacatgaagggtc tggcagccaaagcaatcactcaaagttcaaaccttatcatttttttgctttgttcctcttggcc ttggttttgtacatcagctttgaaaataccatcccagggttaatgctggggttaatttataac taagagtgctctagttttgcaatacaggacatgctataaaaatggaaagatgttgctttctga gaggatcttgctaccagtggaacagccactaaggattctgcagtgagagcagagggccagcta agtggtactctcccagagactgtctgactcacgccacccccctccaccttggacacaggacgct

Name/ SEQ ID NO.	Sequence
	gtggtttctgagccaggtacagtgactcctttcggtaagtgcagtggaagctgtacactgccc aggcaaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttagcccctg tttgctcctccgataactggggtgaccttggttaatattcaccagcagcctccccgttgccc ctctggatccactgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcacca ccactgacctgggacagt
LTP2 SEQ ID NO: 318	aggctcagaggcacacaggagtttctgggctcaccctgccccttccaacccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agagggtctagagcccttaagctagcaggttaatttttaaaaagcagtcaaaagtccaagtgg cccttggcagcatttactctctctgtttgctctggttaataatctcaggagcacaaacattcc agatccaggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactct ctctgtttgctctggttaataatctcaggagcacaaacattccagatccggcgcgccagggct ggaagctacctttgacatcatttcctctgcgaatgcatgtataatttctacagaacctattag aaaggatcacccagcctctgcttttgtacaactttcccttaaaaaactgccaattccactgct gtttggcccaatagtgagaacttttttcctgctgcctcttggtgcttttgcctatggcccctat tctgcctgctgaagacactcttgccagcatggacttaaacccctccagctctgacaatcctct ttctcttttgttttacatgaagggtctggcagccaaagcaatcactcaaagttcaaaccttat cattttttgctttgttcctcttggccttggttttgtacatcagctttgaaaataccatcccag ggttaatgctggggttaatttataactaagagtgctctagttttgcaatacaggacatgctat aaaaatggaaagatgttgctttctgagaggatcttgctaccagtggaacagccactaaggatt ctgcagtgagagcagagggccagctaagtggtactctcccagagactgtctgactcacgccac cccctccaccttggacacaggacgctgtggtttctgagccaggtacagtgactcctttcggta agtgcagtggaagctgtacactgcccaggcaaagcgtccgggcagcgtaggcgggcgactcag atcccagccagtggacttagcccctgtttgctcctccgataactggggtgaccttggttaata ttcaccagcagcctcccccgttgcccctctggatccactgcttaaatacggacgaggacaggg ccctgtctcctcagcttcaggcaccaccactgacctgggacagt
LTP3 SEQ ID NO: 319	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactctctctgt ttgctctggttaataatctcaggagcacaaacattccagatccaggttaatttttaaaaagca gtcaaaagtccaagtggcccttggcagcatttactctctctgtttgctctggttaataatctc aggagcacaaacattccagatccggcgcgccagggctggaagctaccttgacatcatttcct ctgcgaatgcatgtataatttctacagaacctattagaaaggatcacccagcctctgcttttg tacaactttcccttaaaaaactgccaattccactgctgtttggcccaatagtgagaacttttt cctgctgcctcttggtgcttttgcctatggcccctattctgcctgctgaagacactcttgcca gcatggacttaaacccctccagctctgacaatcctctttctcttttgttttacatgaagggtc tggcagccaaagcaatcactcaaagttcaaaccttatcatttttgctttgttcctcttggcc ttggttttgtacatcagctttgaaaataccatcccagggttaatgctggggttaatttataac taagagtgctctagttttgcaatacaggacatgctataaaaatggaaagatgttgctttctga gaggatcttgctaccagtggaacagccactaaggattctgcagtgagagcagagggccagcta agtggtactctcccagagactgtctgactcacgccacccccctccaccttggacacaggacgct gtggtttctgagccaggtacagtgactcctttcggtaagtgcagtggaagctgtacactgccc aggcaaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttagcccctg tttgctcctccgataactggggtgaccttggttaatattcaccagcagcctccccgttgccc ctctggatccactgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcacca ccactgacctgggacagtaaaacaggtaagtccgctgtttgtgtgctgcctctgaagtccaca ctgaacaaacttcagcctactcatgtccctaaaatgggcaaacattgcaagcagcaaacagca aacacacagccctccctgcctgctgaccttggagctggggcagaggtcagagacctctctggc ctctactaaccatgttcatgttttcttttttttttctacaggtcctgggtgacgaacag

Name/ SEQ ID NO.	Sequence
LMTP6 SEQ ID NO: 320	aggctcagaggcacacaggagtttctgggctcaccctgccccttccaacccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccccttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agagggccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccgagatg cctggttataattaacccagacatgtggctgccccccccccccccccaacacctgctgcctctaa aaataaccctgtccctggtggatcccactacgggtttaggctgcccatgtaaggaggcaaggc ctggggacacccgagatgcctggttataattaacccagacatgtggctgccccccccccccccc aacacctgctgcctctaaaaataaccctgtccctggtggatcccactacgggtttaggctgcc catgtaaggaggcaaggcctggggacacccgagatgcctggttataattaacccagacatgtg gctgccccccccccccccaacacctgctgcctctaaaaataaccctgtccctggtggatcccc tgcatgcgaagatcttcgaacaaggctgtgggggactgagggcaggctgtaacaggcttgggg gccagggcttatacgtgcctgggactcccaaagtattactgttccatgttcccggcgaagggc cagctgtcccccgccagctagactcagcacttagtttaggaaccagtgagcaagtcagcccctt ggggcagcccatacaaggccatggggctgggcaagctgcacgcctgggtccggggtgggcacg gtgcccgggcaacgagctgaaagctcatctgctctcaggggcccctccctggggacagccccct cctggctagtcacaccctgtaggctcctctatataacccaggggcacaggggctgccctcatt ctaccaccacctccacagcacagacagacactcaggagccagccagcgtcgagatcttgctac cagtggaacagccactaaggattctgcagtgagagcagagggccagctaagtggtactctccc agagactgtctgactcacgccacccctccaccttggacacaggacgctgtggtttctgagcc aggtacagtgactcctttcggtaagtgcagtggaagctgtacactgcccaggcaaagcgtccg ggcagcgtaggcgggcgactcagatcccagccagtggacttagcccctgtttgctcctccgat aactggggtgaccttggttaatattcaccagcagcctcccccgttgcccctctggatccactg cttaaatacggacgaggacagggccctgtctcctcagcttcaggcaccaccactgacctggga cagt
LMTP13 SEQ ID NO: 321	aggctcagaggcacacaggagtttctgggctcaccctgccccttccaacccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccccttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agaggggtacccggggatcttgctaccagtctagaggccgtccgccctcggcaccatcctcac gacacccaaatatggcgacgggtgaggaatggtggggagttatttttagagcggtgaggaagg tgggcaggcagcaggtgttggcgctctaaaaataactcccgggagttatttttagagcggagg aatggtggacacccaaatatggcgacggttcctcacccgtcgccatatttgggtgtccgccct cggccggggccgcattcctgggggccgggcggtgctcccgcccgcctcgataaaaggctccgg ggccggcggcggcccacgagctacccggaggagcgggaggcgccaagcgtgagtatcgatctt gctaccagtggaacagccactaaggattctgcagtgagagcagagggccagctaagtggtact ctcccagagactgtctgactcacgccacccctccaccttggacacaggacgctgtggtttct gagccaggtacagtgactcctttcggtaagtgcagtggaagctgtacactgcccaggcaaagc gtccgggcagcgtaggcgggcgactcagatcccagccagtggacttagcccctgtttgctcct ccgataactggggtgaccttggttaatattcaccagcagcctcccccgttgcccctctggatc cactgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcaccaccactgacc tgggacagt
LMTP14 SEQ ID NO: 322	gaatggtggacacccaaatatggcgacggttcctcacccgtcgccatatttgggtgtccgccc tcggccggggccgcattcctgggggccgggcggtgctcccgcccgcctcgataaaaggctccg gggccggcggcggcccacgagctacccggaggagcgggaggcgccaagcgatcttgctaccag tggaacagccactaaggattctgcagtgagagcagagggccagctaagtggtactctcccaga gactgtctgactcacgccacccctccaccttggacacaggacgctgtggtttctgagccagg tacagtgactcctttcggtaagtgcagtggaagctgtacactgcccaggcaaagcgtccgggc agcgtaggcgggcgactcagatcccagccagtggacttagcccctgtttgctcctccgataac

Name/ SEQ ID NO.	Sequence
	tggggtgaccttggttaatattcaccagcagcctcccccgttgcccctctggatccactgctt aaatacggacgaggacagggccctgtctcctcagcttcaggcaccaccactgacctgggacag t
LMTP15 SEQ ID NO: 323	aggctcagaggcacacaggagtttctgggctcaccctgccccttccaaccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agagggtctagagaatggtggacacccaaatatggcgacggttcctcacccgtcgccatattt gggtgtccgccctcggccggggccgcattcctgggggccgggcggtgctcccgcccgcctcga taaaaggctccggggccggcggcggcccacgagctacccggaggagcgggaggcgccaagcga tcttgctaccagtggaacagccactaaggattctgcagtgagagcagagggccagctaagtgg tactctcccagagactgtctgactcacgccacccccctccaccttggacacaggacgctgtggt ttctgagccaggtacagtgactcctttcggtaagtgcagtggaagctgtacactgcccaggca aagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttagcccctgtttgc tcctccgataactggggtgaccttggttaatattcaccagcagcctcccccgttgcccctctg gatccactgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcaccaccact gacctgggacagt
LMTP18 SEQ ID NO: 324	aggctcagaggcacacaggagtttctgggctcaccctgccccttccaaccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agagggccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccgagatg cctggttataattaacccagacatgtggctgccccccccccccccaacacctgctgcctctaa aaataaccctgtccctggtggatcccctgcatgcgaagatcttcgaacaaggctgtgggggac tgagggcaggctgtaacaggcttgggggccagggcttatacgtgcctgggactcccaaagtat tactgttccatgttcccggcgaagggccagctgtcccccgccagctagactcagcacttagtt taggaaccagtgagcaagtcagcccttggggcagcccatacaaggccatggggctgggcaagc tgcacgcctgggtccggggtgggcacggtgcccgggcaacgagctgaaagctcatctgctctc aggggcccctccctggggacagcccctcctggctagtcacaccctgtaggctcctctatataa cccaggggcacaggggctgccctcattctaccaccacctccacagcacagacagacactcagg agccagccagcgtcgagatcttgctaccagtggaacagccactaaggattctgcagtgagagc agagggccagctaagtggtactctcccagagactgtctgactcacgccacccccctccaccttg gacacaggacgctgtggtttctgagccaggtacagtgactcctttcggtaagtgcagtggaag ctgtacactgcccaggcaaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtg gacttagcccctgtttgctcctccgataactggggtgaccttggttaatattcaccagcagcc tcccccgttgcccctctggatccactgcttaaatacggacgaggacagggccctgtctcctca gcttcaggcaccaccactgacctgggacagt
LMTP19 SEQ ID NO: 325	aggctcagaggcacacaggagtttctgggctcaccctgccccttccaaccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agagggccctgcatgcgaagatcttcgaacaaggctgtgggggactgagggcaggctgtaaca ggcttgggggccagggcttatacgtgcctgggactcccaaagtattactgttccatgttcccg gcgaagggccagctgtcccccgccagctagactcagcacttagtttaggaaccagtgagcaag tcagcccttggggcagcccatacaaggccatggggctgggcaagctgcacgcctgggtccggg gtgggcacggtgcccgggcaacgagctgaaagctcatctgctctcaggggcccctccctgggg acagcccctcctggctagtcacaccctgtaggctcctctatataacccaggggcacaggggct gccctcattctaccaccacctccacagcacagacagacactcaggagccagccagcgtcgaga

Name/ SEQ ID NO.	Sequence
	tcttgctaccagtggaacagccactaaggattctgcagtgagagcagagggccagctaagtgg tactctcccagagactgtctgactcacgccacccctccaccttggacacaggacgctgtggt ttctgagccaggtacagtgactcctttcggtaagtgcagtggaagctgtacactgcccaggca aagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttagcccctgtttgc tcctccgataactggggtgaccttggttaatattcaccagcagcctcccccgttgcccctctg gatccactgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcaccaccact gacctgggacagt
LMTP20 SEQ ID NO: 326	aggctcagaggcacacaggagtttctgggctcaccctgcccccttccaacccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccccttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agagggcccttcagattaaaaataactgaggtaagggcctgggtaggggaggtggtgtgagac gctcctgtctctcctctatctgcccatcggccctttggggaggaggaatgtgcccaaggacta aaaaaaggccatggagccagaggggcgagggcaacagacctttcatgggcaaaccttggggcc ctgctgaagctttggcccactacgggtttaggctgcccatgtaaggaggcaaggcctggggac acccgagatgcctggttataattaacccagacatgtggctgccccccccccccccaacacctg ctgcctctaaaaataaccctgtccctggtggatcccctgcatgcgaagatcttcgaacaaggc tgtgggggactgagggcaggctgtaacaggcttgggggccagggcttatacgtgcctgggact cccaaagtattactgttccatgttcccggcgaagggccagctgtcccccgccagctagactca gcacttagtttaggaaccagtgagcaagtcagcccttggggcagcccatacaaggccatgggg ctgggcaagctgcacgcctgggtccggggtgggcacggtgcccgggcaacgagctgaaagctc atctgctctcaggggcccctccctggggacagcccctcctggctagtcacaccctgtaggctc ctctatataacccaggggcacaggggctgccctcattctaccaccacctccacagcacagaca gacactcaggagccagccagcgtcgagatcttgctaccagtggaacagccactaaggattctg cagtgagagcagagggccagctaagtggtactctcccagagactgtctgactcacgccacccc ctccaccttggacacaggacgctgtggtttctgagccaggtacagtgactcctttcggtaagt gcagtggaagctgtacactgcccaggcaaagcgtccgggcagcgtaggcgggcgactcagatc ccagccagtggacttagcccctgtttgctcctccgataactggggtgaccttggttaatattc accagcagcctcccccgttgcccctctggatccactgcttaaatacggacgaggacagggccc tgtctcctcagcttcaggcaccaccactgacctgggacagt
LBTP1 SEQ ID NO: 327	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactctctctgt ttgctctggttaataatctcaggagcacaaacattccagatccaggttaatttttaaaaagca gtcaaaagtccaagtggcccttggcagcatttactctctctgtttgctctggttaataatctc aggagcacaaacattccagatccggcgcgccagggctggaagctacctttgtctagaaggctc agaggcacacaggagtttctgggctcaccctgcccccttccaacccctcagttcccatcctcc agcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactcatgtccc taaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgctgacct tggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccactcgacc ccttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtgagaggg gtacccggggatcttgctaccagtggaacagccactaaggattctgcagtgagagcagagggc cagctaagtggtactctcccagagactgtctgactcacgccacccctccaccttggacacag gacgctgtggtttctgagccaggtacaatgactcctttcggtaagtgcagtggaagctgtaca ctgcccaggcaaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttag cccctgtttgctcctccgataactggggtgaccttggttaatattcaccagcagcctcccccg ttgcccctctggatccactgcttaaatacggacgaggacagggccctgtctcctcagcttcag gcaccaccactgacctgggacagt
LBTP2	aggctcagaggcacacaggagtttctgggctcaccctgcccccttccaacccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac

Name/ SEQ ID NO.	Sequence
SEQ ID NO: 328	tcgacccctt ggaatttcgg tggagaggag cagaggttgt cctggcgtgg tttaggtagt gtg agagggcaca catacacgaa cacacatata catatacatt cacatatatg cacacacata c acatatacac gcatacacgt acacacaaat gcacactcac acatgcacac acatacataa tat acacactctc acacatgcac atacacacat acatacacat acatgtgcat gcacacacac aaa tacacatgca tacatccaca ttcacacaga tgcagacaca aatgcacaca cacacacacac acacacacac acacacacac acacacgcac actgccaccc tgaactagtg gtggctaaat gaaca ataagtctcc atcaccagct tgggggggag gtaggtggta gtgtaggtgc cccccattgt gtgat catgttcatt gtatgagttt gtctgtgttc attcatcata gtgacagtcc ccatgtgggt agc agagagtacg tgtgcatgca tcatctccgt gtttgctcat gagtgtgtat gtcagtgtgt tcc agtctttctg tgtgagtgtc gtccccaatc cccccatccc ccccccccca gatctctaat tagtgg tttggggttt gttccttttc cctcctgttc ctttcctcag cagcgcggca gcagcggcgg cag cctcggtggt agcagcagca gcagcagcag cagcagcagc agcagcagca gcagcagcaa cag aagctgccgc gccgctgagt agcagcaagg actccgagtc aagagtaggattgtaggattgga tctgagtggg aacaagagtg agctggcctg agagaggagc agatgcctcc cagcgccctc agg ccacccattg ccagtaatct tcaagccaga cctcttgaga ggagacgggacagccaaccctag cctacccagg tacagacact gggcagttct gggggactgc ccacagatgc ctattggattcct ggggtatgta ggactcccgg gtctaccagc cctttt cacc tttccccata gcaccccaagga agctctgaca acttgcccat attcctgttt cccacccgtc cccctgggca ccccctttttcttct ctccctcccag atcccttctt tggggagctc agcaaatgga gcaggaaatt tggaccctctgc ctccctctct cgccttcctc attggatccg gagtcttctc cgctgggaaa gctgtaattagag ggtggatccc tacagacaga gagcagcccc ccacccccac ccccccagtc ccttctaactt ta gatctcttct ctcccattct cccattctcc ctccctctcc cttctccctc tcccactggctcc tcggttctct ccatctgcct gactccttgg gacccggtcc ccagatcttg ctaccagtggaac agccactaag gattctgcag tgagagcaga gggccagcta agtggtactc tcccagagactgt ctgactcacg ccacccctcc accttggaca caggacgctg tggtttctga gccaggtacagt gactcctttc ggtaagtgca gtggaagctg tacactgccc aggcaaagcg tccgggcagcgta ggcgggcgac tcagatccca gccagtggac ttagcccctg tttgctcctc cgataactggggt gaccttggtt aatattcacc agcagcctcc cccgttgccc ctctggatcc actgcttaaatac ggacgaggac agggccctgt ctcctcagct tcaggcacca ccactgacct gggacagt
SP7 SEQ ID NO: 329	cacacatacacgaacacacatacatatacatacattcacatatatgcacacacatacacatat acacgcatacacgtacacacaaatgcacactcacacatgcacacacatacataatatacacac tctcacacatgcacatacacacatacatacacatacatgtgcatgcacacacacaaatacaca tgcatacatccacattcacacagatgcagacacaaatgcacacacacacacacacacacacac acacacacacacacacacgcacactgccaccctgaactagtggtggctaaatgaacaataagt ctccatcaccagcttgggggggaggtaggtggtagtgtaggtgcccccattgtgtgatcatgtt cattgtatgagtttgtctgtgttcattcatcatagtgacagtccccatgtgggtagcagagag tacgtgtgcatgcatcatctccgtgtttgctcatgagtgtgtatgtcagtgtgttccagtctt tctgtgtgagtgtcgtccccaatccccc atcccccccccc agatctctaattagtggtttggg gtttgttcctttcccctcctgttcctttcctcagcagcgcggcagcagcggcggcagcctcgg tggtagcagcagcagcagcagcagcagcagcagcagcagcagcagcagcagcaacagaagctg ccgcgccgctgagtagcagcaaggactccgagtcaagagtaggattgtaggattggatctgag tgggaacaagagtgagctggcctgagagaggagcagatgcctcccagcgccctcaggccaccc attgccagtaatcttcaagccagacctcttgagaggagacgggacagccaaccctagcctacc caggtacagacactgggcagttctgggggactgcccacagatgcctattggattcctggggta tgtaggactcccgggtctaccagccctttt cacctttccccatagcaccccc aaggaagctct gacaacttgcccatattcctgtttcccacccgtcccctgggcaccccctttttcttctctccct cccagatcccttctttggggagctcagcaaatggagcaggaaatttggaccctctgcctccct ctctcgccttcctcattggatccggagtcttctccgctgggaaagctgtaattagagggtgga tccctacagacagagagcagcccccccacccccacccccagtcccttctaactttagatctc ttctctcccattctcccattctccctccctctcccttctcccctctcccactggctcctcggtt ctctccatctgcctgactccttgggacccggtcccca

Name/ SEQ ID NO.	Sequence
minSP7 SEQ ID NO: 330	cgcggcagcagcggcggcagcctcggtggtagcagcagcagcagcagcagcagcagcagc agcagcagcagcagcaacagaagctgccgcgccgctgagtagcagcaaggactccgagtcaag agtaggattgtaggattggatctgagtgggaacaagagtgagctggcctgagagaggagcaga tgcctcccagcgccctcaggccacccattgccagtaatcttcaagccagacctcttgagagga gacgggacagccaaccctagcctacccaggtacagacactgggcagttctgggggactgccca cagatgcctattggattcctggggtatgtaggactcccgggtctaccagccctttttcaccttt ccccatagcacccccaaggaagctctgacaacttgcccatattcctgtttcccacccgtcccc tgggcacccccttttcttctctccctcccagatcccttctttggggagctcagcaaatggagc aggaaatttggaccctctgcctccctctctcgccttcctcattggatccggagtcttctccgc tgggaaagctgtaattagagggtggatccctacagacagagagcagccccccccacccccaccc cccagtcccttctaactttagatctcttctctcccattctcccattctccctccctctccctt ctccctctcccactggctcctcggttctctccatctgcctgactccttgggacccggtcccca
ApoE.hAAT SEQ ID NO: 412	aggctcagaggcacacaggagtttctgggctcaccctgccccccttccaaccccctcagttccca tcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcctactca tgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctccctgcctgc tgaccttggagctggggcagaggtcagagacctctctgggcccatgccacctccaacatccac tcgacccccttggaatttcggtggagaggagcagaggttgtcctggcgtggtttaggtagtgtg agaggggtacccggggatcttgctaccagtggaacagccactaaggattctgcagtgagagca gagggccagctaagtggtactctcccagagactgtctgactcacgccacccccctccaccttgg acacaggacgctgtggtttctgagccaggtacaatgactcctttcggtaagtgcagtggaagc tgtacactgcccaggcaaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtgg acttagcccctgtttgctcctccgataactggggtgaccttggttaatattcaccagcagcct cccccgttgcccctctggatccactgcttaaatacggacgaggacagggccctgtctcctcag cttcaggcaccaccactgacctgggacagt
CAG/CB7 SEQ ID NO: 411	gacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcccat atatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacc cccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaatagggactttccatt gacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatcaagtgtatcata tgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagt acatgaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctattacca tggtcgaggtgagccccacgttctgcttcactctccccatctccccccccctccccacccccaa ttttgtatttatttatttttaattattttgtgcagcgatgggggcgggggggggggggggggc gcgcgccaggcggggcggggcggggcgaggggcggggcggggcgaggcggagaggtgcggcgg cagccaatcagagcggcgcgctccgaaagtttccttttatggcgaggcggcggcggcggcggc cctataaaaagcgaagcgcgcggcgggcgggagtcgctgcgcgctgccttcgccccgtgcccc gctccgccgccgcctcgcgccgcccgccccggctctgactgaccgcgttactcccacaggtga gcgggcgggacggcccttctcctccgggctgtaattagcgcttggtttaatgacggcttgttt cttttctgtggctgcgtgaaagccttgaggggctccgggagggccctttgtgcgggggggagcg gctcgggggggtgcgtgcgtgtgtgtgtgcgtggggagcgccgcgtgcggctccgcgctgcccg gcggctgtgagcgctgcgggcgcggcgcggggctttgtgcgctccgcagtgtgcgcgagggga gcgcggccgggggcggtgccccgcggtgcgggggggggctgcgaggggaacaaaggctgcgtgc ggggtgtgtgcgtgggggggtgagcaggggggtgtgggcgcgtcggtcgggctgcaacccccccc tgcacccccctccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacggggc gtggcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgccgggcggggcgg ggccgcctcgggccggggagggctcgggggaggggcgcggcggcccccggagcgccggcggct gtcgaggcgcggcgagccgcagccattgccttttatggtaatcgtgcgagagggcgcagggac ttcctttgtcccaaatctgtgcggagccgaaatctgggaggcgccgccgcacccccctctagcg ggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagggccttcgtgcgt cgccgcgccgccgtcccctctccctctccagcctcggggctgtccgcgggggggacggctgcc ttcgggggggacggggcagggcggggttcggcttctggcgtgtgaccggcggctctagagcct

Name/ SEQ ID NO.	Sequence
	ctgctaaccatgttcatgccttcttcttttttcctacagctcctgggcaacgtgctggttattg tgctgtctcatcattttggcaaag
CK8 SEQ ID NO: 413	ccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacacccgagatgcctggt tataattaacccagacatgtggctgccccccccccccccaacacctgctgcctctaaaaataa ccctgtccctggtggatcccactacgggtttaggctgcccatgtaaggaggcaaggcctgggg acacccgagatgcctggttataattaacccagacatgtggctgccccccccccccccaacacc tgctgcctctaaaaataaccctgtccctggtggatcccactacgggtttaggctgcccatgta aggaggcaaggcctggggacacccgagatgcctggttataattaacccagacatgtggctgcc ccccccccccccaacacctgctgcctctaaaaataaccctgtccctggtggatcccctgcatg cgaagatcttcgaacaaggctgtgggggactgagggcaggctgtaacaggcttgggggccagg gcttatacgtgcctgggactcccaaagtattactgttccatgttcccggcgaagggccagctg tcccccgccagctagactcagcacttagtttaggaaccagtgagcaagtcagcccttggggca gcccatacaaggccatggggctgggcaagctgcacgcctgggtccggggtgggcacggtgccc gggcaacgagctgaaagctcatctgctctcaggggcccctccctggggacagcccctcctggc tagtcacaccctgtaggctcctctatataacccaggggcacaggggctgccctcattctacca ccacctccacagcacagacagacactcaggagccagccagcgtcga
mU1a SEQ ID NO: 414	atggaggcggtactatgtagatgagaattcaggagcaaactgggaaaagcaactgcttccaaa tatttgtgatttttacagtgtagttttggaaaaactcttagcctaccaattcttctaagtgtt ttaaaatgtgggagccagtacacatgaagttatagagtgttttaatgaggcttaaatatttac cgtaactatgaaatgctacgcatatcatgctgttcaggctccgtggccacgcaactcatact
EF-1α SEQ ID NO: 415	gggcagagcgcacatcgcccacagtccccgagaagttgggggggaggggtcggcaattgaacgg gtgcctagagaaggtggcgcggggtaaactgggaaagtgatgtcgtgtactggctccgccttt ttcccgagggtgggggagaaccgtatataagtgcagtagtcgccgtgaacgttcttttcgca acgggtttgccgccagaacacag
TBG SEQ ID NO: 423	gggctggaagctacctttgacatcatttcctctgcgaatgcatgtataatttctacagaacct attagaaaggatcacccagcctctgcttttgtacaactttcccttaaaaaactgccaattcca ctgctgtttggcccaatagtgagaacttttttcctgctgcctcttggtgcttttgcctatggcc cctattctgcctgctgaagacactcttgccagcatggacttaaacccctccagctctgacaat cctctttctctttttgttttacatgaagggtctggcagccaaagcaatcactcaaagttcaaac cttatcatttttttgctttgttcctcttggccttggttttgtacatcagctttgaaaataccat cccagggttaatgctggggttaatttataactaagagtgctctagttttgcaatacaggacat gctataaaaat ggaaagat
Chimeric Intron SEQ ID NO: 416	gtaagtatcaaggttacaagacaggtttaaggagaccaatagaaactgggcttgtcgagacag agaagactcttgcgtttctgataggcacctattggtcttactgacatccactttgcctttctc tccacag
VH4 Intron SEQ ID NO: 417	gtgagtatctcagggatccagacatggggatatgggaggtgcctctgatcccagggctcactg tgggtctctctgttcacag
5'ITR SEQ ID NO: 418	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggt cgcccggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggt tcct

Name/ SEQ ID NO.	Sequence
5'-ITR (Deleted D-sequence for self-complimentary AAV) SEQ ID NO: 419	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagtgg
3'-ITR AAV SEQ ID NO: 420	gaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagtggccaa
3'-ITR (Deleted D-sequence for self-complimentary AAV) SEQ ID NO: 421	ttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcag

[0097] 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: 417) or a chimeric intron (SEQ ID NO: 416). In certain embodiments, the viral vectors provided herein comprise a polyadenylation sequence.

[0098] Provided are gene expression cassettes and rAAVs comprising gene expression cassettes in which expression of the transgene is controlled by engineered nucleic acid regulatory elements that have more than one regulatory element (promoter or enhancer), including regulatory elements that are arranged in tandem (two or three copies) that promote liver-specific expression, or both liver-specific expression and muscle-specific expression, or both liver-specific and expression and bone-specific expression. These regulatory elements include for the liver-specific expression, LSPX1 (SEQ ID NO: 315), LSPX2 (SEQ ID NO: 316), LTP1 (SEQ ID NO: 317), LTP2 (SEQ ID NO:

318), or LTP3 (SEQ ID NO: 319), liver and muscle expression, LMTP6 (SEQ ID NO: 320), LMTP13 (SEQ ID NO: 321), LMTP14 (SEQ ID NO: 322), LMTP15 (SEQ ID NO: 323), LMTP18 (SEQ ID NO: 324), LMTP19 (SEQ ID NO: 325), or LMTP20 (SEQ ID NO: 326), or liver and bone expression, LBTP1 (SEQ ID NO: 327) or LBTP2 (SEQ ID NO: 328), the sequences of which are provided in Table 1 *supra*.

5.1.4 Signal Peptides

[0099] 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 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.

[0100] 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: 146) which can be encoded by a nucleotide sequence of SEQ ID NO: 422 (see Table 2, FIGS. 2-19 and FIGS. 29A-29F). 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 eye (including CNS), muscle, or liver are provided in Tables 2, 3 and 4, respectively, below.

Table 2. Signal peptides for expression in eye/CNS tissue

Signal Peptide Origin	SEQ ID NO:	Sequence
Mutant interleukin 2 signal peptide	146	MYRMQLLLLIALSLALVTNS
Mutant interleukin 2 signal peptide coding sequence	422	atgtataggatgcaactgctcctcctgattgctctgagcctggctcttgtgaccaactct
VEGF-A signal peptide	147	MNFLLSWVHWSLALLLYLHHAKWSQA
Fibulin-1 signal peptide	148	MERAAPSRRVPLPLLLLGGLALLAAGVDA
Vitronectin signal peptide	149	MAPLRPLLILALLAWVALA
Complement Factor H signal peptide	150	MRLLAKIICLMLWAICVA
Opticin signal peptide	151	MRLLAFLSLLALVLQETGT
Albumin signal peptide	152	MKWVTFISLLFLFSSAYS
Chymotrypsinogen signal peptide	153	MAFLWLLSCWALLGTTFG
Interleukin-2 signal peptide	154	MYRMQLLSCIALILALVTNS
Trypsinogen-2 signal peptide	155	MNLLLILTFVAAAVA

Table 3. Signal peptides for expression in muscle cells.

Signal Peptide Origin	SEQ ID NO:	Sequence
Human SPARC	156	MRAWIFFLLCLAGRALA
Human Collagen alpha-1(I) chain	157	MFSFVDLRLLLLLAATALLTHG
Human Lactotransferrin	158	MKLVFLVLLFLGALGLCLA
Human Complement C3	159	MGPTSGPSLLLLLLTHLPLALG
Human Lumican	160	MSLSAFTLFLALIGGTSG
Human Gelsolin isoform 1	161	MAPHRPAPALLCALSLALCALSLPVRA

Signal Peptide Origin	SEQ ID NO:	Sequence
Human Pro-cathepsin H	162	MWATLPLLCAGAWLLGVPVCGA
Human SERPINF1	163	MQALVLLLCIGALLGHSSC
Human SERPINE1	164	MQMSPALTCLVLGLALVFGEGSA
Human Cathepsin D	165	MQPSSLLPLALCLLAAPASA
Human TIMP1	166	MAPFEPLASGILLLLWLIAPSRA
Human Fibronectin	167	MLRGPGPGLLLLAVQCLGTAVPSTGASKSKR
Human Complement C1s subcomponent	168	MWCIVLFSLLAWVYA
Human Cathepsin L1	169	MNPTLILAAFCLGIASA
Human Cathepsin B	170	MWQLWASLCCLLVLANA
Human Salivary acidic proline-rich phosphoprotein ½	171	MLLILLSVALLAFSSA
Human Follistatin-related protein 1	172	MWKRWLALALALVAVAWVRA

Table 4. Signal peptides for expression in liver cells.

Signal Peptide Origin	SEQ ID NO:	Sequence
Human Serum albumin	173	MKWVTFISLLFLFSSAYS
Human α-1 Antitrypsin (SERPINA1)	174	MPSSVSWGILLLAGLCCLVPVSLA
Human Apolipoprotein A-1	175	MKAAVLTLAVLFLTGSQA
Human Apolipoprotein A-2	176	MKLLAATVLLLTICSLEG
Human Apolipoprotein B-100	177	MDPPRPALLALLALPALLLLLLAGARA
Human Coagulation Factor IX	178	MQRVNMIMAESPGLITICLLGYLLSAEC
Human Complement C2	179	MGPLMVLFCLLFLYPGLADS
Human Complement Factor H-related Protein 2 (CFHR2)	180	MWLLVSVILISRISSVGG
Human Complement Factor H-related Protein 5 (CFHR5)	181	MLLLFSVILISWVSTVGG

Signal Peptide Origin	SEQ ID NO:	Sequence
Human Fibrinogen α-chain (FGA)	182	MFSMRIVCLVLSVVGTAWT
Human Fibrinogen β-chain (FGB)	183	MKRMVSWSFHKLKTMKHLLLLLLCVFLVKS
Human Fibrinogen γ-chain (FGG)	184	MSWSLHPRNLILYFYALLFLSSTCVA
Human α-2-HS-Glycoprotein (AHSG)	185	MKSLVLLLCLAQLWGCHS
Human Hemopexin (HPX)	186	MARVLGAPVALGLWSLCWSLAIA
Human Kininogen-1	187	MKLITILFLCSRLLLSLT
Human Mannose-binding protein C (MBL2)	188	MSLFPSLPLLLLSMVAASYS
Human Plasminogen (PLMN)	189	MEHKEVVLLLLLFLKSGQG
Human Prothrombin (Coagulation Factor II)	190	MAHVRGLQLPGCLALAALCSLVHS
Human Secreted Phosphoprotein 24	191	MISRMEKMTMMMKILIMFALGMNYWSCSG
Human Anti-thrombin-III (SERPINC1)	192	MYSNVIGTVTSGKRKVYLLSLLLIGFWDCVTC
Human Serotransferrin (TF)	193	MRLAVGALLVCAVLGLCLA

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

[0101] *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, AAV9-based or AAVrh10-based vector).

[0102] *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:

Leader – Heavy chain – Furin site – 2A site – Leader – 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 NO: 231) or a T2A site comprising the amino acid sequence RKRR(GSG)EGRGSLLTCGDVEENPGP (SEQ ID NO: 429), 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: 427), that could be used include but are not limited to:

T2A: (GSG)EGRGSLLTCGDVEENP**GP** (SEQ ID NO: 227);

P2A: (GSG)ATNFSLLKQAGDVEENP**GP** (SEQ ID NO: 228);

E2A: (GSG)QCTNYALLKLAGDVESNP**GP** (SEQ ID NO: 229);

F2A: (GSG)APVKQTLNFDLLKLAGDVESNP**GP** (SEQ ID NO: 230)

(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 nucleotide sequences encoding different parts of the flexible linker are described in **Table. 1-1**.

Table. 1-1

ID	SEQ ID NO:	Sequence
Furin-T2A	424	agaaagagaagaggctctggagaaggcagaggctccctgctgacatgtgg ggatgttgaagagaatcctgggcct

Furin	425	agaaagagaaga
Furin-GSG linker	426	agaaagagaagaggctctgga
GSG	427	ggctctgga
T2A	428	gaaggcagaggctccctgctgacatgtggggatgttgaagagaatcctgggcct

[0103] 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: 222), RRRR (SEQ ID NO: 223), RRKR (SEQ ID NO: 224), or RKKR (SEQ ID NO: 225). 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: 222), RRRR (SEQ ID NO: 223), RRKR (SEQ ID NO: 224), or RKKR (SEQ ID NO: 225). 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, or RXRR, 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.

[0104] *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.

[0105] 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. For constructs such as that in FIG. 1 that contains the CB7 promoter, the chicken β-actin intron, rabbit β-globin polyA signal, and ITRs, the therapeutic antibody encoded may be approximately 752 amino acids. Substitution of smaller expression elements would permit the expression of larger protein products, such as full-length therapeutic antibodies.

5.1.6 Untranslated regions

[0106] 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

[0107] 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: 418 (5'-ITR) or 420 (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: 419 (5'-ITR) or 421 (3'-ITR).

5.1.8 Transgenes

[0108] 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 $F(ab')_2$ 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). FIG. 20 provides alignments of the Fab heavy and light chains of the therapeutic antibodies disclosed herein and highlights in green residues that may be substituted with an asparagine or, in some instances, a serine, resulting in hyperglycosylation. 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".

[0109] In certain embodiments, the transgenes encode either a full-length antibody or an antigen binding fragment thereof with the coding sequence of the heavy and light chains. Such transgenes encoding the full-length antibody comprise the Fab portion and an Fc region. The Fc region is further discussed in Section 5.1.9. Exemplary sequences are provided in FIG. 23 and Table 7.

[0110] In some embodiments, antigen binding fragments are advantageously used. FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F provide the amino acid sequences of the heavy and light chains of the Fab fragments of the therapeutic antibodies (see also Table 5, which provides the amino acid sequences of the Fab heavy and light chains of the therapeutic antibodies). In some embodiments, the transgene for expression of a full-length antibody may comprise the nucleotide sequences encoding the heavy and light chain sequences using nucleotide 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 as described further herein and the light chain. Nucleotide sequences encoding the Fab fragment portions of the heavy and light chains of the therapeutic antibodies disclosed herein are provided in Table 6. Certain of these nucleotide sequences are codon optimized for expression in human cells. Sequences for lanadelumab and adalimumab coding transgenes are provided in Tables 8 and 17, respectively. The transgene may encode a Fab fragment using nucleotide sequences encoding the sequences provided in FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F, 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: 232)). Heavy chain Fab domain sequences that do not contain a CPPCP (SEQ ID NO: 233) 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: 233) 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: 430) of the hinge region, as depicted in FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F 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).

[0111] 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, 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, 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, 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 NO: 231) or a F/T2A sequence (SEQ ID NO: 429) or a flexible peptide linker.

[0112] 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.

[0113] 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

[0114] 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 of FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13,

14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F including the hinge region of the heavy chain and C-terminal of the heavy chain of the Fab fragment, an Fc domain peptide. Table 7 provides the amino acid sequences of the Fc polypeptides for certain of the therapeutic antibodies described herein. Alternatively, an IgG1, IgG2, or IgG4 Fc domain, the sequences of which are provided in FIG. 23 may be utilized. As detailed, the transgene may comprise a nucleotide sequence encoding the Fc polypeptide for the therapeutic antibody linked to the nucleotide sequence encoding the heavy chain Fab fragment at the C terminus of the hinge region as provided in Table 6 (with the amino acid sequences provided in FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F and Table 6).

[0115] 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.

[0116] In certain embodiments, the Fc polypeptide is that of the therapeutic antibody (see Table 7) or is the Fc polypeptide corresponding to the isotype of the therapeutic antibody (isotype is indicated in FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F). 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 Figure 23 for alignment of IgG1, IgG2 and IgG4 Fc domain sequences, numbered according to EU numbering) or may be an IgG3 Fc domain, depending, for example, upon the desired effector activity of the therapeutic antibody. In some embodiments, the engineered heavy chain constant region (CH), which includes the Fc domain, is chimeric. As such, a chimeric CH region combines CH domains derived from more than one immunoglobulin isotype and/or subtype. For example, the chimeric (or hybrid) CH region comprises part or all of an Fc region from IgG, IgA and/or IgM. In other examples, the chimeric CH region comprises part or all a CH2 domain derived from a human IgG1, human IgG2, or human IgG4 molecule, combined with part or all of a CH3 domain derived from a human IgG1, human IgG2, or human IgG4 molecule. In other embodiments, the chimeric CH region contains a chimeric hinge region.

[0117] 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).

[0118] "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.

[0119] 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.

[0120] "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.

[0121] "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.

[0122] "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.

[0123] 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. 23): 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.

[0124] 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. 23) 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.

[0125] 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.

[0126] 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);

[0127] 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 23).

[0128] 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).

[0129] 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).

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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.

[0134] 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

[0135] 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.

[0136] 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.

[0137] 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.

[0138] In vitro assays, *e.g.*, cell culture assays, can be used to measure transgene expression from a vector described herein, thus indicating, *e.g.*, potency of the vector. For example, the PER.C6® Cell Line (Lonza), a cell line derived from human embryonic retinal cells, or retinal pigment epithelial cells, *e.g.*, the retinal pigment epithelial cell line hTERT RPE-1 (available from ATCC®), can be used to assess transgene expression. Once expressed, characteristics of the expressed product can be determined, including determination of the glycosylation and tyrosine sulfation patterns associated with the HuGlyFab. Glycosylation patterns and methods of determining the same are discussed in Section 5.2.1, while tyrosine sulfation patterns and methods of determining the same are discussed in Section 5.2.2. 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 Sections 5.2.1 and 5.2.2.

5.1.10 Compositions

[0139] 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 N-GLYCOSYLATION, TYROSINE SULFATION, AND O-GLYCOSYLATION

[0140] 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 FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F) 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 FIG. 23).

[0141] Alternatively, mutations may be introduced into the Fc domain to alter the glycosylation site at residue N297 (EU numbering, see FIG. 23), 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.

5.2.1 N-Glycosylation

Reverse Glycosylation Sites

[0142] 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

[0143] 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

[0144] In certain embodiments, a nucleic acid encoding a HuPTM mAb, HuGlyFab or HuTPM 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.

[0145] 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

[0146] 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.

[0147] 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.

[0148] Glycosylation of the Fc domain has been characterized and is a single N-linked glycan at asparagine 297 (EU numbering; see FIG. 23). 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.

[0149] 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.

[0150] 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.

[0151] 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.

[0152] 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

[0153] 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.

[0154] 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.

[0155] 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.

[0156] 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.

[0157] 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 retinal cells, human CNS cells, human liver cells or human muscle cells.

[0158] 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.

[0159] 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.

5.2.2 Tyrosine Sulfation

[0160] 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 FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F).

[0161] 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.

[0162] 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.

5.2.3 O-Glycosylation

[0163] 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).

5.3 VECTORED THERAPEUTIC ANTIBODIES

5.3.1 Anti-ABeta HuPTM Constructs and Formulations for Alzheimer's Disease

[0164] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to amyloid beta (Aβ or Abeta) peptides derived from the amyloid precursor protein that may have benefit in treating Alzheimer's disease (AD) and the like. In particular embodiments, the HuPTM mAb is solanezumab, or GSK933776, or lecanemab, or an antigen binding fragment of one of the foregoing. The amino acid sequences of Fab fragments of these antibodies are provided in FIGS. 2A-C, respectively. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an Aβ-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of, AD, to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0165] 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 Aβ 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 Aβ, such as solanezumab, lecanemab, or GSK933776, or variants there of as detailed herein. The transgene may also encode an anti-Aβ antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al., 2016, mAbs 8: 99-112 which is incorporated by reference herein in its entirety).

[0166] In certain embodiments, the anti-Aβ antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of solanezumab (having amino acid sequences of SEQ ID NOs. 1 and 2, respectively, see Table 5 and FIG 2A). The nucleotide sequences may be codon optimized for expression in human cells. The nucleotide sequences may, for example, comprise the nucleotide sequences of SEQ ID NO: 71 (encoding the solanezumab heavy chain Fab portion) and SEQ ID NO: 72 (encoding the solanezumab 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0167] In addition to the Fab fragments, including the heavy and light chain variable domain sequences and C_L and C_H1 sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 sequence, all or a portion of the hinge region. In specific embodiments, the anti-Aβ-antigen binding domain has a heavy chain variable domain and C_H1 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or

EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 2A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 71 by the hinge region encoding sequences set forth in Table 5 (SEQ ID NO: 71). 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. an IgG1 Fc domain, such as SEQ ID NO: 290 of Table 7, SEQ ID No. 283 or as depicted in FIG. 23, 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-Aβ antigen-binding fragment transgene encodes an Aβ 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-Aβ antigen-binding fragment transgene encodes an Aβ 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-Aβ 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 Aβ 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 for example, in the framework regions (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 2A) 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. 20A. In specific embodiments, the Aβ 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 for example, in the framework regions (*e.g.*, those regions outside of the CDRs, which CDRs are underlined in FIG. 2A) 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. 20B.

[0169] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes a hyperglycosylated solanezumab 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: L107N (heavy chain), Q165N or Q165S (light chain), and/or E200N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0170] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six solanezumab 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-Aβ antibody or antigen-binding fragment thereof.

[0171] In certain embodiments, the anti-Aβ antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of GSK933776 (having amino acid sequences of SEQ ID NOs. 3 and 4, respectively, see Table 5 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: 73 (encoding the GSK933776 heavy chain Fab portion) and SEQ ID NO: 74 (encoding the GSK933776 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or a signal sequence found in Table 2.

[0172] In addition to the heavy and light chain variable domain and C_H1 and C_L sequences, the transgenes may comprise, at the C-terminus of the heavy chain $C_H1$sequence, all or a portion of the hinge region. In specific embodiments, the anti-Aβ-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 EPKSCDKTHTCPPCPAPELAGA (SEQ ID NO: 202), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELAGAPSVFL (SEQ ID NO: 204) or EPKSCDKTHLCPPCPAPELAGAPSVFL (SEQ ID NO: 205) as set forth in FIG. 2B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 3 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 73). 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., an IgG1 Fc domain, such as SEQ ID NO. 291 (Table 7), or alternatively, SEQ ID No. 283 or as depicted in FIG. 23, or a mutant or variant thereof. In particular embodiments, the Fc domain has alanine substitutions at positions 235 and 237 (EU numbering). 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-Aβ antigen-binding fragment transgene encodes an Aβ 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-Aβ antigen-binding fragment transgene encodes an Aβ 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-Aβ 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 Aβ 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, e.g., are made 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. 20A. In specific embodiments, the Aβ 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, 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 light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 20B.

[0174] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes a hyperglycosylated GSK933776 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: L110N (heavy chain), Q165N or Q165S (light chain), and/or E200N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0175] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six GSK933776 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-Aβ antibody or antigen-binding fragment thereof.

[0176] In certain embodiments, the anti-Aβ antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of lecanemab (having amino acid sequences of SEQ ID NOs. 360 and 361, respectively, see Table 5 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: 376 (encoding the lecanemab heavy chain Fab portion) and SEQ ID NO: 377 (encoding the lecanemab 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 CNS cells.

The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0177] In addition to the Fab fragments, including the heavy and light chain variable domain sequences and the C_L and C_H1 domains, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 sequence, all or a portion of the hinge region. In specific embodiments, the anti-Aβ-antigen binding domain has a heavy chain variable domain and C_H1 domain of SEQ ID NO: 360 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 2C. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 376 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 376). 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. an IgG1 Fc domain, such as SEQ ID NO: 392 of Table 7, SEQ ID No. 283 or as depicted in FIG. 23, 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*.

[0178] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes an Aβ 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: 361. In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes an Aβ 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: 360. In certain embodiments, the anti-Aβ 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: 361 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: 360. In specific embodiments, the Aβ antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 360 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. 20A. In specific embodiments, the Aβ antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 361 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 light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 20B.

[0179] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes a hyperglycosylated lecanemab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 360 and 361, respectively, with one or more of the following mutations: T119N (heavy chain), Q165N or Q165S (light chain), and/or E200N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0180] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six lecanemab 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-Aβ antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0181] Provided are methods of treating human subjects for AD by administration of a viral vector containing a transgene encoding an anti-Aβ antibody, or antigen binding fragment thereof. The

antibody may be solanezumab, lecanemab, or GSK933776 and is, e.g., a Fab fragment thereof, or other antigen-binding fragment thereof. In other embodiments, the antibody is a full-length or substantially full-length antibody having an Fc region. In certain embodiments, the patient has been diagnosed with and/or has symptoms associated with prodromal AD, *e.g.*, a mild cognitive impairment associated with early AD or even pre-AD. Recombinant vectors used for delivering the transgene are described in Section 5.4.1. Such vectors should have a tropism for human CNS cells and can include non-replicating rAAV, particularly those bearing an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid. The recombinant vectors can be administered in any manner such that the recombinant vector enters the CNS, e.g., by introducing the recombinant vector into the cerebral spinal fluid (CSF). See Section 5.5.1 for details regarding the methods of treatment.

[0182] Subjects to whom such gene therapy is administered can be those responsive to anti-Aβ therapy. In particular embodiments, the methods encompass treating patients who have been diagnosed with AD, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-Aβ antibody or considered a good candidate for therapy with an anti-Aβ antibody. In specific embodiments, the patients have previously been treated with solanezumab, lecanemab, or GSK933776 and have been found to be responsive to solanezumab, lecanemab, and/or GSK933776. To determine responsiveness, the anti-Aβ antibody or antigen-binding fragment transgene product (e.g., produced in human cell culture, bioreactors, etc.) may be administered directly to the subject.

Human Post Translationally Modified Antibodies

[0183] The production of the anti-Aβ HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of AD accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-Aβ HuPTM Fab or HuPTM mAb, intrathecally, particularly intracisternal or lumbar administration, or intravenous administration to human subjects (patients) diagnosed with or having one or more symptoms of AD, to create a permanent depot in the CNS that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced CNS cells.

[0184] The cDNA construct for the anti-Aβ HuPTMmAb or anti-Aβ HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced CNS cells. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146).

[0185] As an alternative, or an additional treatment to gene therapy, the anti-Aβ HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with AD, or for whom therapy for AD is considered appropriate.

[0186] In specific embodiments, the anti-Aβ 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 solanezumab 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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N56, Q104, and/or N154 of the heavy chain (SEQ ID NO:1) or Q105, N163 and/or N215 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 solanezumab has a sulfation group at Y94, Y95 and/or Y101 of the heavy chain (SEQ ID NO: 1) or Y91 and/or Y92 of the light chain (SEQ ID NO: 2). In other embodiments, the anti-Aβ HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the anti-Aβ-HuPTM mAb is a full length mAb with an Fc region, e.g., the Fc domain of SEQ ID NO 290, or alternatively of SEQ ID NO: 283, SEQ ID NO: 284 or SEQ ID NO: 285, or a mutant or variant thereof.

[0187] In specific embodiments, the anti-Aβ 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 GSK933776 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 glycosylation, particularly a 2,6-sialylation, at one or more

of the amino acid positions N32, Q107, and/or N157 of the heavy chain (SEQ ID NO: 3) or N163 and/or N215 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 GSK933776 has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 3) or Y91 and/or Y92 of the light chain (SEQ ID NO: 4). In other embodiments, the anti-Aβ 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 anti-Aβ-HuPTM mAb is a full length mAb with an Fc region, e.g., the Fc domain of SEQ ID NO: 291, or alternatively SEQ ID NO: 283, SEQ ID NO: 284 or SEQ ID NO: 285, or a mutant or variant thereof, and, e.g., has alanine substitutions at positions 235 and 237 (EU numbering).

[0188] In specific embodiments, the anti-Aβ 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 lecanemab 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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions Q116, and/or N166 of the heavy chain (SEQ ID NO: 360) or N163 and/or N215 of the light chain (SEQ ID NO: 361). Alternatively, or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of lecanemab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 360) or Y91 and/or Y92 of the light chain (SEQ ID NO: 361). In other embodiments, the anti-Aβ HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the anti-Aβ-HuPTM mAb is a full length mAb with an Fc region, e.g., the Fc domain of SEQ ID NO 392, or alternatively of SEQ ID NO: 283 or a mutant or variant thereof. In certain embodiments, the HuPTM mAb or Fab is therapeutically effective and is at least 0.5%, 1% or 2% 2,6 sialylated and/or sulfated and may be at least 5%, 10% or even 50% or 100% glycosylated 2,6 sialylation and/or sulfated. The goal of gene therapy treatment provided herein is to slow or arrest the progression of AD, particular cognitive impairment. Efficacy may be monitored by

measuring a reduction in plaque formation and/or an improvement in cognitive function or a reduction in the decline in cognitive function.

[0189] Combinations of delivery of the anti-Aβ HuPTM mAb or antigen-binding fragment thereof, to the CNS 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 AD that could be combined with the gene therapy provided herein include but are not limited to ARICEPT® (donepezil), RAZADYNE® (galantamine), NAMENDA® (rivastigmine), and NAMZARIC® (donepezil and memantine), to name a few, and administration with anti-Aβ agents, including but not limited to solanezumab, GSK933776, or lecanemab, or anti-Tau agents, such as aTAU.

5.3.2. Anti-Sortilin HuPTM Constructs and Formulations for Frontotemporal Dementia

[0190] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to sortilin that may have benefit in treating frontotemporal dementia (FD). In particular embodiments, the HuPTM mAb is AL-001, or an antigen binding fragment of AL-001. The amino acid sequences of the heavy and light chains of Fab fragments of this antibody is provided in FIG. 3. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding a sortilin-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of, FD, to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0191] 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 sortilin 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 sortilin, such as AL-001, or variants thereof as detailed herein. The transgene may also

encode an anti-sortilin antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al., 2016, mAbs 8: 99-112 which is incorporated by reference herein in its entirety).

[0192] In certain embodiments, the anti-sortilin antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of AL-001 (having amino acid sequences of SEQ ID NOs. 5 and 6, respectively, see Table 5 and FIG. 3). 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: 75 (encoding the AL-001 heavy chain Fab portion) and SEQ ID NO: 76 (encoding the AL-001 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2, *supra*.

[0193] In addition to the heavy and light chain variable domain sequences and the C_H1 and C_L domains, the transgenes may comprise, at the C-terminus sequence, all or a portion of the hinge region. In specific embodiments, the anti-sortilin-antigen binding domain has a heavy chain Fab 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 3. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 75 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 75). 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., an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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*.

[0194] In certain embodiments, the anti-sortilin antigen-binding fragment transgene encodes an sortilin 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-sortilin antigen-binding fragment transgene encodes an sortilin 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-sortilin 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 sortilin 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. 3) 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. 20A. In specific embodiments, the sortilin 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. 3) 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. 20B.

[0195] In certain embodiments, the anti-sortilin antigen-binding fragment transgene encodes a hyperglycosylated AL-001 Fab or mAb, 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), Q160N or Q160S (light chain), and/or E199N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0196] In certain embodiments, the anti-sortilin antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six AL-001 CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 3 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-sortilin antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0197] Provided are methods of treating human subjects for FD by administration of a viral vector containing a transgene encoding an anti-sortilin antibody, or antigen binding fragment thereof. The antibody may be AL-001 and is, e.g., a Fab fragment thereof, or other antigen-binding fragment thereof. In certain embodiments, the transgene encodes a full length or substantially full-length Al-001 mAb, including the Fc region. In certain embodiments, the patient has been diagnosed with FD and/or has symptoms associated with FD or prodromal FD, *e.g.*, a mild cognitive impairment associated with early FD or even pre-FD. Recombinant vectors used for delivering the transgene are described in Section 5.4.1. Such vectors should have a tropism for human CNS cells and can include non-replicating rAAV, particularly those bearing an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid. The recombinant vectors can be administered in any manner such that the recombinant vector enters the CNS, e.g., by introducing the recombinant vector into the cerebral spinal fluid (CSF). See Section 5.5.1 for details regarding the methods of treatment.

[0198] Subjects to whom such gene therapy is administered can be those responsive to anti-sortilin therapy. In particular embodiments, the methods encompass treating patients who have been diagnosed with FD, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-sortilin antibody or considered a good candidate for therapy with an anti-sortilin antibody. In specific embodiments, the patients have previously been treated with AL-001, and have been found to be responsive to AL-001. To determine responsiveness, the anti-sortilin antibody or antigen-binding fragment transgene product (e.g., produced in human cell culture, bioreactors, etc.) may be administered directly to the subject.

Human Post Translationally Modified Antibodies

[0199] The production of the anti-sortilin HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of FD accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-sortilin HuPTM Fab or HuPTM mAb, intrathecally, particularly intracisternal or lumbar administration, or intravenous administration to human subjects (patients) diagnosed with or having one or more symptoms of FD, to create a permanent depot in the CNS that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced CNS cells.

[0200] The cDNA construct for the anti-sortilin HuPTM mAb or anti-sortilin HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced CNS cells. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146).

[0201] As an alternative, or an additional treatment to gene therapy, the anti-sortilin HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with FD, or for whom therapy for FD is considered appropriate.

[0202] In specific embodiments, the anti-sortilin 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 AL-001 as set forth in FIG. 3 (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions Q121 and/or N171 of the heavy chain (SEQ ID NO:5) or N32, N158 and/or N210 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 AL-001 has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 5) or Y86 and/or Y87 of the light chain (SEQ ID NO: 6). In other embodiments, the anti-sortilin HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-

Gal moieties. In certain embodiments, the anti-sortilin-HuPTM mAb is a full length mAb with an Fc region, e.g., the Fc domain of SEQ ID NO: 283, SEQ ID NO: 284 or SEQ ID NO: 285, or a mutant or variant thereof.

[0203] In certain embodiments, the HuPTM mAb or Fab is therapeutically effective and is at least 0.5%, 1% or 2% 2,6 sialylated and/or sulfated and may be at least 5%, 10% or even 50% or 100% glycosylated 2,6 sialylation and/or sulfated. The goal of gene therapy treatment provided herein is to slow or arrest the progression of FD, particular cognitive impairment. Efficacy may be monitored by measuring an improvement in cognitive function and/or a reduction in the deterioration in behavior, personality and/or difficulty with producing or comprehending language.

[0204] Combinations of delivery of the anti-sortilin HuPTM mAb or antigen-binding fragment thereof, to the CNS 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 FD that could be combined with the gene therapy provided herein.

5.3.3. Anti-Tau HuPTM Constructs and Formulations for Tauopathies like Alzheimer's Disease, Chronic Traumatic Encephalopathy, Progressive Supranuclear Palsy, or Frontotemporal Dementia

[0205] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to Tau protein (Tau), such as monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau, that may have benefit in treating Alzheimer's Disease (AD), Chronic Traumatic Encephalopathy (CTE), Pick's Complex, primary age-related tauopathy, progressive supranuclear palsy (PSP), FD, and other tauopathies. In particular embodiments, the HuPTM mAb is ABBV-8E12, UCB-0107, and NI-105 (BIIB076), or an antigen binding fragment of one of the foregoing. The amino acid sequences of Fab fragments of these antibodies are provided in FIGS. 4A-C. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding a Tau-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of,

AD, CTE, PSP, FD, or other tauopathies, to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0206] 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 Tau 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 Tau, such as ABBV-8E12, UCB-0107, and NI-105 (BIIB076), or variants there of as detailed herein. The transgene may also encode anti-Tau antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al., 2016, mAbs 8: 99-112 which is incorporated by reference herein in its entirety).

[0207] In certain embodiments, the anti-Tau antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of ABBV-8E12 (having amino acid sequences of SEQ ID NOs. 7 and 8, respectively, see Table 5 and FIG 4A). 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: 77 (encoding the ABBV-8E12 heavy chain Fab portion) and SEQ ID NO: 78 (encoding the ABBV-8E12 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2, *supra*.

[0208] In addition to the heavy and light chain variable domain and C_H1 and C_L sequences, the transgenes may comprise, at the C-terminus of the C_H1 domain, all or a portion of the hinge region. In specific embodiments, the anti-Tau-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 7 with additional hinge region sequence starting after the C-terminal tyrosine (Y), contains all or a portion of the amino acid sequence ESKYGPPCPPCPAPEFLGG (SEQ ID NO: 214), and specifically, ESKYGPPCPPCPA (SEQ ID NO: 216), ESKYGPPCPSCPA (SEQ ID NO: 217), ESKYGPPCPSCPAPEFLGGPSVFL (SEQ ID NO: 218), or ESKYGPPCPPCPAPEFLGGPSVFL

(SEQ ID NO: 219) as set forth in FIG 4A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 77 by the hinge region encoding sequences set forth in Table 5 (SEQ ID NO: 77). 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., an IgG1 or IgG4 Fc domain, such as SEQ ID Nos. 283 or 285, including with a S241P substitution (EU numbering) or as depicted in FIG. 23, 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*.

[0209] In certain embodiments, the anti-Tau antigen-binding fragment transgene encodes a Tau 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-Tau antigen-binding fragment transgene encodes a Tau 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-Tau 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 Tau 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. 4A) 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. 20A. In specific embodiments, the Tau 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. 4A) 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. 20B.

[0210] In certain embodiments, the anti-Tau antigen-binding fragment transgene encodes a hyperglycosylated ABBV-8E12 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: T110N (heavy chain), Q164N or Q164S (light chain), and/or E199N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0211] In certain embodiments, the anti-Tau antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six ABBV-8E12 CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 4A 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-Tau antibody or antigen-binding fragment thereof.

[0212] In certain embodiments, the anti-Tau antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of UCB-0107 (having amino acid sequences of SEQ ID NOs. 9 and 10, respectively, see Table 5 and FIG 4B). 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: 79 (encoding the UCB-0107 heavy chain Fab portion) and SEQ ID NO: 80 (encoding the UCB-0107 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0213] In addition to the heavy and light chain variable domain, 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-Tau-antigen binding domain has

a heavy chain Fab fragment 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 ESKYGPPCPPCPAPEFLGG (SEQ ID NO: 214), and specifically, ESKYGPPCPPCPA (SEQ ID NO: 216), ESKYGPPCPSCPA (SEQ ID NO: 217), ESKYGPPCPSCPAPEFLGGPSVFL (SEQ ID NO: 218), or ESKYGPPCPPCPAPEFLGGPSVFL (SEQ ID NO: 219) as set forth in FIG 4B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 79 by the hinge region encoding sequences set forth in Table 5 (SEQ ID NO: 79). 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., SEQ ID NO. 292 (Table 7), or an IgG4 Fc domain, such as SEQ ID No. 285 or as depicted in FIG. 23, 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*.

[0214] In certain embodiments, the anti-Tau antigen-binding fragment transgene encodes a Tau 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-Tau antigen-binding fragment transgene encodes a Tau 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-Tau 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 Tau 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. 4B) 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. 20A. In specific embodiments, the Tau 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. 4B) 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. 20B.

[0215] In certain embodiments, the anti-Tau antigen-binding fragment transgene encodes a hyperglycosylated UCB-0107 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: M113N (heavy chain), Q165N or Q165S (light chain), and/or E200N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0216] In certain embodiments, the anti-Tau antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six UCB-0107 CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 4B 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-Tau antibody or antigen-binding fragment thereof.

[0217] In certain embodiments, the anti-Tau antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of NI-105 (having amino acid sequences of SEQ ID NOs. 11 and 12, respectively, see Table 5 and FIG 4C). 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: 81 (encoding the NI-105 heavy chain Fab portion) and SEQ ID NO: 82 (encoding the NI-105 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0218] In addition to the heavy and light chain variable domain and C_H1 and C_L sequences, the transgenes may comprise, at the C-terminus of the C_H1 domain sequence, all or a portion of the hinge region. In specific embodiments, the anti-Tau-antigen binding domain has a heavy chain Fab fragment 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 EPKSCDKTHTCPPCPAPELAGA (SEQ ID NO: 202), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELAGAPSVFL (SEQ ID NO: 204) or EPKSCDKTHLCPPCPAPELAGAPSVFL (SEQ ID NO: 205) as set forth in FIG 4C. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 81 by the hinge region encoding sequences set forth in Table 5 (SEQ ID NO: 81). 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., an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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*.

[0219] In certain embodiments, the anti-Tau antigen-binding fragment transgene encodes a Tau 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-Tau antigen-binding fragment transgene encodes a Tau 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-Tau 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 Tau 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. 4C) 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. 20A. In specific embodiments, the Tau 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. 4C) 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. 20B.

[0220] In certain embodiments, the anti-Tau antigen-binding fragment transgene encodes a hyperglycosylated NI-105 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: L119N (heavy chain) and/or Q196N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0221] In certain embodiments, the anti-Tau antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six NI-105 CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 4C 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-Tau antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0222] Provided are methods of treating human subjects for AD, CTE, PSP, FD, or other tauopathies by administration of a viral vector containing a transgene encoding an anti-Tau antibody, or antigen binding fragment thereof. The antibody may be ABBV-8E12, UCB-0107, or NI-105 (BIIB076), and is, for example, a Fab fragment thereof, or other antigen-binding fragment thereof. In certain embodiments, the antibody is a full length or substantially full length mAb with Fc region. In

certain embodiments, the patient has been diagnosed with and/or has symptoms associated with prodromal AD, *e.g.,* a mild cognitive impairment associated with early AD or even pre-AD. Recombinant vectors used for delivering the transgene are described in Section 5.4.1. Such vectors should have a tropism for human CNS cells and can include non-replicating rAAV, particularly those bearing an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid. The recombinant vectors can be administered in any manner such that the recombinant vector enters the CNS, e.g., by introducing the recombinant vector into the cerebral spinal fluid (CSF). See Section 5.5.1 for details regarding the methods of treatment.

[0223] Subjects to whom such gene therapy is administered can be those responsive to anti-Tau therapy. In particular embodiments, the methods encompass treating patients who have been diagnosed with AD, PSP, or FD, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-Tau antibody or considered a good candidate for therapy with an anti-Tau antibody. In specific embodiments, the patients have previously been treated with ABBV-8E12, UCB-0107, and/or NI-105 (BIIB076), and have been found to be responsive to ABBV-8E12, UCB-0107, and/or NI-105 (BIIB076). To determine responsiveness, the anti-Tau antibody or antigen-binding fragment transgene product (e.g., produced in human cell culture, bioreactors, etc.) may be administered directly to the subject.

Human Post Translationally Modified Antibodies

[0224] The production of the anti-Tau HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of AD, PSP, or FD accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-Tau HuPTM Fab or HuPTM mAb, intrathecally, particularly intracisternal or lumbar administration, or intravenous administration to human subjects (patients) diagnosed with or having one or more symptoms of AD, PSP, or FD, to create a permanent depot in the CNS that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced CNS cells.

[0225] The cDNA construct for the anti-Tau HuPTMmAb or anti-Tau HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and

protein sulfation) by the transduced CNS cells. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146).

[0226] As an alternative, or an additional treatment to gene therapy, the anti-Tau HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with AD, PSP, or FD, or for whom therapy for AD, PSP, or FD is considered appropriate.

[0227] In specific embodiments, the anti-Tau 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 ABBV-8E12 as set forth in FIG. 4A (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N57, Q107, N157 and/or N199 of the heavy chain (SEQ ID NO: 7) or N78, Q104, N162, and/or N214 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 ABBV-8E12 has a sulfation group at Y96, Y97 and/or Y104 of the heavy chain (SEQ ID NO: 7) and/or Y90 and/or Y91 of the light chain (SEQ ID NO: 8). In other embodiments, the anti-Tau HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0228] In specific embodiments, the anti-Tau 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 UCB-0107 as set forth in FIG. 4B (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N32, N58, N76, Q110, N160 and/or N202 of the heavy chain (SEQ ID NO: 9) or N99, N163 and/or N215 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 UCB-0107 has a sulfation group at Y93, Y94, Y101 and/or Y102 of the heavy chain (SEQ ID NO: 9) and/or Y91 and/or Y92 of the light chain (SEQ ID NO: 10). In other embodiments, the anti-Tau HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0229] In specific embodiments, the anti-Tau 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 NI-105 as set forth in FIG. 4C (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N77, N107, Q116, and/or N166 of the heavy chain (SEQ ID NO: 11) and/or N172 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 NI-105 has a sulfation group at Y93 and/or Y94 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-Tau HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0230] In certain embodiments, the HuPTM mAb or Fab is therapeutically effective and is at least 0.5%, 1% or 2% 2,6 sialylated and/or sulfated and may be at least 5%, 10% or even 50% or 100% glycosylated 2,6 sialylation and/or sulfated. The goal of gene therapy treatment provided herein is to slow or arrest the progression of AD, PSP, or FD, particularly cognitive impairment, gross or fine motor skill impairment, or vision impairment. Efficacy may be monitored by measuring a reduction

in plaque formation and/or an improvement in cognitive function, with motor skills, or with vision or a reduction in the decline in cognitive function, motor skills, or vision.

[0231] Combinations of delivery of the anti-Tau HuPTM mAb or antigen-binding fragment thereof, to the CNS 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 AD, PSP, or FD that could be combined with the gene therapy provided herein include but are not limited to ARICEPT® (donepezil), RAZADYNE® (galantamine), NAMENDA® (rivastigmine), and NAMZARIC® (donepezil and memantine), to name a few, and administration with anti-Tau agents, including but not limited to anti-tau, such as, but not limited to ABBV-8E12, UCB-0107, or NI-105, and anti-Aβ agents, such as, but not limited to solanezumab, lecanemab, or GSK933776.

5.3.4. Anti-SEMA4D HuPTM Constructs and Formulations for Huntington's Disease

[0232] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to semaphorin 4D (SEMA4D) that may have benefit in treating Huntington's disease (HD) and juvenile Huntington's disease (JHD). In particular embodiments, the HuPTM mAb is VX15/2503, or an antigen binding fragment of VX15/2503. The amino acid sequences of Fab fragments of this antibody is provided in FIG. 5. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an SEMA4D-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of, HD, to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0233] 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 SEMA4D 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 SEMA4D, such as VX15/2503, or variants there of as detailed herein. The

transgene may also encode an anti-SEMA4D antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al., 2016, mAbs 8: 99-112 which is incorporated by reference herein in its entirety).

[0234] In certain embodiments, the anti-SEMA4D antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of VX15/2503 (having amino acid sequences of SEQ ID NOs. 13 and 14, respectively, see Table 5 and FIG. 5). 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: 83 (encoding the VX15/2503 heavy chain Fab portion) and SEQ ID NO: 84 (encoding the VX15/2503 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0235] In addition to the heavy and light chain variable domain and C_H1 and C_L sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 sequence, all or a portion of the hinge region. In specific embodiments, the anti-SEMA4D-antigen binding domain has a heavy chain variable domain and C_H1 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 contains all or a portion of the amino acid sequence ESKYGPPCPPCPAPEFLGG (SEQ ID NO: 214), and specifically, ESKYGPPCPPCPA (SEQ ID NO: 216), ESKYGPPCPSCPA (SEQ ID NO: 217), ESKYGPPCPSCPAPEFLGGPSVFL (SEQ ID NO: 218), or ESKYGPPCPPCPAPEFLGGPSVFL (SEQ ID NO: 219) as set forth in FIG 5. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 83 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 83). 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., an IgG4 Fc domain, such as SEQ ID No. 285 or as depicted in FIG. 23, 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*.

[0236] In certain embodiments, the anti-SEMA4D antigen-binding fragment transgene encodes an SEMA4D 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-SEMA4D antigen-binding fragment transgene encodes an SEMA4D 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-SEMA4D 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 SEMA4D 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. 5) 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. 20A. In specific embodiments, the SEMA4D 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. 5) 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. 20B.

[0237] In certain embodiments, the anti-SEMA4D antigen-binding fragment transgene encodes a hyperglycosylated VX15/2503 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: T113N (heavy chain),

Q156N or Q156S (light chain), and/or E191N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0238] In certain embodiments, the anti-SEMA4D antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six VX15/2503 CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 5 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-SEMA4D antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0239] Provided are methods of treating human subjects for HD or juvenile HD by administration of a viral vector containing a transgene encoding an anti-SEMA4D antibody, or antigen binding fragment thereof. The antibody may be VX15/2503 and is, e.g., a Fab fragment thereof, or other antigen-binding fragment thereof. In certain embodiments, the transgene encodes the full length or substantially full length VX15/2503. In certain embodiments, the patient has been diagnosed with and/or has symptoms associated with HD, *e.g.*, mild involuntary movements, tremors, and/or dystonia associated with early HD or even pre-HD. Recombinant vectors used for delivering the transgene are described in Section 5.4.1. Such vectors should have a tropism for human CNS cells and can include non-replicating rAAV, particularly those bearing an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid. The recombinant vectors can be administered in any manner such that the recombinant vector enters the CNS, e.g., by introducing the recombinant vector into the cerebral spinal fluid (CSF). See Section 5.5.1 for details regarding the methods of treatment.

[0240] Subjects to whom such gene therapy is administered can be those responsive to anti-SEMA4D therapy. In particular embodiments, the methods encompass treating patients who have been diagnosed with HD, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-SEMA4D antibody or considered a good candidate for therapy with an anti-SEMA4D antibody. In specific embodiments, the patients have previously been treated with VX15/2503, and have been found to be responsive to VX15/2503. To determine responsiveness, the

anti-SEMA4D antibody or antigen-binding fragment transgene product (e.g., produced in human cell culture, bioreactors, etc.) may be administered directly to the subject.

Human Post Translationally Modified Antibodies

[0241] The production of the anti-SEMA4D HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of HD accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-SEMA4D HuPTM Fab, intrathecally, particularly intracisternal or lumbar administration, or intravenous administration to human subjects (patients) diagnosed with or having one or more symptoms of HD, to create a permanent depot in the CNS that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced CNS cells.

[0242] The cDNA construct for the anti-SEMA4D HuPTM mAb or anti-SEMA4D HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced CNS cells. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146).

[0243] As an alternative, or an additional treatment to gene therapy, the anti-SEMA4D HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology and administered to patients diagnosed with HD or juvenile HD, or for whom therapy for HD or juvenile HD is considered appropriate.

[0244] In specific embodiments, the anti-SEMA4D 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 VX15/2503 as set forth in FIG. 5 (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N61, Q110, N160 and/or N207 of the heavy chain (SEQ ID NO:13) or N22, Q104, N154 and/or N206 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 VX15/2503 has a sulfation group at Y94, Y95, Y99, Y100, and/or Y101 of the heavy chain (SEQ ID NO: 13) or Y31, Y36, Y90, and/or Y91 of the light chain (SEQ ID NO: 14). In other

embodiments, the anti-SEMA4D HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0245] In certain embodiments, the HuPTM mAb or Fab is therapeutically effective and is at least 0.5%, 1% or 2% 2,6 sialylated and/or sulfated and may be at least 5%, 10% or even 50% or 100% glycosylated 2,6 sialylation and/or sulfated. The goal of gene therapy treatment provided herein is to slow or arrest the progression of HD or juvenile HD, particular the impairment in voluntary movements. Efficacy may be monitored by measuring improvements in movement, dystonia, and/or an improvement in cognitive function or a reduction in the decline in chorea control and cognitive function. In the case of juvenile HD, efficacy may be monitored by measuring improvements in muscle stiffness, dystonia, and/or chorea or a reduction in the decline in muscle and cognitive function.

[0246] Combinations of delivery of the anti-SEMA4D HuPTM mAb or antigen-binding fragment thereof, to the CNS 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 HD or juvenile HD that could be combined with the gene therapy provided herein include but are not limited to speech, physical, and occupational therapy, XENAZINE® (Tetrabenazine), KLONOPIN® (clonazepam), HALDOL® (haloperidol), CLORAZIL® (clozapine), PROZAD® (fluoxetine), ZOLOFT® (sertraline), and PAMELOR® (nortriptyline), and administration with anti-SEMA4D agents, including but not limited to VX15/2503.

5.3.5. Anti-Alpha-Synuclein HuPTM Constructs and Formulations for Parkinson and Synucleinopathies

[0247] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to alpha-synuclein (SNCA) that may have benefit in treating Parkinson disease (PD) and other synucleinopathies such as dementia with Lewy bodies (DLB), pure autonomic failure (PAF), and multiple system atrophy (MSA). In particular embodiments, the HuPTM mAb is prasinezumab, NI-202 (BIIB054), and MED-1341, or an

antigen binding fragment of one of the foregoing. The amino acid sequences of Fab fragments of these antibodies are provided in FIGS. 6A-C. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding a SNCA-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of, PD, DLB, PAF, MSA, to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0248] 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 SNCA 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 SNCA, such as prasinezumab, NI-202 (BIIB054), or MED-1341, or variants there of as detailed herein. The transgene may also encode anti-SNCA antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al., 2016, mAbs 8: 99-112 which is incorporated by reference herein in its entirety).

[0249] In certain embodiments, the anti-SNCA antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of prasinezumab (having amino acid sequences of SEQ ID NOs. 15 and 16, respectively, see Table 5 and FIG. 6A). 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: 85 (encoding the prasinezumab heavy chain Fab portion) and SEQ ID NO: 86 (encoding the prasinezumab 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0250] 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 $C_H1$sequence, all or a

portion of the hinge region. In specific embodiments, the anti-SNCA-antigen binding domain has a heavy chain Fab fragment 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 6A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 85 by the hinge region encoding sequences set forth in Table 5 (SEQ ID NO: 85). 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: 293 (Table 7), or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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*.

[0251] In certain embodiments, the anti-SNCA antigen-binding fragment transgene encodes a SNCA 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-SNCA antigen-binding fragment transgene encodes a SNCA 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-SNCA 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 SNCA antigen-binding fragment comprises a heavy 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. 6A) 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. 20A. In specific embodiments, the SNCA 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. 6A) 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. 20B.

[0252] In certain embodiments, the anti-Tau antigen-binding fragment transgene encodes a hyperglycosylated prasinezumab 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: L119N (heavy chain), Q166N or Q166S (light chain), and/or E201N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0253] In certain embodiments, the anti-SNCA antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six prasinezumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 6A 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-SNCA antibody or antigen-binding fragment thereof.

[0254] In certain embodiments, the anti-SNCA antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of NI-202 (having amino acid sequences of SEQ ID NOs. 17 and 18, respectively, see Table 5 and FIG 6B). 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: 87 (encoding the NI-202 heavy chain Fab portion) and SEQ ID NO: 88 (encoding the NI-202 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0255] 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-SNCA-antigen binding domain has a heavy chain Fab fragment 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 EPKSCDKTHTCPPCPAPELLGG (SEQ ID NO: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 6B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 87 by the hinge region encoding sequences set forth in Table 5 (SEQ ID NO: 87). 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., an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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*.

[0256] In certain embodiments, the anti-SNCA antigen-binding fragment transgene encodes a SNCA 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-SNCA antigen-binding fragment transgene encodes a SNCA 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-SNCA 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 SNCA 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. 6B) 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. 20A. In specific embodiments, the SNCA 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. 6B) 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. 20B.

[0257] In certain embodiments, the anti-SNCA antigen-binding fragment transgene encodes a hyperglycosylated NI-202 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: L119N (heavy chain), Q166N or Q166S (light chain), and/or E199N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0258] In certain embodiments, the anti-SNCA antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six NI-202 CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 6B 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-SNCA antibody or antigen-binding fragment thereof.

[0259] In certain embodiments, the anti-SNCA antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of MED-1341 (having amino acid sequences of SEQ ID NOs. 19 and 20, respectively, see Table 5 and FIG. 6C). 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: 89 (encoding the MEDI-1341 heavy chain Fab portion) and SEQ ID NO: 90 (encoding the MEDI-1341 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0260] In addition to the heavy and light chain variable domain and C_H1 or C_L sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 sequence, all or a portion of the hinge region. In specific embodiments, the anti-SNCA-antigen binding domain has a heavy chain Fab fragment 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 EPKSCDKTHTCPPCPAPEFEGG (SEQ ID NO: 206), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPEFEGGPSVFL (SEQ ID NO: 208) or EPKSCDKTHLCPPCPAPEFEGGPSVFL (SEQ ID NO: 209) as set forth in FIG. 6C. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 89 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 89). 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: 294 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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*.

[0261] In certain embodiments, the anti-SNCA antigen-binding fragment transgene encodes a SNCA 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-SNCA antigen-binding fragment transgene encodes a SNCA 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-SNCA 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 SNCA 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. 6C) 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. 20A. In specific embodiments, the SNCA 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. 6C) 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. 20B.

[0262] In certain embodiments, the anti-SNCA antigen-binding fragment transgene encodes a hyperglycosylated MEDI-1341 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: T117N (heavy chain) and/or Q203N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0263] In certain embodiments, the anti-SNCA antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six MEDI-1341

CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 6C 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-SNCA antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0264] Provided are methods of treating human subjects for PD, DLB, PAF, MSA, or other synulceinopathies by administration of a viral vector containing a transgene encoding an anti-SNCA antibody, or antigen binding fragment thereof. The antibody may be prasinezumab, NI-202 (BIIB054), or MED-1341, and is e.g. a Fab fragment thereof, or other antigen-binding fragment thereof. In other embodiments, the transgene encodes a full length or substantially full-length antibody with Fc region. In certain embodiments, the patient has been diagnosed with and/or has symptoms associated with PD or other synulceinopathies, *e.g.*, a mild cognitive and/or motor skill impairment associated with early PD or even pre-PD. Recombinant vectors used for delivering the transgene are described in Section 5.4.1. Such vectors should have a tropism for human CNS cells and can include non-replicating rAAV, particularly those bearing an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid. The recombinant vectors can be administered in any manner such that the recombinant vector enters the CNS, e.g., by introducing the recombinant vector into the cerebral spinal fluid (CSF). See Section 5.5.1 for details regarding the methods of treatment.

[0265] Subjects to whom such gene therapy is administered can be those responsive to anti-SNCA therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with PD, DLB, PAF, or MSA, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-SNCA antibody or considered a good candidate for therapy with an anti-SNCA antibody. In specific embodiments, the patients have previously been treated with prasinezumab, NI-202 (BIIB054) and/or MED-1341, and have been found to be responsive to prasinezumab, NI-202 (BIIB054) and/or MED-1341. To determine responsiveness, the anti-SNCA antibody or antigen-binding fragment transgene product (e.g., produced in human cell culture, bioreactors, etc.) may be administered directly to the subject.

Human Post Translationally Modified Antibodies

[0266] The production of the anti-SNCA HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of PD, DLB, PAF, or MSA accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-SNCA HuPTM Fab or HuPTM mAb, intrathecally, particularly intracisternal or lumbar administration, or intravenous administration to human subjects (patients) diagnosed with or having one or more symptoms of PD, DLB, PAF, or MSA, to create a permanent depot in the CNS that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced CNS cells.

[0267] The cDNA construct for the anti-SNCA HuPTMmAb or anti-SNCA HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced CNS cells. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146).

[0268] As an alternative, or an additional treatment to gene therapy, the anti-SNCA HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with PD, DLB, PAF, or MSA or for whom therapy for PD, DLB, PAF or MSA is considered appropriate.

[0269] In specific embodiments, the anti-SNCA 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 prasinezumab as set forth in FIG. 6A (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions Q108 and/or N158 of the heavy chain (SEQ ID NO: 15) or N34, N164, and/or N216 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 prasinezumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 15) and/or Y92 and/or Y93 of the light chain (SEQ ID NO: 16). In other embodiments, the anti-SNCA HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays

known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0270] In specific embodiments, the anti-SNCA 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 NI-202 as set forth in FIG. 6B (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N71, Q116, and/or N166 of the heavy chain (SEQ ID NO: 17) or N34, N164 and/or N216 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 NI-202 has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 17) or Y92 and/or Y93 of the light chain (SEQ ID NO: 18). In other embodiments, the anti-SNCA HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0271] In specific embodiments, the anti-SNCA 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 MEDI-1341 as set forth in FIG. 6C (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N77, Q114, and/or N164 of the heavy chain (SEQ ID NO: 19) or N172 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 MED-1341 has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 19) or Y94 and/or Y95 of the light chain (SEQ ID NO: 20). In other embodiments, the anti-SNCA HuPTM mAb or antigen-binding

fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0272] In certain embodiments, the HuPTM mAb or Fab is therapeutically effective and is at least 0.5%, 1% or 2% 2,6 sialylated and/or sulfated and may be at least 5%, 10% or even 50% or 100% glycosylated 2,6 sialylation and/or sulfated. The goal of gene therapy treatment provided herein is to slow or arrest the progression of PD, DLB, PFA, or MSP, particularly cognitive impairment, gross or fine motor skill impairment, or vision impairment. Efficacy may be monitored by measuring an improvement in cognitive function, motor skills (*i.e.* posture, balance, tremor), and/or vision or a reduction in the decline in cognitive function, motor skills, or vision.

[0273] Combinations of delivery of the anti-SNCA HuPTM mAb or antigen-binding fragment thereof, to the CNS 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 PD, DLB, PFA, or MSP that could be combined with the gene therapy provided herein include but are not limited to RYTARY®, SINEMET®, or DUOPA® (carbidopa/levodopa), to name a few, and administration with anti-SNCA agents, including but not limited to anti-SNCA, such as, but not limited to prasinezumab, NI-202 (BIIB054), or MED-1341.

5.3.6. Anti-SOD1 HuPTM Constructs and Formulations for Alzheimer's Disease and Amyotrophic Lateral Sclerosis

[0274] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to superoxide dismutase 1 (SOD1) that may have benefit in treating AD and amyotrophic lateral sclerosis (ALS). In particular embodiments, the HuPTM mAb is NI-204, or an antigen binding fragment of NI-204. The amino acid sequences of Fab fragments of this antibody are provided in FIGS. 7A and B. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an SOD1-binding HuPTM mAb (or an antigen binding fragment and/or a

hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of AD or ALS to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0275] 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 SOD1 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 SOD1, such as NI-204, or variants there of as detailed herein. The transgene may also encode an anti-SOD1 antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al., 2016, mAbs 8: 99-112 which is incorporated by reference herein in its entirety).

[0276] In certain embodiments, the anti-SOD1 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of NI-204 (10D12) (having amino acid sequences of SEQ ID NOs. 21 and 22, respectively, see Table 5 and FIG. 7A). 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: 91 (encoding the NI-202 (10D12) heavy chain Fab portion) and SEQ ID NO: 92 (encoding the NI-202 (10D12) 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0277] In addition to the heavy and light chain variable domain and C_H1 and C_L sequences, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 sequence, all or a portion of the hinge region. In specific embodiments, the anti-SOD1-antigen binding domain has a heavy chain Fab fragment 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 EPKSCDKTHTCPPCPAPEAAGG (SEQ ID NO: 210), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID

NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPEAAGGPSVFL (SEQ ID NO: 212) or EPKSCDKTHLCPPCPAPEAAGGPSVFL (SEQ ID NO: 213) as set forth in FIG 3. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 91 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 91). 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; 295, or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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*.

[0278] In certain embodiments, the anti-SOD1 antigen-binding fragment transgene encodes an SOD1 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-SOD1 antigen-binding fragment transgene encodes an SOD1 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-SOD1 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 SOD1 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. 7A) 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. 20A. In specific embodiments, the SOD1 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. 7A) 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. 20B.

[0279] In certain embodiments, the anti-SOD1 antigen-binding fragment transgene encodes a hyperglycosylated NI-202 (10D12) 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: L121N (heavy chain), Q159N or Q159S (light chain), and/or E194N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0280] In certain embodiments, the anti-SOD1 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six NI-202 (10D12) CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 7A 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-SOD1 antibody or antigen-binding fragment thereof.

[0281] In certain embodiments, the anti-SOD1 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of NI-204 (12G7) (having amino acid sequences of SEQ ID NOs. 23 and 24, respectively, see Table 5 and FIG. 7B). 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: 93 (encoding the NI-202 (12G7) heavy chain Fab portion) and SEQ ID NO: 94 (encoding the NI-202 (12G7) 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0282] 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-SOD1-antigen binding domain has a heavy chain Fab fragment of SEQ ID NO: 23 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPEAAGG (SEQ ID NO: 210), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPEAAGGPSVFL (SEQ ID NO: 212) or EPKSCDKTHLCPPCPAPEAAGGPSVFL (SEQ ID NO: 213) as set forth in FIG 7B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 93 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 93). 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., an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0283] In certain embodiments, the anti-SOD1 antigen-binding fragment transgene encodes an SOD1 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: 24. In certain embodiments, the anti-SOD1 antigen-binding fragment transgene encodes an SOD1 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: 23. In certain embodiments, the anti-SOD1 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: 24 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: 23. In specific embodiments, the SOD1 antigen binding fragment

comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 23 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. 7B) 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. 20A. In specific embodiments, the SOD1 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 24 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. 7B) 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. 20B.

[0284] In certain embodiments, the anti-SOD1 antigen-binding fragment transgene encodes a hyperglycosylated NI-202 (12G7) Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 23 and 24, respectively, with one or more of the following mutations: L118N (heavy chain) and/or Q196N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0285] In certain embodiments, the anti-SOD1 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six NI-202 (12G7) CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 7B 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-SOD1 antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0286] Provided are methods of treating human subjects for AD or ALS by administration of a viral vector containing a transgene encoding an anti-SOD1 antibody, or antigen binding fragment thereof. The antibody may be NI-202 and is, e.g., a Fab fragment thereof, or other antigen-binding fragment thereof. In certain embodiments, the patient has been diagnosed with and/or has symptoms

associated with prodromal AD, *e.g.,* a mild cognitive impairment associated with early AD or even pre-AD, or ALS.

[0287] Recombinant vectors used for delivering the transgene are described in Section 5.4.1. Such vectors should have a tropism for human CNS cells and can include non-replicating rAAV, particularly those bearing an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid. The recombinant vectors can be administered in any manner such that the recombinant vector enters the CNS, e.g., by introducing the recombinant vector into the cerebral spinal fluid (CSF). See Section 5.5.1 for details regarding the methods of treatment.

[0288] Subjects to whom such gene therapy is administered can be those responsive to anti-SOD1 therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with AD or ALS, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-SOD1 antibody or considered a good candidate for therapy with an anti-SOD1 antibody. In specific embodiments, the patients have previously been treated with NI-202 and have been found to be responsive to NI-202. To determine responsiveness, the anti-SOD1 antibody or antigen-binding fragment transgene product (e.g., produced in human cell culture, bioreactors, etc.) may be administered directly to the subject.

Human Post Translationally Modified Antibodies

[0289] The production of the anti-SOD1 HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of AD or ALS accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-SOD1 HuPTM Fab, intrathecally, particularly intracisternal or lumbar administration, or intravenous administration to human subjects (patients) diagnosed with or having one or more symptoms of AD or ALS, to create a permanent depot in the CNS that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced CNS cells.

[0290] The cDNA construct for the anti-SOD1 HuPTMmAb or anti-SOD1 HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced CNS cells. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146).

[0291] As an alternative, or an additional treatment to gene therapy, the anti-SOD1 HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with AD or ALS, or for whom therapy for AD or ALS is considered appropriate.

[0292] In specific embodiments, the anti-SOD1 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 NI-202 (10D12) as set forth in FIG. 7A (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N110 and/or N168 of the heavy chain (SEQ ID NO: 21) or Q99, N157 and/or N209 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 NI-204 has a sulfation group at Y94 of the heavy chain (SEQ ID NO: 21) or Y85 and/or Y86 of the light chain (SEQ ID NO: 22). In other embodiments, the anti-SOD1 HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0293] In specific embodiments, the anti-SOD1 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 NI-202 (12G7) as set forth in FIG. 7B (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N110 and/or N168 of the heavy chain (SEQ ID NO: 23) or Q99, N157 and/or N209 of the light chain (SEQ ID NO: 24). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of NI-204 has a sulfation group at Y94 of the heavy chain (SEQ ID NO: 23) or Y85 and/or Y86 of the light chain (SEQ ID NO: 24). In other embodiments, the anti-SOD1 HuPTM mAb or antigen-binding fragment

thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0294] In certain embodiments, the HuPTM mAb or Fab is therapeutically effective and is at least 0.5%, 1% or 2% 2,6 sialylated and/or sulfated and may be at least 5%, 10% or even 50% or 100% glycosylated 2,6 sialylation and/or sulfated. The goal of gene therapy treatment provided herein is to slow or arrest the progression of AD or ALS. In the case of AD, efficacy may be monitored by measuring a reduction in plaque formation and/or an improvement in cognitive function or a reduction in the decline in cognitive function. In the case of ALS, efficacy may be monitored by measuring an improvement in speech and/or a reduction of clumsiness, abnormal limb fatigue, and/or muscle cramps and twitches.

[0295] Combinations of delivery of the anti-SOD1 HuPTM mAb or antigen-binding fragment thereof, to the CNS 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 AD that could be combined with the gene therapy provided herein include but are not limited to ARICEPT® (donepezil), RAZADYNE® (galantamine), NAMENDA® (rivastigmine), and NAMZARIC® (donepezil and memantine), to name a few, and administration with anti-SOD1 agents, including but not limited to NI-204. Available treatments for ALS that could be combined with the gene therapy provided herein include but are not limited to RILUTEK® (riluzole), RADICAVA® (edaravone), TIGLUTIK® (riluzole), and NUDEXTRA® (dextromethorphan HBr and quinidine sulfate), to name a few, and administration with anti-SOD1 agents, including but not limited to NI-204.

5.3.7. Anti-CGRPR HuPTM Constructs and Formulations for Migraines and Cluster Headaches.

[0296] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to calcitonin gene-related peptide

receptor (CGRPR) that may have benefit in treating migraines and cluster headaches (referred to collectively as headache disorders). In certain embodiments, the HuPTM mAb is eptinezumab, fremanezumab, galcanezumab or an antigen binding fragment of one of the foregoing. The amino acid sequences of Fab fragments of these antibodies are provided in FIGS. 8A-C. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an CGRPR-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of, migraines and cluster headaches, to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0297] 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 CGRPR 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 CGRPR, such as eptinezumab, fremanezumab, galcanezumab or variants thereof as detailed herein or in accordance with the details herein. The transgene may also encode anti-CGRPR antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al., 2016, mAbs 8: 99-112 which is incorporated by reference herein in its entirety).

[0298] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of eptinezumab (having amino acid sequences of SEQ ID NOs. 25 and 26, respectively, see Table 5 and FIG 8A). 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: 95 (encoding the eptinezumab heavy chain Fab portion) and SEQ ID NO: 96 (encoding the eptinezumab 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 CNS cells. The signal sequence may have the amino acid sequence of

MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0299] 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-CGRPR-antigen binding domain has a heavy chain Fab fragment of SEQ ID NO: 25 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 8A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 95 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 95). 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: 296 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0300] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes a CGRPR 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: 26. In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes a CGRPR 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: 25. In certain embodiments, the anti-CGRPR 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: 26 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: 25. In specific embodiments, the CGRPR antigen-binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 25 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. 8A) 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. 20A. In specific embodiments, the CGRPR antigen-binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 26 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. 8A) 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. 20B.

[0301] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes a hyperglycosylated eptinezumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 25 and 26, respectively, with one or more of the following mutations: L106N (heavy chain), Q165N or Q165S (light chain), and/or E200N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0302] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six eptinezumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 8A 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-CGRPR antibody or antigen-binding fragment thereof.

[0303] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of

fremanezumab (having amino acid sequences of SEQ ID NOs. 27 and 28, respectively, see Table 5 and FIG 8B). 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: 97 (encoding the fremanezumab heavy chain Fab portion) and SEQ ID NO: 98 (encoding the fremanezumab 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0304] In addition to the heavy and light chain variable domain and C_H1 and C_L 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-CGRPR-antigen binding domain has a heavy chain Fab fragment of SEQ ID NO: 27 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence ERKCCVECPPCPAPPVAG (SEQ ID NO: 220) or ERKCCVECPPCPA (SEQ ID NO: 221) as set forth in FIG 8B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 97 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 97). 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: 297 (Table 7) or an IgG2 Fc domain, such as SEQ ID No. 284 or as depicted in FIG. 23, 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.

[0305] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes a CGRPR 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: 28. In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes a CGRPR 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: 27. In certain embodiments, the anti-CGRPR 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: 28 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: 27. In specific embodiments, the CGRPR antigen-binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 27 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. 8B) 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. 20A. In specific embodiments, the CGRPR antigen-binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 28 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. 8B) 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. 20B.

[0306] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes a hyperglycosylated fremanezumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 27 and 28, respectively, with one or more of the following mutations: L117N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0307] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six fremanezumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 8B 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-CGRPR antibody or antigen-binding fragment thereof.

[0308] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of galcanezumab (having amino acid sequences of SEQ ID NOs. 29 and 30, respectively, see Table 5 and FIG. 8C). 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: 99 (encoding the galcanezumab heavy chain Fab portion) and SEQ ID NO: 100 (encoding the galcanezumab 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0309] 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-CGRPR-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 29 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence contains all or a portion of the amino acid sequence ESKYGPPCPPCPAPEAAGG (SEQ ID NO: 431) or ESKYGPPCPSCPAPEAAGG (SEQ ID NO: 432) as set forth in FIG 8C. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 99 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 99). 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: 298 (Table 7) or an IgG4 Fc domain, such as SEQ ID No. 285 or as depicted in FIG. 23, 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.

[0310] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes a CGRPR 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: 30. In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes a CGRPR 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: 29. In certain embodiments, the anti-CGRPR 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: 30 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: 29. In specific embodiments, the CGRPR antigen-binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 29 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. 8C) 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. 20A. In specific embodiments, the CGRPR antigen-binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 30 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. 8C) 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. 20B.

[0311] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes a hyperglycosylated galcanezumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 29 and 30, respectively, with one or more of the following mutations: T114N (heavy chain), Q160N or Q160S, and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0312] In certain embodiments, the anti-CGRPR antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six galcanezumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 8C 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-CGRPR antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0313] Provided are methods of treating human subjects for migraines and cluster headaches by administration of a viral vector containing a transgene encoding an anti-CGRPR antibody, or antigen binding fragment thereof. The antibody may be eptinezumab, fremanezumab, or galcanezumab and is, e.g., a Fab fragment thereof, or other antigen-binding fragment thereof or is a full length anti-CGRPR antibody with an Fc region. In certain embodiments, the patient has been diagnosed with and/or has symptoms associated with episodic migraines or chronic migraines. In certain embodiments, the patient has been diagnosed with and/or has symptoms associated with episodic cluster headaches or chronic cluster headaches. Recombinant vectors used for delivering the transgenes are described in Section 5.4.1 and shown in FIGS 8A-C. Such vectors should have a tropism for human CNS cells and can include non-replicating rAAV, particularly those bearing an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid. The recombinant vectors can be administered in any manner such that the recombinant vector enters the CNS, e.g., by introducing the recombinant vector into the cerebral spinal fluid (CSF). See Section 5.5.1 for details regarding the methods of treatment.

[0314] Subjects to whom such gene therapy is administered can be those responsive to anti-CGRPR therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with migraines or cluster headaches or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-CGRPR antibody or considered a good candidate for therapy with an anti-CGRPR antibody. In specific embodiments, the patients have previously been treated with eptinezumab, fremanezumab, or galcanezumab, and have been found to be responsive to

one or more of eptinezumab, fremanezumab, and galcanezumab. To determine responsiveness, the anti-CGRPR antibody or antigen-binding fragment transgene product (e.g., produced in human cell culture, bioreactors, etc.) may be administered directly to the subject.

Human Post Translationally Modified Antibodies

[0315] The production of the anti-CGRPR HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of migraines or cluster headaches accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-CGRPR HuPTM Fab, intrathecally, particularly intracisternal or lumbar administration, or intravenous administration to human subjects (patients) diagnosed with or having one or more symptoms of migraines or cluster headaches, to create a permanent depot in the CNS that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced CNS cells.

[0316] The cDNA construct for the anti-CGRPR HuPTM mAb or anti-CGRPR HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced CNS cells. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146).

[0317] As an alternative, or an additional treatment to gene therapy, the anti-CGRPR HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with migraines or cluster headaches, or for whom therapy for migraines or cluster headaches is considered appropriate.

[0318] In specific embodiments, the anti-CGRPR 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 eptinezumab as set forth in FIG. 8A (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions Q103 and/or N153 of the heavy chain (SEQ ID NO: 25) or N21, N163, and/or N215 of the light chain (SEQ ID NO: 26). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of

eptinezumab has a sulfation group at Y32, Y33 and/or Y93 of the heavy chain (SEQ ID NO: 25) and/or Y87 and/or Y88 of the light chain (SEQ ID NO: 26). In other embodiments, the anti-CGRPR HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0319] In specific embodiments, the anti-CGRPR 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 fremanezumab as set forth in FIG. 8B (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions Q114, N164, N197 and/or N206 of the heavy chain (SEQ ID NO: 27) or N93, Q100, N158, and/or N210 of the light chain (SEQ ID NO: 28). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of fremanezumab has a sulfation group at Y96, Y97 and/or Y203 of the heavy chain (SEQ ID NO: 27) or Y86 and/or Y87 of the light chain (SEQ ID NO: 28). In other embodiments, the anti-CGRPR HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0320] In specific embodiments, the anti-CGRPR 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 galcanezumab as set forth in FIG. 8C (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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions Q111, N161, and/or N203 of the heavy chain (SEQ ID NO: 29) or N158 and/or N210 of the light chain (SEQ ID NO: 30). Alternatively or in addition to, the HuPTM mAb or

antigen binding-fragment thereof with the heavy and light chain variable domain sequences of erenumab has a sulfation group at Y32 and/or Y33 and/or Y93 of the heavy chain (SEQ ID NO: 29) and/or Y86 and/or Y87 and/or Y92 of the light chain (SEQ ID NO: 30). In other embodiments, the anti-CGRPR HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0321] In certain embodiments, the HuPTM mAb or Fab is therapeutically effective and is at least 0.5%, 1% or 2% 2,6 sialylated and/or sulfated and may be at least 5%, 10% or even 50% or 100% glycosylated 2,6 sialylation and/or sulfated. The goal of gene therapy treatment provided herein is to prevent or reduce the intensity or frequency of migraines, cluster headaches, or one or more of the symptoms associated therewith, including nausea, light sensitivity, sound sensitivity, red eye, eyelid edema, forehead and facial sweating, tearing (lacrimation), abnormal small size of the pupil (miosis), nasal congestion, runny nose (rhinorrhea), and drooping eyelid (ptosis). Efficacy may be monitored by measuring a reduction in the intensity or frequency of migraines or cluster headaches, or a reduction in the amount of acute migraine-specific medication used over a defined period of time.

[0322] Combinations of delivery of the anti-CGRPR HuPTM mAb or antigen-binding fragment thereof, to the CNS 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 cluster headaches or migraines that could be combined with the gene therapy provided herein include but are not limited to triptans, ergotamine derivatives and NSAIDs, to name a few, and administration with anti-CGRPR agents, including but not limited to eptinezumab, fremanezumab, and galcanezumab.

5.3.8. Anti-VEGF, anti-EPOR, anti-Aβ and anti-kallikrein HuPTM Constructs and Formulations for Ocular Disorders

[0323] Compositions and methods are described for the delivery of HuPTM mAb and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to vascular endothelial growth factor (VEGF), erythropoietin receptor (EPOR), Aβ peptides derived from the amyloid precursor protein, or

kallikrein, respectively, indicated for treating one or more retinal disorders including diabetic retinopathy, myopic choroidal neovascularization (mCNV), macular degeneration (e.g., neovascular (wet) or dry age-related macular degeneration (nAMD)), macular edema (e.g., macular edema following a retinal vein occlusion (RVO) or diabetic macular edema (DME)). In certain embodiments, the HuPTM mAb has the amino acid sequence of sevacizumab, LKA-651, GSK933776, lecanemab, or lanadelumab, or an antigen binding fragment of one of the foregoing. The amino acid sequences of Fab fragments of sevacizumab, LKA-651, solanezumab, GSK933776, lecanemab, and lanadelumab are provided in FIGS. 9A-C, 2A-C, and 19, respectively. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding a VEGF-binding, EPOR-binding, Aβ-binding, or kallikrein-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof, including an scFv) to patients (human subjects) diagnosed with, or having one or more symptoms of a retinal disorder (e.g. diabetic retinopathy, mCNV, macular degeneration, or macular edema) to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0324] 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 VEGF, EPOR, Aβ or kallikrein, 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 VEGF, EPOR, Aβ, or kallikrein, such as sevacizumab, LKA-651, solanezumab, lecanemab, GSK933776, or lanadelumab, or variants thereof, as detailed herein. The transgene may also encode an anti-VEGF, anti-EPOR, anti- Aβ, anti-kallikrein antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0325] In certain embodiments, the anti-VEGF antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of sevacizumab (having amino acid sequences of SEQ ID NOs. 31 and 32, respectively, see Table 5 and FIG. 9A). 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: 101 (encoding the sevacizumab

heavy chain Fab portion) and SEQ ID NO: 102 (encoding the sevacizumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0326] 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-VEGF antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 31 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200), or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 9A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 101 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 101). 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: 299 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0327] In certain embodiments, the anti-VEGF antigen-binding fragment transgene encodes an VEGF 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: 32. In certain embodiments, the anti-VEGF antigen-

binding fragment transgene encodes an VEGF 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: 31. In certain embodiments, the anti-VEGF 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: 32 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: 31. In specific embodiments, the VEGF antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 31 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. 9A) 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. 20A. In specific embodiments, the VEGF antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 32 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. 9A) 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. 20B.

[0328] In certain embodiments, the anti-VEGF antigen-binding fragment transgene encodes a hyperglycosylated sevacizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 31 and 32, respectively, with one or more of the following mutations: L117N (heavy chain), Q165N or Q165S (light chain), and/or E200N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0329] In certain embodiments, the anti-VEGF antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six sevacizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 9A 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-VEGF antibody or antigen-binding fragment thereof.

[0330] In certain embodiments, the anti-EPOR antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of LKA-651 (NVS2) (having amino acid sequences of SEQ ID NOs. 33 and 34, respectively, see Table 5 and FIG. 9B). 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: 103 (encoding the LKA-651 (NVS2) heavy chain Fab portion) and SEQ ID NO: 104 (encoding the LKA-651 (NVS2) 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0331] 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-EPOR antigen binding domain has a heavy chain variable domain of SEQ ID NO: 33 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200), or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 9B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 103 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 103). 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., an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0332] In certain embodiments, the anti-EPOR antigen-binding fragment transgene encodes an EPOR 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: 34. In certain embodiments, the anti-EPOR antigen-binding fragment transgene encodes an EPOR 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: 33. In certain embodiments, the anti-EPOR 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: 34 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: 33. In specific embodiments, the EPOR antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 33 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. 9B) 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. 20A. In specific embodiments, the EPOR antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 34 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. 9B) 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. 20B.

[0333] In certain embodiments, the anti-EPOR antigen-binding fragment transgene encodes a hyperglycosylated LKA-651 (NVS2) Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 33 and 34, respectively, with one or more of the following mutations: L112N (heavy chain) and/or Q195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0334] In certain embodiments, the anti-EPOR antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six LKA-651 (NVS3) CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 9C 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-EPOR antibody or antigen-binding fragment thereof.

[0335] In certain embodiments, the anti-EPOR antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of LKA-651 (NVS3) (having amino acid sequences of SEQ ID NOs. 35 and 36, respectively, see Table 5 and FIG. 9C). 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: 105 (encoding the LKA-651 (NVS3) heavy chain Fab portion) and SEQ ID NO: 106 (encoding the LKA-651 (NVS3) 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0336] 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-EPOR antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 35 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200), or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 9C. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 105 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 105). 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. an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0337] In certain embodiments, the anti-EPOR antigen-binding fragment transgene encodes an EPOR 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: 36. In certain embodiments, the anti-EPOR antigen-binding fragment transgene encodes an EPOR 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: 35. In certain embodiments, the anti-EPOR 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: 36 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: 35. In specific embodiments, the EPOR antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 35 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. 9C) 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. 20A. In specific embodiments, the EPOR antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 36 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. 9C) 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. 20B.

[0338] In certain embodiments, the anti-EPOR antigen-binding fragment transgene encodes a hyperglycosylated LKA-651 (NVS3) Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 35 and 36, respectively, with one or more of the following mutations: L122N (heavy chain) and/or Q195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0339] In certain embodiments, the anti-EPOR antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six LKA-651 (NVS3) CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 9C 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-EPOR antibody or antigen-binding fragment thereof.

[0340] In certain embodiments, the anti-Aβ antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of solanezumab (having amino acid sequences of SEQ ID NOs. 1 and 2, respectively, see Table 5 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: 71 (encoding the solanezumab heavy chain Fab portion) and SEQ ID NO: 72 (encoding the solanezumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of

MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0341] In addition to the Fab fragments, including the heavy and light chain variable domain sequences and C_L C_H1, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 sequence, all or a portion of the hinge region. In specific embodiments, the anti-Aβ-antigen binding domain has a heavy chain variable domain and C_H1 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 2A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 71 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 71). 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. an IgG1 Fc domain, such as SEQ ID NO: 290 of Table 7, SEQ ID No. 283 or as depicted in FIG. 23, 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*.

[0342] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes an Aβ 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-Aβ antigen-binding fragment transgene encodes an Aβ 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-Aβ 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 Aβ 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 for example, in the framework regions (*e.g.,* those regions outside of the CDRs, which CDRs are underlined in FIG. 2A) 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. 20A. In specific embodiments, the Aβ 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 for example, in the framework regions (*e.g.,* those regions outside of the CDRs, which CDRs are underlined in FIG. 2A) 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. 20B.

[0343] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes a hyperglycosylated solanezumab 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: L107N (heavy chain), Q165N or Q165S (light chain), and/or E200N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0344] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six solanezumab 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-Aβ antibody or antigen-binding fragment thereof.

[0345] In certain embodiments, the anti-Aβ antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of GSK933776 (having amino acid sequences of SEQ ID NOs. 3 and 4, respectively, see Table 5 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: 73 (encoding the GSK933776 heavy chain Fab portion) and SEQ ID NO: 74 (encoding the GSK933776 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0346] 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-Aβ-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 EPKSCDKTHTCPPCPAPELAGA (SEQ ID NO: 202), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELAGAPSVFL (SEQ ID NO: 204) or EPKSCDKTHLCPPCPAPELAGAPSVFL (SEQ ID NO: 205) as set forth in FIG. 2B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 73 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 73). 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: 291 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0347] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes an Aβ 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-Aβ antigen-binding fragment transgene encodes an Aβ 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-Aβ 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 Aβ 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. 20A. In specific embodiments, the Aβ 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, 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 light chain of one or more of the other therapeutic antibodies, for example, as identified by the alignment in FIG. 20B.

[0348] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes a hyperglycosylated GSK933776 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: L110N (heavy chain), Q165N or Q165S (light chain), and/or E200N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0349] In certain embodiments, the anti-Aβ antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six GSK933776 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-Aβ antibody or antigen-binding fragment thereof.

[0350] The anti-kallikrein constructs and HuPTM mAbs and HuPTM Fabs are described in detail in Section 5.3.18, *infra*. Provided are transgenes for expression of the anti-kallikrein antibody lanadelumab, sequences of which are provided in Table 8.

Gene Therapy Methods

[0351] Provided are methods of treating human subjects for one or more retinal disorders (such as diabetic retinopathy, mCNV, macular degeneration, or macular edema) by administration of a viral vector containing a transgene encoding an anti-VEGF antibody or antigen binding fragment thereof. The antibody may be sevacizumab or a Fab fragment thereof or any antigen binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with one or more of the various retinal disorders listed above.

[0352] Also, provided are methods of treating human subjects for one or more retinal disorders (such as diabetic retinopathy, mCNV, macular degeneration, or macular edema) by administration of a viral vector containing a transgene encoding an anti-EPOR antibody or antigen binding fragment thereof. The antibody may be LKA-651, or a Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with one or more of the various retinal disorders listed above.

[0353] Further provided are methods of treating human subjects for dry AMD degeneration by administration of a viral vector containing a transgene encoding an anti-Aβ antibody or antigen binding fragment thereof. The antibody or Fab fragment thereof may be solanezumab, lecanemab, or

GSK933776. In embodiments, the patient has been diagnosed with and/or has symptoms associated with dry AMD.

[0354] Provided are methods of treating human subjects for diabetic retinopathy or diabetic macular edema by administration of a viral vector containing a transgene encoding an anti-kallikrein antibody or antigen binding fragment thereof. The antibody may be lanadelumab, or a Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with one or more of the various retinal disorders listed above. In specific embodiments, the transgene is a lanadelumab coding transgene in Table 8.

[0355] Recombinant vector used for delivering the transgene are described in Section 5.4.3. Such vectors should have a tropism for human retina-type cells and can include non-replicating rAAV, particularly those bearing an AAV8 capsid. Alternatively, vectors bearing an AAV2.7m8 capsid can be used for ocular indications. The recombinant vectors, such as the ones shown in FIGS. 9A-C, 2A-C and 19, can be administered in any manner such that the recombinant vector enters the retina, e.g., by introducing the recombinant vector into the eye. See Section 5.5.3 for details regarding the methods of treatment.

[0356] Subjects to whom such gene therapy is administered can be those responsive to anti-VEGF, anti-EPOR, anti-Aβ or anti-kallikrein antibodies. In certain embodiments, the methods encompass treating patients who have been diagnosed with one or more retinal disorders, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-VEGF, anti-EPOR, anti-Aβ or anti-kallikrein antibody or considered a good candidate for therapy with an anti-VEGF, anti-EPOR, anti- Aβ or anti-kallikrein antibody. In specific embodiments, the patients have previously been treated with sevacizumab, LKA-651, solanezumab, lecanemab, GSK933776 or lanadelumab and have been found to be responsive to sevacizumab, LKA-651, solanezumab, lecanemab, GSK933776 or lanadelumab. To determine responsiveness, the anti-VEGF, anti-EPOR, anti-Aβ or anti-kallikrein, 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

[0357] The production of the anti-VEGF, anti-EPOR, anti-Aβ or anti-kallikrein HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of one or more retinal disorders accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-VEGF, anti-EPOR, anti-Aβ, anti-kallikrein HuPTM Fab, subretinally, intravitreally, or suprachoroidally to human subjects (patients) diagnosed with or having one or more symptoms of one or more retinal disorders, to create a permanent depot in the retina that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced cells of the retina.

[0358] As an alternative, or an additional treatment to gene therapy, the anti-VEGF, anti-EPOR, anti-Aβ or anti-kallikrein HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology and administered to patients diagnosed with a retinal disorder for whom therapy for a retinal disorder is considered appropriate.

[0359] In specific embodiments, the anti-VEGF 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 sevacizumab as set forth in FIG. 9A (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 N32 and/or N164 of the heavy chain (SEQ ID NO: 31) or N22, N163, and/or N215 of the light chain (SEQ ID NO: 32). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of sevacizumab has a sulfation group at Y95 of the heavy chain (SEQ ID NO: 31) and/or Y88 and/or Y89 of the light chain (SEQ ID NO: 32). In other embodiments, the anti-VEGF HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0360] In specific embodiments, the anti-EPOR 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 LKA-651 (NVS2) as set forth in FIG. 9B (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 Q109 and/or N159 of the heavy chain (SEQ ID NO: 33) or N68 and/or N171 of the light chain (SEQ ID NO: 34). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of LKA-651 (NVS2) has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 33) and/or Y85, Y86, and/or Y96 of the light chain (SEQ ID NO: 34). In other embodiments, the anti-EPOR HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0361] In specific embodiments, the anti-EPOR 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 LK-651 (NVS3) as set forth in FIG. 9C (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 N32, N80, and/or N169 of the heavy chain (SEQ ID NO: 35) or N68 and/or N171 of the light chain (SEQ ID NO: 36). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of LKA-651 (NVS3) has a sulfation group at Y97 and/or Y98 of the heavy chain (SEQ ID NO: 35) and/or Y30, Y31, Y85 and/or Y86 of the light chain (SEQ ID NO: 36). In other embodiments, the anti-EPOR HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0362] In specific embodiments, the anti-Aβ 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 solanezumab 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 glycosylation, particularly a 2,6-sialylation, at one or more

of the amino acid positions N56, Q104, and/or N154 of the heavy chain (SEQ ID NO:1) or Q105, N163 and/or N215 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 solanezumab has a sulfation group at Y94, Y95 and/or Y101 of the heavy chain (SEQ ID NO: 1) or Y91 and/or Y92 of the light chain (SEQ ID NO: 2). In other embodiments, the anti-Aβ HuPTM mAb or antigen-binding fragment thereof does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) NeuGc moieties and/or does not contain any detectable (*e.g.*, as detected by assays known in the art, for example, those described in section 5.2, *infra*) alpha-Gal moieties. In certain embodiments, the anti-Aβ-HuPTM mAb is a full length mAb with an Fc region, e.g., the Fc domain of SEQ ID NO: 283, SEQ ID NO: 284 or SEQ ID NO: 285, or a mutant or variant thereof.

[0363] In specific embodiments, the anti-Aβ 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 GSK933776 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 glycosylation, particularly a 2,6-sialylation, at one or more of the amino acid positions N32, Q107, and/or N157 of the heavy chain (SEQ ID NO: 3) or N163 and/or N215 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 GSK933776 has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 3) or Y91 and/or Y92 of the light chain (SEQ ID NO: 4). In other embodiments, the anti-Aβ 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.

[0364] 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 a retinal disorder, and/or to suppress angiogenesis. In the case of retinal disorders, efficacy may be monitored by monitoring vision acuity. For example, efficacy can be monitored by

assessing change in vision acuity from baseline. (see, e.g., U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf. Published May 2007. Accessed October 13, 2017; Oncology Endpoints in a Changing Landscape. Manag. Care. 2016; 1(suppl):1-12).

[0365] Combinations of delivery of the anti-VEGF, anti-EPOR, or anti-Aβ HuPTM mAb or antigen-binding fragment thereof to the retina 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 diabetic retinopathy, mCNV, macular degeneration, or macular edema that could be combined with the gene therapy provided herein include but are not limited to laser photocoagulation, photodynamic therapy with verteporfin, aflibercept, and/or intravitreal steroids and administration with anti-VEGF, anti-EPOR, anti-Aβ agents, including but not limited to sevacizumab, LKA-651 (NVS2), LKA-651 (NVS3), solanezumab, lecanemab, or GSK933776.

5.3.9. Anti-ALK1, Anti-C5, and Anti-Endoglin HuPTM Constructs and Formulations for Ocular Disorders

[0366] Compositions and methods are described for the delivery of HuPTM mAb and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to activin receptor like kinase 1 (ALK1), complement component 5 (C5), or anti-endoglin (ENG), respectively, indicated for treating one or more ocular disorders including retinal diseases caused by increased neovascularization, for example, nAMD (also known as "wet" AMD), dry AMD, retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy (DR), or non-infectious uveitis In certain embodiments, the HuPTM mAb has the amino acid sequence of ascrinvacumab, tesidolumab, ravulizumab, carotuximab, or an antigen binding fragment of one of the foregoing. The amino acid sequences of Fab fragments of ascrinvacumab, tesidolumab, ravulizumab, and carotuximab are provided in FIGS. 10A-D, respectively. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding a ALK1-binding, C5-binding, or ENG-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative,

thereof, including an scFv) to patients (human subjects) diagnosed with, or having one or more symptoms of a ocular disorder (e.g. macular degeneration or macular uveitis) to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0367] 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 ALK1, C5, or ENG 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 ALK1, C5, or ENG, such as ascrinvacumab, tesidolumab, ravulizumab, carotuximab, or variants thereof as detailed herein. The transgene may also encode an anti-ALK1, anti-C5, or anti-ENG antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0368] In certain embodiments, the anti-ALK1 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of ascrinvacumab (having amino acid sequences of SEQ ID NOs. 37 and 38, respectively, see Table 5 and FIG. 10A). 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: 107 (encoding the ascrinvacumab heavy chain Fab portion) and SEQ ID NO: 108 (encoding the ascrinvacumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0369] 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-ALK1 antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 37 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence contains all or a portion of the amino acid sequence ERKCCVECPPCPAPPVAG (SEQ ID NO: 220) or ERKCCVECPPCPA (SEQ ID NO: 221) as set forth in FIG 10A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 107 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 107). 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; 300 (Table 7) or an IgG2 Fc domain, such as SEQ ID No. 284 or as depicted in FIG. 23, 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.

[0370] In certain embodiments, the anti-ALK1 antigen-binding fragment transgene encodes an ALK1 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: 38. In certain embodiments, the anti-ALK1 antigen-binding fragment transgene encodes an ALK1 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: 37. In certain embodiments, the anti-ALK1 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: 38 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: 37. In specific embodiments, the ALK1 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 37 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. 10A) 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. 20A. In specific embodiments, the ALK1 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 38 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. 10A) 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. 20B.

[0371] In certain embodiments, the anti-ALK1 antigen-binding fragment transgene encodes a hyperglycosylated ascrinvacumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 37 and 38, respectively, with one or more of the following mutations: L113N (heavy chain), Q161N or Q161S (light chain), and/or E196N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0372] In certain embodiments, the anti-ALK1 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six ascrinvacumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 10A 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-ALK1 antibody or antigen-binding fragment thereof.

[0373] In certain embodiments, the anti-C5 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of tesidolumab (having amino acid sequences of SEQ ID NOs. 39 and 40, respectively, see Table 5 and FIG. 10B). 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: 109 (encoding the tesidolumab heavy chain Fab portion) and SEQ ID NO: 110 (encoding the tesidolumab 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, one or more cells

forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0374] 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-C5 antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 39 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPEAAGG (SEQ ID NO: 210), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPEAAGGPSVFL (SEQ ID NO: 212), or EPKSCDKTHLCPPCPAPEAAGGPSVFL (SEQ ID NO: 213) as set forth in FIG 10B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 109 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 109). 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: 301 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0375] In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes an C5 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: 40. In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes an C5 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: 39. In certain embodiments,

the anti-C5 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: 40 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: 39. In specific embodiments, the C5 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 39 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. 10B) 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. 20A. In specific embodiments, the C5 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 40 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. 10B) 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. 20B.

[0376] In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes a hyperglycosylated tesidolumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 39 and 40, respectively, with one or more of the following mutations: L111N (heavy chain) and/or Q196N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0377] In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six tesidolumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 10B 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-C5 antibody or antigen-binding fragment thereof.

[0378] In certain embodiments, the anti-ENG antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of carotuximab (having amino acid sequences of SEQ ID NOs. 41 and 42, respectively, see Table 5 and FIG. 10C). 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: 111 (encoding the carotuximab heavy chain Fab portion) and SEQ ID NO: 112 (encoding the carotuximab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0379] 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-ENG antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 41 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200), or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 10C. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 111 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 111). 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: 302 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0380] In certain embodiments, the anti-ENG antigen-binding fragment transgene encodes an ENG 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: 42. In certain embodiments, the anti-ENG antigen-binding fragment transgene encodes an ENG 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: 41. In certain embodiments, the anti-ENG 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: 42 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: 41. In specific embodiments, the ENG antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 41 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, e.g., are made in the framework regions (*e.g.,* those regions outside of the CDRs, which CDRs are underlined in FIG. 10C) 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. 20A. In specific embodiments, the ENG antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 42 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. 10C) 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. 20B.

[0381] In certain embodiments, the anti-ENG antigen-binding fragment transgene encodes a hyperglycosylated carotuximab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 41

and 42, respectively, with one or more of the following mutations: T113N (heavy chain), Q159N or Q159S (light chain), and/or E194N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0382] In certain embodiments, the anti-ENG antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six carotuximab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 10C 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-ENG antibody or antigen-binding fragment thereof.

[0383] In certain embodiments, the anti-C5 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of ravulizumab (having amino acid sequences of SEQ ID NOs. 362 and 363, respectively, see Table 5 and FIG 10D). 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: 378 (encoding the ravulizumab heavy chain Fab portion) and SEQ ID NO: 379 (encoding the ravulizumab 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 CNS cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or the one of the sequences found in Table 2 *supra*.

[0384] In addition to the Fab fragments, including the heavy and light chain variable domain sequences and C_L C_H1, the transgenes may comprise, at the C-terminus of the heavy chain C_H1 sequence, all or a portion of the hinge region. In specific embodiments, the anti-C5-antigen binding domain has a heavy chain variable domain and C_H1 domain of SEQ ID NO: 362 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence ERKCCVECPPCPAPPVAG (SEQ ID NO: 220) or ERKCCVECPPCPA (SEQ ID NO: 221) as set forth in FIG 10D. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 378 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 378). 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. an IgG2 Fc domain, such as SEQ ID NO: 393 of Table 7, SEQ ID No. 284 or as depicted in FIG. 23, 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*.

[0385] In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes an C5 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: 363. In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes an C5 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: 362. In certain embodiments, the anti-C5 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: 363 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: 362. In specific embodiments, the C5 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 362 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. 10D) 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. 20A. In specific embodiments, the C5 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 363 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. 10D) 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. 20B.

[0386] In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes a hyperglycosylated ravulizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 362 and 363, respectively, with one or more of the following mutations: L117N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0387] In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six ravulizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 10D 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-C5 antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0388] Provided are methods of treating human subjects for one or more ocular disorders by administration of a viral vector containing a transgene encoding an anti-ENG, anti-C5, or anti-ALK1 antibody or antigen binding fragment thereof. The antibody or Fab fragment thereof may be ascrinvacumab, tesidolumab, ravulizumab, or carotuximab. In embodiments, the patient has been diagnosed with and/or has symptoms associated with one or more of the various ocular disorders listed above. Recombinant vector used for delivering the transgene are described in Section 5.4.3. Such vectors should have a tropism for human retina-type cells and can include non-replicating rAAV, particularly those bearing an AAV8 capsid. Alternatively, vectors bearing an AAV2.7m8 or AAV9 capsid can be used for ocular indications. The recombinant vectors, such as the ones shown in FIGS. 10A-D, can be administered in any manner such that the recombinant vector enters the retina, e.g., by introducing the recombinant vector into the eye. See Section 5.5.3 for details regarding the methods of treatment.

[0389] Subjects to whom such gene therapy is administered can be those responsive to anti-ALK1, anti-C5, or anti-ENG. In some embodiments, the methods encompass treating patients who have been diagnosed with one or more retinal disorders or, in the case of an anti-C5 antibody, non-

infectious uveitis, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-ALK1, anti-C5, or anti-ENG antibody or considered a good candidate for therapy with an anti-ALK1, anti-C5, or anti-ENG antibody. In specific embodiments, the patients have previously been treated with ascrinvacumab, tesidolumab, ravulizumab, or carotuximab and have been found to be responsive to ascrinvacumab, tesidolumab, ravulizumab, or carotuximab. To determine responsiveness, the anti-ALK1, anti-C5, or anti-ENG 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

[0390] The production of the anti-ALK1, anti-C5, or anti-ENG HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of one or more retinal disorders, or in the of case those derived from anti-C5 for the treatment of non-infectious uveitis, accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-ALK1, anti-C5, or anti-ENG HuPTM Fab, subretinally, intravitreally, or suprachoroidally to human subjects (patients) diagnosed with or having one or more symptoms of one or more retinal disorders or non-infectious uveitis, to create a permanent depot in the retina that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced cells of the retina.

[0391] As an alternative, or an additional treatment to gene therapy, the anti-ALK1, anti-C5, or anti-ENG HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology and administered to patients diagnosed with a retinal or ocular disorder for whom therapy for a retinal or ocular disorder is considered appropriate.

[0392] In specific embodiments, the anti-ALK1 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 ascrinvacumab as set forth in FIG. 10A (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 N62, N78, Q110, N160, N193, and/or N202 of the heavy chain (SEQ

ID NO: 37) or Q101, N159, and/or N211 of the light chain (SEQ ID NO: 38). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of ascrinvacumab has a sulfation group at Y95, Y96, and/or Y199 of the heavy chain (SEQ ID NO: 37) and/or Y87 and/or Y88 of the light chain (SEQ ID NO: 38). In other embodiments, the anti-ALK1 HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0393] In specific embodiments, the anti-C5 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 tesidolumab as set forth in FIG. 10B (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 N59, Q108, and/or N158 of the heavy chain (SEQ ID NO: 39) or N68, N95, and/or N172 of the light chain (SEQ ID NO: 40). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of tesidolumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 39) and/or Y30, Y85, and/or Y86 of the light chain (SEQ ID NO: 40). In other embodiments, the anti-C5 HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0394] In specific embodiments, the anti-C5 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 ravulizumab as set forth in FIG. 10D (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 N63, N106, Q114, N164, N197, and/or N206 of the heavy chain (SEQ ID NO: 362) or N28, Q100, N158, and/or N210 of the light chain (SEQ ID NO: 363). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of ravulizumab has a sulfation group at Y94 and/or Y95 of

the heavy chain (SEQ ID NO: 362) and/or Y86 and/or Y86 of the light chain (SEQ ID NO: 363). In other embodiments, the anti-C5 HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0395] In specific embodiments, the anti-ENG 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 carotuximab as set forth in FIG. 10C (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 Q110 and/or N160 of the heavy chain (SEQ ID NO: 41) or N52, N93, N157, and/or N209 of the light chain (SEQ ID NO: 42). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of carotuximab has a sulfation group at Y95 and/or Y96 of the heavy chain (SEQ ID NO: 41) and/or Y85 and/or Y86 of the light chain (SEQ ID NO: 42). In other embodiments, the anti-ENG HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0396] 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 an ocular disorder. In the case of retinal disorders, efficacy may be monitored by monitoring vision acuity. For example, efficacy can be monitored by assessing change in vision acuity. In the case of uveitis, efficacy may be monitored by monitoring vision acuity, redness of the eye, sensitivity to light, and/or eye pain. For example, efficacy can be monitored by assessing change in vision acuity, redness of the eye, sensitivity to light, and/or eye pain from baseline.

[0397] Combinations of delivery of the anti-ALK1, anti-C5, or anti-ENG HuPTM mAb or antigen-binding fragment thereof to the retina 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 macular degeneration that could be combined with the gene therapy provided herein include but are not limited to laser photocoagulation, photodynamic therapy with verteporfin, aflibercept, anti-VEGF agents, and/or intravitreal steroids and administration with anti-ALK1, anti-C5, or anti-ENG agents, including but not limited to ascrinvacumab, tesidolumab, ravulizumab, or carotuximab. In the case of uveitis, available treatments for a subject 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-ALK1, anti-C5, or anti-ENG agents, including but not limited to ascrinvacumab, tesidolumab, ravulizumab, or carotuximab.

5.3.10. Anti-CC1Q HuPTM Constructs and Formulations for Glaucoma

[0398] Compositions and methods are described for the delivery of HuPTM mAb and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to complement component 1Q (CC1Q) indicated for treating glaucoma. In certain embodiments, the HuPTM mAb has the amino acid sequence of ANX-007 or an antigen binding fragment of the foregoing. The amino acid sequence of Fab fragments of ANX-007 are provided in FIG. 11. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding a CC1Q-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof, including an scFv) to patients (human subjects) diagnosed with, or having one or more symptoms of glaucoma to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0399] 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 CC1Q 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 CC1Q, such as ANX-007, or variants thereof as detailed herein. The transgene may also encode an anti-CC1Q antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0400] In certain embodiments, the anti-CC1Q antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of ANX-007 (having amino acid sequences of SEQ ID NOs. 43 and 44, respectively, see Table 5 and FIG. 11). 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: 113 (encoding the ANX-007 heavy chain Fab portion) and SEQ ID NO: 114 (encoding the ANX-007 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0401] 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-CC1Q antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 43 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200), or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 11. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 113 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 113). 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. an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0402] In certain embodiments, the anti-CC1Q antigen-binding fragment transgene encodes an CC1Q 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: 44. In certain embodiments, the anti-CC1Q antigen-binding fragment transgene encodes an CC1Q 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: 43. In certain embodiments, the anti-CC1Q 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: 44 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: 43. In specific embodiments, the CC1Q antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 43 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. 11) 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. 20A. In specific embodiments, the CC1Q antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 44 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. 11) 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. 20B.

[0403] In certain embodiments, the anti-CC1Q antigen-binding fragment transgene encodes a hyperglycosylated ANX-007 Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 43 and 44, respectively, with one or more of the following mutations: T116N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0404] In certain embodiments, the anti-CC1Q antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six ANX-007 CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 11 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-CC1Q antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0405] Provided are methods of treating human subjects for glaucoma by administration of a viral vector containing a transgene encoding an anti-CC1Q antibody or antigen binding fragment thereof. The antibody or Fab fragment thereof may be ANX-007. In embodiments, the patient has been diagnosed with and/or has symptoms associated with one or more of the various retinal disorders listed above.

[0406] Recombinant vector used for delivering the transgene are described in Section 5.4.3. Such vectors should have a tropism for human retina-type cells and can include non-replicating rAAV, particularly those bearing an AAV8 capsid. Alternatively, vectors bearing an AAV2.7m8 or AAV9 capsid can be used for ocular indications. The recombinant vectors, such as the ones shown in FIG. 11, can be administered in any manner such that the recombinant vector enters the retina, e.g. by introducing the recombinant vector into the eye. See Section 5.5.3 for details regarding the methods of treatment.

[0407] Subjects to whom such gene therapy is administered can be those responsive to anti-CC1Q. In certain embodiments, the methods encompass treating patients who have been diagnosed with glaucoma, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-CC1Q antibody or considered a good candidate for therapy with an anti-CC1Q antibody. In specific embodiments, the patients have previously been treated with ANX-007, and have been found to be responsive to ANX-007. To determine responsiveness, the anti-CC1Q 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

[0408] The production of the anti-CC1Q HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of one or more retinal disorders accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-CC1Q HuPTM Fab, subretinally, intravitreally, or suprachoroidally to human subjects (patients) diagnosed with or having one or more symptoms of glaucoma, to create a permanent depot in the retina that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced cells of the retina.

[0409] As an alternative, or an additional treatment to gene therapy, the anti-CC1Q HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with glaucoma or for whom therapy for glaucoma is considered appropriate.

[0410] In specific embodiments, the anti-CC1Q 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 ANX-007 as set forth in FIG. 11 (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 N59, Q113, and/or N163 of the heavy chain (SEQ ID NO: 43) or N22, N30, Q100, N158, and/or N210 of the light chain (SEQ ID NO: 44). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of ANX-007 has a sulfation group at Y60, Y94, and/or Y95 of the heavy chain (SEQ ID NO: 43) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 44). In other embodiments, the anti-CC1Q HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0411] 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 glaucoma. In the case of glaucoma, efficacy may be monitored by monitoring vision acuity, eye pain, or intraocular pressure (IOP). For example, efficacy can be monitored by assessing change in IOP, vision acuity, and pain from baseline.

[0412] Combinations of delivery of the anti-CC1Q HuPTM mAb or antigen-binding fragment thereof to the retina 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 glaucoma that could be combined with the gene therapy provided herein include but are not limited to prostaglandins (XALATAN®, LUMIGAN®, TRAVATAN Z®, and RESCULA®), alpha-andronergic agonists (IOPIDINE®, ALPHAGAN®, and ALPHAGAN-P®), carbonic anhydrase inhibitors (TRUSOPT®, AZOPT®, DIAMOX®, NEPTAZANE®, and DARANIDE®), parasympathomimetics (PILOCARPINE®, CARBACHOL®, ECHOTHIOPHATE®, DEMACARIUM®), and/or beta-blocker (TIMOPTIC XE®, ISTALOL®, BETOPTIC S®) and administration with anti-CC1Q agents, including but not limited ANX-007.

5.3.11. Anti-TNFα HuPTM Constructs and Formulations for non-infectious uveitis

[0413] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to tumor necrosis factor-alpha (TNFα), such as adalimumab (FIG. 12A), infliximab (FIG. 12B), or golimumab (FIG. 12C) and indicated for treating non-infectious uveitis. In certain embodiments, the HuPTM mAb has the amino acid sequence of adalimumab, infliximab, golimumab, or an antigen binding fragment thereof. Amino acid sequences of Fab fragments of the antibody are provided in FIGS. 12A-C. 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 one or more symptoms of non-infectious uveitis to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0414] 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, 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.).

[0415] 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. 45 and 46, respectively, see Table 5 and FIG. 12A). 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: 115 (encoding the adalimumab heavy chain Fab portion) and SEQ ID NO: 116 (encoding the adalimumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0416] 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: 45 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198),

EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG. 12A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 115 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 115). 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: 303 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0417] 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: 46. 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: 45. 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: 46 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: 45. In specific embodiments, the TNFα antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 45 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. 12A) 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. 20A. In specific embodiments, the TNFα antigen

binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 46 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. 12A) 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. 20B.

[0418] 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: 45 and 46, respectively, with one or more of the following mutations: L116N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0419] 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. 12A 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.

[0420] 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. 47 and 48, respectively, see Table 5 and FIG. 12B). 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: 117 (encoding the infliximab heavy chain Fab portion) and SEQ ID NO: 118 (encoding the infliximab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond

to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0421] 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: 47 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 12B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 117 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 117). 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: 304 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0422] 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: 48. 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: 47. 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: 48 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: 47. In specific embodiments, the TNFα antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 47 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. 12B) 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. 20A. In specific embodiments, the TNFα antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 48 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. 12B) 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. 20B.

[0423] 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: 47 and 48, respectively, with one or more of the following mutations: T115N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 11A (heavy chain) and 20B (light chain)).

[0424] 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. 12B 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.

[0425] 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. 49 and 50, respectively, see Table 5 and FIG. 12C). 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: 119 (encoding the golimumab heavy chain Fab portion) and SEQ ID NO: 120 (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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0426] 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: 49 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG. 12C. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 119 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 119). 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; 305 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0427] 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: 50. 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: 49. 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: 50 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: 49. In specific embodiments, the TNFα antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 49 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. 12C) 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. 20A. In specific embodiments, the TNFα antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 50 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. 12C) 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. 20B.

[0428] 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: 49 and 50, respectively, with one or more of the following mutations: T124N (heavy chain), Q164N or Q164S (light chain), and/or E199N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0429] 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. 12C 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.

Gene Therapy Methods

[0430] 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. In embodiments, the patient has been diagnosed with and/or has symptom(s) associated with non-infectious uveitis. Recombinant vector used for delivering the transgene are described in Section 5.4.3. Such vectors should have a tropism for human retina-type cells and can include non-replicating rAAV, particularly those bearing an AAV8 capsid. Alternatively, vectors bearing an AAV2.7m8 or AAV9 capsid can be used for ocular indications. The recombinant vectors, such as the ones shown in FIG. 12A-C, can be administered in any manner such that the recombinant vector enters the retina, e.g. by introducing the recombinant vector into the eye. See Section 5.5.3 for details regarding the methods of treatment.

[0431] 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 or considered a good candidate for therapy with an anti-TNFα antibody. In specific embodiments, the patients have previously been treated with adalimumab, infliximab, or golimumab, and have been found to be responsive to 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 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

[0432] The production of the anti-TNFα HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of non-infectious uveitis accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-TNFα HuPTM Fab, intravenously to human subjects (patients) diagnosed with or having one or more symptoms of non-infectious uveitis, to create a permanent depot in the retina that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced liver or muscle cells.

[0433] 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. 12A (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:45) or Q100, N158, and/or N210 of the light chain (SEQ ID NO:46). 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:45) and/or Y86 and/or Y87 of the light chain (SEQ ID NO:46). 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.

[0434] 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. 12B (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:47) or N41, N76, N158 and/or N210 of the light chain (SEQ ID NO:48). 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:47) and/or Y86 and/or Y87 of the light chain (SEQ ID NO:48). 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.

[0435] 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. 12C (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:49) or N162 and/or N214 of the light chain (SEQ ID NO:50). 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:49) and/or Y89 and/or Y90 of the light chain (SEQ ID NO:50). 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.

[0436] 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.

[0437] Combinations of delivery of the anti-TNFα HuPTM mAb or antigen-binding fragment thereof, to the liver 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.

5.3.12. Anti-RGMa HuPTM Constructs and Formulations for Multiple Sclerosis

[0438] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to repulsive guidance molecule-A (RGMa) and indicated for treating multiple sclerosis (MS). In certain embodiments, the HuPTM mAb has the amino acid sequence of elezanumab or an antigen binding fragment of the foregoing. The amino acid sequence of Fab fragments of elezanumab is provided in FIG. 13. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an RGMa-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of MS to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0439] 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 RGMa 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 RGMa, such as elezanumab, or variants thereof as detailed herein. The transgene may also encode an RGMa-integrin antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0440] In certain embodiments, the anti-RGMa antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of elezanumab (having amino acid sequences of SEQ ID NOs. 51 and 52, respectively, see Table 5 and FIG. 13). 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: 121 (encoding the elezanumab heavy chain Fab portion) and SEQ ID NO: 122 (encoding the elezanumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0441] In addition to the heavy and light chain variable domain and C_H1 and C_L 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-integrin-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 51 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPEAAGG (SEQ ID NO: 210), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPEAAGGPSVFL (SEQ ID NO: 212) or EPKSCDKTHLCPPCPAPEAAGGPSVFL (SEQ ID NO: 213) as set forth in FIG. 13. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 121 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 121). 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: 306 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0442] In certain embodiments, the anti-integrin antigen-binding fragment transgene encodes an RGMa 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: 52. In certain embodiments, the anti-RGMa antigen-binding fragment transgene encodes an integrin 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: 51. In certain embodiments, the anti-RGMa 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: 52 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: 51. In specific embodiments, the RGMa antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 51 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. 13) 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. 20A. In specific embodiments, the integrin antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 52 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. 13) 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. 20B.

[0443] In certain embodiments, the anti-RGMa antigen-binding fragment transgene encodes a hyperglycosylated elezanumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 51 and 52, respectively, with one or more of the following mutations: L115N (heavy chain) and/or Q197N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0444] In certain embodiments, the anti-RGMa antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six elezanumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 13 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-RGMa antibody or antigen-binding fragment thereof.

[0445] 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: 72), AAV9 capsid (SEQ ID NO: 73) or AAVrh10 capsid (SEQ ID NO: 74); and an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding an anti-RGMa mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver or muscle cells.

Gene Therapy Methods

[0446] Provided are methods of treating human subjects for MS by administration of a viral vector containing a transgene encoding an anti-RGMa antibody, or antigen binding fragment thereof. The antibody may be elenazumab and is, for example, a full length antibody or Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with MS. Recombinant vector used for delivering the transgene are described in Section 5.4.1 and 5.4.2. In some embodiments, such vectors should have a tropism for human liver cells and can include non-replicating rAAV, particularly those bearing an AAV8 or AAV9 capsid. The recombinant vectors, such as those shown in FIG. 13, can be administered in any manner such that the recombinant vector enters the liver or muscle tissue, e.g. by introducing the recombinant vector into the bloodstream. See 5.5.2 for details regarding the methods of treatment. In other embodiments, such vectors should have a tropism for human CNS cells and can include non-replicating rAAV, particularly those bearing an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid. The recombinant vector, such as shown in FIG. 13, can be administered in any manner such

that the recombinant vector enters the CNS, e.g. by introducing the recombinant vector into the cerebral spinal fluid (CSF). See Section 5.5.1 for details regarding the methods of treatment.

[0447] Subjects to whom such gene therapy is administered can be those responsive to anti-RGMa therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with MS, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-RGMa antibody or considered a good candidate for therapy with an anti-RGMa antibody. In specific embodiments, the patients have previously been treated with elezanumab, and have been found to be responsive to elezanumab. To determine responsiveness, the anti-RGMa 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

[0448] The production of the anti-RGMa HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of MS accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-RGMa HuPTM Fab, subcutaneously, intramuscularly, or intravenously to human subjects (patients) diagnosed with or having one or more symptoms of MS, to create a permanent depot in the liver, muscle or CNS tissue that continuously supplies the fully-human post-translationally modified, such as human-glycosylated, sulfated transgene product produced by transduced liver, muscle or CNS cells.

[0449] The cDNA construct for the anti-RGMa HuPTMmAb or anti-RGMa HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced liver or muscle cells. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, in some embodiments, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Tables 2, 3 or 4 that correspond to the proteins secreted by CNS cells, myocytes or hepatocytes, respectively.

[0450] As an alternative, or an additional treatment to gene therapy, the anti-RGMa HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with MS, or for whom therapy for MS is considered appropriate.

[0451] In specific embodiments, the anti-RGMa 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 elezanumab as set forth in FIG. 13 (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, Q112, and/or N162 of the heavy chain (SEQ ID NO:51) or N71 and/or N173 of the light chain (SEQ ID NO:52). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of elezanumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 51) and/or Y88 and/or Y89 of the light chain (SEQ ID NO: 52). In other embodiments, the anti-RGMa HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0452] 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 MS, particularly a reduction in pain and discomfort for the patient and/or improvements in mobility. Efficacy may be monitored by scoring the symptoms or degree of lesions in the affected tissue. For example, with regard to MS, efficacy can be monitored by assessing frequency of relapses (e.g., Annualized Relapse Rate), physical disability status (e.g., scoring Kurtzke Expanded Disability Status Scale (EDSS)), and biological markers, including brain scans using MRI (e.g., evaluation of T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions through magnetic resonance imaging).

[0453] Combinations of delivery of the anti-RGMa HuPTM mAb or antigen-binding fragment thereof, to the CNS, liver, 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 MS that could be combined with the gene therapy provided herein include but are not limited to interferon beta, interferon beta 1a, glatiramer acetate, cyclophosphamide, corticosteroids, immunomodulators (e.g,

azathioprine, 6-mercaptopurine, and/or methotrexate), and mitoxantrone and administration with anti-RGMa agents, including but not limited to elenazumab.

5.3.13 Anti-TTR HuPTM Constructs and Formulations for Amyloidosis

[0454] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to transthyretin (TTR), particularly mis-folded or pathogenic TTR, indicated for treating familial or wild-type amyloido transthyretin (ATTR) amyloidosis, familial amyloid cardiomyopathy (FAC), and/or familial amyloid polyneuropathy (FAP). In certain embodiments, the HuPTM mAb has the amino acid sequence of NI-301 or PRX-004 or an antigen binding fragment thereof. The amino acid sequence of Fab fragments of NI-301 and PRX-004 are provided in FIG. 14A and 14B, respectively. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding a TTR-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of amyloidosis, FAP, and/or FAC to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

[0455] 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 TTR 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 TTR, such as NI-301, PRX-004, or variants thereof as detailed herein. The transgene may also encode an anti-TTR antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0456] In certain embodiments, the anti-TTR antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of NI-301 (having amino acid sequences of SEQ ID NOs. 53 and 54, respectively, see Table 5 and FIG. 14A). 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: 123 (encoding the NI-301 heavy chain Fab portion) and SEQ ID NO: 124 (encoding the NI-301 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0457] 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-TTR antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 53 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG. 14A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 123 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 123). 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., an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0458] In certain embodiments, the anti-TTR antigen-binding fragment transgene encodes an TTR 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: 54. In certain embodiments, the anti-TTR antigen-binding fragment transgene encodes an TTR 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: 53. In certain embodiments, the anti-TTR 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: 54 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: 53. In specific embodiments, the TTR antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 53 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. 14A) 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. 20A. In specific embodiments, the TTR antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 54 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. 14A) 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. 20B.

[0459] In certain embodiments, the anti-TTR antigen-binding fragment transgene encodes a hyperglycosylated NI-301 Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 53 and 54, respectively, with one or more of the following mutations: M115N (heavy chain), Q159N or Q159S (light chain), and/or E194N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0460] In certain embodiments, the anti-TTR antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six NI-301 CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 14A 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-TTR antibody or antigen-binding fragment thereof.

[0461] In certain embodiments, the anti-TTR antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of PRX-004 (having amino acid sequences of SEQ ID NOs. 55 and 56, respectively, see Table 5 and FIG. 14B). 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: 125 (encoding the PRX-004 heavy chain Fab portion) and SEQ ID NO: 126 (encoding the PRX-004 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0462] 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-TTR antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 55 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG. 14B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 125 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 125). 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: 307 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0463] In certain embodiments, the anti-TTR antigen-binding fragment transgene encodes an TTR 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: 56. In certain embodiments, the anti-TTR antigen-binding fragment transgene encodes an TTR 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: 55. In certain embodiments, the anti-TTR 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: 56 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: 55. In specific embodiments, the TTR antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 55 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. 14B) 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. 20A. In specific embodiments, the TTR antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 56 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. 14B) 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. 20B.

[0464] In certain embodiments, the anti-TTR antigen-binding fragment transgene encodes a hyperglycosylated PRX-004 Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 55 and 56, respectively, with one or more of the following mutations: L112N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0465] In certain embodiments, the anti-TTR antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six PRX-004 CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 14B 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-TTR antibody or antigen-binding fragment thereof.

[0466] ***Gene Therapy Methods***

[0467] Provided are methods of treating human subjects for ATTR, FAT, or FAC by administration of a viral vector containing a transgene encoding an anti-TTR antibody or antigen binding fragment thereof. The antibody may be NI-301, PRX-004 and is, e.g., a full length antibody or Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with ATTR, FAC, or FAT.

[0468] Provided are methods of treating human subjects for ATTR, FAC, and FAT by administration of a viral vector containing a transgene encoding an anti-TTR antibody, or antigen binding fragment thereof. The antibody may be NI-301, or PRX-004, and is, e.g., a Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with ATTR, FAT, or FAC. Recombinant vector used for delivering the transgene are described in Section 5.4.1 and 5.4.2. In some embodiments, such vectors should have a tropism for human liver cells and can include non-replicating rAAV, particularly those bearing an AAV8 or AAV9 capsid. The recombinant vectors, such as those shown in FIGS. 14A and 14B, can be administered in any manner such that the recombinant vector enters the liver or muscle tissue, e.g., by introducing the recombinant vector into the bloodstream. See 5.5.2 for details regarding the methods of treatment. In other embodiments, such vectors should have a tropism for human CNS cells and can include non-replicating rAAV, particularly those bearing an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid. The recombinant vector, such as shown in FIGS. 14A and 14B, can be administered in any manner such that the recombinant vector enters the CNS, e.g., by introducing the recombinant vector into the cerebral spinal fluid (CSF). See Section 5.5.1 for details regarding the methods of treatment.

[0469] Subjects to whom such gene therapy is administered can be those responsive to anti-TTR therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with ATTR, FAP, or FAC, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-TTR antibody, or considered a good candidate for therapy with an anti-TTR antibody. In specific embodiments, the patients have previously been treated with PRX-004 or NI-301, and have been found to be responsive to PRX-004 or NI-301. To determine responsiveness, the anti-TTR 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

[0470] The production of the anti-TTR HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of ATTR, FAC, or FAP accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-TTR HuPTM Fab, subcutaneously, intramuscularly, or intravenously to human subjects (patients) diagnosed with ATTR, FAC, or FAP, to create a permanent depot in the muscle or liver that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced cells of the muscle or liver.

[0471] The cDNA construct for the anti-TTR HuPTMmAb or anti-TTR HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced cells of the muscle or liver. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by cells of the muscle or liver, respectively.

[0472] As an alternative, or an additional treatment to gene therapy, the anti-TTR HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with ATTR, FAP, or FAC is considered appropriate.

[0473] In specific embodiments, the anti-TTR 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 NI-301 as set forth in FIG. 14A (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 N58, N78, N83, Q112, and/or N161 of the heavy chain (SEQ ID NO: 53) or Q99, N157, and/or N209 of the light chain (SEQ ID NO: 54). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of NI-301 has a sulfation group at Y95 and/or Y96 of the heavy chain (SEQ ID NO: 53) and/or Y85 and/or Y86 of the light chain (SEQ ID NO: 54). In other embodiments, the anti-TTR HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0474] In specific embodiments, the anti-TTR 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 PRX-004 as set forth in FIG. 14B (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, Q109, and/or N159 of the heavy chain (SEQ ID NO: 55) or N158 and/or N210 of the light chain (SEQ ID NO: 56). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of PRX-004 has a sulfation group at Y93 and/or Y94 of the heavy chain (SEQ ID NO: 55) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 56). In other embodiments, the anti-TTR HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0475] . 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 the disease being treated or alleviate one or more symptoms thereof. In the case of ATTR, efficacy can be monitored by assessing one or more amyloidosis endpoints, including by

measuring the progression of organ damage, the amount of amyloid fibril tissue deposits, and/or improvement in organ function (*i.e.* kidney and liver).

[0476] Combinations of delivery of the anti-TTR HuPTM mAb or antigen-binding fragment thereof to the muscle or liver 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 ATTR that could be combined with the gene therapy provided herein include but are not limited to chemotherapeutic agent(s) (e.g., alkylating agents, antimetabolites, topoisomerase inhibitors, and mitotic inhibitors), lenalidomide (REVLIMID®), pomalidomide (POMALYST®), thalidomide (SYNOVIR®), daraumumab (DARZALEX®), elotuzumab (EMPLICITI®), bortezomib (VELCADE®), ixazomib (NINLARO®), and/or carfilzomib (KYPROLIS®) and administration with anti-TTR agents, including but not limited to NI-301 and PRX-004.

5.3.14 Anti-CTGF HuPTM Constructs and Formulations for Fibrotic Diseases

[0477] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to connective tissue growth factor (CTGF) indicated for treating one or more fibrotic disorders including pulmonary fibrosis, cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), liver cirrhosis, atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, arthrofibrosis, Crohn's disease, mediastinal fibrosis, myelofibrosis (MF), nephrogenic systemic fibrosis (NSF), progressive massive fibrosis (PMF), retroperitoneal fibrosis (RPF). In certain embodiments, the HuPTM mAb has the amino acid sequence of pamrevlumab or an antigen binding fragment thereof. The amino acid sequence of Fab fragments of pamrevlumab is provided in FIG. 15. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an CTGF-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of a fibrotic disorder to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0478] 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 CTGF 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 CTGF, such as pamrevlumab, or variants thereof as detailed herein. The transgene may also encode an anti-CTGF antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0479] In certain embodiments, the anti-CTGF antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of pamrevlumab (having amino acid sequences of SEQ ID NOs. 57 and 58, respectively, see Table 5 and FIG. 15). 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: 127 (encoding the pamrevlumab heavy chain Fab portion) and SEQ ID NO: 128 (encoding the pamrevlumab light chain Fab portion) as set forth in Table 6. In the case of treating fibrotic diseases, 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0480] 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-CTGF antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 57 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence EPKSCDKTHTCPPCPAPEAAGG (SEQ ID NO: 210), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198),

EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPEAAGGPSVFL (SEQ ID NO: 212) or EPKSCDKTHLCPPCPAPEAAGGPSVFL (SEQ ID NO: 213) as set forth in FIG 15. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 127 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 127). 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: 308 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0481] In certain embodiments, the anti-CTGF antigen-binding fragment transgene encodes an CTGF 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: 58. In certain embodiments, the anti-CTGF antigen-binding fragment transgene encodes an CTGF 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: 57. In certain embodiments, the anti-CTGF 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: 58 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: 57. In specific embodiments, the CTGF antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 57 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. 15) 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. 20A. In specific embodiments, the CTGF antigen

binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 58 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. 15) 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. 20B.

[0482] In certain embodiments, the anti-CTGF antigen-binding fragment transgene encodes a hyperglycosylated pamrevlumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 57 and 58, respectively, with one or more of the following mutations: L111N (heavy chain) and/or Q196N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0483] In certain embodiments, the anti-CTGF antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six pamrevlumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 15 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-CTGF antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0484] Provided are methods of treating human subjects for one or more fibrotic disorders (such as IPF) by administration of a viral vector containing a transgene encoding an anti-CTGF antibody or antigen binding fragment thereof. The antibody may be pamrevlumab, and is e.g. a full length or substantially full length antibody or Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with one or more fibrotic disorders.

[0485] Recombinant vector used for delivering the transgene are described in Section 5.4.3. For delivery to the liver, recombinant vector used for delivering the transgene are described in Section 5.4.2. Such vectors should have a tropism for human liver cells and can include non-replicating rAAV, particularly those bearing an AAV8 or AAV9 capsid. The recombinant vectors, such as those shown

in FIG. 15, can be administered in any manner such that the recombinant vector enters the liver, e.g. by introducing the recombinant vector into the bloodstream. See Section 5.5.2 for details regarding the methods of treatment.

[0486] Subjects to whom such gene therapy is administered can be those responsive to anti-CTGF therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with one or more fibrotic disorders, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-CTGF antibody or considered a good candidate for therapy with an anti-CTGF antibody. In specific embodiments, the patients have previously been treated with pamrevlumab, and have been found to be responsive to pamrevlumab. To determine responsiveness, the anti-CTGF 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

[0487] The production of the anti-CTGF HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of one or more fibrotic disorders accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-CTGF HuPTM Fab, subcutaneously, intramuscularly, or intravenously to human subjects (patients) diagnosed with one or more fibrotic disorders, to create a permanent depot in the liver or muscle that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced cells of the liver or muscle.

[0488] The cDNA construct for the anti-CTGF HuPTMmAb or anti-CTGF HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced cells of the muscle or liver. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by cells of the muscle or liver, respectively.

[0489] As an alternative, or an additional treatment to gene therapy, the anti-CTGF HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology and

administered to patients diagnosed with a fibrotic disorder for whom therapy for a fibrotic disorder is considered appropriate.

[0490] In specific embodiments, the anti-CTGF 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 pamrevlumab as set forth in FIG. 15 (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 N59, Q108, and/or N158 of the heavy chain (SEQ ID NO:57) or N68, N95, and/or N172 of the light chain (SEQ ID NO:58). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of pamrevlumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 57) and/or Y30, Y85 and/or Y86 of the light chain (SEQ ID NO: 58). In other embodiments, the anti-CTGF HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0491] 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 the disease being treated or alleviate one or more symptoms thereof. In the case of CF, efficacy can be monitored by assessing Forced Expiratory Volume in 1s (FEV1), decreased frequency of pulmonary exacerbations, quality of life (QoL) improvement, and, for younger patients, growth improvement. (e.g., see VanDevanter and Konstan, "Outcome measurement for clinical trials assessing treatment of cystic fibrosis lung disease," Clin. Investig. 2(2):163-175 (2012)). In the case of pulmonary fibrosis, efficacy can be monitored by assessing the lung vital capacity (LVC), desaturation with exertion, and diffusing capacity of the lungs for carbon monoxide (DLCO). In the case of IPF, efficacy may be monitored by assessing the level of dyspnoea, FVC, DLCO, desaturation during the 6-min walk test, extent of honeycombing on high-resolution computed tomography (HRCT), or presence of pulmonary hypertension or emphysema. In the case of liver cirrhosis, efficacy may be monitored by assessing the hepatic venous pressure gradient (HVPG) and the stage of liver

fibrosis. In the case of atrial fibrosis, efficacy may be monitored by localizing and quantifying the degree of structural remodeling (SRM) and/or fibrosis in the atrium using contrast-media enhanced delayed enhancement MRI (DE-MRI). In the case of endomyocardial fibrosis, efficacy may be monitored by assessing fibrotic lesions of the inner lining of the heart cavities. In the case of arthrofibrosis, efficacy may be monitored by assessing the extent of involvement by fibrosis in the affected joint (e.g., MRI). In the case of Crohn's disease, efficacy may be monitored by assessing the level of serological markers (e.g., fibronectin, CRP, bFGF, ASCA) and/or the degree of fibrotic lesions using advanced imaging technologies. In the case of mediastinal fibrosis, efficacy may be monitored by assessing the presence and/or degree of fibrosis, polymorphic inflammatory infiltrates and phlebitis by using contrast-enhanced CT. In the case of myelofibrosis, efficacy may be monitored by assessing changes in the level of inflammatory cytokine in the serum, blood counts (PLT, WBC, RBC), degree of fibrosis (reticulin and collagen) in the bone marrow, spleen size, and/or constitutional symptoms compared to baseline. In the case of nephrogenic systemic fibrosis, efficacy may be monitored by assessing changes in the glomerular filtration rate (GFR) from baseline, quantification of fibrotic and/or darkened of the skin, and/or reduction in burning, itching and/or severe sharp pains in areas of involvement. In the case of progressive massive fibrosis, efficacy may be monitored by improvement of pulmonary function and/or reduction in the size of conglomerate masses of dense fibrosis in the lungs. In the case of retroperitoneal fibrosis, the efficacy may be monitored by assessing decreased pain in the lower back and/or abdomen, improvement of anemia, abnormal discoloration of the skin, and/or quality of life.

[0492] Combinations of delivery of the anti-CTGF HuPTM mAb or antigen-binding fragment thereof to the muscle or liver 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 CF that could be combined with the gene therapy provided herein include but are not limited to antibiotics, vaccines, and cough medicines (e.g., acetylcysteine and dornasa alfa) and administration with anti-CTGF, including but not limited to pamrevlumab. Available treatments for IPF that could be combined with the gene therapy provided herein include but are not limited to oxygen therapy, pulmonary rehabilitation, Nintedanib (OFEV®), Pirfenidone (ESBRIET®, PIRFENEX®, PIRESPA®), Corticosteroids (prednisone),

Mycophenolate mofetil/mycophenolic acid (CELLCEPT®), and Azathioprine (IMURAN®) and administration with anti-CTGF, including but not limited to pamrevlumab. Available treatments for cirrhosis that could be combined with gene therapy provided herein include but are not limited to diuretics (e.g., spironolactone, metolazone, and frusemide), ammonia reducer, beta blocker, synthetic hormones (e.g., octeotride), antibiotics, and antiviral drugs. Available treatments for atrial fibrosis that could be combined with gene therapy provided herein include but are not limited to physical ablation, beta blockers, blood thinners, calcium channel blockers, corticosteroids (e.g., prednisone), non-steroidal anti-inflammatory drugs, and antiarrhythmics (digoxin). Available treatments for endomyocardial fibrosis that could be combined with gene therapy provided herein include but are not limited to surgery, blood thinners, ACE inhibitors, corticosteroids (e.g., prednisone), non-steroidal anti-inflammatory drugs, diuretics (e.g., spironolactone, metolazone, and frusemide) or other anti-inflammatories, and antiarrhythmics (digoxin). Available treatments for old myocardial infarction that could be combined with gene therapy provided herein include but are not limited to beta blockers, blood thinners, statins, nitroglycerin, and ACE inhibitors. Available treatments for arthrofibrosis that could be combined with gene therapy provided herein include but are not limited to surgery, physical therapy, corticosteroid injections, non-steroidal anti-inflammatory drugs, and cryotherapy. Available treatments for Crohn's disease that could be combined with gene therapy provided herein include but are not limited to vitamin D, anti-inflammatory agents, non-steroidal anti-inflammatory agents, corticosteroids, immunosuppressants (e.g., Remicade®, adalimumab, methotrexate, mercaptopurine, or azathioprine), and antibiotics. Available treatments for mediastinal fibrosis that could be combined with gene therapy provided herein include but are not limited to tamoxifen, anti-inflammatory agents, non-steroidal anti-inflammatory agents (e.g., indocin), corticosteroids, immunosuppressants (e.g., Remicade®, adalimumab, methotrexate, mercaptopurine, or azathioprine). Available treatments for MF that could be combined with gene therapy provided herein include but are not limited to ruxolitinib, thalidomide, androgen therapy, blood transfusions, chemotherapeutics, and radiation treatment of the spleen. Available treatments for NSF that could be combined with gene therapy provided herein include but are not limited to oxygen therapy and bronchodilators. Available treatments for RPF that could be combined with gene therapy provided herein include but are not

limited to corticosteroids, immunosuppressants (e.g, mycophenolate mofetil, methotrexate, azathioprine, or cyclophosphamide), and tamoxifen).

5.3.15. Anti-IL6R, anti-IL6, and anti-CD19 HuPTM Constructs and Formulations for NMO and Non-infectious Uveitis and Detrimental Immune Response

[0493] 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), interleukin-6 (IL6), or cluster of differentiation 19 (CD19), derived from an anti-IL6R, anti-IL6, or anti-CD19 antibody, such as satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, or inebilizumab (FIGS. 16A-I), indicated for treating non-infectious uveitis, neuromyelitis optica (NMO), diabetic retinopathy (DR), or diabetic macular edema (DME). Also described are compositions and methods 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, anti-IL6, or anti-CD19 antibody, such as satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, or gerilimzumab (FIGS. 16A-H), indicated for treating, inhibiting or ameliorating a detrimental immune response, such as inflammation, cytokine release syndrome and the like associated with viral or bacterial infection or administration of an immune-promoting therapeutic, such as an immune-oncology antibody, protein or cell based therapy, such as a CAR-T therapy. In certain embodiments, the HuPTM mAb has the amino acid sequence of satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, inebilizumab, or an antigen binding fragment thereof. Amino acid sequences of Fab fragments of the antibody are provided in FIGS. 16A-I. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an IL6R-binding, IL6-binding, or CD19-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, NMO, DR, or DME, 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

[0494] 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, IL6, or CD19 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, IL6, or CD19, such as satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, inebilizumab, or variants thereof as detailed herein. The transgene may also encode an anti-IL6R, IL6, or anti-CD19 antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0495] 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. 59 and 60, respectively, see Table 5 and FIG. 16A). 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: 129 (encoding the satralizumab heavy chain Fab portion) and SEQ ID NO: 130 (encoding the satralizumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0496] 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: 59 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: 433) or ERKSCVECPPCPA (SEQ ID NO: 434) as set forth

in FIG. 16A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 129 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 129). 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: 309 (Table 7) or an IgG2 Fc domain, such as SEQ ID No. 284 or as depicted in FIG. 23, 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.

[0497] 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: 60. 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: 59. 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: 60 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: 59. In specific embodiments, the IL6R antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 59 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. 16A) 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. 20A. In specific embodiments, the IL6R antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 60 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. 16A) 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. 20B.

[0498] 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: 59 and 60, respectively, with one or more of the following mutations: L114N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0499] 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. 16A 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.

[0500] 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. 61 and 62, respectively, see Table 5 and FIG. 16B). 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: 131 (encoding the sarilumab heavy chain Fab portion) and SEQ ID NO: 132 (encoding the sarilumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0501] 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: 61 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 16B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 131 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 131). 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: 310 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0502] 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: 62. 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: 61. 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: 62 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: 61. In specific embodiments, the IL6R antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 61 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. 16B) 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. 20A. In specific embodiments, the IL6R antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 62 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. 16B) 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. 20B.

[0503] 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: 61 and 62, respectively, with one or more of the following mutations: M111N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0504] 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. 16B 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.

[0505] 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. 341 and 342, respectively, see Table 5 and FIG. 16H). 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: 353 (encoding the tocilizumab heavy chain Fab portion) and SEQ ID NO: 354 (encoding the tocilizumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 infra.

[0506] 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: 341 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDEPKSCDKTHTCPPCPAPELLGG KTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG. 16H. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 353 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 353). 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: 359 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0507] 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: 342. 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: 341. 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: 342 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: 341. In specific embodiments, the IL6R antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 341 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. 16H) 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. 20A. In specific embodiments, the IL6R antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 342 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. 16H) 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. 20B.

[0508] 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: 341 and 342, respectively, with one or more of the following mutations: L115N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0509] 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. 16H 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.

[0510] 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. 331 and 332, respectively, see Table 5 and FIG. 16C). 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: 343 (encoding the siltuximab heavy chain Fab portion) and SEQ ID NO: 344 (encoding the siltuximab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0511] 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: 331 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 16C. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 343 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 343). 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: 355 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0512] 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: 332. 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: 331. 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: 332 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: 331. In specific embodiments, the IL6 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 331 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. 16C) 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. 20A. In specific embodiments, the IL6 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 332 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. 16C) 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. 20B.

[0513] 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: 331 and 332, respectively, with one or more of the following mutations: S114N (heavy chain), Q159N or Q159S (light chain), and/or E194N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0514] 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. 16C 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.

[0515] 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. 333 and 334, respectively, see Table 5 and FIG. 16D). 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: 345 (encoding the clazakizumab heavy chain Fab portion) and SEQ ID NO: 346 (encoding the clazakizumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 infra.

[0516] 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: 333 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 16D. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 345 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 345). 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: 356 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0517] 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: 334. 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: 333. 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: 334 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: 333. In specific embodiments, the IL6 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 333 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. 16D) 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. 20A. In specific embodiments, the IL6 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 334 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. 16D) 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. 20B.

[0518] 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: 333 and 334, respectively, with one or more of the following mutations: L115N (heavy chain), Q163N or Q163S (light chain), and/or E198N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0519] 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. 16D 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.

[0520] 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. 335 and 336, respectively, see Table 5 and FIG. 16E). 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: 347 (encoding the sirukumab heavy chain Fab portion) and SEQ ID NO: 348 (encoding the sirukumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 infra.

[0521] 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: 335 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 16E. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 347 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 347). 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: 357 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0522] 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: 336. 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: 335. 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: 336 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: 335. In specific embodiments, the IL6 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 335 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. 16E) 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. 20A. In specific embodiments, the IL6 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 336 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. 16E) 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. 20B.

[0523] 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: 335 and 336, respectively, with one or more of the following mutations: T114N (heavy chain), Q159N or Q159S (light chain), and/or E194N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0524] 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. 16E 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.

[0525] 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. 337 and 338, respectively, see Table 5 and FIG. 16F). 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: 349 (encoding the olokizumab heavy chain Fab portion) and SEQ ID NO: 350 (encoding the olokizumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 infra.

[0526] 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: 337 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: 214), and specifically, ESKYGPPCPPCPA (SEQ ID NO: 216), ESKYGPPCPSCPA (SEQ ID NO: 217), ESKYGPPCPSCPAPEFLGGPSVFL (SEQ ID NO: 218), or ESKYGPPCPPCPAPEFLGGPSVFL (SEQ ID NO: 219) as set forth in FIG 16F. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 349 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 349). 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: 358 (Table 7) or an IgG4 Fc domain, such as SEQ ID No. 285 or as depicted in FIG. 23, 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.

[0527] 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: 338. 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: 337. 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: 338 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: 337. In specific embodiments, the IL6 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 337 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. 16F) 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. 20A. In specific embodiments, the IL6 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 338 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. 16F) 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. 20B.

[0528] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes a hyperglycosylated olizikumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 337 and 338, respectively, with one or more of the following mutations: L115N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0529] 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. 16F 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.

[0530] 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 gerilimzumab (having amino acid sequences of SEQ ID NOs. 339 and 340, respectively, see Table 5 and FIG. 16G). 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: 351 (encoding the gerilimzumab heavy chain Fab portion) and SEQ ID NO: 352 (encoding the gerilimzumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0531] 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: 339 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG 16G. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 351 by the

hinge region encoding sequences set forth in Table 7 (SEQ ID NO: 351). 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. 283 or as depicted in FIG. 23, 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.

[0532] 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: 340. 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: 339. 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: 340 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: 339. In specific embodiments, the IL6 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 339 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. 16G) 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. 20A. In specific embodiments, the IL6 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 340 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. 16G) 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. 20B.

[0533] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes a hyperglycosylated gerilimzumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 339 and 340, respectively, with one or more of the following mutations: M117N (heavy chain), and/or Q198N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0534] In certain embodiments, the anti-IL6 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six gerilimzumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 16G 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.

[0535] In certain embodiments, the anti-CD19 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of inebilizumab (having amino acid sequences of SEQ ID NOs. 63 and 64, respectively, see Table 5 and FIG. 16I). 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: 133 (encoding the inebilizumab heavy chain Fab portion) and SEQ ID NO: 134 (encoding the inebilizumab 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0536] In addition to the heavy and light chain variable domain and CH1 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-CD19-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 63 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG. 16C. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 133 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 133). 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: 311 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0537] In certain embodiments, the anti-CD19 antigen-binding fragment transgene encodes an CD19 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: 64. In certain embodiments, the anti-CD19 antigen-binding fragment transgene encodes an CD19 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: 63. In certain embodiments, the anti-CD19 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: 64 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: 63. In specific embodiments, the CD19 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 63 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. 16I) 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. 20A. In specific embodiments, the CD19 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 64 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. 16I) 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. 20B.

[0538] In certain embodiments, the anti-CD19 antigen-binding fragment transgene encodes a hyperglycosylated inebilizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 63 and 64, respectively, with one or more of the following mutations: L116N (heavy chain), Q164N or Q164S (light chain), and/or E199N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0539] In certain embodiments, the anti-CD19 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six inebilizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 16I 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-CD19 antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0540] Provided are methods of treating human subjects for NMO by administration of a viral vector containing a transgene encoding an anti-IL6R, anti-IL6, or anti-CD19 antibody, or antigen binding fragment thereof. The antibody may be satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, or inebilizumab, and is, e.g., a full length, substantially full length or Fab fragment thereof, or other antigen-binding fragment thereof.

[0541] Also provided are methods of treating human subjects for non-infectious uveitis, DR, or DME by administration of a viral vector containing a transgene encoding an anti-IL6R antibody, or anti-IL6 antibody, or antigen binding fragment thereof. The antibody may be satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, or gerilimzumab, and is, e.g., a Fab fragment thereof, or other antigen-binding fragment thereof.

[0542] In embodiments, the patient has been diagnosed with and/or has symptom(s) associated with one or more ocular disorders. Recombinant vectors used for delivering the transgene are described in Section 5.4.3. Such vectors should have a tropism for human retina-type cells and can include non-replicating rAAV, particularly those bearing an AAV8 capsid. Alternatively, vectors bearing an AAV2.7m8 or AAV9 capsid can be used for ocular indications. The recombinant vectors, such as the ones shown in FIGS. 16A-I, can be administered in any manner such that the recombinant vector enters the retina, e.g., by introducing the recombinant vector into the eye. See Section 5.5.3 for details regarding the methods of treatment.

[0543] Provided are methods of treating, inhibiting or ameliorating a detrimental immune response in human subjects 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 gerilimzumab, and is, e.g., a full length, substantially full length or Fab fragment thereof, or other antigen-binding fragment thereof.

[0544] In embodiments, the patient has been diagnosed with and/or has symptom(s) associated with a detrimental immune response, such as inflammation or a cytokine storm associated with a viral or bacterial infection or is in need of therapy to manage adverse side effects, including prophylactically, such as inflammation and/or cytokine release syndrome that may be triggered by a bacterial or viral infection, or an immunotherapeutic, such as an immune-oncology therapeutic or an immune cell based therapy, such as, for example, a CAR-T cell based therapy. Viral infections include influenza, coronavirus, such as SARS-CoV-2 or other coronaviral infection, etc. Immunotherapeutics that may trigger adverse effects that may be prevented or ameliorated include BiTE single-chain antibodies, CAR-T therapeutics, such as, but not limited to tisagenlecleucel (KYMRIAH®) or

axicabtagene ciloleucel (YESCARTA®) or other immunooncology therapeutics, such as anti-thymocyte globulin (ATG) , the CD28 superagonist TGN1412, rituximab, obinutuzumab, alemtuzumab, brentuximab, dacetuzumab, ipilimumab, nivolumab or pembrolizumab. oxaliplatin or lenalidomide. Recombinant vectors used for delivering the transgene are described in Section 5.4.2. Such vectors should have a tropism for human muscle or liver cells and can include non-replicating rAAV, particularly those bearing an AAV8 or AAV9 capsid. The recombinant vectors, such as the ones shown in FIGS. 16A-H, can be administered in any manner such that the recombinant vector enters the liver or muscles, e.g., by introducing the recombinant vector into the bloodstream. See Section 5.5.2 for details regarding the methods of treatment.

[0545] Subjects to whom such gene therapy is administered can be those responsive to anti-IL6R, anti-IL6, or anti-CD19 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, anti-IL6, or anti-CD19 antibody or considered a good candidate for therapy with an anti-IL6R, anti-IL6, or anti-CD19 antibody. In specific embodiments, the patients have previously been treated with satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, or inebilizumab, and have been found to be responsive to satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, or inebilizumab. In other embodiments, the patients have been previously treated with an anti-IL6R, anti-IL6, or anti-CD19 antibody. To determine responsiveness, the anti-IL6R, anti-IL6, or anti-CD19 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

[0546] The production of the anti-IL6R, anti-IL6, or anti-CD19 HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of one of more ocular disorders accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-IL6R, anti-IL6, or anti-CD19 HuPTM Fab, subretinally, intravitreally, or suprachoroidally to human subjects (patients) diagnosed with or having one or more symptoms of non-infectious uveitis,

NMO, DR, or DME, to create a permanent depot in the retina that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced cells of the retina. Alternatively, the production of the anti-IL6R, anti-IL6, or anti-CD19 HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment, inhibition or amelioration of a detrimental immune response accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-IL6R or anti-IL6, HuPTM Fab or HuPTM Mab, subcutaneously, intramuscularly or intravenously to human subjects (patients) diagnosed with or having one or more symptoms of a detrimental immune response or to manage side effects of immune therapy, to create a permanent depot in the retina that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced cells of the liver and/or muscle.

[0547] 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. 16A (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:59) or Q100, N158, and/or N210 of the light chain (SEQ ID NO: 60). 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: 59) and/or Y49, Y50, Y86, and/or Y87 of the light chain (SEQ ID NO: 60). 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.

[0548] 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. 16B (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:61) or Q100, N158, and/or N210 of the light chain (SEQ ID NO:62). 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:61) and/or Y86, Y87, and/or Y192 of the light chain (SEQ ID NO:62). 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.

[0549] 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. 16H (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: 341) or Q100, N158, and/or N210 of the light chain (SEQ ID NO: 342). 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: 341) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 342). 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.

[0550] 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. 16C (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: 331) or N60, N157, and/or N209 of the light chain (SEQ ID NO: 332). 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: 331) and/or Y85 and/or Y86 of the light chain (SEQ ID NO: 332). 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.

[0551] 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. 16D (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: 333) or N30, N161, and/or N213 of the light chain (SEQ ID NO: 334). 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: 333) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 334). 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.

[0552] 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. 16E (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: 335) or N157 and/or N209 of the light chain (SEQ ID NO: 336). 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: 335) and/or Y85 and/or Y86 of the light chain (SEQ ID NO: 336). 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.

[0553] 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. 16F (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: 337) or Q100, N158 and/or N210 of the light chain (SEQ ID NO: 338). 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: 337) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 338). 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.

[0554] 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 gerilimzumab as set forth in FIG. 16G (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: 339) or N71 and/or N174 of the light chain (SEQ ID NO: 340). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of gerilimzumab has a sulfation group at Y95 and/or Y96 of the heavy chain (SEQ ID NO: 339) and/or Y88 and/or Y89 of the light chain (SEQ ID NO: 340). 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.

[0555] In specific embodiments, the anti-CD19 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 inebilizumab as set forth in FIG. 16I (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, Q113, and/or N163 of the heavy chain (SEQ ID NO:63) or N80, N162, and/or N214 of the light chain (SEQ ID NO:64). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of inebilizumab has a sulfation group at Y94, and/or Y95 of the heavy chain (SEQ ID NO:63) and/or Y90 and/or Y91 of the light chain (SEQ ID NO:64). In other embodiments, the anti-CD19 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.

[0556] 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 one or more ocular disorders. In the case 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. In the case of NMO, efficacy may be monitored by measuring an improvement in vision and sensation and/or reduction of weakness or paralysis in the legs or arms, painful spasms, and/or uncontrollable vomiting and hiccups. In the case of non-infectious uveitis, efficacy may be monitored by monitoring vision acuity, redness of the eye, sensitivity to light, and/or eye pain. For example, efficacy can be monitored by assessing change in vision acuity, redness of the eye, sensitivity to light, and/or eye pain from baseline. In the case of DR and DME, efficacy may be monitored by monitoring vision acuity. For example, efficacy can be monitored by assessing change in vision acuity from baseline.

[0557] Alternatively, the goal of the gene therapy is to reduce, inhibit or ameliorate a detrimental immune response in a human subject, such as a subject suffering from a viral or bacterial infection, including infection by SARS-coV-2 or COVID19 or in need of management of side effects

from immunotherapy, such as being administered an immune-oncology agent and/or a cell based immune therapy such as a CAR-T cell therapy. Symptoms of a detrimental immune response, including a cytokine release syndrome, include high fever, inflammation, severe fatigue, nausea, and may lead to tissue or organ damage, including multiple organ failure.

[0558] Combinations of delivery of the anti-IL6R, anti-IL6, or anti-CD19 HuPTM mAb or antigen-binding fragment thereof, to the liver 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-IL6R or anti-IL6, including but not limited to sarilumab, satralizumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, or gerilimzumab. Available treatments for a subject with NMO that could be combined with the gene therapy provided herein include but are not limited to, azathioprine (IMRUN®, AZASAN®), methotrexate, mycophenolate mofetil (CELLCEPT®), rituximab (RITUXAN®), corticosteroids (local and/or systemic), and others and administration with anti-IL6R, anti-IL6, or anti-CD19 agents, including but not limited to satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, or inebilizumab.. Available treatments for DR or DME that could be combined with the gene therapy provided herein include but are not limited to laser photocoagulation, photodynamic therapy with verteporfin, aflibercept, and/or intravitreal steroids, anti-VEGF agents, and others and administration with anti-IL6R agents or anti-CD19 agents, including but not limited to sarilumab, satralizumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, or inebilizumab.

5.3.16 Anti-Integrin (β7 subunit) HuPTM Constructs and Formulations for Crohn's Disease and Ulcerative Colitis

[0559] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to integrin β7 subunit (ITGB7) indicated for treating inflammatory bowel disease (IBD) (e.g., UC and CD). In certain embodiments, the HuPTM mAb has the amino acid sequence of etrolizumab or an antigen binding fragment thereof.

The amino acid sequence of Fab fragments of etrolizumab is provided in FIG. 17. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an ITGB7-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of IBD (e.g., UC or CD) to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0560] 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 ITGB7 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 ITGB7, such as etrolizumab, or variants thereof as detailed herein. The transgene may also encode an anti-ITGB7 antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0561] In certain embodiments, the anti-ITGB7 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of etrolizumab (having amino acid sequences of SEQ ID NOs. 65 and 66, respectively, see Table 5 and FIG. 17). 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: 135 (encoding the etrolizumab heavy chain Fab portion) and SEQ ID NO: 136 (encoding the etrolizumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0562] 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-ITGB7 antigen binding domain has a heavy chain variable domain of SEQ ID NO: 65 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG. 17. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 135 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 135). 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: 311 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0563] In certain embodiments, the anti-ITGB7 antigen-binding fragment transgene encodes an ITGB7 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: 66. In certain embodiments, the anti-ITGB7 antigen-binding fragment transgene encodes an ITGB7 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: 65. In certain embodiments, the anti-ITGB7 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: 66 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: 65. In specific embodiments, the ITGB7 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 65 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. 17) 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. 20A. In specific embodiments, the ITGB7 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 66 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. 17) 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. 20B.

[0564] In certain embodiments, the anti-ITGB7 antigen-binding fragment transgene encodes a hyperglycosylated etrolizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 65 and 66, respectively, with one or more of the following mutations: L112N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0565] In certain embodiments, the anti-ITGB7 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six etrolizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 17 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-ITGB7 antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0566] Provided are methods of treating human subjects for IBD by administration of a viral vector containing a transgene encoding an anti-ITGB7 antibody or antigen binding fragment thereof. The antibody may be etrolizumab and is, e.g., a full length or substantially full length antibody or Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with one or more of IBD.

[0567] Recombinant vector used for delivering the transgene are described in Section 5.4.3. Recombinant vectors used for delivering the transgene are described in Section 5.4.2. Such vectors should have a tropism for human liver cells and can include non-replicating rAAV, particularly those bearing an AAV8 or AAV9 capsid. The recombinant vectors, such as those shown in FIG. 17, can be administered in any manner such that the recombinant vector enters the liver, e.g., by introducing the recombinant vector into the bloodstream. See Section 5.5.2 for details regarding the methods of treatment.

[0568] Subjects to whom such gene therapy is administered can be those responsive to anti-ITGB7 therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with IBD, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-ITGB7 antibody, or considered a good candidate for therapy with an anti-ITGB7 antibody. In specific embodiments, the patients have previously been treated with etrolizumab, and have been found to be responsive to etrolizumab. To determine responsiveness, the anti-ITGB7 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

[0569] The production of the anti-ITGB7 HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of IBD accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-ITGB7 HuPTM Fab, subcutaneously, intramuscularly, or intravenously to human subjects (patients) diagnosed with IBD, to create a permanent depot in the muscle or liver that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced cells of the muscle or liver.

[0570] The cDNA construct for the anti-ITGB7 HuPTMmAb or anti-ITGB7 HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced cells of the muscle or liver. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may

have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by cells of the muscle or liver, respectively.

[0571] As an alternative, or an additional treatment to gene therapy, the anti-ITGB7 HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology and administered to patients diagnosed with a retinal disorder or cancer for whom therapy for IBD is considered appropriate.

[0572] In specific embodiments, the anti-ITGB7 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 etrolizumab as set forth in FIG. 17 (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 N60, N76, Q109, and/or N159 of the heavy chain (SEQ ID NO: 65) or Q100, N158, and/or N210 of the light chain (SEQ ID NO: 66). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of etrolizumab has a sulfation group at Y93 and/or Y94 of the heavy chain (SEQ ID NO: 65) and/or Y36, Y86, and/or Y87 of the light chain (SEQ ID NO: 66). In other embodiments, the anti-ITGB7 HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0573] 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 the disease being treated or alleviate one or more symptoms thereof. With regard to CD, efficacy can be monitored by assessing Crohn's Disease Activity Index [CDAI] over the course of treatment (e.g., see Best WR et al. (1976) Gastroenterology, Mar;70(3):439-44, "Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study."). With regard to UC, efficacy can be monitored by assessing a Mayo score and an endoscopy subscore over the course of treatment (e.g., see Lobaton et al., "The Modified Mayo Endoscopic Score (MMES): A New Index for

the Assessment of Extension and Severity of Endoscopic Activity in Ulcerative Colitis Patients," J. Crohns Colitis. 2015 Oct:9(10):846-52.

[0574] Combinations of delivery of the anti-ITGB7 HuPTM mAb or antigen-binding fragment thereof to the muscle or liver 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 IBD that could be combined with the gene therapy provided herein include but are not limited to nonsteroidal anti-inflammatory drugs (e.g., mesalamine, sulfasalazine), steroids (e.g., hydrocortisone, prednisone, budesonide), immunosuppressants (e.g., methotrexate, mercaptopurine, azathioprine), vitamins (e.g., iron, cholecalciferol), antibiotics (e.g., amino salicylic acid, metronidazole), other antibodies (e.g., infliximab, adalimumab) and administration with anti-ITGB7, including but not limited to etrolizumab.

5.3.17. Anti-Sclerostin HuPTM Constructs and Formulations for Osteoporosis

[0575] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to sclerostin (SOST) derived from anti-SOST antibody, such as romosozumab (FIG. 18), and indicated for treating osteoporosis or abnormal bone loss or weakness (e.g., treating giant cell tumor of bone, treating treatment-induced bone loss, slowing the loss of (or increasing) bone mass in breast and prostate cancer patients, preventing skeletal-related events due to bone metastasis or for decreasing bone resorption and turnover. In certain embodiments, the HuPTM mAb has the amino acid sequence of romosozumab or an antigen binding fragment thereof. The amino acid sequence of Fab fragment of this antibody is provided in FIG. 18. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an SOST-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with osteoporosis or suffering bone loss to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0576] 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 SOST 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 SOST, such as romosozumab or variants thereof as detailed herein. The transgene may also encode an anti-SOST antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0577] In certain embodiments, the anti-SOST antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of romosozumab (having amino acid sequences of SEQ ID NOs. 67 and 68, respectively, see Table 5 and FIG. 18). 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: 137 (encoding the heavy chain Fab portion) and SEQ ID NO: 138 (encoding the romosozumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0578] 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-SOST-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 67 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence contains all or a portion of the amino acid sequence ERKCCVECPPCPAPPVAG (SEQ ID NO: 220) or ERKCCVECPPCPA (SEQ ID NO: 221) as set forth in FIG 18. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 137 by the hinge region encoding sequences set forth in Table

6 (SEQ ID NO: 137). 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: 313 (Table 7) or an IgG2 Fc domain, such as SEQ ID No. 284 or as depicted in FIG. 23, 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.

[0579] In certain embodiments, the anti-SOST antigen-binding fragment transgene encodes an SOST 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: 68. In certain embodiments, the anti-SOST antigen-binding fragment transgene encodes an SOST 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: 67. In certain embodiments, the anti-SOST 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: 68 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: 67. In specific embodiments, the SOST antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 67 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. 18) 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. 20A. In specific embodiments, the SOST antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 68 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. 18) 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. 20B.

[0580] In certain embodiments, the anti-SOST antigen-binding fragment transgene encodes a hyperglycosylated romosozumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 67 and 68, respectively, with one or more of the following mutations: T118N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0581] In certain embodiments, the anti-SOST antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six romosozumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 18 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-SOST antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0582] Provided are methods of treating human subjects for osteoporosis or abnormal bone loss (for example, in breast or prostate cancer patients or due to bone metastases) by administration of a viral vector containing a transgene encoding an anti-SOST antibody, or antigen binding fragment thereof. The antibody may be romosozumab, and is e.g. a full length or substantially full length antibody or Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with osteoporosis or abnormal bone loss. Recombinant vectors used for delivering the transgene are described in Section 5.4.2. Such vectors should have a tropism for human liver or muscle cells and can include non-replicating rAAV, particularly those bearing an AAV8 or AAV9 capsid. The recombinant vector, such as shown in FIG. 18, can be administered in any manner such that the recombinant vector enters the liver or muscle tissue, e.g., by introducing the recombinant vector into the bloodstream. See Section 5.5.2 for details regarding the methods of treatment.

[0583] Subjects to whom such gene therapy is administered can be those responsive to anti-SOST therapy. In certain embodiments, the methods encompass treating patients who have been

diagnosed with osteoporosis or abnormal bone loss, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-SOST antibody or considered a good candidate for therapy with an anti-SOST antibody. In specific embodiments, the patients have previously been treated with romosozumab, and have been found to be responsive to romosozumab. To determine responsiveness, the anti-SOST 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

[0584] The production of the anti-SOST HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of osteoporosis or bone loss accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-SOST HuPTM Fab, intravenously to human subjects (patients) diagnosed with or having one or more symptoms of osteoporosis or bone loss, to create a permanent depot in the liver or muscle tissue that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced liver or muscle cells.

[0585] The cDNA construct for the anti-SOST HuPTMmAb or anti-SOST HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced liver or muscle cells. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0586] As an alternative, or an additional treatment to gene therapy, the anti-SOST HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with osteoporosis or bone loss, or for whom therapy for osteoporosis or bone loss is considered appropriate.

[0587] In specific embodiments, the anti-SOST 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 romosozumab as set forth in FIG. 18 (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 Q115, N165, N198, and/or N207 of the heavy chain (SEQ ID NO:67) or N158 and/or N210 of the light chain (SEQ ID NO:68). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of romosozumab has a sulfation group at Y94 and/or Y204 of the heavy chain (SEQ ID NO: 67) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 68). In other embodiments, the anti-SOST HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0588] 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 osteoporosis or bone loss. Efficacy may be monitored by evaluating bone tissue or skeletal events or the lack of skeletal events. For example, with regard to osteoporosis, efficacy can be monitored by a bone mineral content assessment, assessment of radiographs for vertebral fractures, or diagnostic imaging for clinical fractures confirmation.

[0589] Combinations of delivery of the anti-SOST HuPTM mAb or antigen-binding fragment thereof, to the liver 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 osteoporosis or bone loss that could be combined with the gene therapy provided herein include but are not limited to bisphosphonates (e.g., zoledronic acid), parathyroid hormone (e.g., teriparatide [PTH 1–34] and/or full-length PTH 1–84), calcium, vitamin D, anti-RANKL agents, and chemotherapy, cryotherapy, or radiotherapy in patients diagnosed with cancer, and administration with anti-SOST agents, including but not limited to romosozumab.

5.3.18. Anti-pKal HuPTM Constructs and Formulations for Angioedema and Diabetic Retinopathy

[0590] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to kallikrein (pKal), derived from

an anti-pKal antibody and indicated for treating angioedema, such as hereditary angioedema. In other embodiments, compositions and methods are provided for treating diabetic retinopathy and diabetic macular edema. In certain embodiments, the HuPTM mAb has the amino acid sequence of lanadelumab or an antigen binding fragment thereof. The amino acid sequence of Fab fragment of this antibody is provided in FIG. 19. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an pKal-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with angioedema or diabetic retinopathy and diabetic macular edema to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0591] 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 pKal 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 pKal, such as lanadelumab or variants thereof as detailed herein. The transgene may also encode an anti-pKal antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0592] In certain embodiments, the anti-pKal antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of lanadelumab (having amino acid sequences of SEQ ID NOs. 69 and 70, respectively, see Table 5 and FIG. 19). 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: 139 (encoding the lanadelumab heavy chain Fab portion) and SEQ ID NO: 140 (encoding the lanadelumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an

amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively. For diabetic retinopathy and diabetic macular edema indications, the signal sequence may direct expression and secretion in human ocular or retinal cells, for example, one of the signal sequences in Table 5.

[0593] 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-pKal-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 69 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG. 19. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 139 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 139). 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: 314 (Table 7) or an IgG1 Fc domain, such as SEQ ID No. 283 or as depicted in FIG. 23, 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.

[0594] In specific embodiments, provided are constructs encoding a full length lanadelumab, including the Fc domain, particularly nucleotide sequence L01, L02 or L03 (SEQ ID Nos: 141, 286 or 287, respectively) as described in Example 36 and Table 8, herein, which are codon optimized and, in the case of L02 and L03 depleted for CpG dimers. The transgene may also comprises a nucleotide sequence that encodes a signal peptide MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146; 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: 422. The nucleotide sequences encoding the light chain and heavy chain may be separated by a Furin-2A linker (SEQ ID NOs: 231) 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: 429, and as encoded by SEQ ID NO: 424. Expression of the lanadelumab may be directed by a constitutive or a tissue specific promoter. In certain embodiments, the transgene contains a CAG promoter (SEQ ID NO: 411) or a TBG (SEQ ID NO; 423) promoter. Alternatively, the promoter may be a tissue specific promoter (or regulatory sequence including promoter and enhancer elements) such as the APOE.hAAT regulatory sequence (SEQ ID NO: 412), LSPX1 (SEQ ID NO: 315), LSPX3, LTP1 (SEQ ID NO; 317) or LMTP6 (SEQ ID NO: 320) promoter or CK8 (SEQ ID NO: 413) promoter. See FIG. 24A for a schematic showing the genomic configuration. The transgenes may contain elements provided in Table 1. Exemplary transgenes encoding full length lanadelumab are provided in Table 8 and include CAG.LAN.F2A (SEQ ID NO: 436); CAG.LAN.T2A (SEQ ID NO; 437); TBG.LAN.T2A (SEQ ID NO; 438); APOE.hAAT.LAN.T2A (SEQ ID NO: 439); LSPX1.LAN.T2A (SEQ ID NO; 440); LSPX2.LAN.T2A (SEQ ID NO: 441); LTP1.LAN.T2A (SEQ ID NO: 442); and LMTP6.LAN.T2A (SEQ ID NO: 443). ITR sequences are added to the 5' and 3; ends of the constructs to generate the genomes. The transgenes may be packaged into AAV, particularly AAV8.

[0595] In certain embodiments, the anti-pKal antigen-binding fragment transgene encodes an pKal 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: 70. In certain embodiments, the anti-pKal antigen-binding fragment transgene encodes an pKal 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: 69. In certain embodiments, the anti-pKal 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: 70 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: 69. In specific embodiments, the pKal antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 69 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. 19) 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. 20A. In specific embodiments, the pKal antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 70 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. 19) 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. 20B.

[0596] In certain embodiments, the anti-pKal antigen-binding fragment transgene encodes a hyperglycosylated lanadelumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 69 and 70, respectively, with one or more of the following mutations: M117N (heavy chain) and/or Q159N, Q159S, and/or E194N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0597] In certain embodiments, the anti-pKal antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six lanadelumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 19 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-pKal antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0598] Provided are methods of treating human subjects for angioedema by administration of a viral vector containing a transgene encoding an anti-pKal antibody, or antigen binding fragment thereof. The antibody may be lanadelumab and is, e.g., a full length or substantially full length antibody or Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with angioedema. Recombinant

vectors used for delivering the transgene are described in Section 5.4.2 and exemplary transgenes are provided above. Such vectors should have a tropism for human liver or muscle cells and can include non-replicating rAAV, particularly those bearing an AAV8 or AAV9 capsid, preferably AAV8. The recombinant vectors, such as shown in FIG. 19, can be administered in any manner such that the recombinant vector enters the liver or muscle tissue, e.g., by introducing the recombinant vector into the bloodstream, for example by intravenous or intramuscular administration. See Section 5.5.2 for details regarding the methods of treatment.

[0599] Provided are methods of treating human subjects for diabetic retinopathy or diabetic macular edema by administration of a viral vector containing a transgene encoding an anti-pKal antibody, or antigen binding fragment thereof. See also, Section 5.3.8 above, also. The antibody may be lanadelumab and is, e.g., a full length or substantially full length antibody or Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with diabetic retinopathy or diabetic macular edema. Recombinant vectors used for delivering the transgene are described in Section 5.4.3 and exemplary transgenes are provided above. Such vectors should have a tropism for human retinal cells and can include non-replicating rAAV, particularly those bearing an AAV8 or AAV9 capsid. The recombinant vectors, such as shown in FIG. 19, can be administered in any manner such that the recombinant vector enters the retinal tissue, for example as disclosed in Section 5.5.3. In particular embodiments, the transgene is CAG.LAN.F2A (SEQ ID NO: 436); CAG.LAN.T2A (SEQ ID NO; 437); TBG.LAN.T2A (SEQ ID NO; 438); APOE.hAAT.LAN.T2A (SEQ ID NO: 439); LSPX1.LAN.T2A (SEQ ID NO; 440); LSPX2.LAN.T2A (SEQ ID NO: 441); LTP1.LAN.T2A (SEQ ID NO: 442); or LMTP6.LAN.T2A (SEQ ID NO: 443) in an AAV8 vector.

[0600] See Section 5.5.2 and 5.5.4 for details regarding the methods of treatment.

[0601] Examples 51, 53, 54 and 56 herein provide results of serum levels of lanadelumab in mice and rats administered AAV vectors encoding full length lanadelumab to assess different promoters and other regulatory elements, linkers, AAV types, modes of administration, etc. Such results inform dosage of a recombinant AAV vector encoding lanadelumab to achieve serum levels, particularly, steady state serum levels, sufficient for therapeutic efficacy. Steady state serum levels of

sufficient therapeutic efficacy may be determined through clinical studies, for example, as provided in the prescribing information for lanadelumab (*see* TAKHZYRO® Prescribing Information). In particular embodiments, the AAV8 lanadelumab vector is administered to a patient in need thereof, for example, a patient diagnosed with or suffering from HAE, at a dosage (vector genomes) sufficient for to expression of therapeutically effective levels of lanadelumab in the patient serum. In specific embodiments, the administration results in C_{max} of 9 μg/ml to 35 μg/ml, including between 12 μg/ml to 25 μg/ml, or between 20 μg/ml and 35 μg/ml; and a C_{min} of 4 μg/ml to 25 μg/ml or a C_{min} greater than 20 μg/ml, but in certain embodiments less than 200 μg/ml or 500 μg/ml. The serum or plasma concentration is preferably achieved as a steady state concentration, for example, maintaining serum or plasma levels within the C_{max} and C_{min} for at least 1 month, 2 months, 3 months, or greater than 3 months, or 1 year. In specific embodiments, administration of the AAV vector results in steady state lanadelumab plasma concentration of 5 μg/ml to 30 μg/ml or 10 μg/ml to 20 μg/ml; or 15 μg/ml to 30 μg/ml or greater than 20 μg/ml, but in certain embodiments less than 200 μg/ml or 500 μg/ml. In particular embodiments, the the lanadelumab antibody secreted into the plasma exhibits greater a greater than at least 40%, 45%, 50%, 55%, 60%, 65% or 70 reduction in pKal activity as measured by a kinetic enzymatic functional assay, for example, the assay described in Example 57. In certain embodiments, the activity of the lanadelumab antibody is measured at 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks or 12 weeks after administration of the AAV vector. The methods of treatment provided herein reduce the incidence or severity of angioedema occurrences or attacks. In particular embodiments, the angioedema occurs in the skin, the gastrointestinal tract or the upper airway.

[0602] Subjects to whom such gene therapy is administered can be those responsive to anti-pKal therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with angioedema or diabetic retinopathy, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-pKal antibody or considered a good candidate for therapy with an anti-pKal antibody. In specific embodiments, the patients have previously been treated with lanadelumab, and have been found to be responsive to lanadelumab. To determine responsiveness, the anti-pKal 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

[0603] The production of the anti-pKal 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-pKal HuPTM Fab, intravenously to human subjects (patients) diagnosed with or having one or more symptoms of angioedema, to create a permanent depot in the liver or muscle tissue that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced liver or muscle cells.

[0604] In specific embodiments, the anti-pKal 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 lanadelumab as set forth in FIG. 19 (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, Q114 and/or N164 of the heavy chain (SEQ ID NO: 69) or Q99, N157, and/or N209 of the light chain (SEQ ID NO: 70). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of lanadelumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 69) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 70). In other embodiments, the anti-pKal HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0605] In certain embodiments, the HuPTM mAb or Fab (or a hyperglycosylated derivative of either) 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 angioedema, reduce the levels of pain or discomfort for the patient, or reduce levels of autoreactive B cells and immunoglobulin producing plasma cells. Efficacy may be monitored by scoring the function, symptoms, or degree of inflammation in the affected tissue or area of the body, e.g., such as the skin, joints, kidneys, lungs,

blood cells, heart, and brain. For example, efficacy can be monitored by assessing changes in attack severity or frequency.

[0606] Combinations of delivery of the anti-pKal HuPTM mAb or antigen-binding fragment thereof, to the liver or muscle 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 angioedema that could be combined with the gene therapy provided herein include but are not limited to danazol, bradykinin receptor antagonist (e.g., icatibant), plasma kallikrein inhibitor (e.g., ecallantide), C1 esterase inhibitor, conestat alfa, anti-fibrinolytic agents (e.g., tranexamic acid), omalizumab, and fresh frozen plasma transfusions, antihistamines, and corticosteroids and administration with anti-pKal agents, including but not limited to lanadelumab.

5.3.19. Anti-IL and IL-Receptor and Other Targets HuPTM Constructs and Formulations for Autoimmune, Respiratory, and Allergic Diseases

[0607] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to interleukins (IL), interleukin receptors (ILR) (e.g., *IL31RA, IL13, IL5*, or *IL-5*), immunoglobin E (IgE), or thymic stromal lymphopoietin (TSLP), derived from anti-ILs, anti-ILRs, anti-IgE, or anti-TSLP indicated for treating one or more autoimmune-related disorders, respiratory diseases, and allergic diseases, such as atopic dermatitis, chronic idiopathic urticaria, asthma, eosinophilic asthma, or chronic obstructive pulmonary disease (COPD) (collectively referred to hereinafter as "subject AI-Ds"). In particular embodiments, the HuPTM mAb has the amino acid sequence of benralizumab, reslizumab, tralokinumab, nemolizumab, omalizumab, or tezepelumab or an antigen binding fragment of one of the foregoing. The amino acid sequences of Fab fragments of these antibodies are provided in FIGS. 29A to 29F, respectively. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an IL/ILR-binding, IgE-binding, or TSLP-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with, or having one or more symptoms of atopic dermatitis, chronic idiopathic urticaria, asthma, eosphinophilic asthma, or COPD to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0608] 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 IL/ILR, IgE, or TSLP 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 IL/ILR, such as benralizumab, reslizumab, tralokinumab, nemolizumab; IgE, such as omalizumab; or TSLP, such as tezepelumab, or variants thereof as detailed herein. The transgene may also encode an anti-IL/ILR, anti-IgE, or anti-TSLP antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0609] In certain embodiments, the anti-IL5 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of benralizumab (having amino acid sequences of SEQ ID NOs. 364 and 365, respectively, see Table 5 and FIG. 29A). 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: 380 (encoding the benralizumab heavy chain Fab portion) and SEQ ID NO: 381 (encoding the benralizumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0610] 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-IL5-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 364 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198),

EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG. 29A. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 380 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 380). 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: 394 (Table 7) or an IgG1 Fc domain, such as SEQ ID NO: 283 or as depicted in FIG. 23, 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.

[0611] In certain embodiments, the anti-IL5 antigen-binding fragment transgene encodes an IL5 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: 365. In certain embodiments, the anti-IL5 antigen-binding fragment transgene encodes an IL5 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: 364. In certain embodiments, the anti-IL5 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: 365 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: 364. In specific embodiments, the IL5 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 364 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. 29A) 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. 20A. In specific embodiments, the IL5 antigen binding fragment

comprises a light chain comprising an amino acid sequence of SEQ ID NO: 365 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. 29A) 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. 20B.

[0612] In certain embodiments, the anti-IL5 antigen-binding fragment transgene encodes a hyperglycosylated benralizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 364 and 365, respectively, with one or more of the following mutations: L116N (heavy chain) and/or Q160N, Q160S, and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0613] In certain embodiments, the anti-IL5 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six benralizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 29A 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-IL5 antibody or antigen-binding fragment thereof.

[0614] In certain embodiments, the anti-IL5R antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of reslizumab (having amino acid sequences of SEQ ID NOs. 366 and 367, respectively, see Table 4 and FIG. 29B). 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: 382 (encoding the reslizumab heavy chain Fab portion) and SEQ ID NO: 383 (encoding the reslizumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an

amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0615] 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-IL5R-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 366 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: 214), and specifically, ESKYGPPCPPCPA (SEQ ID NO: 216), ESKYGPPCPSCPA (SEQ ID NO: 217), ESKYGPPCPSCPAPEFLGGPSVFL (SEQ ID NO: 218), or ESKYGPPCPPCPAPEFLGGPSVFL (SEQ ID NO: 219) as set forth in FIG. 29B. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 382 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 382). 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: 395 (Table 7) or an IgG4 Fc domain, such as SEQ ID NO: 285 or as depicted in FIG. 23, 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.

[0616] In certain embodiments, the anti-IL5R antigen-binding fragment transgene encodes an IL5R 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: 367. In certain embodiments, the anti-IL5R antigen-binding fragment transgene encodes an IL5R 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: 366. In certain embodiments, the anti-IL5R 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: 367 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: 366. In specific embodiments, the IL5R antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 366 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. 29B) 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. 20A. In specific embodiments, the IL5R antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 367 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. 29B) 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. 20B.

[0617] In certain embodiments, the anti-IL5R antigen-binding fragment transgene encodes a hyperglycosylated reslizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 366 and 367, respectively, with one or more of the following mutations: L111N (heavy chain) and/or Q160N, Q160S, and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0618] In certain embodiments, the anti-IL5R antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six reslizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 29B 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-IL5R antibody or antigen-binding fragment thereof.

[0619] In certain embodiments, the anti-IL13 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of tralokinumab (having amino acid sequences of SEQ ID NOs. 368 and 369, respectively, see Table 5 and FIG. 29C). 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: 384 (encoding the tralokinumab heavy chain Fab portion) and SEQ ID NO: 385 (encoding the tralokinumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0620] 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-IL13-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 368 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: 214), and specifically, ESKYGPPCPPCPA (SEQ ID NO: 216), ESKYGPPCPSCPA (SEQ ID NO: 217), ESKYGPPCPSCPAPEFLGGPSVFL (SEQ ID NO: 218), or ESKYGPPCPPCPAPEFLGGPSVFL (SEQ ID NO: 219) as set forth in FIG. 29C. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 384 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 384). 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: 396 (Table 7) or an IgG4 Fc domain, such as SEQ ID NO: 285 or as depicted in FIG. 23, 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.

[0621] In certain embodiments, the anti-IL13 antigen-binding fragment transgene encodes an IL13 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: 369. In certain embodiments, the anti-IL13 antigen-binding fragment transgene encodes an IL13 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: 368. In certain embodiments, the anti-IL13 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: 369 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: 368. In specific embodiments, the IL13 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 368 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. 29C) 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. 20A. In specific embodiments, the IL13 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 369 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. 29C) 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. 20B.

[0622] In certain embodiments, the anti-IL13 antigen-binding fragment transgene encodes a hyperglycosylated tralokinumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 368 and 369, respectively, with one or more of the following mutations: L117N (heavy chain) and/or Q196N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0623] In certain embodiments, the anti-IL13 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six tralokinumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 29C 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-IL13 antibody or antigen-binding fragment thereof.

[0624] In certain embodiments, the anti-IL31RA antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of nemolizumab (having amino acid sequences of SEQ ID NOs. 370 and 371, respectively, see Table 5 and FIG. 29D). 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: 386 (encoding the nemolizumab heavy chain Fab portion) and SEQ ID NO: 387 (encoding the nemolizumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0625] 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-IL31RA-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 370 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: 433) or ERKSCVECPPCPA (SEQ ID NO: 434) as set forth in FIG. 29D. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 386 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 386). 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: 397 (Table 7) or an IgG2 Fc domain, such as SEQ ID NO: 284 or as depicted in FIG. 23, 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.

[0626] In certain embodiments, the anti-IL31RA antigen-binding fragment transgene encodes an IL31RA 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: 371. In certain embodiments, the anti-IL31RA antigen-binding fragment transgene encodes an IL31RA 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: 370. In certain embodiments, the anti-IL31RA 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: 371 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: 370. In specific embodiments, the IL31RA antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 370 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. 29D) 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. 20A. In specific embodiments, the IL31RA antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 371 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. 29D) 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. 20B.

[0627] In certain embodiments, the anti-IL31RA antigen-binding fragment transgene encodes a hyperglycosylated nemolizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 370 and 371, respectively, with one or more of the following mutations: L116N (heavy chain) and/or Q160N and/or Q160S and/or E195N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0628] In certain embodiments, the anti-IL31RA antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six nemolizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 29D 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-IL31RA antibody or antigen-binding fragment thereof.

[0629] In certain embodiments, the anti-IgE antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of omalizumab (having amino acid sequences of SEQ ID NOs. 372 and 33, respectively, see Table 5 and FIG. 29E). 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: 388 (encoding the omalizumab heavy chain Fab portion) and SEQ ID NO: 389 (encoding the omalizumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0630] 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-IgE-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 372 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: 194), and specifically, EPKSCDKTHL (SEQ ID NO: 196), EPKSCDKTHT (SEQ ID NO: 197), EPKSCDKTHTCPPCPA (SEQ ID NO: 198), EPKSCDKTHLCPPCPA (SEQ ID NO: 199), EPKSCDKTHTCPPCPAPELLGGPSVFL (SEQ ID NO: 200) or EPKSCDKTHLCPPCPAPELLGGPSVFL (SEQ ID NO: 201) as set forth in FIG. 29E. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 388 by the

hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 388). 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: 398 (Table 7) or an IgG1 Fc domain, such as SEQ ID NO: 283 or as depicted in FIG. 23, 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.

[0631] In certain embodiments, the anti-IgE antigen-binding fragment transgene encodes an IgE 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: 373. In certain embodiments, the anti-IgE antigen-binding fragment transgene encodes an IgE 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: 372. In certain embodiments, the anti-IgE 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: 373 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: 372. In specific embodiments, the IgE antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 372 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. 29E) 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. 20A. In specific embodiments, the IgE antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 373 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. 29E) 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. 20B.

[0632] In certain embodiments, the anti-IgE antigen-binding fragment transgene encodes a hyperglycosylated omalizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 372 and 373, respectively, with one or more of the following mutations: L116N (heavy chain) and/or Q164N and/or Q164S and/or E199N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0633] In certain embodiments, the anti-IgE antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six omalizumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 29E 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-IgE antibody or antigen-binding fragment thereof.

[0634] In certain embodiments, the anti-TSLP antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of tezepelumab (having amino acid sequences of SEQ ID NOs. 374 and 375, respectively, see Table 5 and FIG. 29F). 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: 390 (encoding the tezepelumab heavy chain Fab portion) and SEQ ID NO: 391 (encoding the tezepelumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0635] 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-TSLP-antigen binding domain

has a heavy chain Fab domain of SEQ ID NO: 374 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence ERKCCVECPPCPAPPVAG (SEQ ID NO: 220) or ERKCCVECPPCPA (SEQ ID NO: 221) as set forth in FIG. 29E. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 390 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 390). 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 an IgG2 Fc domain, such as SEQ ID NO: 284 or as depicted in FIG. 23, 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.

[0636] In certain embodiments, the anti-TSLP antigen-binding fragment transgene encodes an TSLP 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: 375. In certain embodiments, the anti-TSLP antigen-binding fragment transgene encodes an TSLP 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: 374. In certain embodiments, the anti-TSLP 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: 375 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: 374. In specific embodiments, the TSLP antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 374 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. 29F) 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. 20A. In specific embodiments, the TSLP antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 375 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. 29F) 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. 20B.

[0637] In certain embodiments, the anti-TSLP antigen-binding fragment transgene encodes a hyperglycosylated tezepelumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 374 and 375, respectively, with one or more of the following mutations: M117N (heavy chain) and/or and/or Q196N (light chain) (see FIGS. 20A (heavy chain) and 20B (light chain)).

[0638] In certain embodiments, the anti-TSLP antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six tezepelumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 29F 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-TSLP antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0639] Provided are methods of treating human subjects for angioedema by administration of a viral vector containing a transgene encoding an anti-IL/ILR, anti-IgE, or anti-TSLP antibody, or antigen binding fragment thereof. The antibody may be benralizumab, reslizumab, tralokinumab, nemolizumab, omalizumab, or tezepelumab and is, e.g., a full length or substantially full length antibody or Fab fragment thereof, or other antigen-binding fragment thereof. In embodiments, the patient has been diagnosed with and/or has symptoms associated with AI-Ds. Recombinant vectors used for delivering the transgene are described in Section 5.4.2. Such vectors should have a tropism for human liver or muscle cells and can include non-replicating rAAV, particularly those bearing an AAV8 or AAV9 capsid. The recombinant vectors, such as shown in FIGS, 29A-29F, can be

administered in any manner such that the recombinant vector enters the liver or muscle tissue, e.g., by introducing the recombinant vector into the bloodstream. See Section 5.5.2 for details regarding the methods of treatment.

[0640] Subjects to whom such gene therapy is administered can be those responsive to anti-IL/ILR, anti-IgE, or anti-TSLP therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with AI-Ds, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-IL/ILR, anti-IgE, or anti-TSLP antibody or considered a good candidate for therapy with an anti-IL/ILR, anti-IgE, or anti-TSLP antibody In specific embodiments, the patients have previously been treated with dupilumab, ixekizumab, secukinumab, ustekinumab, mepolizumab, benralizumab, reslizumab, tralokinumab, nemolizumab, omalizumab, or tezepelumab and have been found to be responsive to dupilumab, ixekizumab, secukinumab, ustekinumab, mepolizumab, benralizumab, reslizumab, tralokinumab, nemolizumab, omalizumab, or tezepelumab. To determine responsiveness, the anti-IL/ILR, anit-IgE, or anti-TSLP 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

[0641] The production of the anti-IL/ILR, anti-IgE, or anti-TSLP 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-IL/ILR, anti-IgE, or anti-TSLP HuPTM Fab, intravenously to human subjects (patients) diagnosed with or having one or more symptoms of angioedema, to create a permanent depot in the liver or muscle tissue that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced liver or muscle cells.

[0642] In specific embodiments, the anti-IL5 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 benralizumab as set forth in FIG. 29A (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 Q113 and/or N163 of the heavy chain (SEQ ID NO: 364) or Q100, N158, and/or N210 of the light chain (SEQ ID NO: 365). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of benralizumab has a sulfation group at Y94 of the heavy chain (SEQ ID NO: 364) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 365). In other embodiments, the anti-IL5 HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0643] In specific embodiments, the anti-IL5R 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 reslizumab as set forth in FIG. 29B (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 N35, Q108, N158, and/or N200 of the heavy chain (SEQ ID NO: 366) or Q100, N158, and/or N210 of the light chain (SEQ ID NO: 367). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of reslizumab has a sulfation group at Y93 and/or Y94 of the heavy chain (SEQ ID NO: 366) and/or Y86 and/or Y87 of the light chain (SEQ ID NO: 367). In other embodiments, the anti-IL5R HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0644] In specific embodiments, the anti-IL13 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 tralokinumab as set forth in FIG. 29C (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, N164, and/or N206 of the heavy chain (SEQ ID NO: 368) or N68 and/or N172 of the light chain (SEQ ID NO: 369). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences

of tralokinumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 368) and/or Y86 the light chain (SEQ ID NO: 369). In other embodiments, the anti-IL13 HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0645] In specific embodiments, the anti-IL31RA 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 nemolizumab as set forth in FIG. 29D (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 Q113, N163, N196, and/or N205 of the heavy chain (SEQ ID NO: 370) or N158 and/or N210 of the light chain (SEQ ID NO: 371). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of nemolizumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 370) and/or Y86 and/or Y87 the light chain (SEQ ID NO: 371). In other embodiments, the anti-IL31RA HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0646] In specific embodiments, the anti-IL31RA 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 nemolizumab as set forth in FIG. 29D (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 Q113, N163, N196, and/or N205 of the heavy chain (SEQ ID NO: 370) or N158 and/or N210 of the light chain (SEQ ID NO: 371). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of nemolizumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 370) and/or Y86 and/or Y87 the light chain (SEQ ID NO: 371). In other embodiments, the anti-IL31RA HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc

moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0647] In specific embodiments, the anti-IgE 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 omalizumab as set forth in FIG. 29E (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 N36, N59, N77, Q113, and/or N159 of the heavy chain (SEQ ID NO: 372) or Q104, N162, and/or N214 of the light chain (SEQ ID NO: 373). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of omalizumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 372) and/or Y90 and/or Y91 the light chain (SEQ ID NO: 373). In other embodiments, the anti-IgE HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0648] In specific embodiments, the anti-TSLP 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 tezepelumab as set forth in FIG. 29F (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, N80, Q114, N164, N197, and/or N206 of the heavy chain (SEQ ID NO: 374) or N68 and/or N172 of the light chain (SEQ ID NO: 375). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of tezepelumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 374) and/or Y85 and/or Y86 the light chain (SEQ ID NO: 375). In other embodiments, the anti-TSLP HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0649] In certain embodiments, the HuPTM mAb or Fab (or a hyperglycosylated derivative of either) 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 AI-Ds, reduce the levels of pain or discomfort for the patient.

[0650] Efficacy may be monitored by scoring the symptoms or degree of inflammation in the affected tissue or area of the body, e.g., such as the skin. With regard to atopic dermatitis, efficacy can be monitored by assessing changes in the affected skin or in the quality of the patient's life over the course of treatment. One or more standardized assessments can be used to assess the change. (see e.g., Physician Global Assessment (PGA), lattice system, NPF Psoriasis Score (NPF-PS), Medical Outcome Survey Short Form 36 (SF-36), the Euro QoL, Dermatology Life Quality Index (DLQI), and the Skindex; Schram et al. (2012) Allergy; 67: 99–106: "EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference" describing standardized assessments including Eczema Area and Severity Index (EASI) and the Severity Scoring of Atopic Dermatitis Index (SCORAD)). With regard to COPD and asthma, efficacy may be monitored by assessing changes in symptoms or by measuring airway function by peak expiratory flow (PEV) or spirometry (e.g. FEV_1). With regard to eosinophilic asthma, efficacy can be monitored by assessing changes in asthma exacerbations, and in lung function (e.g. airflow obstruction, forced vital capacity, and residual volume), and asthma control. With regard to chronic idiopathic urticaria, efficacy can be monitored by assessing changes in the affected skin or changes in the degree of swelling of the lips, eyelids, or throat.

[0651] Combinations of delivery of the anti-IL/ILR, anti-IgE, or anti-TSLP HuPTM mAb or antigen-binding fragment thereof, to the liver or muscle 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 subject AI-Ds that could be combined with the gene therapy provided herein include but are not limited to antihistamines, H2 blockers, topical corticosteroids, or antidepressants for chronic idiopathic urticaria, aminosalicylates, immunomodulatory agents (e.g., azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX)), oral or topical corticosteroids (e.g., prednisone or

budesonide), topical calcineurin inhibitors, inhaled corticosteroids for asthma or COPD, leukotriene modifiers, high-dose inhaled corticosteroids, and oral corticosteroids, and/or topical steroids for atopic dermatitis and administration with anti-IL/ILR, anti-IgE, or anti-TSLP agents, including but not limited to dupilumab, ixekizumab, secukinumab, ustekinumab, mepolizumab, benralizumab, reslizumab, tralokinumab, nemolizumab, omalizumab, or tezepelumab.

5.3.20 HuPTM Constructs and Formulations for Non-infectious Uveitis

[0652] 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), interleukin-6 (IL6), TNFα, or C5, derived from an anti-IL6R, anti-IL6, anti-TNFα, or anti-C5 antibody, such as satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, tesidolumab, ravulizumab, adalimumab, infliximab, or golimumab (FIGS. 10B and 10D, 12A-12C, and 16A-I,), indicated for treating uveitis, preferably non-infectious posterior uveitis (NIU).

[0653] In certain embodiments, provided are methods of treating panuveitis or intermediate uveitis, including associated with NIU. Accordingly, methods of treatment of NIU and panuveitis and intermediate uveitis are also provided. Uveitis is inflammation in the eye and may be associated with systemic autoimmune disorders, including Behcet's disease, sarcoidosis, juvenile chronic arthritis, Vogt-Koyanagi-Harada syndrome, multiple sclerosis, and other autoimmune indications, particularly T cell-mediated autoimmune indications. In other embodiments, the NIU is associated with ocular autoimmune disease, such as, birdshot retinochoroidopathy, multifocal choroiditis, and other white dot syndromes. Methods of treatment include methods of inhibiting, and reducing the progression of vision loss and ocular damage, such as macular scarring or atrophy, lamellar macular hole formation and optic atrophy. In particular, the method of treatment may improve visual acuity (for example, defined by the best corrected visual acuity (BCVA) score or slow the loss of visual acuity and or ocular damage. Other manifestations of NIU include vitreous haze, macular retinitis and vasculitis. Accordingly, provided are methods of treating, reducing the severity of and reducing the progression of vitreous haze, macular retinitis and/or vasculitis associated with NIU by administering the HuPTM.

[0654] In certain embodiments, the HuPTM mAb has the amino acid sequence of satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, tesidolumab, ravulizumab, adalimumab, infliximab, or golimumab, or an antigen binding fragment thereof. Amino acid sequences of Fab fragments of the antibody are provided in FIGS. 10B, 10D, 12A-12C, or 16A-I. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an IL6R-binding, IL6-binding, TNFα-binding, or C5-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 to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0655] 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, IL6, TNFα, or C5 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, IL6, TNFα, or C5, such as satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, tesidolumab, ravulizumab, adalimumab, infliximab, golimumab, or variants thereof as detailed herein. The transgene may also encode an anti-IL6R, anti-IL6, anti-TNFα, or anti-C5 antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.). Transgenes are described in detail in Sections 5.3.9, 5.3.11, or 5.3.15 above.

[0656] In preferred embodiments, the antibody that binds to TNFα is adalimumab, or variants thereof as described herein. For example, a full length or Fab adalimumab antibody may be delivered by administering an adeno-associated virus (AAV) vector encoding an adalimumab mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof), such as CAG.adalimumab.IgG (SEQ ID NO: 451) or CAG.adalimumab.Fab (SEQ ID NO: 453).

[0657] Sequences encoding the anti-C5, anti-IL6R, anti-IL6, or and TNF-α antigen binding fragment transgenes can be found in Table 5 (amino acid) or Table 6 (nucleotide) or FIG. 10A, 10D,

12A-12C, or 16A-16I. 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, one or more cells forming the retina. The signal sequence may have the amino acid sequence of MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 2 that correspond to the proteins secreted by one or more cells forming the retina. Alternatively, the signal sequence may be appropriate for expression in muscle or liver cells, such as those listed in Tables 3 and 4 *infra*.

[0658] The anti-C5, anti-IL6, anti-IL6R, or anti-TNFα antigen binding domain can have heavy chain Fab domain of SEQ ID NOS: 39, 362, 45, 47, 49, 331, 333, 335, 337, 339, 341, 59, or 61 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequences as set forth in FIGS. 10B, 10D, 12A-C, or 16A-16I and as described in detail in Sections 5.3.9, 5.3.11, or 5.3.15.

[0659] 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 NOS: 301, 303, 304, 305, 309, 310, 355-359, or 394-398 (Table 7) or an IgG1, IgG2, or IgG4 Fc domain, such as SEQ ID No. 283, 284, or 285 or as depicted in FIG. 23, 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.

[0660] The anti-C5, anti-IL6, anti-IL6R, or anti-TNFα antigen binding domain can have light chain Fab domain of SEQ ID NOS: 40, 363, 46, 48, 50, 332, 334, 336, 338, 340, 342, 60, or 62 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequences as set forth in FIGS. 10B, 10D, 12A-C, or 16A-16I and as described in detail in Sections 5.3.9, 5.3.11, or 5.3.15.

[0661] In certain embodiments, the anti-C5, anti-IL6, anti-IL6R, or anti-TNFα antigen-binding fragment transgene encodes an C5, IL6, IL6R, or 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 sequences set forth in SEQ ID

NOS: 40, 363, 46, 48, 50, 332, 334, 336, 338, 340, 342, 60, or 62. In certain embodiments, the anti-C5, anti-IL6, anti-IL6R, or anti-TNFα antigen-binding fragment transgene encodes an C5, IL6, IL6R, or 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 sequences set forth in SEQ ID NOS: 39, 362, 45, 47, 49, 331, 333, 335, 337, 339, 341, 59, or 61. In certain embodiments, the anti-C5, anti-IL6, anti-IL6R, or 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 sequences set forth in SEQ ID NOS: 40, 363, 46, 48, 50, 332, 334, 336, 338, 340, 342, 60, or 62 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: 39, 362, 45, 47, 49, 331, 333, 335, 337, 339, 341, 59, or 61. In specific embodiments, the anti-C5, anti-IL6, anti-IL6R, or anti-TNFα antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NOS: 39, 362, 45, 47, 49, 331, 333, 335, 337, 339, 341, 59, or 61 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 FIGS. 10B, 10D, 12A-C, or 16A-I) 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. 20A. In specific embodiments, the C5, IL6, IL6R, or TNFα antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NOS: 40, 363, 46, 48, 50, 332, 334, 336, 338, 340, 342, 60, or 62 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. 10B, 10D, 12A-C, or 16A-I) 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. 20B.

[0662] In certain embodiments, the anti-C5, anti-IL6, anti-IL6R, or anti-TNFα antigen-binding fragment transgene encodes a hyperglycosylated Fab, comprising a heavy chain and a light

chain of SEQ ID NOs: 39 and 40, 362 and 363, 45 and 46, 47 and 48, 49 and 50, 331 and 332, 333 and 334, 335 and 336, 337 and 338, 339 and 340, 341 and 342, 59 and 60, or 61 and 62, respectively, with one or more of the following mutations as indicated in FIGS. 20A (heavy chain) and 20B (light chain).

[0663] In certain embodiments, the anti-C5, anti-IL6, anti-IL6R, or anti-TNFα antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six CDRs which are underlined in the heavy and light chain variable domain sequences of FIGS. 10B, 10D, 12A-12C, or 16A-16I 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-C5, anti-IL6, anti-IL6R, or anti-TNFα antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0664] Also provided are methods of treating human subjects for non-infectious uveitis by administration of a viral vector containing a transgene encoding an anti-IL6R, anti-IL6, anti-TNFα, or anti-C5 antibody, or antigen binding fragment thereof. The antibody may be satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, tesidolumab, ravulizumab, adalimumab, infliximab, or golimumab, and is, e.g., a Fab fragment thereof, or other antigen-binding fragment thereof.

[0665] In embodiments, the patient has been diagnosed with and/or has symptom(s) associated with non-infectious uveitis. Recombinant vectors used for delivering the transgene are described in Section 5.4.3. Such vectors should have a tropism for human retina-type cells and can include non-replicating rAAV, particularly those bearing an AAV8 capsid. Alternatively, vectors bearing an AAV2.7m8 or AAV9 capsid can be used for ocular indications. The recombinant vectors, such as the ones shown in FIGS. 10B, 10D, 12A-C, or 16A-I, can be administered in any manner such that the recombinant vector enters the retina, e.g., by introducing the recombinant vector into the eye. See Section 5.5.3 for details regarding the methods of treatment.

[0666] Subjects to whom such gene therapy is administered can be those responsive to anti-IL6R, anti-IL6, anti-TNFα, or anti-C5 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 anti-IL6R, anti-IL6, anti-TNFα, or anti-C5 antibody or considered a good candidate for therapy with an anti-IL6R, anti-IL6, anti-TNFα, or anti-C5 antibody. In specific embodiments, the patients have previously been treated with satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, tesidolumab, ravulizumab, adalimumab, infliximab, or golimumab, or inebilizumab, and have been found to be responsive to satralizumab, sarilumab, tocilizumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, tesidolumab, ravulizumab, adalimumab, infliximab, or golimumab. In other embodiments, the patients have been previously treated with an anti-IL6R, anti-IL6, anti-TNFα, or anti-C5 antibody. To determine responsiveness, the anti-IL6R, anti-IL6, anti-TNFα, or anti-C5 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

[0667] The production of the anti-IL6R, anti-IL6, anti-TNFα, or anti-C5 HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of non-infectious uveitis accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-IL6R, anti-IL6, anti-TNFα, or anti-C5 HuPTM Fab, subretinally, intravitreally, or suprachoroidally to human subjects (patients) diagnosed with or having one or more symptoms of non-infectious uveitis, to create a permanent depot in the retina that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced cells of the retina.

[0668] 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. Efficacy may also be assessed by monitoring best corrected visual acuity (BCVA) and/or performing applanation tonometry, slit-lamp examination of the anterior and posterior segments, dilated indirect ophthalmoscopy, and optical coherence tomography (OTC), and comparing to baseline values.

[0669] In specific embodiments, the anti-C5, anti-IL6, anti-IL6R, or 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 as set forth in FIG. 10B, 10D, 12A-12C, or 16A-16I (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. Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences has a sulfation group of the heavy chain and/or of the light chain. In other embodiments, the anti-C5, anti-IL6, anti-IL6R, or anti-TNFα HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region. See Sections 5.3.9, 5.3.11, or 5.3.15 for a detailed description of Y-sulfation sites and other post-translational modifications.

[0670] 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 monitoring vision acuity, redness of the eye, sensitivity to light, and/or eye pain. For example, efficacy can be monitored by assessing change in vision acuity, redness of the eye, sensitivity to light, and/or eye pain from baseline.

[0671] Combinations of delivery of the anti-IL6, anti-IL6R, anti-TNFα, or anti-C5 HuPTM mAb or antigen-binding fragment thereof, to the retina 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 (oral and/or inhaled)), and others and administration with anti-TNFα, anti-IL6, anti-IL6R, or anti-C5 agents, including but not limited to adalimumab, infliximab, or golimumab.

Constructs for delivery to Retinal Cell Types

[0672] Sections 5.3.9, 5.3.11, and 5.3.15 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 C5, TNFα, IL6R, and IL6. Such recombinant vectors used for delivering the transgene can have a tropism for one or more human retina cell types. Such vectors can include non-replicating recombinant adeno-associated virus vectors ("rAAV"), e.g., those bearing an AAV8 capsid. Alternatively, an AAV vector bearing an AAV2.7m8 capsid can be used. 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.

[0673] In preferred embodiments, provided are constructs for gene therapy administration to a human subject, comprising an AAV vector, which comprises a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143) or an AAV2.7m8 capsid (SEQ ID NO: 142); and a viral or artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs) wherein the expression cassette comprises a transgene encoding the heavy and light chains of the therapeutic antibody, operably linked to one or more regulatory sequences that control expression of the transgene in human cells (e.g., retina cell or liver cell types) that express and deliver the therapeutic antibody in a therapeutically appropriate manner as disclosed herein. In certain embodiments, the encoded AAV8 or AAV2.7m8 capsid has the sequence of SEQ ID NO: 143 or 142 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, particularly substitutions with amino acid residues found in the corresponding position in other AAV capsids, for example, in the SUBS row of FIG. 21 which provides

a comparison of the amino acid sequences of the capsid sequences of various AAVs, highlighting amino acids appropriate for substitution at different positions within the capsid sequence.

[0674] In some embodiments, the HuPTM mAb or antigen binding fragment thereof, including the HuPTM Fab transgene should be controlled by appropriate expression control elements for expression of the HuPTM Fab or HuPTM Mab in human retina or liver cell types, for example, CB7 promoter (a chicken β-actin promoter and CMV enhancer/CAG, SEQ ID NO: 411), or tissue-specific promoters, and can include other expression control elements that enhance expression of the transgene driven by the vector. Promoter sequences and sequences of other regulatory elements, such as introns, are provided in Table 1.

[0675] Gene therapy constructs for antibodies or Fabs are designed such that both the heavy and light chains are expressed. More specifically, 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. The leader sequence for each of the heavy and light chains is, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Section 5.1.5, supra, provides specific IRES, 2A, and other linker sequences that can be used with the methods and compositions provided herein. In specific embodiments, the linker is a Furin-2A linker, for example a Furin-F2A linker RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 231) or a Furin-T2A linker RKRR(GSG)EGRGSLLTCGDVEENPGP (SEQ ID NO: 429). In specific embodiments, the transgene is a nucleotide sequence that encodes the following: Signal sequence-heavy chain Fab portion-Furin-(F/T)2A linker-signal sequence-light chain Fab portion. See FIGS. 10B and 10D for sequences for tesidolumab and ravulizumab Fab expression, respectively; FIGS. 12A to 12C for a sequence for adalimumab, infliximab, and golimumab Fab expression, respectively; and FIGS. 16A to 16I for sequences for satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, and tocilizumab, inebilizumab Fab expression, respectively. In an alternative embodiment, the construct also comprises the nucleotide sequence encoding the Fc domain for the therapeutic antibody (see Table 7 or FIG. 23) for expression of the full length mAb. Nucleotide sequences for adalimumab mAb and Fab single chain construct transgenes are described in Table 17.

Nucleic acid sequences coding for the component sequences of the heavy and light chains of adalimumab, either the full length (SEQ ID NOS: 444 and 448) or Fab fragments (components encoded by SEQ ID NOS: 445 and 446 (heavy chain) and 498-450 (light chain) are also provided.

[0676] In a specific embodiment, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) Control elements, which include a) the CB7 promoter (SEQ ID NO: 411), comprising the CMV enhancer/chicken β-actin promoter, b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy and light chains of the C5-binding, TNFα-binding, IL6R-binding, and IL6-binding Fab, separated by a self-cleaving furin (F)/(F/T)2A linker (SEQ ID NOS: 231 or 429, respectively), ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is provided in FIG. 1.

[0677] In a preferred embodiment, the construct described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) Control elements, which include a) the CB7 promoter (SEQ ID NO: 411), comprising the CMV enhancer/chicken β-actin promoter, b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the component sequences of the heavy and light chains of adalimumab, either the full length (SEQ ID NOS: 444 and 448) or Fab fragments (components encoded by SEQ ID NOS: 445 and 446 (heavy chain) and 498-450 (light chain), separated by a self-cleaving furin (F)/T2A linker (SEQ ID NOS: 429), ensuring expression of equal amounts of the heavy and the light chain polypeptides.

[0678] 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: 143) or of an AAV2.7m8 (SEQ ID NO: 142); and an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats, wherein the expression cassette comprises a transgene encoding an anti-C5 anti-TNFα, anti-IL6R, and anti-IL6 mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in one or more retina cell types (such as 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).

[0679] In a preferred embodiment, provided is an AAV comprising a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143); and an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding an adalimumab mAb (SEQ ID NO: 451), or an antigen-binding fragment thereof (SEQ ID NO: 453), operably linked to one or more regulatory sequences that control expression of the transgene in one or more retina cell types (such as 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).

Administration for delivering to retinal type cells

[0680] Therapeutically effective doses of the recombinant vector described above should be administered in any manner such that the recombinant vector enters the retina, e.g., by introducing the recombinant vector directly into the eye. In specific, embodiments, the vector is administered subretinally (a surgical procedure performed by trained retinal surgeons that involves a partial vitrectomy with the subject under local anesthesia, and injection of the gene therapy into the retina, or intravitreally, or suprachoroidally such as by microinjection or microcannulation. Subretinal, intravitreal 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. The expression of the encoded anti-C5, anti-TNFα, anti-IL6R, and anti-IL6 antibody results in delivery and maintenance of the transgene product in the retina. Pharmaceutical compositions suitable for administration comprise a suspension of the recombinant vector comprising the transgene encoding the anti-C5, anti-TNFα, anti-IL6R, and anti-IL6 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.

Full Length Expression of mAb in Retinal Cell Types

[0681] In a specific embodiment for expressing an intact or substantially intact mAb in retinal 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) the CB7 promoter, comprising the CMV enhancer/chicken β-actin promoter, b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy chain Fab of an anti-C5 (e.g., tesidolumab, ravulizumab), anti-TNFα (e.g., adalimumab, infliximab, and golimumab), anti-IL6R (e.g., satralizumab, sarilumab, and tocilizumab), anti-IL6 (e.g. siltuximab, clazakizumab, sirukumab, olokizumab, and gerilimzumab), an Fc polypeptide associated with the therapeutic antibody (Table 6 and X) or of the same IgG isotype as the native form of the therapeutic antibody, such as an IgG isotype amino acid sequence from FIG. 23, and a light chain of an anti-C5 (e.g., tesidolumab and ravulizumab), anti-TNFα (e.g., adalimumab, infliximab, and golimumab), anti-IL6R (e.g., satralizumab, sarilumab, and tocilizumab), and anti-IL6 (e.g. siltuximab, clazakizumab, sirukumab, olokizumab, and gerilimzumab), wherein the heavy chain (Fab and Fc polypeptide) and light chain are separated by a self-cleaving furin (F)/(T/F)2A or flexible linker, ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is provided in FIG. 1.

[0682] 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: 143) or of an AAV2.7m8 (SEQ ID NO: 142); 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-C5, anti-TNFα, anti-IL6R, or anti-IL6 mAb, operably linked to one or more regulatory sequences that control expression of the transgene in one or more retina cell types (such as 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).

5.3.21. Anti-C5 HuPTM Constructs and Formulations for Myasthenia Gravis

[0683] Compositions and methods are described for the delivery of HuPTM mAbs and antigen-binding fragments thereof, such as HuPTM Fabs, that bind to complement component 5 (anti-C5) derived from anti-C5 antibody, such as ravulizumab (FIG. 10D), and indicated for treating myasthenia gravis. In certain embodiments, the HuPTM mAb has the amino acid sequence of romosozumab or an antigen binding fragment thereof. The amino acid sequence of Fab fragment of this antibody is provided in FIG. 10D. Delivery may be accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding an C5-binding HuPTM mAb (or an antigen binding fragment and/or a hyperglycosylated derivative or other derivative, thereof) to patients (human subjects) diagnosed with myasthenia gravis to create a permanent depot that continuously supplies the human PTM, e.g., human-glycosylated, transgene product.

Transgenes

[0684] 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 C5 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 C5, such as ravulizumab or variants thereof as detailed herein. The transgene may also encode an anti-C5 antigen binding fragment that contains additional glycosylation sites (*e.g.*, see Courtois et al.).

[0685] In certain embodiments, the anti-C5 antigen-binding fragment transgene comprises the nucleotide sequences encoding the heavy and light chains of the Fab portion of ravulizumab (having amino acid sequences of SEQ ID NOs. 362 and 363, respectively, see Table 5 and FIG. 10D). 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: 378 (encoding the ravulizumab heavy chain Fab portion) and SEQ ID NO: 379 (encoding the ravulizumab 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 liver cells (e.g., hepatocytes) or muscle cells. The signal sequence may have the amino acid sequence of

MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0686] 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-C5-antigen binding domain has a heavy chain Fab domain of SEQ ID NO: 362 with additional hinge region sequence starting after the C-terminal valine (V), contains all or a portion of the amino acid sequence contains all or a portion of the amino acid sequence ERKCCVECPPCPAPPVAG (SEQ ID NO: 220) or ERKCCVECPPCPA (SEQ ID NO: 221) as set forth in FIG 10D. These hinge regions may be encoded by nucleotide sequences at the 3' end of SEQ ID NO: 378 by the hinge region encoding sequences set forth in Table 6 (SEQ ID NO: 378). 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: 393 (Table 7) or an IgG2 Fc domain, such as SEQ ID No. 284 or as depicted in FIG. 23, 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.

[0687] In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes an C5 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: 363. In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes an C5 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: 362. In certain embodiments, the anti-C5 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: 363 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: 362. In specific embodiments, the C5 antigen binding fragment comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 362 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. 10D) 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. 20A. In specific embodiments, the C5 antigen binding fragment comprises a light chain comprising an amino acid sequence of SEQ ID NO: 363 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. 10D) 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. 20B.

[0688] In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes a hyperglycosylated ravulizumab Fab, comprising a heavy chain and a light chain of SEQ ID NOs: 363 and 362, respectively, with one or more of the following mutations L117N (heavy chain), Q160N or Q160S (light chain), and/or E195N (light chain) (see FIGS. 20A (heavy chain) and B (light chain)).

[0689] In certain embodiments, the anti-C5 antigen-binding fragment transgene encodes an antigen-binding fragment and comprises the nucleotide sequences encoding the six romosozumab CDRs which are underlined in the heavy and light chain variable domain sequences of FIG. 10D 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-C5 antibody or antigen-binding fragment thereof.

Gene Therapy Methods

[0690] Provided are methods of treating human subjects for myasthenia gravis by administration of a viral vector containing a transgene encoding an anti-C5 antibody, or antigen binding fragment thereof. The antibody may be ravulizumab, and is e.g. a full length or substantially full length antibody or Fab fragment thereof, or other antigen-binding fragment thereof. In

embodiments, the patient has been diagnosed with and/or has symptoms associated with myasthenia gravis. Recombinant vectors used for delivering the transgene are described in Section 5.4.2. Such vectors should have a tropism for human liver or muscle cells and can include non-replicating rAAV, particularly those bearing an AAV8 or AAV9 capsid. The recombinant vector, such as shown in FIG. 10D, can be administered in any manner such that the recombinant vector enters the liver or muscle tissue, e.g., by introducing the recombinant vector into the bloodstream. See Section 5.5.2 for details regarding the methods of treatment.

[0691] Subjects to whom such gene therapy is administered can be those responsive to anti-C5 therapy. In certain embodiments, the methods encompass treating patients who have been diagnosed with myasthenia gravis, or have one or more symptoms associated therewith, and identified as responsive to treatment with an anti-C5 antibody or considered a good candidate for therapy with an anti-C5 antibody. In specific embodiments, the patients have previously been treated with ravulizumab, and have been found to be responsive to ravulizumab. To determine responsiveness, the anti-C5 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

[0692] The production of the anti-C5 HuPTM mAb or HuPTM Fab, should result in a "biobetter" molecule for the treatment of myasthenia gravis accomplished via gene therapy – e.g., by administering a viral vector or other DNA expression construct encoding the anti-C5 HuPTM Fab, intravenously to human subjects (patients) diagnosed with or having one or more symptoms of osteoporosis or bone loss, to create a permanent depot in the liver or muscle tissue that continuously supplies the fully-human post-translationally modified, e.g., human-glycosylated, sulfated transgene product produced by transduced liver or muscle cells.

[0693] The cDNA construct for the anti-C5 HuPTMmAb or anti-C5 HuPTM Fab should include a signal peptide that ensures proper co- and post-translational processing (glycosylation and protein sulfation) by the transduced liver or muscle cells. For example, the signal sequence may be MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Alternatively, the signal sequence may have an

amino acid sequence selected from any one of the signal sequences set forth in Table 3 or 4 that correspond to the proteins secreted by myocytes or hepatocytes, respectively.

[0694] As an alternative, or an additional treatment to gene therapy, the anti-C5 HuPTM mAb or HuPTM Fab can be produced in human cell lines by recombinant DNA technology, and administered to patients diagnosed with osteoporosis or bone loss, or for whom therapy for osteoporosis or bone loss is considered appropriate.

[0695] In specific embodiments, the anti-C5 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 ravulizumab as set forth in FIG. 10D (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 N63, N106, Q114, N164, N197, and/or N206 of the heavy chain (SEQ ID NO: 362) or N28, Q100, N158, and/or N210 of the light chain (SEQ ID NO: 363). Alternatively or in addition to, the HuPTM mAb or antigen binding-fragment thereof with the heavy and light chain variable domain sequences of ravulizumab has a sulfation group at Y94 and/or Y95 of the heavy chain (SEQ ID NO: 362) and/or Y86 and/or Y86 of the light chain (SEQ ID NO: 363). In other embodiments, the anti-C5 HuPTM mAb or antigen-binding fragment thereof does not contain detectable NeuGc moieties and/or does not contain detectable alpha-Gal moieties. In certain embodiments, the HuPTM mAb is a full length or substantially full length mAb with an Fc region.

[0696] 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 myasthenia gravis. Efficacy may be monitored by evaluating changes in endurance or fatigability from baseline, e.g. by using the Quantitative Myasthenia Gravis Score (QMGS), Manual Muscle Test (MMT), and/or Myasthenia Muscle Score (see Barnett C *et al*. Neurol Clin. 2018 May; 36(2): 339–353.). For example, the QMSC score assesses changes in ptosis, diplopia, orbicularis oculi weakness, swallowing a cup of water, speech, percent predicted forced vital capacity, grip strength (2 items), arm endurance (2 items), leg endurance (2 items), and neck flexion endurance.

[0697] Combinations of delivery of the anti-C5 HuPTM mAb or antigen-binding fragment thereof, to the liver 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 myasthenia gravis that could be combined with the gene therapy provided herein include but are not limited to pyridostigmine, corticosteroids, or immunosuppressants, and administration with anti-C5 agents, including but not limited to ravulizumab.

TABLE 5. Table of Fab Fragment Amino Acid Sequences

mAb	Chain/ SEQ ID NO.	Sequence
Solanezumab	Heavy/ SEQ ID NO: 1	EVQLVESGGG LVQPGGSLRL SCAASGFTFS RYSMSWVRQA PGKGLELVAQ INSVGNSTYY PDTVKGRFTI SRDNAKNTLY LQMNSLRAED TAVYYCASGD YWGQGTLVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKKV EPKSCD +/- KTHT(or KTHL) +/-CPPCPA +/- PELLGGPSVFL
Solanezumab	Light/ SEQ ID NO: 2	DVVMTQSPLS LPVTLGQPAS ISCRSSQSLI YSDGNAYLHW FLQKPGQSPR LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHVP WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
GSK933776	Heavy/ SEQ ID NO: 3	EVQLVESGGG LVQPGGSLRL SCA A/V SGFTFS DNGMAWVRQA PGKGLEWVSF ISNLAYSIDY ADTVTGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCVSGT WFAYWGQGTL VTVSSASTKG PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KKVEPKSCD +/- KTHT (or KTHL)+/- CPPCPA +/- PELAGAPSVFL
GSK933776	Light/ SEQ ID NO: 4	DIVMTQSPLS LPVTPGEPAS ISCRVSQSLL HSNGYTYLHW YLQKPGQSPQ LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQTRHVP YTFGGGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC

mAb	Chain/ SEQ ID NO.	Sequence
AL-001	Heavy/ SEQ ID NO: 5	QVQLVQSGAE VKKPGASVKV SCKASGYTFT KYYMSWVRQA PGQGLEWMGI INPIGGSTSY AQKFQGRVTM TRDTSTSTVY MELSSLRSED TAVYYCARDP SGIALAGPAS RGYQGMDVWG QGTTVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCD +/- KTHT (or KTHL) +/-CPPCPA +/- PELLGGPSVFL
AL-001	Light/ SEQ ID NO: 6	EIVMTQSPAT LSVSPGERAT LSCRASQSVS SNLAWYQQKP GQAPRLLIYG ASTRATGIPA RFSGSGSGTE FTLTISSLQS EDFAVYYCQQ ARLGPWTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
ABBV-8E12	Heavy/ SEQ ID NO: 7	EVKVVESGGG LVQPGGSMKL SCVVSGFTFS NYWVNWVRQA PGKGLEWVAQ IRLKSDNYAT HYEESVKGRF TISRDDSKSS VYLQMNNLRA EDSGIYYCTN WEDYWGQGTT VTVSSASTKG PSVFPLAPCS RSTSESTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS LGTKTYTCNV DHKPSNTKVD KRVESKY +/- GPPCPPCPA (or GPPCPSCPA)+/- PEFLGGPSVFL
ABBV-8E12	Light/ SEQ ID NO: 8	DIVLTQSPDS LAVSLGERAT ISCRASQSVS TSRYSYIHWY QQKPGQFPKL LIKYASNLES GVPSRFSGSG SGTDFTLNIH PLEPEDFATY YCHHSWEIPL TFGQGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
UCB-0107	Heavy/ SEQ ID NO: 9	EVQLQESGPG LVKPSETLSL TCTVSGFSLT SNDIAWIRQP PGKGLEWMGT IWTDGSTNYN A/T AVQSRVTIS VDTSKNQFSL KLSSVTAADT AVYYCARHRL YYGAFDYWGQ GTMVTVSSAS TKGPSVFPLA PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTKTYT CNVDHKPSNT KVDKRVESKY +/- GPPCPPCPA (or GPPCPSCPA)+/- PEFLGGPSVFL
UCB-0107	Light/ SEQ ID NO: 10	DIVMTQTPLS LSVTPGQPAS ISCRSSQSLE YSDGYTYLEW YLQKPGQSPQ LLIYEVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCFQATHNP YTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC

mAb	Chain/ SEQ ID NO.	Sequence
NI-105	Heavy/ SEQ ID NO: 11	QVQLVESGGG VVQPGRSLRV SCAASGFTFS SYDMHWVRQA PGKGLEWVAV IWFDGSNEFY ADSVKGRFTI SRDNSKNTLF QMNSLRAEDT AVYYCARDLG ASVTTSNAEN FHHWGQGTLV TVSSASTKGP SVFPLAPSSK STSGGTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL GTQTYICNVN HKPSNTKVDK KVEPKSCD +/- KTHT (or KTHL)+/- CPPCPA +/- PELAGAPSVFL
NI-105	Light/ SEQ ID NO: 12	SYELTQPPSV SVSPGQTARI TCSGDALPKR YVYWYQQKSG QAPVLVIYED SKRPSGIPET FSGSSSGTMA TLTISGAQVE DEADYYCYST DSNGHHWVFG GGTKLTVLGQ PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TCS
VX15/2503	Heavy/ SEQ ID NO: 13	QVQLVQSGAE VKKPGSSVKV SCKASGYSFS DYYMHWVRQA PGQGLEWMGQ INPTTGGASY NQKFKGKATI TVDKSTSTAY MELSSLRSED TAVYYCARYY YGRHFDVWGQ GTTVTVSSAS TKGPSVFPLA PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVTVSSVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKY +/- GPPCPPCPA(or GPPCPSCPA) +/- PEFLGGPSVFL
VX15/2503	Light/ SEQ ID NO: 14	DIVMTQSPDS LAVSLGERAT INCKASQSVD YDGDSYMNWY QQKPGQPPKL LIYAASNLES GVPDRFSGSG SGTDFTLTIS SLQAEDVAVY YCQQSNEDPY TFGQGTKLEI KFIFPPSDEQ LKSGTASVVC LLNNFYPREA KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC EVTHQGLSSP VTKSFNRGEC
Prasinezumab	Heavy/ SEQ ID NO: 15	EVQLVESGGG LVQPGGSLRL SCAASGFTFS NYGMSWVRQA PGKGLEWVAS ISSGGGSTYY PDNVKGRFTI SRDDAKNSLY LQMNSLRAED TAVYYCARGG AGIDYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD +/- KTHT(or KTHL) +/-CPPCPA +/- PELLGGPSVFL
Prasinezumab	Light/ SEQ ID NO: 16	DIQMTQSPSS LSASVGDRVT ITCKSIQTLL YSSNQKNYLA WFQQKPGKAP KLLIYWASIR KSGVPSRFSG SGSGTDFTLT ISSLQPEDLA TYYCQQYYSY PLTFGGGTKL EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC EVTHQGLSSP VTKSFNRGEC

mAb	Chain/ SEQ ID NO.	Sequence
NI-202	Heavy/ SEQ ID NO: 17	EVQLVESGAE VKKPGASVKV SCKASGYTFT NYAMHWVRQA PGQRLEWMGW INAGNGKRKY SQKFQDRVTI NRDTSASTIY MELSSLGSED TAVYYCAREE DHAGSGSYLS MDVWGQGTLV TVSSASTKGP SVFPLAPSSK STSGGTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL GTQTYICNVN HKPSNTKVDK RVEPKSCD +/- KTHT(or KTHL) +/- CPPCPA +/- PELLGGPSVFL
NI-202	Light/ SEQ ID NO: 18	DIQMTQSPSS LSASVGDRVT ITCKSIQTLL YSSNQKNYLA WFQQKPGKAP KLLIYWASIR KSGVPSRFSG SGSGTDFTLT ISSLQPEDLA TYYCQQYYSY PLTFGGGTKL EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC EVTHQGLSSP VTKSFNRGEC
MEDI-1341/TAK 341	Heavy/ SEQ ID NO: 19	EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSS ISHLGGSTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAGGA NHGKYYYGMD KWGQGTTVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKRV EPKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PEFEGGPSVFL
MEDI-1341/TAK 341	Light/ SEQ ID NO: 20	QAVLTQPASL SASPGASASL TCTLRSGAPL PKYRIYWYQQ KPGSPPQYLL RYKSDADKHQ GSGVPSRFSG SKDASANAGI LLISGLQSED EADYYCMVWD HGVWYFGGGT KLTVLGQPKA APSVTLFPPS SEELQANKAT LVCLISDFYP GAVTVAWKAD SSPVKAGVET TTPSKQSNNK YAASSYLSLT PEQWKSHRSY SCQVTHEGST VEKTVAPTEC S
NI-204.10D12	Heavy/ SEQ ID NO: 21	EVQLVESGGD LVRPGGSLRL SCVASGFTFS NYWMHWVRQA PGQRPVWVSR TNTDGRNTAY ADYAKGRFTI SRDNAKSTLY LQLNSLRAED TAVYFCARLR RNVADQITHN YYMDVWGKGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PEAAGGPSVFL
NI-204.10D12	Light/ SEQ ID NO: 22	DIQMTQSPSS LSASVGDRVT ACRASQSVGT YLNWYQQKRG KAPKLLIFAA SSLQSGVPSR FSGSGSGTDF TLTISSLQPE DFATYYCQQS YSSPPTFGQG TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC
NI-204.12G7	Heavy/ SEQ ID NO: 23	QVQLVQSGAE VKKPGASVTL SCKASGYTFT AYYIHWVRQA REQGLEWMGV INPSTGTTFY AQNFPDRVSV TRDTSTSTVF MELHNLKSED TAVYYCARAI SEHGSGSYSP YYWGQGTLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV

mAb	Chain/ SEQ ID NO.	Sequence
		TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCD +/- KTHT (or KTHL)+/- CPPCPA +/- PEAAGGPSVFL
NI-204.12G7	Light/ SEQ ID NO: 24	SYELTQPPSV SVSLGQMAAI TCSGEALPKK YGYWYQQKPG QVPVLLIYRD VERPSGVPDR FSGSSSGTMV TLTISGVQAE DEADYYCLSA DSSGTWVFGG GTKLTVLGQP KANPTVTLFP PSSEELQANK ATLVCLISDF YPGAVTVAWK ADGSPVKAGV ETTKPSKQSN NKYAASSYLS LTPEQWKSHR SYSCQVTHEG STVEKTVAPT ECS
Eptinezumab	Heavy/ SEQ ID NO: 25	EVQLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWVRQA PGKGLEWVGV IGINGATYYA SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDARVE PKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Eptinezumab	Light/ SEQ ID NO: 26	QVLTQSPSSL SASVGDRVTI NCQASQSVYH NTYLAWYQQK PGKVPKQLIY DASTLASGVP SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
Fremanezumab	Heavy/ SEQ ID NO: 27	EVQLVESGGG LVQPGGSLRL SCAASGFTFS NYWISWVRQA PGKGLEWVAE IRSESDASAT HYAEAVKGRF TISRDNAKNS LYLQMNSLRA EDTAVYYCLA YFDYGLAIQN YWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVE +/- CPPCPA +/- PPVAG
Fremanezumab	Light/ SEQ ID NO: 28	EIVLTQSPAT LSLSPGERAT LSCKASKRVT TYVSWYQQKP GQAPRLLIYG ASNRYLGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCSQ SYNYPYTFGQ GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Galcanezumab	Heavy/ SEQ ID NO: 29	QVQLVQSGAE VKKPGSSVKV SCKASGYTFG NYWMQWVRQA PGQGLEWMGA IYEGTGKTVY IQKFADRVTI TADKSTSTAY MELSSLRSED TAVYYCARLS DYVSGFGYWG QGTTVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY TCNVDHKPSN TKVDKRVESK Y+/-GPPCPPCPA (or GPPCPSCPA) +/- PEAAGGPSVFL

mAb	Chain/ SEQ ID NO.	Sequence
Galcanezumab	Light/ SEQ ID NO: 30	DIQMTQSPSS LSASVGDRVT ITCRASKDIS KYLNWYQQKP GKAPKLLIYY TSGYHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GDALPPTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Sevacizumab	Heavy/ SEQ ID NO: 31	EVQLVESGGG LVKPGGSLRL SCAASGFSFS NNDVMCWVRQ APGKGLEWIG CIMTTDVVTE YANWAKSRFT VSRDSAKNSV YLQMNSLRAE DTAVYFCARD SVGSPLMSFD LWGPGTLVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKKV EPKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Sevacizumab	Light/ SEQ ID NO: 32	DIQMTQSPSS LSASVGDRVT INCQASQSIY NNNELSWYQQ KPGKPPKLLI YRASTLASGV PSRFSGSGSG TDFTLTISSL QPEDVATYYC GGYKSYSNDG NGFGGGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
LKA-651 NVS2	Heavy/ SEQ ID NO: 33	EVQLVQSGAE VKKPGESLKI SCKGSGYSFT SYWIGWVRQM PGKGLEWMGW IDPYRSEIRY SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARVS SEPFDSWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKRVEPKSC D +/- KTHT (or KTHL) CPPCPA +/- PELLGGPSVFL
LKA-651 NVS2	Light/ SEQ ID NO: 34	SYVLTQPPSV SVAPGKTARI TCSGDKLGDH YAYWYQQKPG QAPVLVIYDD SKRPSGIPER FSGSNSGNTA TLTISRVEAG DEADYYCATW TFEGDYVFGG GTKLTVLGQP KAAPSVTLFP PSSEELQANK ATLVCLISDF YPGAVTVAWK ADSSPVKAGV ETTTPSKQSN NKYAASSYLS LTPEQWKSHR SYSCQVTHEG STVEKTVAPT ECS
LKA-651 NVS3	Heavy/ SEQ ID NO: 35	QVQLQQSGPG LVKPSQTLSL TCAISGDSVS SNTAAWNWIR QSPSRGLEWL GVIYYRSKWY NDYAVSVKSR ITINPDTSKN QFSLQLNSVT PEDTAVYYCA RSVPGGDPGL EHAFAYWGRG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKRVEPKSC D +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL

mAb	Chain/ SEQ ID NO.	Sequence
LKA-651 NVS3	Light/ SEQ ID NO: 36	SYVLTQPPSV SVAPGKTARI TCSGDNLGTY YVEWYQQKPG QAPVLVIYDD SDRPSGIPER FSGSNSGNTA TLTISRVEAG DEADYYCASF ASWSDSVFGG GTKLTVLGQP KAAPSVTLFP PSSEELQANK ATLVCLISDF YPGAVTVAWK ADSSPVKAGV ETTTPSKQSN NKYAASSYLS LTPEQWKSHR SYSCQVTHEGS TVEKTVAPTE CS
Ascrinvacumab	Heavy/ SEQ ID NO: 37	QVQLQESGPG LVKPSQTLSL TCTVSGGSIS SGEYYWNWIR QHPGKGLEWI GYIYYSGSTY YNPSLKSRVT ISVDTSKNQF SLKLSSVTAA DTAVYYCARE SVAGFDYWGQ GTLVTVSSAS TKGPSVFPLA PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSNFGTQTYT CNVDHKPSNT KVDKTVERKC CVE +/- CPPCPA +/- PPVAG
Ascrinvacumab	Light/ SEQ ID NO: 38	EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GTSSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPITFG QGTRLEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGN SQESVTEQDS KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
Tesidolumab	Heavy/ SEQ ID NO: 39	EVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IGPFFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARDT PYFDYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PEAAGGPSVFL
Tesidolumab	Light/ SEQ ID NO: 40	SYELTQPLSV SVALGQTARI TCSGDSIPNY YVYWYQQKPG QAPVLVIYDD SNRPSGIPER FSGSNSGNTA TLTISRAQAG DEADYYCQSF DSSLNAEVFG GGTKLTVLGQ PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TECS
Carotuximab	Heavy/ SEQ ID NO: 41	EVKLEESGGG LVQPGGSMKL SCAASGFTFS DAWMDWVRQS PEKGLEWVAE IRSKASNHAT YYAESVKGRF TISRDDSKSS VYLQMNSLRA EDTGIYYCTR WRRFFDSWGQ GTTLTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKKVEPKS CD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Carotuximab	Light/ SEQ ID NO: 42	QIVLSQSPAI LSASPGEKVT MTCRASSSVS YMHWYQQKPG SSPKPWIYAT SNLASGVPVR FSGSGSGTSY SLTISRVEAE DAATYYCQQW SSNPLTFGAG TKLELKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE

mAb	Chain/ SEQ ID NO.	Sequence
		SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC
ANX-007	Heavy/ SEQ ID NO: 43	QVQLVQSGAE LKKPGASVKV SCKSSGYHFT SYWMHWVKQA PGQGLEWIGV IHPNSGSINY NEKFESRVTI TVDKSTSTAY MELSSLRSED TAVYYCAGER DSTEVLPMDY WGQGTTVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKRVE PKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
ANX-007	Light/ SEQ ID NO: 44	DVQITQSPSS LSASLGERAT INCRASKSIN KYLAWYQQKP GKAPKLLIYS GSTLQSGIPA RFSGSGSGTD FTLTISSLEP EDFAMYYCQQ HNEYPLTFGQ GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Adalimumab	Heavy/ SEQ ID NO: 45	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: 46	DIQMTQSPSS LSASVGDRVT ITCRASQGIR NYLAWYQQKP GKAPKLLIYA ASTLQSGVPS RFSGSGSGTD FTLTISSLQP EDVATYYCQR YNRAPYTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Infliximab	Heavy/ SEQ ID NO: 47	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 KT HL)+/- CPPCPA +/- PELLGGPSVFL
Infliximab	Light/ SEQ ID NO: 48	DILLTQSPAI LSVSPGERVS FSCRASQFVG SSIHWYQQRT NGSPRLLIKY ASESMSGIPS RFSGSGSGTD FTLSINTVES EDIADYYCQQ SHSWPFTFGS GTNLEVKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

mAb	Chain/ SEQ ID NO.	Sequence
Golimumab	Heavy/ SEQ ID NO: 49	SKLQVQLVES GGGVVQPGRS LRLSCAASGF IFSSYAMHWV RQAPGNGLEW VAFMSYDGSN KKYADSVKGR FTISRDNSKN TLYLQMNSLR AEDTAVYYCA RDRGIAAGGN YYYYGMDVWG QGTTVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCD +/- KT HT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Golimumab	Light/ SEQ ID NO: 50	AGSEIVLTQS PATLSLSPGE RATLSCRASQ SVYSYLAWYQ QKPGQAPRLL IYDASNRATG IPARFSGSGS GTDFTLTISS LEPEDFAVYY CQQRSNWPPF TFGPGTKVDI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
Elezanumab	Heavy/ SEQ ID NO: 51	EVQLVQSGAE VKKPGASVKV SCKASGYTFT SHGISWVRQA PGQGLDWMGW ISPYSGNTNY AQKLQGRVTM TTDTSTSTAY MELSSLRSED TAVYYCARVG SGPYYYMDVW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCD +/- KTHT (or KT HL)+/- CPPCPA +/- PEAAGGPSVFL
Elezanumab	Light/ SEQ ID NO: 52	QSALTQPRSV SGSPGQSVTI SCTGTSSSVG DSIYVSWYQQ HPGKAPKLML YDVTKRPSGV PDRFSGSKSG NTASLTISGL QAEDEADYYC YSYAGTDTLF GGGTKVTVLG QPKAAPSVTL FPPSSEELQA NKATLVCLIS DFYPGAVTVA WKADSSPVKA GVETTTPSKQ SNNKYAASSY LSLTPEQWKS HRSYSCQVTH EGSTVEKTVA PTECS
NI-301	Heavy/ SEQ ID NO: 53	QVQLQESGPG LVKPSETLSL TCSVSGGSII SRSSYWGWIR QPPGKGLEWI GGIYHSGNTY DNPSLKSRLT MSVDTSKNQF SLNLRSVTAA DTAVYYCARI VPGGDAFDIW GQGTMVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCD +/- KTHT (or KTHL)+/- CPPCPA +/- PELLGGPSVFL
NI-301	Light/ SEQ ID NO: 54	DIQMTQSPSS LSASVGDRVT ACRASQSVGT YLNWYQQKRG KAPKLLIFAA SSLQSGVPSR FSGSGSGTDF TLTISSLQPE DFATYYCQQS YSSPPTFGQG TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

mAb	Chain/ SEQ ID NO.	Sequence
PRX-004	Heavy/ SEQ ID NO: 55	EVQLVESGGG LIQPGGSLRL SCAASGFTFS NYAMSWVRQA PGKGLEWVSS ISSGGSTYYP DSVKGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARYYY GQYFDFWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKRVEPKSC D +/- KT HT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
PRX-004	Light/ SEQ ID NO: 56	DIVMTQSPSS LSASVGDRVT ITCKASQDVS TTVAWYQQKP GKAPKLLIYS ASYRSTGVPS RFSGSGSGTD FTLTISSLQP EDFAVYYCQQ HYSTPLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Pamrevlumab	Heavy/ SEQ ID NO: 57	EVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IGPFFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARDT PYFDYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKRVEPKSCD +/- KTHT (or KTHL)+/- CPPCPA +/- PEAAGGPSVFL
Pamrevlumab	Light/ SEQ ID NO: 58	SYELTQPLSV SVALGQTARI TCSGDSIPNY YVYWYQQKPG QAPVLVIYDD SNRPSGIPER FSGSNSGNTA TLTISRAQAG DEADYYCQSF DSSLNAEVFG GGTKLTVLGQ PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TECS
Satralizumab	Heavy/ SEQ ID NO: 59	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
Satralizumab	Light/ SEQ ID NO: 60	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: 61	EVQLVESGGG LVQPGRSLRL SCAASRFTFD DYAMHWVRQA PGKGLEWVSG ISWNSGRIGY ADSVKGRFTI SRDNAENSLF LQMNGLRAED TALYYCAKGR DSFDIWGQGT MVTVSSASTK

mAb	Chain/ SEQ ID NO.	Sequence
		GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD +/- KTHT (or KTHL)+ /- CPPCPA +/- PELLGGPSVFL
Sarilumab	Light/ SEQ ID NO: 62	DIQMTQSPSS VSASVGDRVT ITCRASQGIS SWLAWYQQKP GKAPKLLIYG ASSLESGVPS RFSGSGSGTD FTLTISSLQP EDFASYYCQQ ANSFPYTFGQ GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Inebilizumab	Heavy/ SEQ ID NO: 63	EVQLVESGGG LVQPGGSLRL SCAASGFTFS SSWMNWVRQA PGKGLEWVGR IYPGDGDTNY NVKFKGRFTI SRDDSKNSLY LQMNSLKTED TAVYYCARSG FITTVRDFDY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKRVE PKSCD +/- KTHT (or K THL)+/- CPPCPA+/- PELLGGPSVFL
Inebilizumab	Light/ SEQ ID NO: 64	EIVLTQSPD FQSVTPKEK VTITCRASE SVDTFGISF MNWFQQKPD QSPKLLIHE ASNQGSGVP SRFSGSGSG TDFTLTINS LEAEDAATY YCQQSKEVP FTFGGGTKV EIKRTVAAP SVFIFPPSD EQLKSGTAS VVCLLNNFY PREAKVQWK VDNALQSGN SQESVTEQD SKDSTYSLS STLTLSKAD YEKHKVYAC EVTHQGLSS PVTKSFNRGEC
Etrolizumab	Heavy/ SEQ ID NO: 65	EVQLVESGGG LVQPGGSLRL SCAASGFFIT NNYWGWVRQA PGKGLEWVGY ISYSGSTSYN PSLKSRFTIS RDTSKNTFYL QMNSLRAEDT AVYYCARTGS SGYFDFWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Etrolizumab	Light/ SEQ ID NO: 66	DIQMTQSPSS LSASVGDRVT ITCRASESVD DLLHWYQQKP GKAPKLLIKY ASQSISGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GNSLPNTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Romosozumab	Heavy/ SEQ ID NO: 67	EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVRQA PGQGLEWMGE INPNSGGAGY NQKFKGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARLG YDDIYDDWYF DVWGQGTTVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSNFG TQTYTCNVDH KPSNTKVDKT VERKCCVE +/- CPPCPA+/- PPVAG

mAb	Chain/ SEQ ID NO.	Sequence
Romosozumab	Light/ SEQ ID NO: 68	DIQMTQSPSS LSASVGDRVT ITCRASQDIS NYLNWYQQKP GKAPKLLIYY TSRLLSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GDTLPYTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Lanadelumab	Heavy/ SEQ ID NO: 69	EVQLLESGGG LVQPGGSLRL SCAASGFTFS HYIMMWVRQA PGKGLEWVSG IYSSGGITVY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAYRR IGVPRRDEFD IWGQGTMVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKRV EPKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Lanadelumab	Light/ SEQ ID NO: 70	DIQMTQSPST LSASVGDRVT ITCRASQSIS SWLAWYQQKP GKAPKLLIYK ASTLESGVPS RFSGSGSGTE FTLTISSLQP DDFATYYCQQ YNTYWTFGQG TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC
Siltuximab	Heavy/ SEQ ID NO: 331	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: 332	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: 333	EVQLVESGGG LVQPGGSLRL SCAASGFSLS NYYVTWVRQA PGKGLEWVGI IYGSDETAYA TSAIGRFTIS RDNSKNTLYL QMNSLRAEDT AVYYCARDDS SDWDAKFNLW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Clazakizumab	Light/ SEQ ID NO: 334	AIQMTQSPSS LSASVGDRVT ITCQASQSIN NELSWYQQKP GKAPKLLIYR ASTLASGVPS RFSGSGSGTD FTLTISSLQP DDFATYYCQQ GYSLRNIDNA FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG

mAb	Chain/ SEQ ID NO.	Sequence
		NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC
Sirukumab	Heavy/ SEQ ID NO: 335	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: 336	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: 337	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: 338	DIQMTQSPSS LSASVGDRVT ITCQASQDIG ISLSWYQQKP GKAPKLLIYN ANNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCLQ HNSAPYTFGQ GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Gerilimzumab	Heavy/ SEQ ID NO: 339	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
Gerilimzumab	Light/ SEQ ID NO: 340	QSALTQPPSV SGTPGQSVTI SCAGANNDIG TYAYVSWYQQ LPGTAPKLMI YKVTTRASGI PDRFSGSKSG NTASLTISGL QAEDEADYYC ASYRNFNNAV FGTGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS

mAb	Chain/ SEQ ID NO.	Sequence
Tocilizumab	Heavy/ SEQ ID NO: 341	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: 342	DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY TSRLHSGVPS RFSGSGSGTD FTFTISSLQP EDIATYYCQQ GNTLPYTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Lecanemab	Heavy/ SEQ ID NO: 360	EVQLVESGGG LVQPGGSLRL SCSASGFTFS SFGMHWVRQA PGKGLEWVAY ISSGSSTIYY GDTVKGRFTI SRDNAKNSLF LQMSSLRAED TAVYYCAREG GYYYGRSYYT MDYWGQGTTV TVSSASTKGP SVFPLAPSSK STSGGTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL GTQTYICNVN HKPSNTKVDK RVEPKSCD +/- KTHT +/- CPPCPA +/- PELLGGPSVFL
Lecanemab	Light/ SEQ ID NO: 361	DVVMTQSPLS LPVTPGAPAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLRI SRVEAEDVGI YYCFQGSHVP PTFGPGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
Ravulizumab	Heavy/ SEQ ID NO:362	QVQLVQSGAE VKKPGASVKV SCKASGHIFS NYWIQWVRQA PGQGLEWMGE ILPGSGHTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVE +/- CPPCPA+/- PPVAG
Ravulizumab	Light/ SEQ ID NO: 363	DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Benralizumab	Heavy/ SEQ ID NO: 364	EVQLVQSGAE VKKPGASVKV SCKASGYTFT SYVIHWVRQR PGQGLAWMGY INPYNDGTKY NERFKGKVTI TSDRSTSTVY MELSSLRSED TAVYLCGREG IRYYGLLGDY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV

mAb	Chain/ SEQ ID NO.	Sequence
		SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKKV EPKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Benralizumab	Light/ SEQ ID NO: 365	DIQMTQSPSS LSASVGDRVT ITCGTSEDII NYLNWYQQKP GKAPKLLIYH TSRLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GYTLPYTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Reslizumab	Heavy/ SEQ ID NO:366	EVQLVESGGG LVQPGGSLRL SCAVSGLSLT SNSVNWIRQA PGKGLEWVGL IWSNGDTDYN SAIKSRFTIS RDTSKSTVYL QMNSLRAEDT AVYYCAREYY GYFDYWGQGT LVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTKTYTCN VDHKPSNTKV DKRV ESKY+/- GPPCPPCPA (or GPPCP SCPA) +/- PEFLGGPSVFL
Reslizumab	Light/ SEQ ID NO: 367	DIQMTQSPSS LSASVGDRVT ITCLASEGIS SYLAWYQQKP GKAPKLLIYG ANSLQTGVPS RFSGSGSATD YTLTISSLQP EDFATYYCQQ SYKFPNTFGQ GTKVEVKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Tralokinumab	Heavy/ SEQ ID NO: 368	QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYGLSWVRQA PGQGLEWMGW ISANNGDTNY GQEFQGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARDS SSSWARWFFD LWGRGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK PSNTKVDKRV ESKY+/- *GPPCPPCP A (or GPPCPSCPA) +/- PEFLGG*PSVFL
Tralokinumab	Light/ SEQ ID NO:369	SYVLTQPPSV SVAPGKTARI TCGGNIIGSK LVHWYQQKPG QAPVLVIYDD GDRPSGIPER FSGSNSGNTA TLTISRVEAG DEADYYCQVW DTGSDPVVFG GGTKLTVLGQ PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TECS
Nemolizumab	Heavy/ SEQ ID NO: 370	QVQLVQSGAE VKKPGASVKV SCKASGYTFT GYIMNWVRQA PGQGLEWMGL INPYNGGTDY NPQFQDRVTI TADKSTSTAY MELSSLRSED TAVYYCARDG YDDGPYTLET WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSNFGTQ TYTCNVDHKP SNTKVDKTVERK SCVE +/- CPPCPA +/-P PVAG

mAb	Chain/ SEQ ID NO.	Sequence
Nemolizumab	Light/ SEQ ID NO: 371	DIQMTQSPSS LSASVGDRVT ITCQASEDIY SFVAWYQQKP GKAPKLLIYN AQTEAQGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQH HYDSPLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
Omalizumab	Heavy/ SEQ ID NO: 372	EVQLVESGGG LVQPGGSLRL SCAVSGYSIT SGYSWNWIRQ APGKGLEWVA SITYDGSTNY ADSVKGRFTI SRDDSKNTFY LQMNSLRAED TAVYYCARGS HYFGHWHFAV WGQGTLVTVS SGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKA EPKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Omalizumab	Light/ SEQ ID NO: 373	DIQLTQSPSS LSASVGDRVT ITCRASQSVD YDGDSYMNWY QQKPGKAPKL LIYAASYLES GVPSRFSGSG SGTDFTLTIS SLQPEDFATY YCQQSHEDPY TFGQGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
Tezepelumab	Heavy/ SEQ ID NO:374	QMQLVESGGG VVQPGRSLRL SCAASGFTFR TYGMHWVRQA PGKGLEWVAV IWYDGSNKHY ADSVKGRFTI TRDNSKNTLN LQMNSLRAED TAVYYCARAP QWELVHEAFD IWGQGTMVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVE +/- CPPCPA +/- P PVAG
Tezepelumab	Light/ SEQ ID NO: 375	SYVLTQPPSV SVAPGQTARI TCGGNNLGSK SVHWYQQKPG QAPVLVVYDD SDRPSWIPER FSGSNSGNTA TLTISRGEAG DEADYYCQVW DSSSDHVVFG GGTKLTVLGQ PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TECS

TABLE 6. Table of Fab Fragment Nucleic Acid Sequences

mAb	Chain/ SEQ ID NO.	Sequence
Solanezumab	Heavy/ SEQ ID NO: 71	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGGTACAGCATGAG CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGCTGGTGGCCCAGATCAAC AGCGTGGGCAACAGCACCTACTACCCCGACACCGTGAAGGGCAGGTTCACCA TCAGCAGGGACAACGCCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAG GGCCGAGGACACCGCCGTGTACTACTGCGCCAGCGGCGACTACTGGGGCCAG GGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCC CCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGC GCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCC TGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCA GACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAG AAGGTGGAGCCCAAGAGCTGCGAC +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Solanezumab	Light/ SEQ ID NO: 72	GACGTGGTGATGACCCAGAGCCCCCTGAGCCTGCCCGTGACCCTGGGCCAGC CCGCCAGCATCAGCTGCAGGAGCAGCCAGAGCCTGATCTACAGCGACGGCAA CGCCTACCTGCACTGGTTCCTGCAGAAGCCCGGCCAGAGCCCCAGGCTGCTG ATCTACAAGGTGAGCAACAGGTTCAGCGGCGTGCCCGACAGGTTCAGCGGCA GCGGCAGCGGCACCGACTTCACCCTGAAGATCAGCAGGGTGGAGGCCGAGGA CGTGGGCGTGTACTACTGCAGCCAGAGCACCCACGTGCCCTGGACCTTCGGC CAGGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCA TCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTG CCTGCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCA AGGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTA CGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGC CCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
GSK933776	Heavy/ SEQ ID NO: 73	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCC(GCC/GTG)AGCGGCTTCACCTTCAGCGACAACGG CATGGCCTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCTTC ATCAGCAACCTGGCCTACAGCATCGACTACGCCGACACCGTGACCGGCAGGT TCACCATCAGCAGGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAG CCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGTGAGCGGCACCTGGTTC GCCTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGG GCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCAC CGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTG AGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGC TGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAG CAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAAC ACCAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGCGAC +/- AAGACCC ACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGGCCGGCGCCCCCAGCGTGTTCCTG

mAb	Chain/ SEQ ID NO.	Sequence
GSK933776	Light/ SEQ ID NO: 74	GACATCGTGATGACCCAGAGCCCCCTGAGCCTGCCCGTGACCCCCGGCGAGC CCGCCAGCATCAGCTGCAGGGTGAGCCAGAGCCTGCTGCACAGCAACGGCTA CACCTACCTGCACTGGTACCTGCAGAAGCCCGGCCAGAGCCCCCAGCTGCTG ATCTACAAGGTGAGCAACAGGTTCAGCGGCGTGCCCGACAGGTTCAGCGGCA GCGGCAGCGGCACCGACTTCACCCTGAAGATCAGCAGGGTGGAGGCCGAGGA CGTGGGCGTGTACTACTGCAGCCAGACCAGGCACGTGCCCTACACCTTCGGC GGCGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCA TCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTG CCTGCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCA AGGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTA CGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGC CCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
AL-001	Heavy/ SEQ ID NO: 75	CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCG TGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCACCAAGTACTACATGAG CTGGGTGAGGCAGGCCCCCGGCCAGGGCCTGGAGTGGATGGGCATCATCAAC CCCATCGGCGGCAGCACCAGCTACGCCCAGAAGTTCCAGGGCAGGGTGACCA TGACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGAGCAGCCTGAG GAGCGAGGACACCGCCGTGTACTACTGCGCCAGGGACCCCAGCGGCATCGCC CTGGCCGGCCCCGCCAGCAGGGGCTACCAGGGCATGGACGTGTGGGGCCAGG GCACCACCGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCC CCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGC CTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCG CCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCT GTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAG ACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGA GGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
AL-001	Light/ SEQ ID NO: 76	GAGATCGTGATGACCCAGAGCCCCGCCACCCTGAGCGTGAGCCCCGGCGAGA GGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCAACCTGGCCTG GTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGGCGCCAGC ACCAGGGCCACCGGCATCCCCGCCAGGTTCAGCGGCAGCGGCAGCGGCACCG AGTTCACCCTGACCATCAGCAGCCTGCAGAGCGAGGACTTCGCCGTGTACTA CTGCCAGCAGGCCAGGCTGGGCCCCTGGACCTTCGGCGGCGGCACCAAGGTG GAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC
ABBV-8E12	Heavy/ SEQ ID NO: 77	GAGGTGAAGGTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCA TGAAGCTGAGCTGCGTGGTGAGCGGCTTCACCTTCAGCAACTACTGGGTGAA CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGGCCCAGATCAGG CTGAAGAGCGACAACTACGCCACCCACTACGAGGAGAGCGTGAAGGGCAGGT TCACCATCAGCAGGGACGACAGCAAGAGCAGCGTGTACCTGCAGATGAACAA CCTGAGGGCCGAGGACAGCGGCATCTACTACTGCACCAACTGGGAGGACTAC TGGGGCCAGGGCACCACCGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCA

mAb	Chain/ SEQ ID NO.	Sequence
		GCGTGTTCCCCCTGGCCCCCTGCAGCAGGAGCACCAGCGAGAGCACCGCCGC CCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGG AACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGCAGA GCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCT GGGCACCAAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACACCAAG GTGGACAAGAGGGTGGAGAGCAAGTAC +/- GGCCCCCCCTGCCCCCCCTG CCCCGCC (GGCCCCCCCCTGCCCCAGCTGCCCCGCC)+/- CCCGAGTTCCTGGGCGGCCCCAGCGTGTTCCTG
ABBV-8E12	Light/ SEQ ID NO: 78	GACATCGTGCTGACCCAGAGCCCCGACAGCCTGGCCGTGAGCCTGGGCGAGA GGGCCACCATCAGCTGCAGGGCCAGCCAGAGCGTGAGCACCAGCAGGTACAG CTACATCCACTGGTACCAGCAGAAGCCCGGCCAGTTCCCCAAGCTGCTGATC AAGTACGCCAGCAACCTGGAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCG GCAGCGGCACCGACTTCACCCTGAACATCCACCCCCTGGAGCCCGAGGACTT CGCCACCTACTACTGCCACCACAGCTGGGAGATCCCCCTGACCTTCGGCCAG GGCACCAAGCTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGG ACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
UCB-0107	Heavy/ SEQ ID NO: 79	GAGGTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAGCGAGACCC TGAGCCTGACCTGCACCGTGAGCGGCTTCAGCCTGACCAGCAACGACATCGC CTGGATCAGGCAGCCCCCCGGCAAGGGCCTGGAGTGGATGGGCACCATCTGG ACCGACGGCAGCACCAACTACAAC(GCC/ACC)GCCGTGCAGAGCAGGGTGA CCATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGT GACCGCCGCCGACACCGCCGTGTACTACTGCGCCAGGCACAGGCTGTACTAC GGCGCCTTCGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCAGCGCCA GCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCTGCAGCAGGAGCACCAG CGAGAGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCC GTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCC CCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGT GCCCAGCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAG CCCAGCAACACCAAGGTGGACAAGAGGGTGGAGAGCAAGTAC +/- GGCCCC CCCTGCCCCCCCTGCCCCGCC (GGCCCCCCCTGCCCCAGCTGCCCCGCC) +/- CCCGAGTTCCTGGGCGGCCCCAGCGT GTTCCTG
UCB-0107	Light/ SEQ ID NO: 80	GACATCGTGATGACCCAGACCCCCCTGAGCCTGAGCGTGACCCCCGGCCAGC CCGCCAGCATCAGCTGCAGGAGCAGCCAGAGCCTGGAGTACAGCGACGGCTA CACCTACCTGGAGTGGTACCTGCAGAAGCCCGGCCAGAGCCCCCAGCTGCTG ATCTACGAGGTGAGCAACAGGTTCAGCGGCGTGCCCGACAGGTTCAGCGGCA GCGGCAGCGGCACCGACTTCACCCTGAAGATCAGCAGGGTGGAGGCCGAGGA CGTGGGCGTGTACTACTGCTTCCAGGCCACCCACAACCCCTACACCTTCGGC CAGGGCACCAAGCTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCA TCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTG CCTGCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCA

mAb	Chain/ SEQ ID NO.	Sequence
		AGGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTA CGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGC CCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
NI-105	Heavy/ SEQ ID NO: 81	CAGGTGCAGCTGGTGGAGAGCGGCGGCGGCGTGGTGCAGCCCGGCAGGAGCC TGAGGGTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACGACATGCA CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGGCCGTGATCTGG TTCGACGGCAGCAACGAGTTCTACGCCGACAGCGTGAAGGGCAGGTTCACCA TCAGCAGGGACAACAGCAAGAACACCCTGTTCCAGATGAACAGCCTGAGGGC CGAGGACACCGCCGTGTACTACTGCGCCAGGGACCTGGGCGCCAGCGTGACC ACCAGCAACGCCGAGAACTTCCACCACTGGGGCCAGGGCACCCTGGTGACCG TGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAG CAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTAC TTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCG TGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAG CGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAAC GTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAGCCCAAGA GCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGGCCGGCGCCCCCAGC GTGTTCCTG
NI-105	Light/ SEQ ID NO: 82	AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGTGAGCCCCGGCCAGACCG CCAGGATCACCTGCAGCGGCGACGCCCTGCCCAAGAGGTACGTGTACTGGTA CCAGCAGAAGAGCGGCCAGGCCCCCGTGCTGGTGATCTACGAGGACAGCAAG AGGCCCAGCGGCATCCCCGAGACCTTCAGCGGCAGCAGCAGCGGCACCATGG CCACCCTGACCATCAGCGGCGCCCAGGTGGAGGACGAGGCCGACTACTACTG CTACAGCACCGACAGCAACGGCCACCACTGGGTGTTCGGCGGCGGCACCAAG CTGACCGTGCTGGGCCAGCCCAAGGCCGCCCCCAGCGTGACCCTGTTCCCCC CCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAG CGACTTCTACCCCGGCGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCC GTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACAACAAGT ACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAG GAGCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAGAAGACCGTG GCCCCCACCTGCAGC
VX15/2503	Heavy/ SEQ ID NO: 83	CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCAGCAGCG TGAAGGTGAGCTGCAAGGCCAGCGGCTACAGCTTCAGCGACTACTACATGCA CTGGGTGAGGCAGGCCCCCGGCCAGGGCCTGGAGTGGATGGGCCAGATCAAC CCCACCACCGGCGGCGCCAGCTACAACCAGAAGTTCAAGGGCAAGGCCACCA TCACCGTGGACAAGAGCACCAGCACCGCCTACATGGAGCTGAGCAGCCTGAG GAGCGAGGACACCGCCGTGTACTACTGCGCCAGGTACTACTACGGCAGGCAC TTCGACGTGTGGGGCCAGGGCACCACCGTGACCGTGAGCAGCGCCAGCACCA AGGGCCCCAGCGTGTTCCCCCTGGCCCCCTGCAGCAGGAGCACCAGCGAGAG CACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC GTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCG TGACCGTGAGCAGCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGT GGTGACCGTGCCCAGCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTG GACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGAGCAAGTAC +/-GGCCCCCCCTGCCCCCCCTGCCCCGCC (GGCCCCCCCTGCCCCAGCTGCCCCGCC) +/- CCCGAGTTCCTGGGCG GCCCCAGCGTGTTCCTG

mAb	Chain/ SEQ ID NO.	Sequence
VX15/2503	Light/ SEQ ID NO: 84	GACATCGTGATGACCCAGAGCCCCGACAGCCTGGCCGTGAGCCTGGGCGAGA GGGCCACCATCAACTGCAAGGCCAGCCAGAGCGTGGACTACGACGGCGACAG CTACATGAACTGGTACCAGCAGAAGCCCGGCCAGCCCCCCAAGCTGCTGATC TACGCCGCCAGCAACCTGGAGAGCGGCGTGCCCGACAGGTTCAGCGGCAGCG GCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGGCCGAGGACGT GGCCGTGTACTACTGCCAGCAGAGCAACGAGGACCCCTACACCTTCGGCCAG GGCACCAAGCTGGAGATCAAGTTCATCTTCCCCCCCAGCGACGAGCAGCTGA AGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCAGGGA GGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCAG GAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCA CCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGA GGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGC GAGTGC
Prasinezumab	Heavy/ SEQ ID NO: 85	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAACTACGGCATGAG CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGGCCAGCATCAGC AGCGGCGGCGGCAGCACCTACTACCCCGACAACGTGAAGGGCAGGTTCACCA TCAGCAGGGACGACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAG GGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGGCGGCGCCGGCATCGAC TACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCC CCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGC CGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGC TGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGC AGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGCT GGGCGGCCCCAGCGTGTTCCTG
Prasinezumab	Light/ SEQ ID NO: 86	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GGGTGACCATCACCTGCAAGAGCATCCAGACCCTGCTGTACAGCAGCAACCA GAAGAACTACCTGGCCTGGTTCCAGCAGAAGCCCGGCAAGGCCCCCAAGCTG CTGATCTACTGGGCCAGCATCAGGAAGAGCGGCGTGCCCAGCAGGTTCAGCG GCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGA GGACCTGGCCACCTACTACTGCCAGCAGTACTACAGCTACCCCCTGACCTTC GGCGGCGGCACCAAGCTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGT TCATCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGT GTGCCTGCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTG GACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACA GCAAGGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGA CTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGC AGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
NI-202	Heavy/ SEQ ID NO: 87	GAGGTGCAGCTGGTGGAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCG TGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCACCAACTACGCCATGCA CTGGGTGAGGCAGGCCCCCGGCCAGAGGCTGGAGTGGATGGGCTGGATCAAC GCCGGCAACGGCAAGAGGAAGTACAGCCAGAAGTTCCAGGACAGGGTGACCA TCAACAGGGACACCAGCGCCAGCACCATCTACATGGAGCTGAGCAGCCTGGG CAGCGAGGACACCGCCGTGTACTACTGCGCCAGGGAGGAGGACCACGCCGGC AGCGGCAGCTACCTGAGCATGGACGTGTGGGGCCAGGGCACCCTGGTGACCG TGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAG

mAb	Chain/ SEQ ID NO.	Sequence
		CAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTAC TTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCG TGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAG CGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAAC GTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGCCCAAGA GCTGCGAC +/-AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/-CCCGAGCTGCTGGGCGGCCCCAGCGTGTT CCTG
NI-202	Light/ SEQ ID NO: 88	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GGGTGACCATCACCTGCAAGAGCATCCAGACCCTGCTGTACAGCAGCAACCA GAAGAACTACCTGGCCTGGTTCCAGCAGAAGCCCGGCAAGGCCCCCAAGCTG CTGATCTACTGGGCCAGCATCAGGAAGAGCGGCGTGCCCAGCAGGTTCAGCG GCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGA GGACCTGGCCACCTACTACTGCCAGCAGTACTACAGCTACCCCCTGACCTTC GGCGGCGGCACCAAGCTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGT TCATCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGT GTGCCTGCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTG GACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACA GCAAGGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGA CTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGC AGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
MEDI-1341/TAK 341	Heavy/ SEQ ID NO: 89	GAGGTGCAGCTGCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCTACGCCATGAG CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGC CACCTGGGCGGCAGCACCTACTACGCCGACAGCGTGAAGGGCAGGTTCACCA TCAGCAGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAG GGCCGAGGACACCGCCGTGTACTACTGCGCCGGCGGCGCCAACCACGGCAAG TACTACTACGGCATGGACAAGTGGGGCCAGGGCACCACCGTGACCGTGAGCA GCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAG CACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCC GAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACA CCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGT GACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAAC CACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCG AC +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGTTCGAGGGCGGCCCCAGCG TGTTCCTG
MEDI-1341/TAK 341	Light/ SEQ ID NO: 90	CAGGCCGTGCTGACCCAGCCCGCCAGCCTGAGCGCCAGCCCCGGCGCCAGCG CCAGCCTGACCTGCACCCTGAGGAGCGGCGCCCCCCTGCCCAAGTACAGGAT CTACTGGTACCAGCAGAAGCCCGGCAGCCCCCCCCAGTACCTGCTGAGGTAC AAGAGCGACGCCGACAAGCACCAGGGCAGCGGCGTGCCCAGCAGGTTCAGCG GCAGCAAGGACGCCAGCGCCAACGCCGGCATCCTGCTGATCAGCGGCCTGCA GAGCGAGGACGAGGCCGACTACTACTGCATGGTGTGGGACCACGGCGTGTGG TACTTCGGCGGCGGCACCAAGCTGACCGTGCTGGGCCAGCCCAAGGCCGCCC CCAGCGTGACCCTGTTCCCCCCCAGCAGCGAGGAGCTGCAGGCCAACAAGGC CACCCTGGTGTGCCTGATCAGCGACTTCTACCCCGGCGCCGTGACCGTGGCC TGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCA GCAAGCAGAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCC

mAb	Chain/ SEQ ID NO.	Sequence
		CGAGCAGTGGAAGAGCCACAGGAGCTACAGCTGCCAGGTGACCCACGAGGGC AGCACCGTGGAGAAGACCGTGGCCCCCACCGAGTGCAGC
NI-204.10D12	Heavy/ SEQ ID NO: 91	GAGGTGCAGCTGGTGGAGAGCGGCGGCGACCTGGTGAGGCCCGGCGGCAGCC TGAGGCTGAGCTGCGTGGCCAGCGGCTTCACCTTCAGCAACTACTGGATGCA CTGGGTGAGGCAGGCCCCCGGCCAGAGGCCCGTGTGGGTGAGCAGGACCAAC ACCGACGGCAGGAACACCGCCTACGCCGACTACGCCAAGGGCAGGTTCACCA TCAGCAGGGACAACGCCAAGAGCACCCTGTACCTGCAGCTGAACAGCCTGAG GGCCGAGGACACCGCCGTGTACTTCTGCGCCAGGCTGAGGAGGAACGTGGCC GACCAGATCACCCACAACTACTACATGGACGTGTGGGGCAAGGGCACCCTGG TGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCC CAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAG GACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCA GCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCT GAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATC TGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAGC CCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGGCCGCCGGCGGCCCCAGC GTGTTCCTG
NI-204.10D12	Light/ SEQ ID NO: 92	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GGGTGACCGCCTGCAGGGCCAGCCAGAGCGTGGGCACCTACCTGAACTGGTA CCAGCAGAAGAGGGGCAAGGCCCCCAAGCTGCTGATCTTCGCCGCCAGCAGC CTGCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACT TCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTG CCAGCAGAGCTACAGCAGCCCCCCCACCTTCGGCCAGGGCACCAAGGTGGAG ATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCGACG AGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTA CCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGC AACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCC TGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGCTTC AACAGGGGCGAGTGC
NI-204.12G7	Heavy/ SEQ ID NO: 93	CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCG TGACCCTGAGCTGCAAGGCCAGCGGCTACACCTTCACCGCCTACTACATCCA CTGGGTGAGGCAGGCCAGGGAGCAGGGCCTGGAGTGGATGGGCGTGATCAAC CCCAGCACCGGCACCACCTTCTACGCCCAGAACTTCCCCGACAGGGTGAGCG TGACCAGGGACACCAGCACCAGCACCGTGTTCATGGAGCTGCACAACCTGAA GAGCGAGGACACCGCCGTGTACTACTGCGCCAGGGCCATCAGCGAGCACGGC AGCGGCAGCTACAGCCCCTACTACTGGGGCCAGGGCACCCTGGTGACCGTGA GCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAA GAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTC CCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGC ACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGT GGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTG AACCACAAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAGCCCAAGAGCT GCGAC +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGGCCGCCGGCGGCCCCAGCGT GTTCCTG

mAb	Chain/ SEQ ID NO.	Sequence
NI-204.12G7	Light/ SEQ ID NO: 94	AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGTGAGCCTGGGCCAGATGG CCGCCATCACCTGCAGCGGCGAGGCCCTGCCCAAGAAGTACGGCTACTGGTA CCAGCAGAAGCCCGGCCAGGTGCCCGTGCTGCTGATCTACAGGGACGTGGAG AGGCCCAGCGGCGTGCCCGACAGGTTCAGCGGCAGCAGCAGCGGCACCATGG TGACCCTGACCATCAGCGGCGTGCAGGCCGAGGACGAGGCCGACTACTACTG CCTGAGCGCCGACAGCAGCGGCACCTGGGTGTTCGGCGGCGGCACCAAGCTG ACCGTGCTG
Eptinezumab	Heavy/ SEQ ID NO: 95	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGTGAGCGGCATCGACCTGAGCGGCTACTACATGAA CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGGGCGTGATCGGC ATCAACGGCGCCACCTACTACGCCAGCTGGGCCAAGGGCAGGTTCACCATCA GCAGGGACAACAGCAAGACCACCGTGTACCTGCAGATGAACAGCCTGAGGGC CGAGGACACCGCCGTGTACTTCTGCGCCAGGGGCGACATCTGGGGCCAGGGC ACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCC TGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCT GGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCC CTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGT ACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGAC CTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACGCCAGG GTGGAGCCCAAGAGCTGCGAC +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGCTGGGCGGCCCCAGCGTGACCCTG
Eptinezumab	Light/ SEQ ID NO: 96	CAGGTGCTGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGG TGACCATCAACTGCCAGGCCAGCCAGAGCGTGTACCACAACACCTACCTGGC CTGGTACCAGCAGAAGCCCGGCAAGGTGCCCAAGCAGCTGATCTACGACGCC AGCACCCTGGCCAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCA CCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACGTGGCCACCTA CTACTGCCTGGGCAGCTACGACTGCACCAACGGCGACTGCTTCGTGTTCGGC GGCGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCA TCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTG CCTGCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCA AGGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTA CGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGC CCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
Fremanezumab	Heavy/ SEQ ID NO: 97	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAACTACTGGATCAG CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGGCCGAGATCAGG AGCGAGAGCGACGCCAGCGCCACCCACTACGCCGAGGCCGTGAAGGGCAGGT TCACCATCAGCAGGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAG CCTGAGGGCCGAGGACACCGCCGTGTACTACTGCCTGGCCTACTTCGACTAC GGCCTGGCCATCCAGAACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCA GCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCTGCAGCAGGAG CACCAGCGAGAGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCC GAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACA CCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGT GACCGTGCCCAGCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTGGAC CACAAGCCCAGCAACACCAAGGTGGACAAGACCGTGGAGAGGAAGTGCTGCG TGGAG +/- TGCCCCCCCTGCCCCGCC +/- CCCCCCGTGGCCGGC

mAb	Chain/ SEQ ID NO.	Sequence
Fremanezumab	Light/ SEQ ID NO: 98	GAGATCGTGCTGACCCAGAGCCCCGCCACCCTGAGCCTGAGCCCCGGCGAGA GGGCCACCCTGAGCTGCAAGGCCAGCAAGAGGGTGACCACCTACGTGAGCTG GTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGGCGCCAGC AACAGGTACCTGGGCATCCCCGCCAGGTTCAGCGGCAGCGGCAGCGGCACCG ACTTCACCCTGACCATCAGCAGCCTGGAGCCCGAGGACTTCGCCGTGTACTA CTGCAGCCAGAGCTACAACTACCCCTACACCTTCGGCCAGGGCACCAAGCTG GAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC
Galcanezumab	Heavy/ SEQ ID NO: 99	CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCAGCAGCG TGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCGGCAACTACTGGATGCA GTGGGTGAGGCAGGCCCCCGGCCAGGGCCTGGAGTGGATGGGCGCCATCTAC GAGGGCACCGGCAAGACCGTGTACATCCAGAAGTTCGCCGACAGGGTGACCA TCACCGCCGACAAGAGCACCAGCACCGCCTACATGGAGCTGAGCAGCCTGAG GAGCGAGGACACCGCCGTGTACTACTGCGCCAGGCTGAGCGACTACGTGAGC GGCTTCGGCTACTGGGGCCAGGGCACCACCGTGACCGTGAGCAGCGCCAGCA CCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCTGCAGCAGGAGCACCAGCGA GAGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTG ACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCG CCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCC CAGCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGCCC AGCAACACCAAGGTGGACAAGAGGGTGGAGAGCAAGTAC +/- GGCCCCCCC TGCCCCCCCTGCCCCGCC (GGCCCCCCCTGCCCCAGCTGCCCCGCC) +/- CCCGAGGCCGCCGGCGGCCCCAGCGTGTTC CTG
Galcanezumab	Light/ SEQ ID NO: 100	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GGGTGACCATCACCTGCAGGGCCAGCAAGGACATCAGCAAGTACCTGAACTG GTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACTACACCAGC GGCTACCACAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCG ACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTA CTGCCAGCAGGGCGACGCCCTGCCCCCCACCTTCGGCGGCGGCACCAAGGTG GAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC
Sevacizumab	Heavy/ SEQ ID NO: 101	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGAAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCAGCTTCAGCAACAACGACGTGAT GTGCTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGATCGGCTGCATC ATGACCACCGACGTGGTGACCGAGTACGCCAACTGGGCCAAGAGCAGGTTCA CCGTGAGCAGGGACAGCGCCAAGAACAGCGTGTACCTGCAGATGAACAGCCT GAGGGCCGAGGACACCGCCGTGTACTTCTGCGCCAGGGACAGCGTGGGCAGC CCCCTGATGAGCTTCGACCTGTGGGGCCCCGGCACCCTGGTGACCGTGAGCA GCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAG

mAb	Chain/ SEQ ID NO.	Sequence
		CACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCC GAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACA CCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGT GACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAAC CACAAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGCG AC +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/-CCCGAGCTGCTGGGCGGCCCCAGCGTGTT CCTG
Sevacizumab	Light/ SEQ ID NO: 102	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GGGTGACCATCAACTGCCAGGCCAGCCAGAGCATCTACAACAACAACGAGCT GAGCTGGTACCAGCAGAAGCCCGGCAAGCCCCCCAAGCTGCTGATCTACAGG GCCAGCACCCTGGCCAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCG GCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACGTGGCCAC CTACTACTGCGGCGGCTACAAGAGCTACAGCAACGACGGCAACGGCTTCGGC GGCGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCA TCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTG CCTGCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCA AGGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTA CGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGC CCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
LKA-651/NVS2	Heavy/ SEQ ID NO: 103	GAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGAGAGCC TGAAGATCAGCTGCAAGGGCAGCGGCTACAGCTTCACCAGCTACTGGATCGG CTGGGTGAGGCAGATGCCCGGCAAGGGCCTGGAGTGGATGGGCTGGATCGAC CCCTACAGGAGCGAGATCAGGTACAGCCCCAGCTTCCAGGGCCAGGTGACCA TCAGCGCCGACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAA GGCCAGCGACACCGCCATGTACTACTGCGCCAGGGTGAGCAGCGAGCCCTTC GACAGCTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGG GCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCAC CGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTG AGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGC TGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAG CAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCGAC +/- AAGACCCA CACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
LKA-651/NVS2	Light/ SEQ ID NO: 104	AGCTACGTGCTGACCCAGCCCCCCAGCGTGAGCGTGGCCCCCGGCAAGACCG CCAGGATCACCTGCAGCGGCGACAAGCTGGGCGACCACTACGCCTACTGGTA CCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACGACGACAGCAAG AGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCG CCACCCTGACCATCAGCAGGGTGGAGGCCGGCGACGAGGCCGACTACTACTG CGCCACCTGGACCTTCGAGGGCGACTACGTGTTCGGCGGCGGCACCAAGCTG ACCGTGCTGGGCCAGCCCAAGGCCGCCCCCAGCGTGACCCTGTTCCCCCCCA GCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGA CTTCTACCCCGGCGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCCGTG AAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACAACAAGTACG CCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGGAG CTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAGAAGACCGTGGCC CCCACCGAGTGCAGC

mAb	Chain/ SEQ ID NO.	Sequence
LKA-651/NVS3	Heavy/ SEQ ID NO: 105	CAGGTGCAGCTGCAGCAGAGCGGCCCCGGCCTGGTGAAGCCCAGCCAGACCC TGAGCCTGACCTGCGCCATCAGCGGCGACAGCGTGAGCAGCAACACCGCCGC CTGGAACTGGATCAGGCAGAGCCCCAGCAGGGGCCTGGAGTGGCTGGGCGTG ATCTACTACAGGAGCAAGTGGTACAACGACTACGCCGTGAGCGTGAAGAGCA GGATCACCATCAACCCCGACACCAGCAAGAACCAGTTCAGCCTGCAGCTGAA CAGCGTGACCCCCGAGGACACCGCCGTGTACTACTGCGCCAGGAGCGTGCCC GGCGGCGACCCCGGCCTGGAGCACGCCTTCGCCTACTGGGGCAGGGGCACCC TGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGC CCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTG AAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGA CCAGCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAG CCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTAC ATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGG AGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGCTGGGCGGCCCCAG CGTGTTCCTG
LKA-651/NVS3	Light/ SEQ ID NO: 106	AGCTACGTGCTGACCCAGCCCCCCAGCGTGAGCGTGGCCCCCGGCAAGACCG CCAGGATCACCTGCAGCGGCGACAACCTGGGCACCTACTACGTGGAGTGGTA CCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACGACGACAGCGAC AGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCG CCACCCTGACCATCAGCAGGGTGGAGGCCGGCGACGAGGCCGACTACTACTG CGCCAGCTTCGCCAGCTGGAGCGACAGCGTGTTCGGCGGCGGCACCAAGCTG ACCGTGCTGGGCCAGCCCAAGGCCGCCCCCAGCGTGACCCTGTTCCCCCCCA GCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGA CTTCTACCCCGGCGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCCGTG AAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACAACAAGTACG CCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGGAG CTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAGAAGACCGTGGCC CCCACCGAGTGCAGC
Ascrinvacumab	Heavy/ SEQ ID NO: 107	ACCTGCACCGTGAGCGGCGGCAGCATCAGCAGCGGCGAGTACTACTGGAACT GGATCAGGCAGCACCCCGGCAAGGGCCTGGAGTGGATCGGCTACATCTACTA CAGCGGCAGCACCTACTACAACCCCAGCCTGAAGAGCAGGGTGACCATCAGC GTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCCG CCGACACCGCCGTGTACTACTGCGCCAGGGAGAGCGTGGCCGGCTTCGACTA CTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCC AGCGTGTTCCCCCTGGCCCCCTGCAGCAGGAGCACCAGCGAGAGCACCGCCG CCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTG GAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGCAG AGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAACT TCGGCACCCAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACACCAA GGTGGACAAGACCGTGGAGAGGAAGTGCTGCGTGGAG +/- TGCCCCCCCTGCCCCGCC +/- CCCCCCGTGGCCGGC
Ascrinvacumab	Light/ SEQ ID NO: 108	GAGATCGTGCTGACCCAGAGCCCCGGCACCCTGAGCCTGAGCCCCGGCGAGA GGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGAGCAGCAGCTACCTGGC CTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTACGGCACC AGCAGCAGGGCCACCGGCATCCCCGACAGGTTCAGCGGCAGCGGCAGCGGCA CCGACTTCACCCTGACCATCAGCAGGCTGGAGCCCGAGGACTTCGCCGTGTA

mAb	Chain/ SEQ ID NO.	Sequence
		CTACTGCCAGCAGTACGGCAGCAGCCCCATCACCTTCGGCCAGGGCACCAGG CTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCA GCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAA CTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCT ACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAA GGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAG AGCTTCAACAGGGGCGAGTGC
Tesidolumab	Heavy/ SEQ ID NO: 109	GAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCAGCAGCG TGAAGGTGAGCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTACGCCATCAG CTGGGTGAGGCAGGCCCCCGGCCAGGGCCTGGAGTGGATGGGCGGCATCGGC CCCTTCTTCGGCACCGCCAACTACGCCCAGAAGTTCCAGGGCAGGGTGACCA TCACCGCCGACGAGAGCACCAGCACCGCCTACATGGAGCTGAGCAGCCTGAG GAGCGAGGACACCGCCGTGTACTACTGCGCCAGGGACACCCCCTACTTCGAC TACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCC CCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGC CGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGC TGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGC AGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGGCCGCCGGCGGCCCCAGCGTGTTCCTG
Tesidolumab	Light/ SEQ ID NO: 110	AGCTACGAGCTGACCCAGCCCCTGAGCGTGAGCGTGGCCCTGGGCCAGACCG CCAGGATCACCTGCAGCGGCGACAGCATCCCCAACTACTACGTGTACTGGTA CCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACGACGACAGCAAC AGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCG CCACCCTGACCATCAGCAGGGCCCAGGCCGGCGACGAGGCCGACTACTACTG CCAGAGCTTCGACAGCAGCCTGAACGCCGAGGTGTTCGGCGGCGGCACCAAG CTGACCGTGCTGGGCCAGCCCAAGGCCGCCCCCAGCGTGACCCTGTTCCCCC CCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAG CGACTTCTACCCCGGCGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCC GTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACAACAAGT ACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAG GAGCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAGAAGACCGTG GCCCCCACCGAGTGCAGC
Carotuximab	Heavy/ SEQ ID NO: 111	GAGGTGAAGCTGGAGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCA TGAAGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCGACGCCTGGATGGA CTGGGTGAGGCAGAGCCCCGAGAAGGGCCTGGAGTGGGTGGCCGAGATCAGG AGCAAGGCCAGCAACCACGCCACCTACTACGCCGAGAGCGTGAAGGGCAGGT TCACCATCAGCAGGGACGACAGCAAGAGCAGCGTGTACCTGCAGATGAACAG CCTGAGGGCCGAGGACACCGGCATCTACTACTGCACCAGGTGGAGGAGGTTC TTCGACAGCTGGGGCCAGGGCACCACCCTGACCGTGAGCAGCGCCAGCACCA AGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGG CACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC GTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCG TGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAG

mAb	Chain/ SEQ ID NO.	Sequence
		CAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGC AACACCAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGCGAC +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTC CTG
Carotuximab	Light/ SEQ ID NO: 112	CAGATCGTGCTGAGCCAGAGCCCCGCCATCCTGAGCGCCAGCCCCGGCGAGA AGGTGACCATGACCTGCAGGGCCAGCAGCAGCGTGAGCTACATGCACTGGTA CCAGCAGAAGCCCGGCAGCAGCCCCAAGCCCTGGATCTACGCCACCAGCAAC CTGGCCAGCGGCGTGCCCGTGAGGTTCAGCGGCAGCGGCAGCGGCACCAGCT ACAGCCTGACCATCAGCAGGGTGGAGGCCGAGGACGCCGCCACCTACTACTG CCAGCAGTGGAGCAGCAACCCCCTGACCTTCGGCGCCGGCACCAAGCTGGAG CTGAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCGACG AGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTA CCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGC AACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCC TGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGCTTC AACAGGGGCGAGTGC
ANX-007	Heavy/ SEQ ID NO: 113	CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGCTGAAGAAGCCCGGCGCCAGCG TGAAGGTGAGCTGCAAGAGCAGCGGCTACCACTTCACCAGCTACTGGATGCA CTGGGTGAAGCAGGCCCCCGGCCAGGGCCTGGAGTGGATCGGCGTGATCCAC CCCAACAGCGGCAGCATCAACTACAACGAGAAGTTCGAGAGCAGGGTGACCA TCACCGTGGACAAGAGCACCAGCACCGCCTACATGGAGCTGAGCAGCCTGAG GAGCGAGGACACCGCCGTGTACTACTGCGCCGGCGAGAGGGACAGCACCGAG GTGCTGCCCATGGACTACTGGGGCCAGGGCACCACCGTGACCGTGAGCAGCG CCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCAC CAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG CCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCT TCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGAC CGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCAC AAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCGAC+ /- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTT CCTG
ANX-007	Light/ SEQ ID NO: 114	GACGTGCAGATCACCCAGAGCCCCAGCAGCCTGAGCGCCAGCCTGGGCGAGA GGGCCACCATCAACTGCAGGGCCAGCAAGAGCATCAACAAGTACCTGGCCTG GTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACAGCGGCAGC ACCCTGCAGAGCGGCATCCCCGCCAGGTTCAGCGGCAGCGGCAGCGGCACCG ACTTCACCCTGACCATCAGCAGCCTGGAGCCCGAGGACTTCGCCATGTACTA CTGCCAGCAGCACAACGAGTACCCCCTGACCTTCGGCCAGGGCACCAAGCTG GAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC

mAb	Chain/ SEQ ID NO.	Sequence
Adalimumab	Heavy/ SEQ ID NO: 115	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCAGGAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCGACGACTACGCCATGCA CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCGCCATCACC TGGAACAGCGGCCACATCGACTACGCCGACAGCGTGGAGGGCAGGTTCACCA TCAGCAGGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAG GGCCGAGGACACCGCCGTGTACTACTGCGCCAAGGTGAGCTACCTGAGCACC GCCAGCAGCCTGGACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCG CCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCAC CAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG CCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCT TCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGAC CGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCAC AAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGCGAC+ /- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTT CCTG
Adalimumab	Light/ SEQ ID NO: 116	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GGGTGACCATCACCTGCAGGGCCAGCCAGGGCATCAGGAACTACCTGGCCTG GTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCGCCAGC ACCCTGCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCG ACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACGTGGCCACCTACTA CTGCCAGAGGTACAACAGGGCCCCCTACACCTTCGGCCAGGGCACCAAGGTG GAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC
Infliximab	Heavy/ SEQ ID NO: 117	GAGGTGAAGCTGGAGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCA TGAAGCTGAGCTGCGTGGCCAGCGGCTTCATCTTCAGCAACCACTGGATGAA CTGGGTGAGGCAGAGCCCCGAGAAGGGCCTGGAGTGGGTGGCCGAGATCAGG AGCAAGAGCATCAACAGCGCCACCCACTACGCCGAGAGCGTGAAGGGCAGGT TCACCATCAGCAGGGACGACAGCAAGAGCGCCGTGTACCTGCAGATGACCGA CCTGAGGACCGAGGACACCGGCGTGTACTACTGCAGCAGGAACTACTACGGC AGCACCTACGACTACTGGGGCCAGGGCACCACCCTGACCGTGAGCAGCGCCA GCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAG CGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCC GTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCC CCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGT GCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAG CCCAGCAACACCAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCG TGTTCCTG
Infliximab	Light/ SEQ ID NO: 118	GACATCCTGCTGACCCAGAGCCCCGCCATCCTGAGCGTGAGCCCCGGCGAGA GGGTGAGCTTCAGCTGCAGGGCCAGCCAGTTCGTGGGCAGCAGCATCCACTG GTACCAGCAGAGGACCAACGGCAGCCCCAGGCTGCTGATCAAGTACGCCAGC GAGAGCATGAGCGGCATCCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCG

mAb	Chain/ SEQ ID NO.	Sequence
		ACTTCACCCTGAGCATCAACACCGTGGAGAGCGAGGACATCGCCGACTACTA CTGCCAGCAGAGCCACAGCTGGCCCTTCACCTTCGGCAGCGGCACCAACCTG GAGGTGAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC
Golimumab	Heavy/ SEQ ID NO: 119	AGCAAGCTGCAGGTGCAGCTGGTGGAGAGCGGCGGCGGCGTGGTGCAGCCCG GCAGGAGCCTGAGGCTGAGCTGCGCCGCCAGCGGCTTCATCTTCAGCAGCTA CGCCATGCACTGGGTGAGGCAGGCCCCCGGCAACGGCCTGGAGTGGGTGGCC TTCATGAGCTACGACGGCAGCAACAAGAAGTACGCCGACAGCGTGAAGGGCA GGTTCACCATCAGCAGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAA CAGCCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGACAGGGGC ATCGCCGCCGGCGGCAACTACTACTACTACGGCATGGACGTGTGGGGCCAGG GCACCACCGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCC CCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGC CTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCG CCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCT GTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAG ACCTACATCTGCAACGTGAACCACAAGCCCAGC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTG CTGGGCGGCCCCAGCGTGTTCCTG
Golimumab	Light/ SEQ ID NO: 120	GCCGGCAGCGAGATCGTGCTGACCCAGAGCCCCGCCACCCTGAGCCTGAGCC CCGGCGAGAGGGCCACCCTGAGCTGCAGGGCCAGCCAGAGCGTGTACAGCTA CCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAGGCTGCTGATCTAC GACGCCAGCAACAGGGCCACCGGCATCCCCGCCAGGTTCAGCGGCAGCGGCA GCGGCACCGACTTCACCCTGACCATCAGCAGCCTGGAGCCCGAGGACTTCGC CGTGTACTACTGCCAGCAGAGGAGCAACTGGCCCCCCTTCACCTTCGGCCCC GGCACCAAGGTGGACATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGG ACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
Elezanumab	Heavy/ SEQ ID NO: 121	GAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCG TGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCACCAGCCACGGCATCAG CTGGGTGAGGCAGGCCCCCGGCCAGGGCCTGGACTGGATGGGCTGGATCAGC CCCTACAGCGGCAACACCAACTACGCCCAGAAGCTGCAGGGCAGGGTGACCA TGACCACCGACACCAGCACCAGCACCGCCTACATGGAGCTGAGCAGCCTGAG GAGCGAGGACACCGCCGTGTACTACTGCGCCAGGGTGGGCAGCGGCCCCTAC TACTACATGGACGTGTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCA GCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAG CGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCC GTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCC CCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGT GCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAG

mAb	Chain/ SEQ ID NO.	Sequence
		CCCAGCAACACCAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGGCCGCCGGCGGCCCCAGCGTGT TCCTG
Elezanumab	Light/ SEQ ID NO: 122	CAGAGCGCCCTGACCCAGCCCAGGAGCGTGAGCGGCAGCCCCGGCCAGAGCG TGACCATCAGCTGCACCGGCACCAGCAGCAGCGTGGGCGACAGCATCTACGT GAGCTGGTACCAGCAGCACCCCGGCAAGGCCCCCAAGCTGATGCTGTACGAC GTGACCAAGAGGCCCAGCGGCGTGCCCGACAGGTTCAGCGGCAGCAAGAGCG GCAACACCGCCAGCCTGACCATCAGCGGCCTGCAGGCCGAGGACGAGGCCGA CTACTACTGCTACAGCTACGCCGGCACCGACACCCTGTTCGGCGGCGGCACC AAGGTGACCGTGCTGGGCCAGCCCAAGGCCGCCCCCAGCGTGACCCTGTTCC CCCCCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGAT CAGCGACTTCTACCCCGGCGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGC CCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACAACA AGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCA CAGGAGCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAGAAGACC GTGGCCCCCACCGAGTGCAGC
NI-301	Heavy/ SEQ ID NO: 123	CAGGTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAGCGAGACCC TGAGCCTGACCTGCAGCGTGAGCGGCGGCAGCATCATCAGCAGGAGCAGCTA CTGGGGCTGGATCAGGCAGCCCCCCGGCAAGGGCCTGGAGTGGATCGGCGGC ATCTACCACAGCGGCAACACCTACGACAACCCCAGCCTGAAGAGCAGGCTGA CCATGAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAACCTGAGGAGCGT GACCGCCGCCGACACCGCCGTGTACTACTGCGCCAGGATCGTGCCCGGCGGC GACGCCTTCGACATCTGGGGCCAGGGCACCATGGTGACCGTGAGCAGCGCCA GCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAG CGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCC GTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCC CCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGT GCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAG CCCAGCAACACCAAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTG TTCCTG
NI-301	Light/ SEQ ID NO: 124	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GGGTGACCGCCTGCAGGGCCAGCCAGAGCGTGGGCACCTACCTGAACTGGTA CCAGCAGAAGAGGGGCAAGGCCCCCAAGCTGCTGATCTTCGCCGCCAGCAGC CTGCAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCGACT TCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTG CCAGCAGAGCTACAGCAGCCCCCCCACCTTCGGCCAGGGCACCAAGGTGGAG ATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCGACG AGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTA CCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGC AACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCC TGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGCTTC AACAGGGGCGAGTGC

mAb	Chain/ SEQ ID NO.	Sequence
PRX-004	Heavy/ SEQ ID NO: 125	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGATCCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAACTACGCCATGAG CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGC AGCGGCGGCAGCACCTACTACCCCGACAGCGTGAAGGGCAGGTTCACCATCA GCAGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAGGGC CGAGGACACCGCCGTGTACTACTGCGCCAGGTACTACTACGGCCAGTACTTC GACTTCTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGG GCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCAC CGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTG AGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGC TGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAG CAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTT CCTG
PRX-004	Light/ SEQ ID NO: 126	GACATCGTGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GGGTGACCATCACCTGCAAGGCCAGCCAGGACGTGAGCACCACCGTGGCCTG GTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACAGCGCCAGC TACAGGAGCACCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCG ACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCGTGTACTA CTGCCAGCAGCACTACAGCACCCCCCTGACCTTCGGCGGCGGCACCAAGGTG GAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC
Pamrevlumab	Heavy/ SEQ ID NO: 127	GAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCAGCAGCG TGAAGGTGAGCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTACGCCATCAG CTGGGTGAGGCAGGCCCCCGGCCAGGGCCTGGAGTGGATGGGCGGCATCGGC CCCTTCTTCGGCACCGCCAACTACGCCCAGAAGTTCCAGGGCAGGGTGACCA TCACCGCCGACGAGAGCACCAGCACCGCCTACATGGAGCTGAGCAGCCTGAG GAGCGAGGACACCGCCGTGTACTACTGCGCCAGGGACACCCCCTACTTCGAC TACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCC CCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGC CGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGC TGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGC AGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGGCCGCCGGCGGCCCCAGCGTGTTCCTG
Pamrevlumab	Light/ SEQ ID NO: 128	AGCTACGAGCTGACCCAGCCCCTGAGCGTGAGCGTGGCCCTGGGCCAGACCG CCAGGATCACCTGCAGCGGCGACAGCATCCCCAACTACTACGTGTACTGGTA CCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACGACGACAGCAAC AGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCG CCACCCTGACCATCAGCAGGGCCCAGGCCGGCGACGAGGCCGACTACTACTG

mAb	Chain/ SEQ ID NO.	Sequence
		CCAGAGCTTCGACAGCAGCCTGAACGCCGAGGTGTTCGGCGGCGGCACCAAG CTGACCGTGCTGGGCCAGCCCAAGGCCGCCCCCAGCGTGACCCTGTTCCCCC CCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAG CGACTTCTACCCCGGCGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCC GTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACAACAAGT ACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAG GAGCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAGAAGACCGTG GCCCCCACCGAGTGCAGC
Satralizumab	Heavy/ SEQ ID NO: 129	CAGGTGCAGCTGCAGGAGAGCGGCCCCGGCCTGGTGAAGCCCAGCGAGACCC TGAGCCTGACCTGCGCCGTGAGCGGCCACAGCATCAGCCACGACCACGCCTG GAGCTGGGTGAGGCAGCCCCCCGGCGAGGGCCTGGAGTGGATCGGCTTCATC AGCTACAGCGGCATCACCAACTACAACCCCAGCCTGCAGGGCAGGGTGACCA TCAGCAGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAG GGCCGAGGACACCGCCGTGTACTACTGCGCCAGGAGCCTGGCCAGGACCACC GCCATGGACTACTGGGGCGAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCA CCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGG CGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTG ACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCG CCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCC CAGCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTGGACCACAAGCCC AGCAACACCAAGGTGGACAAGACCGTGGAGAGGAAGAGCTGCGTGGAG +/- TGCCCCCCCTGCCCCGCC +/- CCCCCCGTGGCCGGC
Satralizumab	Light/ SEQ ID NO: 130	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GCGTGACCATCACCTGCCAGGCCAGCACCGACATCAGCAGCCACCTGAACTG GTACCAGCAGAAGCCCGGCAAGGCCCCCGAGCTGCTGATCTACTACGGCAGC CACCTGCTGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCG ACTTCACCTTCACCATCAGCAGCCTGGAGGCCGAGGACGCCGCCACCTACTA CTGCGGCCAGGGCAACAGGCTGCCCTACACCTTCGGCCAGGGCACCAAGGTG GAGATCGAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC
Sarilumab	Heavy/ SEQ ID NO: 131	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCAGGAGCC TGAGGCTGAGCTGCGCCGCCAGCAGGTTCACCTTCGACGACTACGCCATGCA CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCGGCATCAGC TGGAACAGCGGCAGGATCGGCTACGCCGACAGCGTGAAGGGCAGGTTCACCA TCAGCAGGGACAACGCCGAGAACAGCCTGTTCCTGCAGATGAACGGCCTGAG GGCCGAGGACACCGCCCTGTACTACTGCGCCAAGGGCAGGGACAGCTTCGAC ATCTGGGGCCAGGGCACCATGGTGACCGTGAGCAGCGCCAGCACCAAGGGCC CCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGC CGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGAGC TGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGC AGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC

mAb	Chain/ SEQ ID NO.	Sequence
		(or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Sarilumab	Light/ SEQ ID NO: 132	GACATCCAGATGACCCAGAGCCCCAGCAGCGTGAGCGCCAGCGTGGGCGACA GGGTGACCATCACCTGCAGGGCCAGCCAGGGCATCAGCAGCTGGCTGGCCTG GTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGGCGCCAGC AGCCTGGAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCG ACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCAGCTACTA CTGCCAGCAGGCCAACAGCTTCCCCTACACCTTCGGCCAGGGCACCAAGCTG GAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC
Inebilizumab	Heavy/ SEQ ID NO: 133	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCAGCAGCTGGATGAA CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGGGCAGGATCTAC CCCGGCGACGGCGACACCAACTACAACGTGAAGTTCAAGGGCAGGTTCACCA TCAGCAGGGACGACAGCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAA GACCGAGGACACCGCCGTGTACTACTGCGCCAGGAGCGGCTTCATCACCACC GTGAGGGACTTCGACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCG CCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCAC CAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG CCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCT TCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGAC CGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCAC AAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCGAC+ /- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGT TCCTG
Inebilizumab	Light/ SEQ ID NO: 134	GAGATCGTGCTGACCCAGAGCCCCGACTTCCAGAGCGTGACCCCCAAGGAGA AGGTGACCATCACCTGCAGGGCCAGCGAGAGCGTGGACACCTTCGGCATCAG CTTCATGAACTGGTTCCAGCAGAAGCCCGACCAGAGCCCCAAGCTGCTGATC CACGAGGCCAGCAACCAGGGCAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCG GCAGCGGCACCGACTTCACCCTGACCATCAACAGCCTGGAGGCCGAGGACGC CGCCACCTACTACTGCCAGCAGAGCAAGGAGGTGCCCTTCACCTTCGGCGGC GGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGG ACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
Etrolizumab	Heavy/ SEQ ID NO: 135	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCTTCATCACCAACAACTACTGGGG CTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGGGCTACATCAGC TACAGCGGCAGCACCAGCTACAACCCCAGCCTGAAGAGCAGGTTCACCATCA GCAGGGACACCAGCAAGAACACCTTCTACCTGCAGATGAACAGCCTGAGGGC

mAb	Chain/ SEQ ID NO.	Sequence
		CGAGGACACCGCCGTGTACTACTGCGCCAGGACCGGCAGCAGCGGCTACTTC GACTTCTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGG GCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCAC CGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTG AGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGC TGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAG CAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAAC ACCAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGCGAC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGT TCCTG
Etrolizumab	Light/ SEQ ID NO: 136	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GGGTGACCATCACCTGCAGGGCCAGCGAGAGCGTGGACGACCTGCTGCACTG GTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCAAGTACGCCAGC CAGAGCATCAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCG ACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTA CTGCCAGCAGGGCAACAGCCTGCCCAACACCTTCGGCCAGGGCACCAAGGTG GAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC
Romosozumab	Heavy/ SEQ ID NO: 137	GAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAGCCCGGCGCCAGCG TGAAGGTGAGCTGCAAGGCCAGCGGCTACACCTTCACCGACTACAACATGCA CTGGGTGAGGCAGGCCCCCGGCCAGGGCCTGGAGTGGATGGGCGAGATCAAC CCCAACAGCGGCGGCGCCGGCTACAACCAGAAGTTCAAGGGCAGGGTGACCA TGACCACCGACACCAGCACCAGCACCGCCTACATGGAGCTGAGGAGCCTGAG GAGCGACGACACCGCCGTGTACTACTGCGCCAGGCTGGGCTACGACGACATC TACGACGACTGGTACTTCGACGTGTGGGGCCAGGGCACCACCGTGACCGTGA GCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCTGCAGCAG GAGCACCAGCGAGAGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTC CCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGC ACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGT GGTGACCGTGCCCAGCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTG GACCACAAGCCCAGCAACACCAAGGTGGACAAGACCGTGGAGAGGAAGTGCT GCGTGGAG+/- TGCCCCCCCTGCCCCGCC +/- CCCCCCGTGGCCGGC
Romosozumab	Light/ SEQ ID NO: 138	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GGGTGACCATCACCTGCAGGGCCAGCCAGGACATCAGCAACTACCTGAACTG GTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACTACACCAGC AGGCTGCTGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCG ACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTA CTGCCAGCAGGGCGACACCCTGCCCTACACCTTCGGCGGCGGCACCAAGGTG GAGATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCG ACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTT CTACCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACA GCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGT

mAb	Chain/ SEQ ID NO.	Sequence
		GTACGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGC TTCAACAGGGGCGAGTGC
Lanadelumab	Heavy/ SEQ ID NO: 139	GAGGTGCAGCTGCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCC TGAGGCTGAGCTGCGCCGCCAGCGGCTTCACCTTCAGCCACTACATCATGAT GTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCGGCATCTAC AGCAGCGGCGGCATCACCGTGTACGCCGACAGCGTGAAGGGCAGGTTCACCA TCAGCAGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGAG GGCCGAGGACACCGCCGTGTACTACTGCGCCTACAGGAGGATCGGCGTGCCC AGGAGGGACGAGTTCGACATCTGGGGCCAGGGCACCATGGTGACCGTGAGCA GCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAG CACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCC GAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACA CCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGT GACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAAC CACAAGCCCAGCAACACCAAGGTGGACAAGAGGGTGGAGCCCAAGAGCTGCG AC+/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGT TCCTG
Lanadelumab	Light/ SEQ ID NO: 140	GACATCCAGATGACCCAGAGCCCCAGCACCCTGAGCGCCAGCGTGGGCGACA GGGTGACCATCACCTGCAGGGCCAGCCAGAGCATCAGCAGCTGGCTGGCCTG GTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACAAGGCCAGC ACCCTGGAGAGCGGCGTGCCCAGCAGGTTCAGCGGCAGCGGCAGCGGCACCG AGTTCACCCTGACCATCAGCAGCCTGCAGCCCGACGACTTCGCCACCTACTA CTGCCAGCAGTACAACACCTACTGGACCTTCGGCCAGGGCACCAAGGTGGAG ATCAAGAGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCGACG AGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTA CCCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGC AACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCC TGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGAGCAGCCCCGTGACCAAGAGCTTC AACAGGGGCGAGTGC
Lanadelumab L01	SEQ ID NO: 141	ATGTACCGGATGCAGCTGCTGCTGCTCATTGCCCTGTCTCTGGCCCTGGTCA CCAATAGCGAAGTCCAGCTGCTGGAATCTGGCGGCGGACTTGTTCAACCTGG CGGCTCTCTGAGACTGAGCTGTGCCGCTTCCGGCTTCACCTTCAGCCACTAT ATCATGATGTGGGTCCGACAGGCCCCTGGCAAAGGCCTTGAATGGGTGTCCG GCATCTATAGCAGCGGCGGCATCACAGTGTACGCCGACTCTGTGAAGGGCAG ATTCACCATCAGCCGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAAC AGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGCGCCTATAGAAGAATCG GCGTGCCCAGACGGGACGAGTTCGATATTTGGGGCCAGGGCACCATGGTCAC CGTGTCTAGCGCCTCTACAAAGGGCCCTAGCGTGTTCCCTCTGGCTCCTAGC AGCAAGAGCACAAGCGGAGGAACAGCCGCTCTGGGCTGTCTGGTCAAGGACT ACTTTCCCGAGCCTGTGACCGTGTCCTGGAATAGCGGAGCACTGACAAGCGG CGTGCACACCTTTCCAGCTGTGCTGCAAAGCAGCGGCCTGTACTCTCTGAGC AGCGTGGTCACAGTGCCAAGCTCTAGCCTGGGCACCCAGACCTACATCTGCA ATGTGAACCACAAGCCTAGCAACACCAAGGTGGACAAGAGAGTGGAACCCAA GAGCTGCGACAAGACCCACACCTGTCCTCCATGTCCTGCTCCAGAACTGCTC GGCGGACCTTCCGTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTGATGA TCAGCAGAACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGA TCCCGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCC

mAb	Chain/ SEQ ID NO.	Sequence
		AAGACCAAGCCTAGAGAGGAACAGTACAACAGCACCTACAGAGTGGTGTCCG TGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAA GGTGTCCAACAAGGCCCTGCCTGCTCCTATCGAGAAAACCATCAGCAAGGCC AAGGGCCAGCCTAGGGAACCCCAGGTTTACACACTGCCTCCAAGCCGGGAAG AGATGACCAAGAACCAGGTGTCCCTGACCTGCCTCGTGAAGGGCTTCTACCC TTCCGATATCGCCGTGGAATGGGAGAGCAATGGCCAGCCAGAGAACAACTAC AAGACAACCCCTCCTGTGCTGGACAGCGACGGCTCATTCTTCCTGTACAGCA AGCTGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCAGCTGCAG CGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGTCTGAGCCTG TCTCCAGGCCTGCGGAAGAGAAGGGCTCCTGTGAAGCAGACCCTGAACTTCG ACCTGCTGAAACTGGCCGGCGACGTGGAAAGCAACCCCGGACCTATGTATAG AATGCAGCTCCTCCTGCTGATCGCACTGAGCCTGGCTCTCGTGACCAACAGC GACATCCAGATGACACAGAGCCCCAGCACACTGTCTGCCAGCGTGGGAGACA GAGTGACCATCACCTGTAGAGCCAGCCAGTCCATCTCCTCTTGGCTGGCCTG GTATCAGCAAAAGCCTGGCAAGGCCCCTAAGCTGCTGATCTACAAGGCCTCC ACACTGGAAAGCGGGGTGCCCTCCAGATTTTCTGGCAGCGGATCTGGCACCG AGTTCACCCTGACCATCAGTAGCCTGCAGCCTGACGACTTCGCCACCTACTA CTGCCAGCAGTACAATACCTACTGGACCTTCGGCCAGGGAACAAAGGTGGAA ATCAAGCGGACTGTGGCCGCTCCAAGCGTGTTCATCTTTCCACCTAGCGACG AGCAGCTGAAGTCCGGCACAGCCTCTGTTGTGTGCCTGCTGAACAACTTCTA CCCCAGAGAAGCCAAGGTGCAGTGGAAAGTGGACAATGCCCTGCAGAGCGGC AACTCCCAAGAGAGCGTGACAGAGCAGGACTCCAAGGATTCCACCTACAGCC TGTCTAGCACCCTGACACTGAGCAAGGCCGACTACGAGAAGCACAAAGTGTA TGCCTGCGAAGTGACCCACCAGGGCCTTAGCTCTCCAGTGACCAAGAGCTTC AACCGGGGCGAGTGTTGATAA
Siltuximab	Heavy/ SEQ ID NO: 343	gaagtgcagctggtggaaagcggcggcaaactgctgaaaccgggcggcagcc tgaaactgagctgcgcggcgagcggctttacctttagcagctttgcgatgag ctggtttcgccagagcccggaaaaacgcctggaatgggtggcggaaattagc agcggcggcagctatacctattatccggataccgtgaccggccgctttacca ttagccgcgataacgcgaaaaacaccctgtatctggaaatgagcagcctgcg cagcgaagataccgcgatgtattattgcgcgcgcggcctgtggggctattat gcgctggattattggggccagggcaccagcgtgaccgtgagcagcgcgagca ccaaaggcccgagcgtgtttccgctggcgccgagcagcaaaagcaccagcgg cggcaccgcggcgctgggctgcctggtgaaagattattttccggaaccggtg accgtgagctggaacagcggcgcgctgaccagcggcgtgcatacctttccgg cggtgctgcagagcagcggcctgtatagcctgagcagcgtggtgaccgtgcc gagcagcagcctgggcacccagacctatatttgcaacgtgaaccataaaccg agcaacaccaaagtggataaaaaagtggaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Siltuximab	Light/ SEQ ID NO: 344	cagattgtgctgattcagagcccggcgattatgagcgcgagcccgggcgaaa aagtgaccatgacctgcagcgcgagcagcagcgtgagctatatgtattggta tcagcagaaaccgggcagcagcccgcgcctgctgatttatgataccagcaac ctggcgagcggcgtgccggtgcgctttagcggcagcggcagcggcaccagct atagcctgaccattagccgcatggaagcggaagatgcggcgacctattattg ccagcagtggagcggctatccgtatacctttggcggcggcaccaaactggaa attaaacgcaccgtggcggcgccgagcgtgtttatttttccgccgagcgatg aacagctgaaaagcggcaccgcgagcgtggtgtgcctgctgaacaacttta

mAb	Chain/ SEQ ID NO.	Sequence
		tccgcgcgaagcgaaagtgcagtggaaagtggataacgcgctgcagagcggc aacagccaggaaagcgtgaccgaacaggatagcaaagatagcacctatagcc tgagcagcaccctgaccctgagcaaagcggattatgaaaaacataaagtgta tgcgtgcgaagtgacccatcagggcctgagcagcccggtgaccaaaagcttt aaccgcggcgaatgc
Clazakizumab	Heavy/ SEQ ID NO: 345	gaagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcc tgcgcctgagctgcgcggcgagcggctttagcctgagcaactattatgtgac ctgggtgcgccaggcgccgggcaaaggcctggaatgggtgggcattatttat ggcagcgatgaaaccgcgtatgcgaccagcgcgattggccgctttaccatta gccgcgataacagcaaaaacaccctgtatctgcagatgaacagcctgcgcgc ggaagataccgcggtgtattattgcgcgcgcgatgatagcagcgattgggat gcgaaatttaacctgtggggccagggcaccctggtgaccgtgagcagcgcga gcaccaaaggcccgagcgtgtttccgctggcgccgagcagcaaaagcaccag cggcggcaccgcggcgctgggctgcctggtgaaagattattttccggaaccg gtgaccgtgagctggaacagcggcgcgctgaccagcggcgtgcatacctttc cggcggtgctgcagagcagcggcctgtatagcctgagcagcgtggtgaccgt gccgagcagcagcctgggcacccagacctatatttgcaacgtgaaccataaa ccgagcaacaccaaagtggataaacgcgtggaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Clazakizumab	Light/ SEQ ID NO: 346	gcgattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatc gcgtgaccattacctgccaggcgagccagagcattaacaacgaactgagctg gtatcagcagaaaccgggcaaagcgccgaaactgctgatttatcgcgcgagc accctggcgagcggcgtgccgagccgctttagcggcagcggcagcggcaccg attttaccctgaccattagcagcctgcagccggatgattttgcgacctatta ttgccagcagggctatagcctgcgcaacattgataacgcgtttggcggcggc accaaagtggaaattaaacgcaccgtggcggcgccgagcgtgtttatttttc cgccgagcgatgaacagctgaaaagcggcaccgcgagcgtggtgtgcctgct gaacaacttttatccgcgcgaagcgaaagtgcagtggaaagtggataacgcg ctgcagagcggcaacagccaggaaagcgtgaccgaacaggatagcaaagata gcacctatagcctgagcagcaccctgaccctgagcaaagcggattatgaaaa acataaagtgtatgcgtgcgaagtgacccatcagggcctgagcagcccggtg accaaaagctttaaccgcggcgaatgcgaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Sirukumab	Heavy/ SEQ ID NO: 347	Gaagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcc tgcgcctgagctgcgcggcgagcggctttacctttagcccgtttgcgatgag ctgggtgcgccaggcgccgggcaaaggcctggaatgggtggcgaaaattagc ccgggcggcagctggacctattatagcgataccgtgaccggccgctttacca ttagccgcgataacgcgaaaaacagcctgtatctgcagatgaacagcctgcg cgcggaagataccgcggtgtattattgcgcgcgccagctgtggggctattat gcgctggatatttggggccagggcaccaccgtgaccgtgagcagcgcgagca ccaaaggcccgagcgtgtttccgctggcgccgagcagcaaaagcaccagcgg cggcaccgcggcgctgggctgcctggtgaaagattattttccggaaccggtg accgtgagctggaacagcggcgcgctgaccagcggcgtgcataccttccgg cggtgctgcagagcagcggcctgtatagcctgagcagcgtggtgaccgtgcc

mAb	Chain/ SEQ ID NO.	Sequence
		gagcagcagcctgggcacccagacctatatttgcaacgtgaaccataaaccg agcaacaccaaagtggataaaaaagtggaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Sirukumab	Light/ SEQ ID NO: 348	gaaattgtgctgacccagagcccggcgaccctgagcctgagcccgggcgaac gcgcgaccctgagctgcagcgcgagcattagcgtgagctatatgtattggta tcagcagaaaccgggccaggcgccgcgcctgctgatttatgatatgagcaac ctggcgagcggcattccggcgcgctttagcggcagcggcagcggcaccgatt ttaccctgaccattagcagcctggaaccggaagattttgcggtgtattattg catgcagtggagcggctatccgtatacctttggcggcggcaccaaagtggaa attaaacgcaccgtggcggcgccgagcgtgtttatttttccgccgagcgatg aacagctgaaaagcggcaccgcgagcgtggtgtgcctgctgaacaacttta tccgcgcgaagcgaaagtgcagtggaaagtggataacgcgctgcagagcggc aacagccaggaaagcgtgaccgaacaggatagcaaagatagcacctatagcc tgagcagcaccctgaccctgagcaaagcggattatgaaaaacataaagtgta tgcgtgcgaagtgacccatcagggcctgagcagcccggtgaccaaaagcttt aaccgcggcgaatgc
Olokizumab	Heavy/ SEQ ID NO: 349	Gaagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcc tgcgcctgagctgcgcggcgagcggctttaactttaacgattattttatgaa ctgggtgcgccaggcgccgggcaaaggcctggaatgggtggcgcagatgcgc aacaaaaactatcagtatggcacctattatgcggaaagcctggaaggccgct ttaccattagccgcgatgatagcaaaaacagcctgtatctgcagatgaacag cctgaaaaccgaagataccgcggtgtattattgcgcgcgcgaaagctattat ggctttaccagctattggggccagggcaccctggtgaccgtgagcagcgcga gcaccaaaggcccgagcgtgtttccgctggcgccgtgcagccgcagcaccag cgaaagcaccgcggcgctgggctgcctggtgaaagattattttccggaaccg gtgaccgtgagctggaacagcggcgcgctgaccagcggcgtgcatacctttc cggcggtgctgcagagcagcggcctgtatagcctgagcagcgtggtgaccgt gccgagcagcagcctgggcaccaaaacctatacctgcaacgtggatcataaa ccgagcaacaccaaagtggataaacgcgtgGAGAGCAAGTAC +/- GGCCCCCCCTGCCCCCCCTG CCCCGCC (GGCCCCCCCTGCCCCAGCTGCCCCGCC)+/- CCCGAGTTCCTGGGCGGCCCCAGCGTGTTCCTG
Olokizumab	Light/ SEQ ID NO: 350	gatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatc gcgtgaccattacctgccaggcgagccaggatattggcattagcctgagctg gtatcagcagaaaccgggcaaagcgccgaaactgctgatttataacgcgaac aacctggcggatggcgtgccgagccgctttagcggcagcggcagcggcaccg attttaccctgaccattagcagcctgcagccggaagattttgcgacctatta ttgcctgcagcataacagcgcgccgtatacctttggccagggcaccaaactg gaaattaaacgcaccgtggcggcgccgagcgtgtttatttttccgccgagcg atgaacagctgaaaagcggcaccgcgagcgtggtgtgcctgctgaacaactt ttatccgcgcgaagcgaaagtgcagtggaaagtggataacgcgctgcagagc ggcaacagccaggaaagcgtgaccgaacaggatagcaaagatagcacctata gcctgagcagcaccctgaccctgagcaaagcggattatgaaaaacataaagt gtatgcgtgcgaagtgacccatcagggcctgagcagcccggtgaccaaaagc tttaaccgcggcgaatgc

mAb	Chain/ SEQ ID NO.	Sequence
Gerilimzumab	Heavy/ SEQ ID NO: 351	Gaagtgcagctgcaggaaagcggcccgggcctggtgaaaccgagccagaccc tgagcctgacctgcaccgtgagcggcggcagcattaccagccgctattatgc gtggagctggattcgccagccgccgggcaaaggcctggaatggattggcgtg attgattatgatggcgatacctattatagcccgagcctgaaaagccgcgtga gcattagctgggataccagcaaaaaccagtttagcctgaaactgagcagcgt gaccccggcggataccgcggtgtattattgcgcgcgcgatccggatgtggtg accggctttcattatgattattggggccagggcaccatggtgaccgtgagca gcgcgagcaccaaaggcccgagcgtgtttccgctggcgccgagcagcaaaag caccagcggcggcaccgcggcgctgggctgcctggtgaaagattattttccg gaaccggtgaccgtgagctggaacagcggcgcgctgaccagcggcgtgcata cctttccggcggtgctgcagagcagcggcctgtatagcctgagcagcgtggt gaccgtgccgagcagcagcctgggcacccagacctatatttgcaacgtgaac cataaaccgagcaacaccaaagtggataaaaaagtggaaccgaaaagctgcg at +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Gerilimzumab	Light/ SEQ ID NO: 352	cagagcgcgctgacccagccgccgagcgtgagcggcaccccgggccagagcg tgaccattagctgcgcgggcgcgaacaacgatattggcacctatgcgtatgt gagctggtatcagcagctgccgggcaccgcgccgaaactgatgatttataaa gtgaccacccgcgcgagcggcattccggatcgctttagcggcagcaaaagcg gcaacaccgcgagcctgaccattagcggcctgcaggcggaagatgaagcgga ttattattgcgcgagctatcgcaactttaacaacgcggtgtttggcaccggc accaaactgaccgtgctgggccagccgaaagcggcgccgagcgtgaccctgt ttccgccgagcagcgaagaactgcaggcgaacaaagcgaccctggtgtgcct gattagcgatttttatccgggcgcggtgaccgtggcgtggaaagcggatagc agcccggtgaaagcgggcgtggaaaccaccaccccgagcaaacagagcaaca acaaatatgcggcgagcagctatctgagcctgaccccggaacagtggaaaag ccatcgcagctatagctgccaggtgacccatgaaggcagcaccgtggaaaaa accgtggcgccgaccgaatgcagc
Tocilizumab	Heavy/ SEQ ID NO: 353	Caggtgcagctgcaggaaagcggcccgggcctggtgcgcccgagccagaccc tgagcctgacctgcaccgtgagcggctatagcattaccagcgatcatgcgtg gagctgggtgcgccagccgccgggccgcggcctggaatggattggctatatt agctatagcggcattaccacctataacccgagcctgaaaagccgcgtgacca tgctgcgcgataccagcaaaaaccagtttagcctgcgcctgagcagcgtgac cgcggcggataccgcggtgtattattgcgcgcgcagcctggcgcgcaccacc gcgatggattattggggccagggcagcctggtgaccgtgagcagcgcgagca ccaaaggcccgagcgtgtttccgctggcgccgagcagcaaaagcaccagcgg cggcaccgcggcgctgggctgcctggtgaaagattattttccggaaccggtg accgtgagctggaacagcggcgcgctgaccagcggcgtgcataccttccgg cggtgctgcagagcagcggcctgtatagcctgagcagcgtggtgaccgtgcc gagcagcagcctgggcacccagacctatatttgcaacgtgaaccataaaccg agcaacaccaaagtggataaaaaagtggaaccgaaaagctgcgat +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC+/- CCCGAGCTGCTGGGCGGCCCCAGCGTGTTCCTG
Tocilizumab	Light/ SEQ ID NO: 354	gatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatc gcgtgaccattacctgccgcgcgagccaggatattagcagctatctgaactg gtatcagcagaaaccgggcaaagcgccgaaactgctgatttattataccagc cgcctgcatagcggcgtgccgagccgctttagcggcagcggcagcggcaccg

mAb	Chain/ SEQ ID NO.	Sequence
		attttacctttaccattagcagcctgcagccggaagatattgcgacctatta ttgccagcagggcaacaccctgccgtatacctttggccagggcaccaaagtg gaaattaaacgcaccgtggcggcgccgagcgtgtttatttttccgccgagcg atgaacagctgaaaagcggcaccgcgagcgtggtgtgcctgctgaacaactt ttatccgcgcgaagcgaaagtgcagtggaaagtggataacgcgctgcagagc ggcaacagccaggaaagcgtgaccgaacaggatagcaaagatagcacctata gcctgagcagcaccctgaccctgagcaaagcggattatgaaaaacataaagt gtatgcgtgcgaagtgacccatcagggcctgagcagcccggtgaccaaaagc tttaaccgcggcgaatgc
Lecanemab	Heavy/ SEQ ID NO: 376	Gaagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcc tgcgcctgagctgcagcgcgagcggctttacctttagcagctttggcatgca ttgggtgcgccaggcgccgggcaaaggcctggaatgggtggcgtatattagc agcggcagcagcaccatttattatggcgataccgtgaaaggccgctttacca ttagccgcgataacgcgaaaaacagcctgtttctgcagatgagcagcctgcg cgcggaagataccgcggtgtattattgcgcgcgcgaaggcggctattattat ggccgcagctattataccatggattattggggccagggcaccaccgtgaccg tgagcagcgcgagcaccaaaggcccgagcgtgtttccgctggcgccgagcag caaaagcaccagcggcggcaccgcggcgctgggctgcctggtgaaagattat tttccggaaccggtgaccgtgagctggaacagcggcgcgctgaccagcggcg tgcataccttccggcggtgctgcagagcagcggcctgtatagcctgagcag cgtggtgaccgtgccgagcagcagcctgggcacccagacctatatttgcaac gtgaaccataaaccgagcaacaccaaagtggataaacgcgtggaaccgaaaa gctgcgat +/- AAGACCC ACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGGCCGGCGCCCCCAGCGTGTTCCTG
Lecanemab	Light/ SEQ ID NO: 377	Gatgtggtgatgacccagagcccgctgagcctgccggtgaccccgggcgcgc cggcgagcattagctgccgcagcagccagagcattgtgcatagcaacggcaa cacctatctggaatggtatctgcagaaaccgggccagagcccgaaactgctg atttataaagtgagcaaccgctttagcggcgtgccggatcgctttagcggca gcggcagcggcaccgattttaccctgcgcattagccgcgtggaagcggaaga tgtgggcatttattattgctttcagggcagccatgtgccgccgacctttggc ccgggcaccaaactggaaattaaacgcaccgtggcggcgccgagcgtgttta tttttccgccgagcgatgaacagctgaaaagcggcaccgcgagcgtggtgtg cctgctgaacaacttttatccgcgcgaagcgaaagtgcagtggaaagtggat aacgcgctgcagagcggcaacagccaggaaagcgtgaccgaacaggatagca agatagcacctatagcctgagcagcaccctgaccctgagcaaagcggatta tgaaaaacataaagtgtatgcgtgcgaagtgacccatcagggcctgagcagc ccggtgaccaaaagctttaaccgcggcgaatgc
Ravulizumab	Heavy/ SEQ ID NO: 378	caggtgcagctggtgcagagcggcgcggaagtgaaaaaaccgggcgcgagcg tgaaagtgagctgcaaagcgagcggccatatttttagcaactattggattca gtgggtgcgccaggcgccgggccagggcctggaatggatgggcgaaattctg ccgggcagcggccataccgaatataccgaaaactttaaagatcgcgtgacca tgacccgcgataccagcaccagcaccgtgtatatggaactgagcagcctgcg cagcgaagataccgcggtgtattattgcgcgcgctatttttttggcagcagc ccgaactggtattttgatgtgtggggccagggcaccctggtgaccgtgagca gcgcgagcaccaaaggcccgagcgtgtttccgctggcgccgtgcagccgcag caccagcgaaagcaccgcggcgctgggctgcctggtgaaagattattttccg

mAb	Chain/ SEQ ID NO.	Sequence
		gaaccggtgaccgtgagctggaacagcggcgcgctgaccagcggcgtgcata cctttccggcggtgctgcagagcagcggcctgtatagcctgagcagcgtggt gaccgtgccgagcagcaactttggcacccagacctatacctgcaacgtggat cataaaccgagcaacaccaaagtggataaaaccgtggaacgcaaatgctgcg tggaa +/- TGCCCCCCCTGCCCCGCC +/- CCCCCCGTGGCCGGC
Ravulizumab	Light/ SEQ ID NO: 379	Gatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatc gcgtgaccattacctgcggcgcgagcgaaaacatttatggcgcgctgaactg gtatcagcagaaaccgggcaaagcgccgaaactgctgatttatggcgcgacc aacctggcggatggcgtgccgagccgctttagcggcagcggcagcggcaccg attttaccctgaccattagcagcctgcagccggaagattttgcgacctatta ttgccagaacgtgctgaacaccccgctgacctttggccagggcaccaaagtg gaaattaaacgcaccgtggcggcgccgagcgtgtttatttttccgccgagcg atgaacagctgaaaagcggcaccgcgagcgtggtgtgcctgctgaacaactt ttatccgcgcgaagcgaaagtgcagtggaaagtggataacgcgctgcagagc ggcaacagccaggaaagcgtgaccgaacaggatagcaaagatagcacctata gcctgagcagcaccctgaccctgagcaaagcggattatgaaaaacataaagt gtatgcgtgcgaagtgacccatcagggcctgagcagcccggtgaccaaaagc tttaaccgcggcgaatgc
Benralizumab	Heavy/ SEQ ID NO: 380	Gaagtgcagctggtgcagagcggcgcggaagtgaaaaaaccgggcgcgagcg tgaaagtgagctgcaaagcgagcggctatacctttaccagctatgtgattca ttgggtgcgccagcgcccgggccagggcctggcgtggatgggctatattaac ccgtataacgatggcaccaaatataacgaacgctttaaaggcaaagtgacca ttaccagcgatcgcagcaccagcaccgtgtatatggaactgagcagcctgcg cagcgaagataccgcggtgtatctgtgcggccgcgaaggcattcgctattat ggcctgctgggcgattattggggccagggcaccctggtgaccgtgagcagcg cgagcaccaaaggcccgagcgtgtttccgctggcgccgagcagcaaaagcac cagcggcggcaccgcggcgctgggctgcctggtgaaagattatttccggaa ccggtgaccgtgagctggaacagcggcgcgctgaccagcggcgtgcatacct ttccggcggtgctgcagagcagcggcctgtatagcctgagcagcgtggtgac cgtgccgagcagcagcctgggcacccagacctatatttgcaacgtgaaccat aaaccgagcaacaccaaagtggataaaaaagtggaaccgaaaagctgcgat +/- AAGACCC ACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGGCCGGCGCCCCCAGCGTGTTCCTG
Benralizumab	Light/ SEQ ID NO: 381	Gatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatc gcgtgaccattacctgcggcaccagcgaagatattattaactatctgaactg gtatcagcagaaaccgggcaaagcgccgaaactgctgatttatcataccagc cgcctgcagagcggcgtgccgagccgctttagcggcagcggcagcggcaccg attttaccctgaccattagcagcctgcagccggaagattttgcgacctatta ttgccagcagggctataccctgccgtatacctttggccagggcaccaaagtg gaaattaaacgcaccgtggcggcgccgagcgtgtttatttttccgccgagcg atgaacagctgaaaagcggcaccgcgagcgtggtgtgcctgctgaacaactt ttatccgcgcgaagcgaaagtgcagtggaaagtggataacgcgctgcagagc ggcaacagccaggaaagcgtgaccgaacaggatagcaaagatagcacctata gcctgagcagcaccctgaccctgagcaaagcggattatgaaaaacataaagt

mAb	Chain/ SEQ ID NO.	Sequence
		gtatgcgtgcgaagtgacccatcagggcctgagcagcccggtgaccaaaagc tttaaccgcggcgaatgc
Reslizumab	Heavy/ SEQ ID NO: 382	Gaagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcc tgcgcctgagctgcgcggtgagcggcctgagcctgaccagcaacagcgtgaa ctggattcgccaggcgccgggcaaaggcctggaatgggtgggcctgatttgg agcaacggcgataccgattataacagcgcgattaaaagccgctttaccatta gccgcgataccagcaaaagcaccgtgtatctgcagatgaacagcctgcgcgc ggaagataccgcggtgtattattgcgcgcgcgaatattatggctattttgat tattggggccagggcaccctggtgaccgtgagcagcgcgagcaccaaaggcc cgagcgtgtttccgctggcgccgtgcagccgcagcaccagcgaaagcaccgc ggcgctgggctgcctggtgaaagattattttccggaaccggtgaccgtgagc tggaacagcggcgcgctgaccagcggcgtgcatacctttccggcggtgctgc agagcagcggcctgtatagcctgagcagcgtggtgaccgtgccgagcagcag cctgggcaccaaaacctatacctgcaacgtggatcataaaccgagcaacacc aaagtggataaacgcgtggaaagcaaatat GAGAGCAAGTAC +/- GGCCCCCCCTGCCCCCCCTG CCCCGCC (GGCCCCCCCTGCCCCAGCTGCCCCGCC)+/- CCCGAGTTCCTGGGCGGCCCCAGCGTGTTCCTG
Reslizumab	Light/ SEQ ID NO: 383	Gatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatc gcgtgaccattacctgcctggcgagcgaaggcattagcagctatctggcgtg gtatcagcagaaaccgggcaaagcgccgaaactgctgatttatggcgcgaac agcctgcagaccggcgtgccgagccgctttagcggcagcggcagcgcgaccg attataccctgaccattagcagcctgcagccggaagattttgcgacctatta ttgccagcagagctataaatttccgaacacctttggccagggcaccaaagtg gaagtgaaacgcaccgtggcggcgccgagcgtgtttatttttccgccgagcg atgaacagctgaaaagcggcaccgcgagcgtggtgtgcctgctgaacaactt ttatccgcgcgaagcgaaagtgcagtggaaagtggataacgcgctgcagagc ggcaacagccaggaaagcgtgaccgaacaggatagcaaagatagcacctata gcctgagcagcaccctgaccctgagcaaagcggattatgaaaaacataaagt gtatgcgtgcgaagtgacccatcagggcctgagcagcccggtgaccaaaagc tttaaccgcggcgaatgc
Tralokinumab	Heavy/ SEQ ID NO: 384	Caggtgcagctggtgcagagcggcgcggaagtgaaaaaaccgggcgcgagcg tgaaagtgagctgcaaagcgagcggctatacctttaccaactatggcctgag ctgggtgcgccaggcgccgggccagggcctggaatggatgggctggattagc gcgaacaacggcgataccaactatggccaggaatttcagggccgcgtgacca tgaccaccgataccagcaccagcaccgcgtatatggaactgcgcagcctgcg cagcgatgataccgcggtgtattattgcgcgcgcgatagcagcagcagctgg gcgcgctggtttttgatctgtggggccgcggcaccctggtgaccgtgagca gcgcgagcaccaaaggcccgagcgtgtttccgctggcgccgtgcagccgcag caccagcgaaagcaccgcggcgctgggctgcctggtgaaagattattttccg gaaccggtgaccgtgagctggaacagcggcgcgctgaccagcggcgtgcata cctttccggcggtgctgcagagcagcggcctgtatagcctgagcagcgtggt gaccgtgccgagcagcagcctgggcaccaaaacctatacctgcaacgtggat cataaaccgagcaacaccaaagtggataaacgcgtg GAGAGCAAGTAC +/- GGCCCCCCCTGCCCCCCCTG CCCCGCC

mAb	Chain/ SEQ ID NO.	Sequence
		(GGCCCCCCCCTGCCCCAGCTGCCCCGCC)+/- CCCGAGTTCCTGGGCGGCCCCAGCGTGTTCCTG
Tralokinumab	Light/ SEQ ID NO: 385	Agctatgtgctgacccagccgccgagcgtgagcgtggcgccgggcaaaaccg cgcgcattacctgcggcggcaacattattggcagcaaactggtgcattggta tcagcagaaaccgggccaggcgccggtgctggtgatttatgatgatggcgat cgcccgagcggcattccggaacgctttagcggcagcaacagcggcaacaccg cgaccctgaccattagccgcgtggaagcgggcgatgaagcggattattattg ccaggtgtgggataccggcagcgatccggtggtgtttggcggcggcaccaaa ctgaccgtgctgggccagccgaaagcggcgccgagcgtgaccctgtttccgc cgagcagcgaagaactgcaggcgaacaaagcgaccctggtgtgcctgattag cgatttttatccgggcgcggtgaccgtggcgtggaaagcggatagcagcccg gtgaaagcgggcgtggaaaccaccaccccgagcaaacagagcaacaacaaat atgcggcgagcagctatctgagcctgaccccggaacagtggaaaagccatcg cagctatagctgccaggtgacccatgaaggcagcaccgtggaaaaaaccgtg gcgccgaccgaatgcagc
Nemolizumab	Heavy/ SEQ ID NO: 386	Caggtgcagctggtgcagagcggcgcggaagtgaaaaaaccgggcgcgagcg tgaaagtgagctgcaaagcgagcggctatacctttaccggctatattatgaa ctgggtgcgccaggcgccgggccagggcctggaatggatgggcctgattaac ccgtataacggcggcaccgattataacccgcagtttcaggatcgcgtgacca ttaccgcggataaaagcaccagcaccgcgtatatggaactgagcagcctgcg cagcgaagataccgcggtgtattattgcgcgcgcgatggctatgatgatggc ccgtataccctggaaacctggggccagggcaccctggtgaccgtgagcagcg cgagcaccaaaggcccgagcgtgtttccgctggcgccgagcagcaaaagcac cagcggcggcaccgcggcgctgggctgcctggtgaaagattattttccggaa ccggtgaccgtgagctggaacagcggcgcgctgaccagcggcgtgcatacct ttccggcggtgctgcagagcagcggcctgtatagcctgagcagcgtggtgac cgtgccgagcagcaactttggcacccagacctatacctgcaacgtggatcat aaaccgagcaacaccaaagtggataaaaccgtggaa cgcaaaagctgcgtggaa +/- TGCCCCCCCTGCCCCGCC +/- CCCCCCGTGGCCGGC
Nemolizumab	Light/ SEQ ID NO: 387	Gatattcagatgacccagagcccgagcagcctgagcgcgagcgtgggcgatc gcgtgaccattacctgccaggcgagcgaagatatttatagctttgtggcgtg gtatcagcagaaaccgggcaaagcgccgaaactgctgatttataacgcgcag accgaagcgcagggcgtgccgagccgctttagcggcagcggcagcggcaccg attttaccctgaccattagcagcctgcagccggaagattttgcgacctatta ttgccagcatcattatgatagcccgctgacctttggcggcggcaccaaagtg gaaattaaacgcaccgtggcggcgccgagcgtgtttatttttccgccgagcg atgaacagctgaaaagcggcaccgcgagcgtggtgtgcctgctgaacaactt ttatccgcgcgaagcgaaagtgcagtggaaagtggataacgcgctgcagagc ggcaacagccaggaaagcgtgaccgaacaggatagcaaagatagcacctata gcctgagcagcaccctgaccctgagcaaagcggattatgaaaaacataaagt gtatgcgtgcgaagtgacccatcagggcctgagcagcccggtgaccaaaagc tttaaccgcggcgaatgc

mAb	Chain/ SEQ ID NO.	Sequence
Omalizumab	Heavy/ SEQ ID NO: 388	Gaagtgcagctggtggaaagcggcggcggcctggtgcagccgggcggcagcc tgcgcctgagctgcgcggtgagcggctatagcattaccagcggctatagctg gaactggattcgccaggcgccgggcaaaggcctggaatgggtggcgagcatt acctatgatggcagcaccaactatgcggatagcgtgaaaggccgctttacca ttagccgcgatgatagcaaaaacacctttatctgcagatgaacagcctgcg cgcggaagataccgcggtgtattattgcgcgcgcggcagccattattttggc cattggcattttgcggtgtggggccagggcaccctggtgaccgtgagcagcg gcccgagcgtgtttccgctggcgccgagcagcaaaagcaccagcggcggcac cgcggcgctgggctgcctggtgaaagattattttccggaaccggtgaccgtg agctggaacagcggcgcgctgaccagcggcgtgcataccttccggcggtgc tgcagagcagcggcctgtatagcctgagcagcgtggtgaccgtgccgagcag cagcctgggcacccagacctatatttgcaacgtgaaccataaaccgagcaac accaaagtggataaaaaagcg +/- AAGACCCACACC (or AAGACCCACCTG) +/- TGCCCCCCCTGCCCCGCC +/- CCCGAGCTGGCCGGCGCCCCCAGCGTGTTCCTG
Omalizumab	Light/ SEQ ID NO: 389	Gatattcagctgacccagagcccgagcagcctgagcgcgagcgtgggcgatc gcgtgaccattacctgccgcgcgagccagagcgtggattatgatggcgatag ctatatgaactggtatcagcagaaaccgggcaaagcgccgaaactgctgatt tatgcggcgagctatctggaaagcggcgtgccgagccgctttagcggcagcg gcagcggcaccgatttaccctgaccattagcagcctgcagccggaagattt tgcgacctattattgccagcagagccatgaagatccgtatacctttggccag ggcaccaaagtggaaattaaacgcaccgtggcggcgccgagcgtgtttattt ttccgccgagcgatgaacagctgaaaagcggcaccgcgagcgtggtgtgcct gctgaacaacttttatccgcgcgaagcgaaagtgcagtggaaagtggataac gcgctgcagagcggcaacagccaggaaagcgtgaccgaacaggatagcaaag atagcacctatagcctgagcagcaccctgaccctgagcaaagcggattatga aaaacataaagtgtatgcgtgcgaagtgacccatcagggcctgagcagcccg gtgaccaaaagctttaaccgcggcgaatgc
Tezepelumab	Heavy/ SEQ ID NO: 390	Cagatgcagctggtggaaagcggcggcggcgtggtgcagccgggccgcagcc tgcgcctgagctgcgcggcgagcggctttacctttcgcacctatggcatgca ttgggtgcgccaggcgccgggcaaaggcctggaatgggtggcggtgatttgg tatgatggcagcaacaaacattatgcggatagcgtgaaaggccgctttacca ttacccgcgataacagcaaaaacaccctgaacctgcagatgaacagcctgcg cgcggaagataccgcggtgtattattgcgcgcgcgccgcagtgggaactg gtgcatgaagcgtttgatatttggggccagggcaccatggtgaccgtgagca gcgcgagcaccaaaggcccgagcgtgtttccgctggcgccgtgcagccgcag caccagcgaaagcaccgcggcgctgggctgcctggtgaaagattattttccg gaaccggtgaccgtgagctggaacagcggcgcgctgaccagcggcgtgcata cctttccggcggtgctgcagagcagcggcctgtatagcctgagcagcgtggt gaccgtgccgagcagcaactttggcacccagacctatacctgcaacgtggat cataaaccgagcaacaccaaagtggataaaaccgtg +/- TGCCCCCCCTGCCCCGCC +/- CCCCCCGTGGCCGGC
Tezepelumab	Light/ SEQ ID NO: 391	agctatgtgctgacccagccgccgagcgtgagcgtggcgccgggccagaccg cgcgcattacctgcggcggcaacaacctgggcagcaaaagcgtgcattggta tcagcagaaaccgggccaggcgccggtgctggtggtgtatgatgatagcgat cgcccgagctggattccggaacgctttagcggcagcaacagcggcaacaccg cgaccctgaccattagccgcggcgaagcgggcgatgaagcggattattattg ccaggtgtgggatagcagcagcgatcatgtggtgtttggcggcggcaccaaa

mAb	Chain/ SEQ ID NO.	Sequence
		ctgaccgtgctgggccagccgaaagcggcgccgagcgtgaccctgtttccgc cgagcagcgaagaactgcaggcgaacaaagcgaccctggtgtgcctgattag cgattttatccgggcgcggtgaccgtggcgtggaaagcggatagcagcccg gtgaaagcgggcgtggaaaccaccaccccgagcaaacagagcaacaacaaat atgcggcgagcagctatctgagcctgaccccggaacagtggaaaagccatcg cagctatagctgccaggtgacccatgaaggcagcaccgtggaaaaaaccgtg gcgccgaccgaatgcagc

TABLE 7. Table of Fc Domain Amino Acid Sequences

mAb	Chain/ SEQ ID NO.	Sequence
Solanezumab	Fc domain/ SEQ ID NO: 290	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
GSK933776	Fc domain/ SEQ ID NO: 291	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
UCB-0107	Fc domain/ SEQ ID NO: 292	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK
Prasinezumab	Fc domain/ SEQ ID NO: 293	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
MEDI-1341/TAK 341	Fc domain/ SEQ ID NO: 294	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPASI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK

mAb	Chain/ SEQ ID NO.	Sequence
NI-204.10D12	Fc domain/ SEQ ID NO: 295	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Eptinezumab	Fc domain/ SEQ ID NO: 296	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYASTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Fremanezumab	Fc domain/ SEQ ID NO: 297	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV VSVLTVVHQD WLNGKEYKCK VSNKGLPSSI EKTISKTKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Galcanezumab	Fc domain/ SEQ ID NO: 298	FPPKPKDTL MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLGK
Sevacizumab	Fc domain/ SEQ ID NO: 299	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Ascrinvacumab	Fc domain/ SEQ ID NO: 300	PSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Tesidolumab	Fc domain/ SEQ ID NO: 301	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Carotuximab	Fc domain/ SEQ ID NO: 302	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Adalimumab	Fc domain/	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK

mAb	Chain/ SEQ ID NO.	Sequence
	SEQ ID NO: 303	VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Infliximab	Fc domain/ SEQ ID NO: 304	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Golimumab	Fc domain/ SEQ ID NO: 305	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Elezanumab	Fc domain/ SEQ ID NO: 306	FPPKPKDQLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVLHEAL HNHYTQKSLS LSPGK
PRX-004	Fc domain/ SEQ ID NO: 307	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Pamrevlumab	Fc domain/ SEQ ID NO: 308	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Satralizumab	Fc domain/ SEQ ID NO: 309	PSVFL 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: 310	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Inebilizumab	Fc domain/	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK

mAb	Chain/ SEQ ID NO.	Sequence
	SEQ ID NO: 311	
Etrolizumab	Fc domain/ SEQ ID NO: 312	FPPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SREEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPG
Romosozumab	Fc domain/ SEQ ID NO: 313	PSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Lanadelumab	Fc domain/ SEQ ID NO: 314	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPG
Siltuximab	Fc domain/ SEQ ID NO: 355	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: 356	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: 357	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Olokizumab	Fc domain/ SEQ ID NO: 358	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK
Tocilizumab	Fc domain/ SEQ ID NO: 359	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPG
Lecanemab	Fc domain/	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ

mAb	Chain/ SEQ ID NO.	Sequence
	SEQ ID No: 392	VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Ravulizumab	Fc Domain/ SEQ ID NO: 393	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVLHEAL HSHYTQKSLS LSLGK
Benralizumab	Fc Domain/ SEQ ID NO: 394	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK
Reslizumab	Fc Domain/ SEQ ID NO: 395	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK
Tralokinumab	Fc Domain/ SEQ ID NO: 396	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK
Nemolizumab	Fc Domain/ SEQ ID NO: 397	FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG SFFLYSKLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSP
Omalizumab	Fc Domain/ SEQ ID NO: 398	FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK

5.4 Delivery of Gene Therapy Constructs

5.4.1 Constructs for delivery to CNS

[0698] Sections 5.3.1, 5.3.2, 5.3.3, 5.3.4, 5.3.5., 5.3.6., and 5.3.7. 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 Aβ, sortilin, Tau protein, SEMA4D, alpha-synuclein, SOD1, and CGRPR, respectively. Such recombinant vector used for delivering the transgene should have a tropism for human CNS cells, such as glial and neuronal cells. Such vectors can include non-replicating recombinant adeno-associated virus vectors ("rAAV"), particularly those bearing an AAV9, AAVrh10, AAVrh20, AAVrh39, or AAVcy5 capsid. 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.

[0699] In specific embodiments, provided are constructs for gene therapy administration to a human subject, comprising an AAV vector, which comprises a viral capsid that is at least 95% identical to the amino acid sequence of an AAV9 capsid (SEQ ID NO: 144); and a viral or artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs) wherein the expression cassette comprises a transgene encoding the heavy and light chains of the therapeutic antibody, operably linked to one or more regulatory sequences that control expression of the transgene in human cells that express and deliver the therapeutic antibody in a therapeutically appropriate manner as disclosed herein, particularly expressed from CNS cells. In certain embodiments, the encoded AAV9 capsid has the sequence of SEQ ID NO: 144 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, particularly substitutions with amino acid residues found in the corresponding position in other AAV capsids, for example, in the SUBS row of FIG. 21 which provides a comparison of the amino acid sequences of the capsid sequences of various AAVs, highlighting amino acids appropriate for substitution at different positions within the capsid sequence.

[0700] In other specific embodiments, provided are constructs for gene therapy administration to a human subject, comprising an AAV vector, which comprises a viral capsid that is at least 95% identical to the amino acid sequence of an AAVrh10 capsid (SEQ ID NO: 145); and a viral or artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs) wherein the expression cassette comprises a transgene encoding the heavy and light chains of the therapeutic antibody, operably linked to one or more regulatory sequences that control expression of the transgene in human cells that express and deliver the therapeutic antibody in a therapeutically appropriate manner as disclosed herein, particularly from CNS cells. In certain embodiments, the encoded

AAVrh10 capsid has the sequence of SEQ ID NO: 145 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, particularly substitutions with amino acid residues found in the corresponding position in other AAV capsids, for example, in the SUBS row of FIG. 21 which provides a comparison of the amino acid sequences of the capsid sequences of various AAVs, highlighting amino acids appropriate for substitution at different positions within the capsid sequence.

[0701] In some embodiments, the HuPTM mAb or antigen binding fragment thereof, including the HuPTM Fab transgene should be controlled by appropriate expression control elements for expression of the HuPTM mAb or HuPTM Fab in human CNS cells, for example, the CB7 promoter (a chicken β-actin promoter and CMV enhancer), RSV promoter, GFAP promoter (glial fibrillary acidic protein), MBP promoter (myelin basic protein), MMT promoter, EF-1α, U86 promoter, RPE65 promoter or opsin promoter, an inducible promoter, for example, a hypoxia-inducible promoter or a drug inducible promoter, such as a promoters induced by rapamycin and related agents, and other expression control elements that enhance expression of the transgene driven by the vector (e.g., introns such as the chicken β-actin intron, minute virus of mice (MVM) intron, human factor IX intron (e.g., FIX truncated intron 1), β-globin splice donor/immunoglobulin heavy chain spice acceptor intron, adenovirus splice donor /immunoglobulin splice acceptor intron, SV40 late splice donor /splice acceptor (19S/16S) intron, and hybrid adenovirus splice donor/IgG splice acceptor intron and polyA signals such as the rabbit β-globin polyA signal, human growth hormone (hGH) polyA signal, SV40 late polyA signal, synthetic polyA (SPA) signal, and bovine growth hormone (bGH) polyA signal). See, e.g., Powell and Rivera-Soto, 2015, Discov. Med., 19(102):49-57.

[0702] Gene therapy constructs are designed such that both the heavy and light chains are expressed. More specifically, 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. The leader sequence for each of the heavy and light chains is, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146) or one of the leader sequences provided in Table 2.. Section 5.1.5, *supra*, provides specific IRES, 2A, and other linker

sequences that can be used with the methods and compositions provided herein. In specific embodiments, the linker is a Furin-2A linker, for example a Furin-F2A linker RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 231. In preferred embodiments, the linker is a Furin-2A linker, for example a Furin-T2A linker RKRR(GSG)EGRGSLLTCGDVEENPGP (SEQ ID NO: 429). In specific embodiments, the transgene is a nucleotide sequence that encodes the following: Signal sequence-heavy chain Fab portion-Furin-2A linker-signal sequence-light chain Fab portion. See, e.g., FIGS. 2A-2C for sequences for Solanezumab, lecanemab, and GSK933776 Fab expression, respectively; FIG. 3 for sequence for AL-001 Fab expression; FIGS. 4A-4C for the sequence for ABBV-8E12, UCB-0107, and NI-105 Fab expression, respectively; FIG. 5 for the sequence for VX15/2503 Fab expression; FIGS. 6A-C for the sequence for prasinezumab, NI-202, and MED-1341 Fab expression, respectively; FIGS. 7A-B for the sequence for NI-204 Fab expression; and FIG. 8A-C for the sequence for eptinezumab, fremanezumab, and galcanezumab Fab expression, respectively. In an alternative embodiment, the construct also comprises the nucleotide sequence encoding the Fc domain for the therapeutic antibody (see Table 7 or FIG. 23) for expression of the full length mAb.

[0703] In a specific embodiment, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) Control elements, which include a) the CB7 promoter, comprising the CMV enhancer/chicken β-actin promoter, b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy and light chains of the Aβ-binding, sortilin-binding, Tau protein-binding, SEMA4D-binding, alpha-synuclein-binding, SOD1-binding, or CGRPR-binding Fab, separated by a self-cleaving furin (F)/2A linker, ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is provided in FIG. 1.

[0704] In specific embodiments, provided are AAV vectors comprising a viral capsid that is at least 95% identical to the amino acid sequence of an AAV9 capsid (SEQ ID NO: 144) or AAVrh10 (SEQ ID NO: 145); and an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding an anti-Aβ, anti-sortilin, anti-Tau protein, anti-SEMA4D, anti-alpha-synuclein, anti-SOD1, or anti-

CGRPR mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human CNS cells.

5.4.2 Constructs for delivery to Liver or Muscle Cells

[0705] Sections 5.3.8, 5.3.9, 5.3.10, 5.3.11, 5.3.12, 5.3.13, 5.3.14, 5.3.15, 5.3.16, 5.3.17, 5.3.18, 5.3.19, 5.3.20, and 5.3.21 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 VEGF, EpoR, ALK-1, C5, ENG, CC1Q, TNFα, RGMa, TTR, CTGF, IL6R, IL6, CD19, ITGF7, SOST, pKal, IL-6, IL-6R, IL/ILR, IgE, or TSLP. Such recombinant vector used for delivering the transgene can have a tropism for human liver or muscle cells. Such vectors can include non-replicating recombinant adeno-associated virus vectors ("rAAV"), e.g., those bearing an AAV8 or AAV9 capsid. 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.

[0706] In specific embodiments, provided are constructs for gene therapy administration to a human subject, comprising an AAV vector, which comprises a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143); and a viral or artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs) wherein the expression cassette comprises a transgene encoding the heavy and light chains of the therapeutic antibody, operably linked to one or more regulatory sequences that control expression of the transgene in human cells (e.g., human muscle or liver cells) that express and deliver the therapeutic antibody in a therapeutically appropriate manner as disclosed herein. In certain embodiments, the encoded AAV8 capsid has the sequence of SEQ ID NO: 143 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, particularly substitutions with amino acid residues found in the corresponding position in other AAV capsids, for example, in the SUBS row of FIG. 21 which provides a comparison of the amino acid sequences of the capsid sequences of various AAVs, highlighting amino acids appropriate for substitution at different positions within the capsid sequence.

[0707] In specific embodiments, provided are constructs for gene therapy administration to a human subject, comprising an AAV vector, which comprises a viral capsid that is at least 95% identical

to the amino acid sequence of an AAV9 capsid (SEQ ID NO: 144); and a viral or artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs) wherein the expression cassette comprises a transgene encoding the heavy and light chains of the therapeutic antibody, operably linked to one or more regulatory sequences that control expression of the transgene in human cells (e.g., human muscle or liver cells) that express and deliver the therapeutic antibody in a therapeutically appropriate manner as disclosed herein. In certain embodiments, the encoded AAV9 capsid has the sequence of SEQ ID NO: 144 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, particularly substitutions with amino acid residues found in the corresponding position in other AAV capsids, for example, in the SUBS row of FIG. 21 which provides a comparison of the amino acid sequences of the capsid sequences of various AAVs, highlighting amino acids appropriate for substitution at different positions within the capsid sequence.

[0708] In other embodiments, the HuPTM mAb or antigen binding fragment thereof, including the HuPTM Fab transgene should be controlled by appropriate expression control elements for expression of the HuPTM Fab in human liver or muscle cells, for example, the CB7 promoter (a chicken β-actin promoter and CMV enhancer, SEQ ID NO: 411), EF-1 alpha promoter (SEQ ID NO: 415), mU1a (SEQ ID NO: 414), or liver specific promoters such as the TBG (Thyroxine-binding Globulin) promoter (SEQ ID NO: 423), the APOA2 promoter, the SERPINA1 (hAAT) promoter, the ApoE.hAAT promoter (SEQ ID NO: 412), or the MIR122 promoter, or muscle specific promoters, such as the human desmin promoter, the CK8 promoter (SEQ ID NO: 413), or the human Pitx3 promoter, or inducible promoters, such as hypoxia-inducible promoters or rapamycin-inducible promoter, and can include other expression control elements that enhance expression of the transgene driven by the vector (e.g., introns such as the chicken β-actin intron, minute virus of mice (MVM) intron, human factor IX intron (e.g., FIX truncated intron 1), β-globin splice donor/immunoglobulin heavy chain spice acceptor intron, adenovirus splice donor /immunoglobulin splice acceptor intron, SV40 late splice donor /splice acceptor (19S/16S) intron, and hybrid adenovirus splice donor/IgG splice acceptor intron and polyA signals such as the rabbit β-globin polyA signal, human growth hormone (hGH) polyA signal, SV40 late polyA signal, synthetic polyA (SPA) signal, and bovine

growth hormone (bGH) polyA signal). See, e.g., Powell and Rivera-Soto, 2015, Discov. Med., 19(102):49-57.

[0709] In some embodiments, transgene expression is controlled by tissue-specific promoters or regulatory elements that promote tissue-specificity, for example, for liver-specific expression, LSPX1 (SEQ ID NO: 315), LSPX2 (SEQ ID NO: 316), LTP1 (SEQ ID NO: 317), LTP2 (SEQ ID NO: 318), or LTP3 (SEQ ID NO: 319), for liver and muscle expression, LMTP6 (SEQ ID NO: 320), LMTP13 (SEQ ID NO: 321), LMTP14 (SEQ ID NO: 322), LMTP15 (SEQ ID NO: 323), LMTP18 (SEQ ID NO: 324), LMTP19 (SEQ ID NO: 325), or LMTP20 (SEQ ID NO: 326), or for liver and bone expression, LBTP1 (SEQ ID NO: 327) or LBTP2 (SEQ ID NO: 328), the sequences of which are provided in Table 1.

[0710] Gene therapy constructs are designed such that both the heavy and light chains are expressed. More specifically, 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. The leader sequence for each of the heavy and light chains is, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Section 5.1.5, supra, provides specific IRES, 2A, and other linker sequences that can be used with the methods and compositions provided herein. In specific embodiments, the linker is a Furin-2A linker, for example, a Furin-F2A linker RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 231) or a Furin-T2A linker RKRR(GSG)EGRGSLLTCGDVEENPGP (SEQ ID NO: 429). In specific embodiments, the transgene is a nucleotide sequence that encodes the following: Signal sequence-heavy chain Fab portion-Furin-2Alinker-signal sequence-light chain Fab portion. See, e.g., FIG. 2B for sequences of GSK933776 Fab expression; FIGS. 9A to 9C for sequences for sevacizumab and LKA-651 Fab expression, respectively; FIGS. 10A to 10D for a sequence for ascrinvacumab, tesidolumab, ravulizumab, and carotuximab Fab expression, respectively; FIG. 11 for sequences for ANX-007 Fab expression; FIGS. 12A to 12C for a sequence for adalimumab, infliximab, and golimumab Fab expression; FIG. 13 for sequence for elezanumab Fab expression; FIGS. 14A and 14B for sequences for NI-301 and PRX-004 Fab expression, respectively; FIG. 15 for a sequence for

pamrevlumab Fab expression; FIGS. 16A to 16I for sequences for satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, tocilizumab, and inebilizumab Fab expression, respectively; FIG. 17 for a sequence for etrolizumab Fab expression; FIG. 18 for a sequence for romosozumab Fab expression; FIG. 19 for a sequence for lanadelumab Fab expression; and FIG. 29A to 29F for a sequence for benralizumab, reslizumab, tralokinumab, nemolizumab, omalizumab, and tezepelumab Fab expression respectively. In an alternative embodiment, the construct also comprises the nucleotide sequence encoding the Fc domain for the therapeutic antibody (see Table 7 or FIG. 23) for expression of the full length mAb. In specific embodiments, transgene sequences of expression of lanadelumab are provided in Table 8.

[0711] In a specific embodiment, 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, e.g., a hypoxia-inducible promoter, or a tissue-specific promoter, e.g. ApoE.hAAT, LSPX1, LMTP6, or CK8 or other disclosed in Table 1, b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy and light chains of the VEGF-binding, EpoR-binding, ALK-1-binding, C5-binding, ENG-binding, CC1Q-binding, TNF-α binding, RGMa-binding, TTR-binding, CTGF-binding, IL6R-binding, IL6-binding, CD19-binding, ITGF7-binding, SOST-binding, pKal-binding, IL-6 or IL6R-binding, IL/ILR-binding, IgE-binding, or TSLP-binding Fab, separated by a self-cleaving furin (F)/2A linker or T2A linker, ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is provided in FIG. 1.

[0712] In a specific embodiment, 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, e.g., a hypoxia-inducible promoter or a tissue-specific promoter (e.g. ApoE.hAAT or LSPX1), b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy and light chains of the VEGF-binding, EpoR-binding, ALK-1-binding, C5-binding, ENG-binding, CC1Q-binding, TNF-α binding, RGMa-binding, TTR-binding, CTGF-binding, IL6R-binding, IL6-binding, CD19-binding, ITGF7-binding, SOST-binding, pKal-binding, IL-6 or IL-6R, IL/ILR-binding, IgE-binding, or TSLP-binding

Fab, separated by a self-cleaving furin (F)/2A linker or a T2A linker, ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is provided in FIG. 1.

[0713] 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: 143); and an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding an anti-VEGF, anti-EpoR, anti-ALK-1, anti-C5, anti-ENG, anti-CC1Q, anti-TNF-α anti-RGMa, anti-TTR, anti-CTGF, anti-IL6R, anti-IL6, anti-CD19, anti-ITGF7, anti-SOST, anti-pKal, IL-6 or IL-6R, anti-IL/ILR, anti-IgE, or anti-TSLP mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver or muscle cells.

[0714] In specific embodiments, provided are AAV vectors comprising a viral capsid that is at least 95% identical to the amino acid sequence of an AAV9 (SEQ ID NO: 144); and an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene encoding an anti-VEGF, anti-EpoR, anti-ALK-1, anti-C5, anti-ENG, anti-CC1Q, anti-TNF-α anti-RGMa, anti-TTR, anti-CTGF, anti-IL6R, anti-IL6, anti-CD19, anti-ITGF7, anti-SOST, anti-pKal, IL-6 or IL-6R, anti-IL/ILR, anti-IgE, or anti-TSLP mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human muscle cells.

[0715] In certain embodiments, a rAAV comprises a transgene encoding an anti-kallikrein antibody, such as lanadelumab, and the construct comprises the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) regulatory control elements, a) promoter/enhancers, such as any one of Sp7 (SEQ ID NO: 329), minSP7 (SEQ ID NO: 329), ApoE.hAAT (SEQ ID NO: 412), LSPX1 (SEQ ID NO: 315), LSPX2 (SEQ ID NO: 316), LTP1 (SEQ ID NO: 317), LTP2 (SEQ ID NO: 318), LTP3 (SEQ ID NO: 319), LMTP6 (SEQ ID NO: 320), LMTP13 (SEQ ID NO: 321), LMTP14 (SEQ ID NO: 322), LMTP15 (SEQ ID NO: 323), LMTP18 (SEQ ID NO: 324), LMTP19 (SEQ ID NO: 325), LMTP20 (SEQ ID NO: 326), LBTP1 (SEQ ID NO: 327), or LBTP2 (SEQ ID NO: 328) as in Table 1, b) a poly A signal, and c) optionally an intron; and (3) nucleic acid sequences coding for the heavy and light chain of lanadelumab (L01 (SEQ ID NO:

141), L02 (SEQ ID NO: 286), or L03 (SEQ ID NO: 287), Table 8) wherein the heavy chain (Fab and Fc region) and the light chain are separated by a self-cleaving furin (F)/F2A (SEQ ID NO: 231) or furin (F)/T2A (SEQ ID NO: 429) or flexible linker, ensuring expression of equal amounts of the heavy and the light chain polypeptides. In specific embodiments, the transgene expressing lanadelumab has the sequence of SEQ ID NO: 435 to 443.

5.4.3 Constructs for delivery to Retinal Cell Types

[0716] Sections 5.3.8, 5.3.9, 5.3.10, 5.3.11, 5.3.15, 5.3.19, and 5.3.20 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 VEGF, EpoR, Aβ peptides, kallikrein, ALK-1, C5, ENG, CC1Q, TNFα, IL6R, IL6, and CD19. Such recombinant vectors used for delivering the transgene can have a tropism for one or more human retina cell types. Such vectors can include non-replicating recombinant adeno-associated virus vectors ("rAAV"), e.g., those bearing an AAV8 capsid. Alternatively, an AAV vector bearing an AAV2.7m8 capsid can be used. 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.

[0717] In specific embodiments, provided are constructs for gene therapy administration to a human subject, comprising an AAV vector, which comprises a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143); and a viral or artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs) wherein the expression cassette comprises a transgene encoding the heavy and light chains of the therapeutic antibody, operably linked to one or more regulatory sequences that control expression of the transgene in human cells (e.g., retina cell or liver cell types) that express and deliver the therapeutic antibody in a therapeutically appropriate manner as disclosed herein. In certain embodiments, the encoded AAV8 capsid has the sequence of SEQ ID NO: 143 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, particularly substitutions with amino acid residues found in the corresponding position in other AAV capsids, for example, in the SUBS row of FIG. 21 which provides a comparison of the amino acid sequences of the capsid

sequences of various AAVs, highlighting amino acids appropriate for substitution at different positions within the capsid sequence.

[0718] In specific embodiments, provided are constructs for gene therapy administration to a human subject, comprising an AAV vector, which comprises a viral capsid that is at least 95% identical to the amino acid sequence of an AAV2.7m8 capsid (SEQ ID NO: 142); and a viral or artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs) wherein the expression cassette comprises a transgene encoding the heavy and light chains of the therapeutic antibody, operably linked to one or more regulatory sequences that control expression of the transgene in human cells (e.g., retina cell or liver cell types) that express and deliver the therapeutic antibody in a therapeutically appropriate manner as disclosed herein. In certain embodiments, the encoded AAV2.7m8 capsid has the sequence of SEQ ID NO: 142 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, particularly substitutions with amino acid residues found in the corresponding position in other AAV capsids, for example, in the SUBS row of FIG. 21 which provides a comparison of the amino acid sequences of the capsid sequences of various AAVs, highlighting amino acids appropriate for substitution at different positions within the capsid sequence.

[0719] In some embodiments, the HuPTM mAb or antigen binding fragment thereof, including the HuPTM Fab transgene should be controlled by appropriate expression control elements for expression of the HuPTM Fab or HuPTM Mab in human retina or liver cell types, for example, CB7 promoter (a chicken β-actin promoter and CMV enhancer, SEQ ID NO: 411), or tissue-specific promoters such as RPE-specific promoters e.g., the RPE65 promoter, or cone-specific promoters, e.g., the opsin promoter, or liver specific promoters, such as, the TBG (Thyroxine-binding Globulin) promoter (SEQ ID NO: 423), the APOA2 promoter, the SERPINA1 (hAAT) promoter, the ApoE.hAAT promoter (SEQ ID NO: 412), or the MIR122 promoter, or inducible promoters, for example, hypoxia-induced promoters and drug inducible promoters such as promoters induced by rapamycin and related agents; and can include other expression control elements that enhance expression of the transgene driven by the vector (e.g., introns such as the chicken β-actin intron, minute virus of mice (MVM) intron, human factor IX intron (e.g., FIX truncated intron 1), β-globin splice donor/immunoglobulin heavy chain spice acceptor intron, adenovirus splice donor /immunoglobulin

splice acceptor intron, SV40 late splice donor /splice acceptor (19S/16S) intron, and hybrid adenovirus splice donor/IgG splice acceptor intron and polyA signals such as the rabbit β-globin polyA signal, human growth hormone (hGH) polyA signal, SV40 late polyA signal, synthetic polyA (SPA) signal, and bovine growth hormone (bGH) polyA signal). See, e.g., Powell and Rivera-Soto, 2015, Discov. Med., 19(102):49-57. In some embodiments, transgene expression is controlled by tissue-specific promoters or regulatory elements that promote tissue-specificity, for example, for liver-specific expression, LSPX1 (SEQ ID NO: 315), LSPX2 (SEQ ID NO: 316), LTP1 (SEQ ID NO: 317), LTP2 (SEQ ID NO: 318), or LTP3 (SEQ ID NO: 319), for liver and muscle expression, LMTP6 (SEQ ID NO: 320), LMTP13 (SEQ ID NO: 321), LMTP14 (SEQ ID NO: 322), LMTP15 (SEQ ID NO: 323), LMTP18 (SEQ ID NO: 324), LMTP19 (SEQ ID NO: 325), or LMTP20 (SEQ ID NO: 326), or for liver and bone expression, LBTP1 (SEQ ID NO: 327) or LBTP2 (SEQ ID NO: 328), the sequences of which are provided in Table 1.

[0720] Gene therapy constructs for antibodies or Fabs are designed such that both the heavy and light chains are expressed. More specifically, 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. The leader sequence for each of the heavy and light chains is, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). Section 5.1.5, supra, provides specific IRES, 2A, and other linker sequences that can be used with the methods and compositions provided herein. In specific embodiments, the linker is a Furin-2A linker, for example a Furin-F2A linker RKRR(GSG)APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 231) or a Furin-T2A linker RKRR(GSG)EGRGSLLTCGDVEENPGP (SEQ ID NO: 429). In specific embodiments, the transgene is a nucleotide sequence that encodes the following: Signal sequence-heavy chain Fab portion-Furin-(F/T)2A linker-signal sequence-light chain Fab portion. See FIGS. 2A-C for sequences for solanezumab, GSK933776, and lecanemab Fab expression, respectively; FIGS. 9A to 9C for sequences for sevacizumab and LKA-651 Fab expression, respectively; FIGS. 10A to 10D for a sequence for ascrinvacumab, tesidolumab, ravulizumab, and carotuximab Fab expression, respectively; FIG. 11 for sequences for ANX-007 Fab expression; FIGS. 12A to 12C for a sequence

for adalimumab, infliximab, and golimumab Fab expression, respectively; FIGS. 16A to 16I for sequences for satralizumab, sarilumab, siltuximab, clazakizumab, sirukumab, olokizumab, gerilimzumab, and tocilizumab, inebilizumab Fab expression, respectively; and FIG. 19 for lanadelumab Fab expression (and see also Table 8 for nucleotide sequences encoding lanadelumab and lanadelumab transgenes). In an alternative embodiment, the construct also comprises the nucleotide sequence encoding the Fc domain for the therapeutic antibody (see Table 7 or FIG. 23) for expression of the full length mAb (and Table 8 for lanadelumab).

[0721] In a specific embodiment, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) Control elements, which include a) the CB7 promoter, comprising the CMV enhancer/chicken β-actin promoter, b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy and light chains of the VEGF-binding, EpoR-binding, anti-Aβ, ALK-1-binding, C5-binding, ENG-binding, CC1Q-binding, TNFα-binding, kallikrein-binding, IL6R-binding, IL6-binding, and CD19-binding Fab, separated by a self-cleaving furin (F)/2A linker, ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is provided in FIG. 1.

[0722] In another embodiment, the constructs described herein comprise the following components: (1) AAV2 inverted terminal repeats that flank the expression cassette; (2) Control elements, which include a) the CB7 promoter, comprising the CMV enhancer/chicken β-actin promoter, b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy and light chains of the VEGF-binding, EpoR-binding, Aβ-binding, ALK-1-binding, C5-binding, ENG-binding, CC1Q-binding, TNFα-binding, kallikrein-binding, IL6R-binding, IL6-binding, and CD19-binding Fab, separated by flexible peptide linker, ensuring proper folding and solubility.

[0723] 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: 143) or of an AAV2.7m8 (SEQ ID NO: 142); and an artificial genome comprising an expression cassette flanked by AAV inverted terminal repeats (ITRs), wherein the expression cassette comprises a transgene

encoding an anti-VEGF, anti-EpoR, anti-Aβ, anti-ALK-1, anti-C5, anti-ENG, anti-CC1Q, anti-TNFα, anti-kallikrein, anti-IL6R, anti-IL6, and anti-CD19 mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in one or more retina cell types (such as 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).

5.5 Dose Administration

5.5.1 Administration for delivering to CNS.

[0724] Sections 5.3.1, 5.3.2, 5.3.3, 5.3.4, 5.3.5., 5.3.6., and 5.3.7. 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 Aβ, sortilin, Tau protein, SEMA4D, alpha-synuclein, SOD1, and CGRPR, respectively. Therapeutically effective doses of any such recombinant vector should be administered in any manner such that the recombinant vector enters the CNS, e.g. by introducing the recombinant vector into the cerebral spinal fluid (CSF). In specific, embodiments, the vector is administered intrathecally, specifically intracisternally (such as to the cisterna magna) or, alternatively, lumbar delivery. Alternatively, the recombinant vector may be administered intravenously. In particular, recombinant AAV9 vectors have been shown to cross the blood-brain barrier and, as such, may be useful to deliver the anti-Aβ, anti-sortilin, anti-Tau, anti-SEMA4D, anti-alpha-synuclein, anti-SOD1, or anti-CGRPR, antibody transgene product to the CNS. Specifically, a scAAV9 may be particularly useful for intravenous administration. Intrathecal, including intracisternal or lumbar administration, or intravenous administration should result expression of the soluble transgene product in cells of the CNS. The expression of the transgene product (e.g., the encoded anti-Aβ, anti-sortilin, anti-Tau, anti-SEMA4D, anti-alpha-synuclein, anti-SOD1, or anti-CGRPR antibody) results in delivery and maintenance of the transgene product in the CNS. 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 samples of the CSF.

[0725] Pharmaceutical compositions suitable for intrathecal, intracisternal, lumbar or intravenous administration comprise a suspension of the recombinant vector comprising the transgene encoding the anti-Aβ, anti-sortilin, anti-Tau, anti-SEMA4D, anti-alpha-synuclein, anti-SOD1, or anti-CGRPR 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.

5.5.2 Administration for delivering to liver or muscle tissue

[0726] Sections 5.3.8, 5.3.9, 5.3.10, 5.3.11, 5.3.12, 5.3.13, 5.3.14, 5.3.15, 5.3.16, 5.3.17, 5.3.18, 5.3.19, 5.3.20, and 5.3.21, 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 VEGF, EpoR, Aβ, ALK-1, C5, ENG, CC1Q, TNFα, RGMa, TTR, CTGF, IL6R, IL6, CD19, ITGF7, SOST, pKal, IL/ILR, IgE, or TSLP. Therapeutically effective doses of any such recombinant vector should be administered in any manner such that the recombinant vector enters the liver or muscle (e.g., skeletal muscle), e.g. by introducing the recombinant vector into the bloodstream. Alternatively, the vector may be administered directly to the liver through hepatic blood flow, e.g., via the suprahepatic veins or via the hepatic artery. In specific, embodiments, the vector is administered subcutaneously, intramuscularly or intravenously. Intramuscular, subcutaneous, intravenous or hepatic administration should result in expression of the soluble transgene product in cells of the liver or muscle. Alternatively, the vector may be administered directly to the liver through hepatic blood flow, e.g., via the suprahepatic veins or via the hepatic artery. The expression of the transgene product (e.g., the encoded anti-VEGF, anti-EpoR, anti-Aβ, anti-ALK1, anti-C5, anti-ENG, anti-CC1Q, anti-TNFα, anti-RGMa, anti-TTR, anti-CTGF, anti-IL6R, anti-CD19, anti-ITGF7, anti-SOST, anti-pKal, anti-IL/ILR, anti-IgE, or anti-TSLP antibody) results in delivery and maintenance of the transgene product in the liver or muscle.

[0727] 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.

[0728] 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.

[0729] 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.

[0730] In specific embodiments, doses that maintain a plasma concentration of the anti-CD19 transgene product at a C_{min} of at least 1 μg/ml (e.g., C_{min} of 1 to 10 μg/ml or 10 to 100 μg/ml or 100 to 300 μg/ml) are provided.

[0731] In specific embodiments, doses that maintain a plasma concentration of the anti-SOST transgene product at a C_{min} of at least 1 μg/ml (e.g., C_{min} of 1 to 10 μg/ml or 10 to 100 μg/ml or 100 to 200 μg/ml) are desired.

[0732] In specific embodiments, doses that maintain a plasma concentration of the sarilumab antibody, or antigen-binding fragment thereof, at a C_{min} of at least 5 μg/ml (e.g., C_{min} of 5 to 20 μg/ml or 20 to 50 μg/ml), preferably at a C_{min} of about 15 μg/mL to 20 μg/mL, are provided.

[0733] In specific embodiments, doses that maintain a plasma concentration of the tocilizumab antibody, or antigen-binding fragment thereof, at a C_{min} of at least 1 μg/ml (e.g., C_{min} of 1 to 10 μg/ml or 10 to 20 μg/ml) are provided.

[0734] In specific embodiments, doses that maintain a plasma concentration of the siltuximab antibody, or an antigen-binding fragment thereof, at a C_{min} of at least 20 μg/ml (e.g., C_{min} of 20 to 100 μg/ml or 100 to 200 μg/ml), preferably at a C_{min} of about 80 μg/mL to 90 μg/mL, are provided.

[0735] In specific embodiments, doses that maintain a plasma concentration of the anti-CTGF antibody transgene product at a C_{min} of at least 100 μg/mL(e.g., C_{min} of 100 to 200 μg/ml or 200 to 300 μg/mL) are provided.

[0736] In specific embodiments, doses that maintain a plasma concentration of the anti-ENG antibody transgene product at a C_{min} of at least 10 μg/mL are desired, such as C_{min} of 10 to 100 μg/ml or 100 to 300 μg/ml or 300 to 600 μg/ml are provided.

[0737] In specific embodiments, doses that maintain a plasma concentration of the anti-C5 antibody transgene product at a C_{min} of at least 10 μg/mL (e.g., C_{min} of 10 to 100 μg/ml or 100 to 200 μg/mL or 200 to 300 μg/mL) are provided.

[0738] In specific embodiments, doses that maintain a plasma concentration of the ravulizumab antibody, or antigen-binding fragment thereof, at a C_{min} of at least 200 μg/mL (e.g., C_{min} of 200 to 300 μg/ml or 300 to 400 μg/mL or 400 to 600 μg/mL), preferably at a C_{min} of about 350 to 450 μg/mL in complement-inhibitor naïve patients and at a C_{min} of about 450 to 550 μg/mL are provided.

[0739] In specific embodiments, doses that maintain a plasma concentration of the anti-IL/ILR antibody transgene product at a C_{min} of at least 0.1 μg/mL (e.g., C_{min} of 0.1 to 10 μg/ml or 10 to 20 μg/mL or 20 to 100 μg/mL) are provided.

[0740] In specific embodiments, doses that maintain a plasma concentration of the anti-IgE antibody transgene product at a C_{min} of at least 100 μg/mL (e.g., C_{min} of 100 to 200 μg/ml or 200 to 300 μg/mL or 300 to 400 μg/mL) are provided.

[0741] In specific embodiments, doses that maintain a plasma concentration of the anti-TSLP antibody transgene product at a C_{min} of at least 70 μg/mL (e.g., C_{min} of 70 to 150 μg/ml or 100 to 200 μg/mL or 200 to 350 μg/mL) are provided.

[0742] In specific embodiments, doses that maintain a plasma concentration of the lanadelumab antibody, or antigen-binding fragment thereof, at a C_{min} of at least 10 μg/mL (e.g., C_{min} of 10 to 50 μg/ml or 50 to 100 μg/mL or 100 to 200 μg/mL), preferably at a C_{min} of about 20 to 30 μg/mL, are provided.

[0743] 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.

[0744] Pharmaceutical compositions suitable for intravenous, intramuscular, subcutaneous or hepatic administration comprise a suspension of the recombinant vector comprising the transgene

encoding the anti-VEGF, anti-EpoR, anti-Aβ, anti-ALK-1, anti-C5, anti-ENG, anti-CC1Q, anti-TNFα, anti-RGMa, anti-TTR, anti-CTGF, anti-IL6R, anti-IL6, anti-CD19, anti-ITGF7, anti-SOST, anti-pKal, anti-IL/ILR, anti-IgE, or anti-TSLP 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.

5.5.3 Administration for delivering to retinal type cells

[0745] Therapeutically effective doses of the recombinant vector should be administered in any manner such that the recombinant vector enters the retina, e.g., by introducing the recombinant vector directly into the eye. In specific, embodiments, the vector is administered subretinally (a surgical procedure performed by trained retinal surgeons that involves a partial vitrectomy with the subject under local anesthesia, and injection of the gene therapy into the retina; see, e.g., Campochiaro et al., 2016, Hum Gen Ther Sep 26 epub:doi: 10.1089/hum.2016.117, which is incorporated by reference herein in its entirety), or intravitreally, or suprachoroidally such as by microinjection or microcannulation. (See, e.g., Patel et al., 2012, Invest Ophth & Vis Sci 53:4433-4441; Patel et al., 2011, Pharm Res 28:166-176; Olsen, 2006, Am J Ophth 142:777-787 each of which is incorporated by reference in its entirety). Subretinal, intravitreal 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.

[0746] The expression of the transgene product (e.g., the encoded anti-VEGF, anti-EpoR, anti-Aβ, anti-pKal, anti-ALK-1, anti-C5, anti-ENG, anti-CC1Q, anti-TNFα, anti-IL6R, anti-IL6, and anti-CD19 Antibody) results in delivery and maintenance of the transgene product in the retina. Pharmaceutical compositions suitable for administration comprise a suspension of the recombinant vector comprising the transgene encoding the anti-VEGF, anti-EpoR, anti-Aβ, anti-pKal, anti-ALK-1, anti-C5, anti-ENG, anti-CC1Q, anti-TNFα, anti-IL6R, anti-IL6, and anti-CD19 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

[0747] 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. In specific embodiments, doses and routes of administration of a vector comprising the transgene encoding an adalimumab antibody, or antigen-binding fragment thereof, should result in expression of the adalimumab antibody, or antigen-binding fragment thereof, that achieve and maintain an intravitreal concentration of the adalimumab antibody, or antigen-binding fragment thereof, at an equivalent level to the intravitreal concentration achieved by monthly intravitreal injections of Humira at a dose of 1.5 mg.

[0748] In specific embodiments, doses that maintain a plasma concentration of the infliximab antibody, or antigen-binding fragment thereof, at a C_{min} 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.

[0749] In specific embodiments, doses that maintain a plasma concentration of the sarilumab antibody, or antigen-binding fragment thereof, at a C_{min} of at least 5 μg/ml (e.g., C_{min} of 5 to 20 μg/ml or 20 to 50 μg/ml), preferably at a C_{min} of about 15 μg/mL to 20 μg/mL, are provided.

[0750] In specific embodiments, doses and routes of administration of a vector comprising the transgene encoding an satralizumab antibody, or antigen-binding fragment thereof, should result in expression of the satralizumab antibody, or antigen-binding fragment thereof, that achieve and maintain an intravitreal concentration of the satralizumab antibody, or antigen-binding fragment thereof, at an equivalent level to the intravitreal concentration achieved by monthly subcutaneous injections of SA237 (Roche) at a dose of 120 mg.

[0751] In specific embodiments, doses that maintain a plasma concentration of the tocilizumab antibody, or antigen-binding fragment thereof, at a C_{min} of at least 1 μg/ml (e.g., C_{min} of 1 to 10 μg/ml or 10 to 20 μg/ml) are provided. In specific embodiments, doses and routes of administration of a vector comprising the transgene encoding a tocilizumab antibody, or antigen-binding fragment thereof, should result in expression of the tocilizumab antibody, or antigen-binding fragment thereof, that

achieve and maintain a systemic concentration of the adalimumab antibody, or antigen-binding fragment thereof, at an equivalent level to the systemic concentration achieved by monthly intravenous injections of RoActemra at a dose of 4 mg/kg or 8 mg/kg.

[0752] In specific embodiments, doses that maintain a plasma concentration of the siltuximab antibody, or an antigen-binding fragment thereof, at a C_{min} of at least 20 μg/ml (e.g., C_{min} of 20 to 100 μg/ml or 100 to 200 μg/ml), preferably at a C_{min} of about 80 μg/mL to 90 μg/mL, are provided.

[0753] In specific embodiments, doses that maintain a plasma concentration of the ravulizumab antibody, or antigen-binding fragment thereof, at a C_{min} of at least 200 μg/mL (e.g., Cmin of 200 to 300 μg/ml or 300 to 400 μg/mL or 400 to 600 μg/mL), preferably at a C_{min} of about 350 to 450 μg/mL in complement-inhibitor naïve patients and at a C_{min} of about 450 to 550 μg/mL are provided.

[0754] In specific embodiments, doses that maintain a plasma concentration of the lanadelumab antibody, or antigen-binding fragment thereof, at a C_{min} of at least 10 μg/mL (e.g., C_{min} of 10 to 50 μg/ml or 50 to 100 μg/mL or 100 to 200 μg/mL), preferably at a C_{min} of about 20 to 30 μg/mL, are provided.

5.6 Constructs and Methods for Expression of HuPTM mAb

[0755] Examples 36 and 37 demonstrate that full length heavy and light chains of lanadelumab were expressed from an AAV vector transgene in human HEK293 cells and secreted into the cell supernatant (FIGS. 24B-24D). Mice administered recombinant AAV8 and recombinant AAV9 vectors that carry a transgene encoding the full length heavy and light chains of lanadelumab had lanadelumab present in serum as detectable by ELISA seven weeks after administration (FIG. 25). Accordingly, provided herein are AAV constructs, vectors, methods of manufacture and methods of treatment comprising transgenes that 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. 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 fragments of which depicted in FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F herein and including, in certain embodiments, the associated Fc domain provided in Table 7. In other embodiments, the transgenes encode the full-length forms of the Fab fragments of therapeutic antibodies depicted in one of FIGS. 2A-2F, 3A-3E, 4A, 4B, 5A-5C, 6, 7A, 7B, 8A-8H, 9A or 9B of PCT application no. PCT/US2018/056346, filed October 17, 2018, incorporated herein by reference (which Figures are included as an Appendix hereto), with an Fc domain.

[0756] 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.

[0757] 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 7 or an exemplary Fc domain of an IgG1, IgG2 or IgG4 isotype as set forth in FIG. 23. In specific embodiments, the HuPTM mAb comprises a Fc polypeptide comprising an amino acid sequence of an Fc polypeptide in Table 7 or FIG. 23 with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more amino acid substitutions, insertions or deletions. In

some embodiments, the HuPTM mAb comprises a Fc polypeptide of a sequence that is a variant of the Fc polypeptide sequence in Table 7 or FIG. 23 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.

[0758] In specific embodiments, provided are recombinant AAV constructs such as the construct shown in FIG. 1 or FIG. 24A, 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 one of FIGS. 2A-2C, 3, 4A-4C, 5, 6A-6C, 7A-7B, 8A-8C, 9A-9C, 10A-10D, 11, 12A-12C, 13, 14A-14B, 15, 16A-16I, 17, 18, 19, and 29A-29F or FIGS. 2A-2F, 3A-3E, 4A, 4B, 5A-5C, 6, 7A, 7B, 8A-8H, 9A or 9B of PCT application no. PCT/US2018/056346, filed October 17, 2018 (copies of these figures are included in an Appendix hereto and are incorporated herein by reference also), yet have a heavy chain that further comprises an Fc domain polypeptide C terminal to the hinge region of the heavy chain (including the corresponding Fc domain set forth in Table 7 or an IgG1, IgG2 or IgG4 Fc domain as in FIG. 23). 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.

[0759] Provided are recombinant AAV vectors that comprise the constructs encoding the full-length antibodies. The rAAVs include but are not limited to AAV based vectors comprising capsid components from one or more of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAVrh10 or AAVrh20. In preferred embodiments, AAV based vectors provided herein comprise capsids from one or more of AAV8, AAV9, AAV10, AAV11, AAVrh10 or AAVrh20 serotypes. The AAV serotype may be advantageously selected for tropism to a particular tissue type as detailed herein.

[0760] 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.

5.6.1. Full length expression of HuPTM mAb in CNS Cells

[0761] In a specific embodiments for expressing an intact or substantially intact mAb in retinal 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) the CB7 promoter, comprising the CMV enhancer/chicken β-actin promoter, b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy chain Fab of an anti-Aβ mAb (e.g., solanezumab, lecanemab, and GSK933776), anti-sortilin mAb (e.g., AL-001), anti-Tau protein mAb (e.g., ABBV-8E12, UCB-0107, NI-105 (BIIB076), and aTAU), anti-SEMA4D mAb (e.g., VX15/2503), anti-alpha-synuclein mAb (e.g., prasinezumab, NI-202 (BIIB054) and MED-1341), anti-SOD1 mAb (e.g., NI-204), or anti-CGRPR mAb (e.g., eptinezumab, fremanezumab, and galcanezumab, the Fc polypeptide may be the Fc associated with the therapeutic antibody (Table 7) or of the same isotype as the native form of the therapeutic antibody, such as an IgG isotype amino acid sequence from FIG. 23; and the light chain Fab of an anti-Aβ mAb (e.g., solanezumab, lecanemab, and GSK933776,), anti-sortilin mAb (e.g., AL-001), anti-Tau protein mAb (e.g., ABBV-8E12, UCB-0107, NI-105 (BIIB076), and aTAU), anti-SEMA4D mAb (e.g., VX15/2503), anti-alpha-synuclein mAb (e.g., prasinezumab, NI-202 (BIIB054) and MED-1341), anti-SOD1 mAb (e.g., NI-204), or anti-CGRPR mAb (e.g., eptinezumab, fremanezumab, and galcanezumab, wherein the heavy chain (Fab and Fc polypeptide) and the light chain are separated by a self-cleaving furin (F)/ 2A or T2A or flexible linker, ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is provided in FIG. 1.

[0762] In specific embodiments, provided are AAV vectors comprising a viral capsid that is at least 95% identical to, or is identical to, the amino acid sequence of an AAV9 capsid (SEQ ID NO: 144) or AAVrh10 (SEQ ID NO: 145); 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-Aβ, anti-sortilin, anti-Tau protein, anti-SEMA4D, anti-alpha-synuclein, anti-SOD1, or anti-CGRPR mAb, operably linked to one or more

regulatory sequences that control expression of the transgene in human CNS cells. Methods of producing HuPTM mAbs and methods of treatment, prevention or amelioration of symptoms of a disease or conditions amenable to treatment, prevention or amelioration of symptoms with the therapeutic antibody by administration of an rAAV encoding the HuPTM mAb or with the HuPTM mAb are also provided.

5.6.2 Full Length Expression of mAB in Liver or Muscle Cells

[0763] In a specific embodiments for expressing an intact or substantially intact mAb in muscle or liver 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 hypoxia-inducible promoter, b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy chain Fab of an anti-VEGF (e.g., sevacizumab), anti-EpoR (e.g., LKA-651,), anti-ALK1 (e.g., ascrinvacumab), anti-C5 (e.g., tesidolumab and ravulizumab), anti-endoglin (e.g., carotuximab), anti-CC1Q (e.g., ANX-007), anti-TNFα (e.g., adalimumab, infliximab, and golimumab), anti-RGMa (e.g., elezanumab), anti-TTR (e.g., NI-301 and PRX-004), anti-CTGF (e.g., pamrevlumab), anti-IL6R (e.g., satralizumab, sarilumab, and tocilizumab), anti-IL6 (e.g. siltuximab, clazakizumab, sirukumab, olokizumab, and gerilimzumab), anti-CD19 (e.g., inebilizumab), anti-ITGF7 mAb (e.g., etrolizumab), anti-SOST mAb (e.g., romosozumab), anti-pKal mAb (e.g., lanadelumab), anti-IL/ILR (e.g. benralizumab, reslizumab, tralokinumab, and nemolizumab), anti-IgE (e.g. omalizumab), or anti-TSLP (e.g. Tezepelumab); an Fc polypeptide associated with the therapeutic antibody (Table 7) or of the same isotype as the native form of the therapeutic antibody, such as an IgG isotype amino acid sequence from FIG 23; and the light chain of an anti-VEGF (e.g., sevacizumab), anti-EpoR (e.g., LKA-651,), anti-ALK1 (e.g., ascrinvacumab), anti-C5 (e.g., tesidolumab and ravulizumab), anti-CD105 or anti-ENG (e.g., carotuximab), anti-CC1Q (e.g., ANX-007), anti-TNFα (e.g., adalimumab, infliximab, and golimumab), anti-RGMa (e.g., elezanumab), anti-TTR (e.g., NI-301 and PRX-004), anti-CTGF (e.g., pamrevlumab), anti-IL6R (e.g., satralizumab, sarilumab, and tocilizumab), anti-IL6 (e.g. siltuximab, clazakizumab, sirukumab, olokizumab, and gerilimzumab), anti-CD19 (e.g., inebilizumab), anti-ITGF7 mAb (e.g., etrolizumab), anti-SOST mAb (e.g., romosozumab), anti-pKal mAb (e.g., lanadelumab), anti-IL/ILR (e.g. benralizumab, reslizumab, tralokinumab, and nemolizumab), anti-

IgE (e.g. omalizumab), or anti-TSLP (e.g. Tezepelumab); 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. An exemplary construct is provided in FIG. 1.

[0764] 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: 143); 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-VEGF, anti-EpoR, anti-ALK-1, anti-Aβ anti-C5, anti-ENG, anti-CC1Q, anti-TNFα, anti-RGMa, anti-TTR, anti-CTGF, anti-CD19, anti-ITGF7, anti-SOST, anti-pKal mAb, anti-IL6R, anti-IL6,, anti-IL/ILR, anti-IgE, or anti-TSLP; operably linked to one or more regulatory sequences that control expression of the transgene in human liver or muscle cells.

[0765] In specific embodiments, provided are AAV vectors comprising a viral capsid that is at least 95% identical to the amino acid sequence of an AAV9 (SEQ ID NO: 144); 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-VEGF, anti-EpoR, anti-Aβ, anti-ALK-1, anti-C5, anti-ENG, anti-CC1Q, anti-TNFα, anti-RGMa, anti-TTR, anti-CTGF, anti-IL6R, anti-IL6, anti-CD19, anti-ITGF7, anti-SOST, anti-pKal mAb, anti-IL/ILR, anti-ITGA4, anti-IgE, or anti-TSLP, operably linked to one or more regulatory sequences that control expression of the transgene in human muscle cells.

5.6.3 Full Length Expression of mAb in Retinal Cell Types

[0766] In a specific embodiments for expressing an intact or substantially intact mAb in retinal 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) the CB7 promoter, comprising the CMV enhancer/chicken β-actin promoter, b) a chicken β-actin intron and c) a rabbit β-globin poly A signal; and (3) nucleic acid sequences coding for the heavy chain Fab of an anti-VEGF (e.g., sevacizumab), anti-EpoR (e.g., LKA-651,), anti-Aβ (e.g., solanezumab, lecanemab, and GSK933776) anti-ALK1 (e.g., ascrinvacumab), anti-C5 (e.g., tesidolumab, ravulizumab), anti-

CD105 or anti-ENG (e.g., carotuximab), anti-CC1Q (e.g., ANX-007), anti-TNFα (e.g., adalimumab, infliximab, and golimumab), anti-IL6R (e.g., satralizumab, sarilumab, and tocilizumab), anti-IL6 (e.g. siltuximab, clazakizumab, sirukumab, olokizumab, and gerilimzumab), anti-CD19 (e.g., inebilizumab), , an Fc polypeptide associated with the therapeutic antibody (Table 6) or of the same IgG isotype as the native form of the therapeutic antibody, such as an IgG isotype amino acid sequence from FIG. 23, and a light chain of an anti-VEGF (e.g., sevacizumab), anti-Aβ (e.g., solanezumab, lecanemab, and GSK933776), anti-EpoR (e.g., LKA-651), anti-ALK1 (e.g., ascrinvacumab), anti-C5 (e.g., tesidolumab and ravulizumab), anti-CD105 or anti-Endoglin (e.g., carotuximab), anti-CC1Q (e.g., ANX-007), anti-TNFα (e.g., adalimumab, infliximab, and golimumab), anti-IL6R (e.g., satralizumab, sarilumab, and tocilizumab), anti-CD19 (e.g., inebilizumab), and anti-IL6 (e.g. siltuximab, clazakizumab, sirukumab, olokizumab, and gerilimzumab), wherein the heavy chain (Fab and Fc polypeptide) and light chain are separated by a self-cleaving furin (F)/F2A or flexible linker, ensuring expression of equal amounts of the heavy and the light chain polypeptides. An exemplary construct is provided in FIG. 1.

[0767] 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: 143) or of an AAV2.7m8 (SEQ ID NO: 142); 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-VEGF, anti-fD, anti-MMP9, anti-EpoR, anti-Aβ, anti-ALK-1, anti-C5, anti-ENG, anti-CC1Q, anti-TNFα, anti-IL6R, anti-IL6, or anti-CD19 mAb, operably linked to one or more regulatory sequences that control expression of the transgene in one or more retina cell types (such as 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).

6. EXAMPLES

6.1 EXAMPLE 1: Solanezumab Fab cDNA-Based Vector

[0768] A solanezumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of

solanezumab (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 codon optimized for expression in human CNS cells. Nucleotide sequences may be the nucleotide sequence of SEQ ID NOs. 71 and 72, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain ad heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 2A for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.2 EXAMPLE 2: GSK933776 Fab cDNA-Based Vector

[0769] A GSK933776 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of GSK933776 (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 is codon optimized for expression in human CNS cells. Nucleotide sequences may be the nucleotide sequence of SEQ ID NOs. 73 and 74, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 2B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.3 EXAMPLE 3: AL-001 Fab cDNA-Based Vector

[0770] An AL-001 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of AL-001 (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 is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 75 and 76, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS

(SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 3 for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.4 EXAMPLE 4: ABBV-8E12 Fab cDNA-Based Vector

[0771] An ABBV-8E12 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of ABBV-8E12 (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 is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs: 77 and 78, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 4A for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.5 EXAMPLE 5: UCB-0107 Fab cDNA-Based Vector

[0772] An UCB-0107 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of UCB-0107 (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 is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 79 and 80, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 4B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.6 EXAMPLE 6: NI-105 Fab cDNA-Based Vector

[0773] A NI-105 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of NI-105 (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 is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 81 and 82, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 4C for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.7 EXAMPLE 7: VX15/2503 Fab cDNA-Based Vector

[0774] A VX15/2503 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of VX15/2503 (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 is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs: 83 and 84, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 5 for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.8 EXAMPLE 8: Prasinezumab Fab cDNA-Based Vector

[0775] A prasinezumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of prasinezumab (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 is codon optimized for expression in

human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 85 and 86, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 6A for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.9 EXAMPLE 9: NI-202 Fab cDNA-Based Vector

[0776] A NI-202 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of NI-202 (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 is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOS: 87 and 88, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 6B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.10 EXAMPLE 10: MEDI-1341/TAK 341 Fab cDNA-Based Vector

[0777] A MEDI-1341/ TAK 341 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of MEDI-1341/ TAK 341 (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 is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOS: 89 and 90, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID Nos: 227-230) to create a bicistronic vector. See FIG. 6C for amino acid sequence of a transgene

product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.11 EXAMPLE 11: NI-204.10D12 Fab cDNA-Based Vector

[0778] A NI-204.10D12 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of NI-204.10D12 (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 is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs: 91 and 92, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 7A for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.12 EXAMPLE 12: NI-204.12G7 Fab cDNA-Based Vector

[0779] A NI-204.12G7 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of NI-204.12G7 (amino acid sequences being SEQ ID NOs. 23 and 24, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs: 93 and 94, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 7B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.13 EXAMPLE 13: Eptinezumab Fab cDNA-Based Vector

[0780] An eptinezumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of eptinezumab (amino acid sequences being SEQ ID NOs. 25 and 26, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs: 95 and 96, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 8A for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.14 EXAMPLE 14: Fremanezumab Fab cDNA-Based Vector

[0781] A fremanezumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of fremanezumab (amino acid sequences being SEQ ID NOs. 27 and 28, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOS: 97 and 98, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 8B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.15 EXAMPLE 15: Galcanezumab Fab cDNA-Based Vector

[0782] A galcanezumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of galcanezumab (amino acid sequences being SEQ ID NOs. 29 and 30, respectively). The nucleotide

sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 99 and 100, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 8C for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.16 EXAMPLE 16: Sevacizumab Fab cDNA-Based Vector

[0783] A sevacizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of sevacizumab (amino acid sequences being SEQ ID NOs. 31 and 32, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 101 and 102, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 9A for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.17 EXAMPLE 17: LKA-651 (NVS2) Fab cDNA-Based Vector

[0784] A LKA-651 (NVS2) Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of LKA-651 (NVS2) (amino acid sequences being SEQ ID NOs. 33 and 34, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 103 and 104, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light

chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 9B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.18 EXAMPLE 18: LKA-651 (NVS3) Fab cDNA-Based Vector

[0785] A LKA-651 (NVS3) Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of LKA-651 (NVS3) (amino acid sequences being SEQ ID NOs. 35 and 36, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 105 and 106, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 9C for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.19 EXAMPLE 19: Ascrinvacumab Fab cDNA-Based Vector

[0786] An ascrinvacumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of ascrinvacumab (amino acid sequences being SEQ ID NOs. 37 and 38, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 107 and 108, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 10A for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.20 EXAMPLE 20: Tesidolumab Fab cDNA-Based Vector

[0787] A tesidolumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of tesidolumab (amino acid sequences being SEQ ID NOs. 39 and 40, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 109 and 110, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 10B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.21 EXAMPLE 21: Carotuximab Fab cDNA-Based Vector

[0788] A carotuximab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of carotuximab (amino acid sequences being SEQ ID NOs. 41 and 42, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOS: 111 and 112, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 10C for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.22 EXAMPLE 22: ANX-007 Fab cDNA-Based Vector

[0789] An ANX-007 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of ANX-007 (amino acid sequences being SEQ ID NOs. 43 and 44, respectively). The nucleotide

sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 113 and 114, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 11 for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.23 EXAMPLE 23: Adalimumab Fab cDNA-Based Vector

[0790] An adalimumab Fab cDNA-based vector is 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. 45 and 46, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 115 and 116, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 12A for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.24 EXAMPLE 24: Infliximab Fab cDNA-Based Vector

[0791] 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. 47 and 48, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 117 and 118, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light

chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 12B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.25 EXAMPLE 25: Golimumab Fab cDNA-Based Vector

[0792] 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. 49 and 50, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 119 and 120, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 12C for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.26 EXAMPLE 26: Elezanumab Fab cDNA-Based Vector

[0793] An elezanumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of elezanumab (amino acid sequences being SEQ ID NOs. 51 and 52, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOS: 121 and 122, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 13 for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.27 EXAMPLE 27: NI-301 Fab cDNA-Based Vector

[0794] An NI-301 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of NI-301 (amino acid sequences being SEQ ID NOs. 53 and 54, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 123 and 124, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 14A for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.28 EXAMPLE 28: PRX-004 Fab cDNA-Based Vector

[0795] A PRX-004 Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of PRX-004 (amino acid sequences being SEQ ID NOs. 55 and 56, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 125 and 126, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 14B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.29 EXAMPLE 29: Pamrevlumab Fab cDNA-Based Vector

[0796] A pamrevlumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of pamrevlumab (amino acid sequences being SEQ ID NOs. 57 and 58, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 127 and 128, respectively.

The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 15 for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.30 EXAMPLE 30: Satralizumab Fab cDNA-Based Vector

[0797] A 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. 59 and 60, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 129 and 130, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 16A for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.31 EXAMPLE 31: Sarilumab Fab cDNA-Based Vector

[0798] 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. 61 and 62, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 131 and 132, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG.

16B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.32 EXAMPLE 32: Inebilizumab Fab cDNA-Based Vector

[0799] An inebilizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of inebilizumab (amino acid sequences being SEQ ID NOs. 63 and 64, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOs. 133 and 134, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 16C for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.33 EXAMPLE 33: Etrolizumab Fab cDNA-Based Vector

[0800] An etrolizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of etrolizumab (amino acid sequences being SEQ ID NOs. 65 and 66, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain is codon optimized for expression in human CNS cells and may be the nucleotide sequence of SEQ ID NOS: 135 and 136, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 17 for amino acid sequence of a transgene product. The vector

additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.34 EXAMPLE 34: Romosozumab Fab cDNA-Based Vector

[0801] A romosozumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of romosozumab (amino acid sequences being SEQ ID NOs. 67 and 68, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOS: 137 and 138, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 18 for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.35 EXAMPLE 35: Siltuximab Fab cDNA-Based Vector

[0802] 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. 331 and 332, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light and may be the nucleotide sequence of SEQ ID NOs: 343 and 344, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 16C for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.36 EXAMPLE 36: Clazakizumab Fab cDNA-Based Vector

[0803] 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. 333 and 334, respectively). The nucleotide

sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 345 and 346, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 16D for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.37 EXAMPLE 37: Sirukumab Fab cDNA-Based Vector

[0804] A 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. 335 and 336, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 347 and 348, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 16E for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.38 EXAMPLE 38: Olokizumab Fab cDNA-Based Vector

[0805] A 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. 337 and 338, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 349 and 350, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 16F for amino acid sequence of

a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.39 EXAMPLE 39: Gerilimzumab Fab cDNA-Based Vector

[0806] A gerilimzumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of gerilimzumab (amino acid sequences being SEQ ID NOs. 339 and 340, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 351 and 352, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 16G for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.40 EXAMPLE 40: Tocilizumab Fab cDNA-Based Vector

[0807] 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. 341 and 342, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 353 and 354, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 16H for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.41 EXAMPLE 41: Lecanemab Fab cDNA-Based Vector

[0808] A lecanemab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of lecanemab (amino acid sequences being SEQ ID NOs. 360 and 361, respectively). The nucleotide

sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 376 and 377, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 2C for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.42 EXAMPLE 42: Ravulizumab Fab cDNA-Based Vector

[0809] A ravulizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of ravulizumab (amino acid sequences being SEQ ID NOs. 362 and 363, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 378 and 379, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 10D for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.43 EXAMPLE 43: Benralizumab Fab cDNA-Based Vector

[0810] A benralizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of benralizumab (amino acid sequences being SEQ ID NOs. 364 and 365, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 380 and 381, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 29A for amino acid sequence of

a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.44 EXAMPLE 44: Reslizumab Fab cDNA-Based Vector

[0811] A reslizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of reslizumab (amino acid sequences being SEQ ID NOs. 366 and 367, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 382 and 383, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 29B for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.45 EXAMPLE 45: Tralokinumab Fab cDNA-Based Vector

[0812] A tralokinumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of tralokinumab (amino acid sequences being SEQ ID NOs. 368 and 369, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 384 and 385, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 29C for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.46 EXAMPLE 46: Nemolizumab Fab cDNA-Based Vector

[0813] A nemolizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of nemolizumab (amino acid sequences being SEQ ID NOs. 370 and 371, respectively). The nucleotide

sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 386 and 387, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 29D for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.47 EXAMPLE 47: Omalizumab Fab cDNA-Based Vector

[0814] A omalizumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of omalizumab (amino acid sequences being SEQ ID NOs. 372 and 373, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 388 and 389, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 29E for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.48 EXAMPLE 48: Tezepelumab Fab cDNA-Based Vector

[0815] A tezepelumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of tezepelumab (amino acid sequences being SEQ ID NOs. 374 and 375, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs: 390 and 391, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 29F for amino acid sequence of

a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.49 EXAMPLE 49: Lanadelumab Fab cDNA-Based Vector

[0816] A lanadelumab Fab cDNA-based vector is constructed comprising a transgene comprising nucleotide sequences encoding the Fab portion of the heavy and light chain sequences of lanadelumab (amino acid sequences being SEQ ID NOs. 69 and 70, respectively). The nucleotide sequence coding for the Fab portion of the heavy and light chain may be the nucleotide sequence of SEQ ID NOs. 139 and 140, respectively. The transgene also comprises nucleotide sequences that encodes a signal peptide, e.g., MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain are separated by IRES elements or 2A cleavage sites (SEQ ID NOs: 227-230) to create a bicistronic vector. See FIG. 19 for amino acid sequence of a transgene product. The vector additionally includes a constitutive promoter, such as CB7 or an inducible promoter, such as a hypoxia-inducible promoter.

6.50 EXAMPLE 50: Protein expression analysis of Lanadelumab in cell lysates and supernatant

[0817] Cell culture studies were performed to assess the expression of full length mAb sequences (containing Fc region) from AAV constructs in human cells.

Methods

[0818] A lanadelumab cDNA-based vector was constructed comprising a transgene comprising a nucleotide sequence encoding the heavy and light chain sequences of lanadelumab (amino acid sequences being SEQ ID NOs. 69 and 70, respectively). The nucleotide sequence coding for the heavy and light chain of lanadelumab was codon optimized to generate the three nucleotide sequences provided in Table 8 below, L01 (SEQ ID NO: 141), L02 (SEQ ID NO: 286), and L03 (SEQ ID NO: 287). L02 and L03 also have reduced incidence of CpG dimers in the sequence. The transgene also comprised a nucleotide sequence that encodes the signal peptide MYRMQLLLLIALSLALVTNS (SEQ ID NO: 146). The nucleotide sequences encoding the light chain and heavy chain were separated by a Furin-F2A linker (SEQ ID NOs: 231) or a Furin T2A linker (SEQ ID NO: 429) to create a bicistronic vector. The vector additionally included a constitutive CAG promoter (SEQ ID NO: 411).

See FIG. 24A for a schematic showing the genomic configuration and sequences of the constructs are provided in Table 8 (SEQ ID NOS: 435-437)

[0819] Table 1 above provides the sequences of composite nucleic acid regulatory sequences that may be incorporated into expression cassettes and be operably linked to the transgene to promote liver-specific expression (LSPX1, LSPX2, LTP1, LTP2, or LTP3, SEQ ID NOS: 315-319, respectively), liver and muscle expression (LMTP6, LMTP13, LMTP15, LMTP18, LMTP19 or LMTP20, SEQ ID NOS: 320-326 respectively), liver and bone expression (LTBP1 or LPTP2, SEQ ID NOS: 327-328, respectively) Other promoter sequences provided, include the ApoE.hAAT (SEQ ID NO: 412, Table 1 above) promoter, wherein four copies of the liver-specific apolipoprotein E (ApoE) enhancer were placed upstream of the human alpha 1-antitrypsin (hAAT) promoter.).

Table 8

Name/ SEQ ID NO.	Sequence
L01 SEQ ID NO: 141	ATGTACCGGATGCAGCTGCTGCTGCTCATTGCCCTGTCTCTGGCCCTGGTCACCAATAGC GAAGTCCAGCTGCTGGAATCTGGCGGCGGACTTGTTCAACCTGGCGGCTCTCTGAGACTG AGCTGTGCCGCTTCCGGCTTCACCTTCAGCCACTATATCATGATGTGGGTCCGACAGGCC CCTGGCAAAGGCCTTGAATGGGTGTCCGGCATCTATAGCAGCGGCGGCATCACAGTGTAC GCCGACTCTGTGAAGGGCAGATTCACCATCAGCCGGGACAACAGCAAGAACACCCTGTAC CTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGCGCCTATAGAAGA ATCGGCGTGCCCAGACGGGACGAGTTCGATATTTGGGGCCAGGGCACCATGGTCACCGTG TCTAGCGCCTCTACAAAGGGCCCTAGCGTGTTCCCTCTGGCTCCTAGCAGCAAGAGCACA AGCGGAGGAACAGCCGCTCTGGGCTGTCTGGTCAAGGACTACTTTCCCGAGCCTGTGACC GTGTCCTGGAATAGCGGAGCACTGACAAGCGGCGTGCACACCTTTCCAGCTGTGCTGCAA AGCAGCGGCCTGTACTCTCTGAGCAGCGTGGTCACAGTGCCAAGCTCTAGCCTGGGCACC CAGACCTACATCTGCAATGTGAACCACAAGCCTAGCAACACCAAGGTGGACAAGAGAGTG GAACCCAAGAGCTGCGACAAGACCCACACCTGTCCTCCATGTCCTGCTCCAGAACTGCTC GGCGGACCTTCCGTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTGATGATCAGCAGA ACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGATCCCGAAGTGAAGTTC AATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAG TACAACAGCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAAC GGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCTCCTATCGAGAAAACC ATCAGCAAGGCCAAGGGCCAGCCTAGGGAACCCCAGGTTTACACACTGCCTCCAAGCCGG GAAGAGATGACCAAGAACCAGGTGTCCCTGACCTGCCTCGTGAAGGGCTTCTACCCTTCC GATATCGCCGTGGAATGGGAGAGCAATGGCCAGCCAGAGAACAACTACAAGACAACCCCT CCTGTGCTGGACAGCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAGTCC AGATGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCAC TACACCCAGAAGAGTCTGAGCCTGTCTCCAGGCCTGCGGAAGAGAAGGGCTCCTGTGAAG CAGACCCTGAACTTCGACCTGCTGAAACTGGCCGGCGACGTGGAAAGCAACCCCGGACCT ATGTATAGAATGCAGCTCCTCCTGCTGATCGCACTGAGCCTGGCTCTCGTGACCAACAGC GACATCCAGATGACACAGAGCCCCAGCACACTGTCTGCCAGCGTGGGAGACAGAGTGACC ATCACCTGTAGAGCCAGCCAGTCCATCTCCTCTTGGCTGGCCTGGTATCAGCAAAAGCCT GGCAAGGCCCCTAAGCTGCTGATCTACAAGGCCTCCACACTGGAAAGCGGGGTGCCCTCC

Name/ SEQ ID NO.	Sequence
	AGATTTTCTGGCAGCGGATCTGGCACCGAGTTCACCCTGACCATCAGTAGCCTGCAGCCT GACGACTTCGCCACCTACTACTGCCAGCAGTACAATACCTACTGGACCTTCGGCCAGGGA ACAAAGGTGGAAATCAAGCGGACTGTGGCCGCTCCAAGCGTGTTCATCTTTCCACCTAGC GACGAGCAGCTGAAGTCCGGCACAGCCTCTGTTGTGTGCCTGCTGAACAACTTCTACCCC AGAGAAGCCAAGGTGCAGTGGAAAGTGGACAATGCCCTGCAGAGCGGCAACTCCCAAGAG AGCGTGACAGAGCAGGACTCCAAGGATTCCACCTACAGCCTGTCTAGCACCCTGACACTG AGCAAGGCCGACTACGAGAAGCACAAAGTGTATGCCTGCGAAGTGACCCACCAGGGCCTT AGCTCTCCAGTGACCAAGAGCTTCAACCGGGGCGAGTGTTGATAA
L02 SEQ ID NO: 286	ATGTACAGAATGCAGCTGCTGCTGCTCATTGCCCTGTCTCTGGCCCTGGTCACCAATTCT GAGGTCCAGCTGCTTGAGAGTGGTGGTGGACTGGTTCAGCCTGGTGGCAGCCTGAGACTG TCTTGTGCTGCCTCTGGCTTCACCTTCAGCCACTATATCATGATGTGGGTCAGACAGGCC CCTGGCAAAGGCCTGGAATGGGTGTCAGGCATCTACAGCAGTGGTGGCATCACAGTGTAT GCTGACTCTGTGAAGGGCAGATTCACCATCAGCAGAGACAACAGCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGAGAGCTGAGGACACAGCAGTGTACTACTGTGCCTATAGAAGA ATTGGGGTGCCCAGAAGGGATGAGTTTGACATCTGGGGCCAGGGCACCATGGTTACAGTG TCCTCTGCCAGCACAAAGGGCCCCTCTGTTTTTCCACTGGCTCCCAGCAGCAAGAGCACC AGTGGTGGAACAGCTGCCCTGGGCTGTCTGGTCAAGGATTACTTCCCTGAGCCTGTGACT GTGTCCTGGAACTCTGGGGCTCTGACTTCTGGGGTGCACACCTTTCCAGCTGTGCTGCAG TCCTCTGGCCTGTACTCTCTGTCCTCTGTGGTCACAGTGCCTAGCTCTAGCCTGGGCACA CAGACCTACATCTGCAATGTGAACCACAAGCCTAGCAACACCAAGGTGGACAAGAGAGTG GAACCCAAGAGCTGTGACAAGACCCACACCTGTCCTCCATGTCCTGCTCCAGAACTGCTT GGAGGCCCTTCTGTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTGATGATCAGCAGA ACCCCTGAAGTGACCTGTGTGGTGGTTGATGTGTCCCATGAGGACCCAGAAGTGAAGTTC AATTGGTATGTGGATGGGGTTGAAGTGCACAATGCCAAGACCAAGCCTAGAGAGGAACAG TACAACAGCACCTACAGAGTGGTTTCTGTGCTGACAGTGCTGCACCAGGACTGGCTGAAT GGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCTCCTATTGAGAAAACC ATCTCCAAGGCCAAGGGCCAGCCAAGAGAACCCCAGGTTTACACCCTGCCACCTAGCAGA GAAGAGATGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTTAAGGGCTTCTACCCCTCT GACATTGCTGTGGAATGGGAGAGCAATGGCCAGCCTGAAAACAACTACAAGACAACCCCT CCTGTGCTGGACTCTGATGGCTCATTCTTCCTGTACAGCAAGCTGACTGTGGACAAGTCC AGATGGCAGCAGGGAAATGTGTTCAGCTGCTCTGTGATGCATGAGGCCCTGCACAACCAC TACACCCAGAAAAGTCTGTCTCTGTCCCCTGGCAGAAAGAGAAGAGGCTCTGGAGAAGGC AGAGGCTCCCTGCTGACATGTGGGGATGTTGAAGAGAATCCTGGGCCTATGTATAGGATG CAACTGCTCCTCCTGATTGCTCTGAGCCTGGCTCTTGTGACCAACTCTGACATCCAGATG ACACAGAGCCCCTCCACACTGTCTGCATCTGTGGGAGACAGAGTGACCATCACCTGTAGA GCCAGCCAGTCTATCTCTAGCTGGCTGGCCTGGTATCAGCAAAAGCCTGGCAAGGCCCCT AAGCTGCTGATCTACAAGGCCAGCACACTTGAGTCAGGGGTGCCCTCCAGATTTTCTGGC TCTGGATCTGGCACAGAGTTCACCCTGACCATCAGCTCCCTGCAGCCAGATGACTTTGCC ACCTACTACTGCCAGCAGTACAATACCTACTGGACCTTTGGCCAGGGAACAAAGGTGGAA ATCAAGAGAACAGTGGCTGCCCCATCTGTGTTCATCTTCCCACCATCTGATGAACAGCTG AAGTCTGGCACTGCCTCTGTTGTGTGCCTGCTGAACAACTTTTACCCCAGAGAAGCCAAG GTGCAGTGGAAAGTGGATAATGCCCTGCAGTCTGGCAATAGCCAAGAATCTGTGACAGAG CAGGACTCCAAGGATTCCACCTACAGCCTGAGCAGCACCCTGACACTGAGCAAGGCTGAC TATGAGAAGCACAAAGTGTATGCCTGTGAAGTGACACACCAGGGACTGAGCAGCCCAGTG ACCAAGAGCTTCAACAGGGGAGAGTGCTGATAA
L03 SEQ ID NO: 287	ATGTACAGAATGCAGCTGCTGCTGCTCATTGCCCTGTCTCTGGCCCTGGTCACCAATTCT GAGGTCCAGCTGCTTGAGAGTGGTGGTGGACTGGTTCAGCCTGGTGGCAGCCTGAGACTG TCTTGTGCTGCCTCTGGCTTCACCTTCAGCCACTATATCATGATGTGGGTCAGACAGGCC CCTGGCAAAGGCCTGGAATGGGTGTCAGGCATCTACAGCAGTGGTGGCATCACAGTGTAT GCTGACTCTGTGAAGGGCAGATTCACCATCAGCAGAGACAACAGCAAGAACACCCTGTAC

Name/ SEQ ID NO.	Sequence
	CTGCAGATGAACTCCCTGAGAGCTGAGGACACAGCAGTGTACTACTGTGCCTATAGAAGA ATTGGGGTGCCCAGAAGGGATGAGTTTGACATCTGGGGCCAGGGCACCATGGTTACAGTG TCCTCTGCCAGCACAAAGGGCCCCTCTGTTTTTCCACTGGCTCCCAGCAGCAAGAGCACC AGTGGTGGAACAGCTGCCCTGGGCTGTCTGGTCAAGGATTACTTCCCTGAGCCTGTGACT GTGTCCTGGAACTCTGGGGCTCTGACCTCTGGGGTGCACACCTTTCCAGCTGTGCTGCAG TCCTCTGGCCTGTACTCTCTGTCCTCTGTGGTCACAGTGCCTAGCTCTAGCCTGGGCACA CAGACCTACATCTGCAATGTGAACCACAAGCCTAGCAACACCAAGGTGGACAAGAGAGTG GAACCCAAGAGCTGTGACAAGACCCACACCTGTCCTCCATGTCCTGCTCCAGAACTGCTT GGAGGCCCTTCTGTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTGATGATCAGCAGA ACCCCTGAAGTGACCTGTGTGGTGGTTGATGTGTCCCATGAGGACCCAGAAGTGAAGTTC AATTGGTATGTGGATGGGGTTGAAGTGCACAATGCCAAGACCAAGCCTAGAGAGGAACAG TACAACAGCACCTACAGAGTGGTTTCTGTGCTGACAGTGCTGCACCAGGACTGGCTGAAT GGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCTCCTATTGAGAAAACC ATCTCCAAGGCCAAGGGCCAGCCAAGAGAACCCCAGGTTTACACCCTGCCACCTAGCAGA GAAGAGATGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTTAAGGGCTTCTACCCCTCT GACATTGCTGTGGAATGGGAGAGCAATGGCCAGCCTGAAAACAACTACAAGACAACCCCT CCTGTGCTGGACTCTGATGGCTCATTCTTCCTGTACAGCAAGCTGACTGTGGACAAGTCC AGATGGCAGCAGGGAAATGTGTTCAGCTGCTCTGTGATGCATGAGGCCCTGCACAACCAC TACACCCAGAAAAGTCTGTCTCTGTCCCCTGGCAGAAAGAGAAGAGGATCAGGGGCCCCA GTGAAGCAGACCCTGAACTTTGATCTGCTGAAGCTGGCTGGGGATGTTGAGAGCAACCCT GGACCTATGTATAGGATGCAACTGCTCCTCCTGATTGCTCTGAGCCTGGCTCTTGTGACC AACTCTGACATCCAGATGACACAGAGCCCCTCCACACTGTCTGCATCTGTGGGAGACAGA GTGACCATCACCTGTAGAGCCAGCCAGTCTATCTCTTCCTGGCTGGCCTGGTATCAGCAA AAGCCTGGCAAGGCCCCTAAGCTGCTGATCTACAAGGCCAGCACACTTGAGTCAGGGGTG CCCTCCAGATTTTCTGGCTCTGGATCTGGCACAGAGTTCACCCTGACCATCAGCTCCCTG CAGCCAGATGACTTTGCCACCTACTACTGCCAGCAGTACAATACCTACTGGACCTTTGGC CAGGGAACAAAGGTGGAAATCAAGAGAACAGTGGCTGCCCCATCTGTGTTCATCTTCCCA CCATCTGATGAACAGCTGAAGTCTGGCACTGCCTCTGTTGTGTGCCTGCTGAACAACTTT TACCCTAGAGAAGCCAAGGTGCAGTGGAAAGTGGATAATGCCCTGCAGTCTGGCAATAGC CAAGAATCTGTGACAGAGCAGGACTCCAAGGATTCCACCTACAGCCTGAGCAGCACCCTG ACACTGAGCAAGGCTGACTATGAGAAGCACAAAGTGTATGCCTGTGAAGTGACACACCAG GGACTGAGCAGCCCAGTGACCAAGAGCTTCAACAGGGGAGAGTGCTGATAA
CAG.LAN.F2A (CAG.L01) SEQ ID NO: 435	ctagtcgacattgattattgactagttattaatagtaatcaattacggggtcattagttc atagcccatatatggagttccgcgttacataacttacggtaaatggcccgcctggctgac cgcccaacgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaa tagggactttccattgacgtcaatgggtggagtatttacggtaaactgcccacttggcag tacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggc ccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatct acgtattagtcatcgctattaccatggtcgaggtgagccccacgttctgcttcactctcc ccatctccccccccctccccacccccaattttgtatttatttatttttttaattattttgtg cagcgatgggggcgggggggggggggggcgcgcgccaggcggggcggggcggggcgagg ggcggggcggggcgaggcggagaggtgcggcggcagccaatcagagcggcgcgctccgaa agtttccttttatggcgaggcggcggcggcggccctataaaaagcgaagcgcgcggc gggcgggagtcgctgcgcgctgccttcgccccgtgccccgctccgccgccgcctcgcgcc gcccgccccggctctgactgaccgcgttactcccacaggtgagcgggcgggacggccctt ctcctccgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggctgc gtgaaagccttgaggggctccgggagggccctttgtgcgggggggagcggctcgggggggtg cgtgcgtgtgtgtgtgcgtggggagcgccgcgtgcggctccgcgctgcccggcggctgtg agcgctgcgggcgcggcgcggggctttgtgcgctccgcagtgtgcgcgaggggagcgcgg ccgggggcggtgccccgcggtgcgggggggggctgcgaggggaacaaaggctgcgtgcggg

Name/ SEQ ID NO.	Sequence
	gtgtgtgcgtgggggggtgagcaggggtgtgggcgcgtcggtcgggctgcaacccccccc tgcacccccctccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacgg ggcgtggcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgccgggcg gggcggggccgcctcgggccggggagggctcgggggaggggcgcggcggcccccggagcg ccggcggctgtcgaggcgcggcgagccgcagccattgccttttatggtaatcgtgcgaga gggcgcagggacttcctttgtcccaaatctgtgcggagccgaaatctgggaggcgccgcc gcacccccctctagcgggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgggcg gggagggccttcgtgcgtcgccgcgccgccgtccccttctccctctccagcctcggggct gtccgcgggggacggctgccttcgggggggacggggcagggcggggttcggcttctggc gtgtgaccggcggctctagagcctctgctaaccatgttcatgccttcttcttttcctac agctcctgggcaacgtgctggttattgtgctgtctcatcattttggcaaagaattcgcta gcgggcactttgcactggaacttacaacacccgagcaaggacgcgactctccaccatgta ccggatgcagctgctgctgctcattgccctgtctctggccctggtcaccaatagcgaagt ccagctgctggaatctggcggcggacttgttcaacctggcggctctctgagactgagctg tgccgcttccggcttcaccttcagccactatatcatgatgtgggtccgacaggcccctgg caaaggccttgaatgggtgtccggcatctatagcagcggcggcatcacagtgtacgccga ctctgtgaagggcagattcaccatcagccgggacaacagcaagaacaccctgtacctgca gatgaacagcctgagagccgaggacaccgccgtgtactactgcgcctatagaagaatcgg cgtgcccagacgggacgagttcgatatttggggccagggcaccatggtcaccgtgtctag cgcctctacaaagggccctagcgtgttccctctggctcctagcagcaagagcacaagcgg aggaacagccgctctgggctgtctggtcaaggactactttcccgagcctgtgaccgtgtc ctggaatagcggagcactgacaagcggcgtgcacacctttccagctgtgctgcaaagcag cggcctgtactctctgagcagcgtggtcacagtgccaagctctagcctgggcacccagac ctacatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagagagtggaacc caagagctgcgacaagacccacacctgtcctccatgtcctgctccagaactgctcggcgg accttccgtgttcctgtttcctccaaagcctaaggacaccctgatgatcagcagaacccc tgaagtgacctgcgtggtggtggatgtgtcccacgaggatcccgaagtgaagttcaattg gtacgtggacggcgtggaagtgcacaacgccaagaccaagcctagagaggaacagtacaa cagcacctacagagtggtgtccgtgctgaccgtgctgcaccaggattggctgaacggcaa agagtacaagtgcaaggtgtccaacaaggccctgcctgctcctatcgagaaaaccatcag caaggccaagggccagcctagggaaccccaggtttacacactgcctccaagccgggaaga gatgaccaagaaccaggtgtccctgacctgcctcgtgaagggcttctacccttccgatat cgccgtggaatgggagagcaatggccagccagagaacaactacaagacaacccctcctgt gctggacagcgacggctcattcttcctgtacagcaagctgacagtggacaagtccagatg gcagcagggcaacgtgttcagctgcagcgtgatgcacgaggccctgcacaaccactacac ccagaagagtctgagcctgtctccaggcctgcggaagagaagggctcctgtgaagcagac cctgaacttcgacctgctgaaactggccggcgacgtggaaagcaaccccggacctatgta tagaatgcagctcctcctgctgatcgcactgagcctggctctcgtgaccaacagcgacat ccagatgacacagagccccagcacactgtctgccagcgtgggagacagagtgaccatcac ctgtagagccagccagtccatctcctcttggctggcctggtatcagcaaaagcctggcaa ggcccctaagctgctgatctacaaggcctccacactggaaagcggggtgccctccagatt ttctggcagcggatctggcaccgagttcaccctgaccatcagtagcctgcagcctgacga cttcgccacctactactgccagcagtacaatacctactggaccttcggccagggaacaaa ggtggaaatcaagcggactgtggccgctccaagcgtgttcatctttccacctagcgacga gcagctgaagtccggcacagcctctgttgtgtgcctgctgaacaacttctaccccagaga agccaaggtgcagtggaaagtggacaatgccctgcagagcggcaactcccaagagagcgt gacagagcaggactccaaggattccacctacagcctgtctagcaccctgacactgagcaa ggccgactacgagaagcacaaagtgtatgcctgcgaagtgacccaccagggccttagctc tccagtgaccaagagcttcaaccggggcgagtgttgataaagcggccgcggtacctctag agtcgacccgggcggcctcgaggacggggtgaactacgcctgaggatccgatcttttcc

Name/ SEQ ID NO.	Sequence
	ctctgccaaaaattatggggacatcatgaagccccttgagcatctgacttctggctaata aaggaaatttattttcattgcaatagtgtgttggaatttttttgtgtctctcactcg
CAG.LANv2.F2A (CAG.L03) SEQ ID NO: 436	gacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcc catatatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgccca acgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaataggga ctttccattgacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatc aagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcct ggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtat tagtcatcgctattaccatggtcgaggtgagccccacgttctgcttcactctccccatct ccccccccctccccaccccccaattttgtatttatttatttttttaattattttgtgcagcga tgggggcgggggggggggggggcgcgcgccaggcggggcggggcggggcgaggggcggg gcggggcgaggcggagaggtgcggcggcagccaatcagagcggcgcgctccgaaagtttc cttttatggcgaggcggcggcggcggcggccctataaaaagcgaagcgcgcggcgggcgg gagtcgctgcgcgctgccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgc cccggctctgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctc cgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggctgcgtgaaa gccttgaggggctccgggagggccctttgtgcgggggggagcggctcgggggggtgcgtgcg tgtgtgtgtgcgtggggagcgccgcgtgcggctccgcgctgcccggcggctgtgagcgct gcgggcgcggcgcggggctttgtgcgctccgcagtgtgcgcgaggggagcgcggccgggg gcggtgccccgcggtgcgggggggggctgcgaggggaacaaaggctgcgtgcggggtgtgt gcgtgggggggtgagcaggggggtgtgggcgcgtcggtcgggctgcaacccccccctgcacc ccctccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacggggcgtg gcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgccgggcgggggcgg ggccgcctcgggccggggagggctcgggggaggggcgcggcggcccccggagcgccggcg gctgtcgaggcgcggcgagccgcagccattgccttttatggtaatcgtgcgagagggcgc agggacttcctttgtcccaaatctgtgcggagccgaaatctgggaggcgccgccgcaccc cctctagcgggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagg gccttcgtgcgtcgccgcgccgccgtcccctctccctctccagcctcggggctgtccgc gggggacggctgccttcgggggggacggggcagggcggggttcggcttctggcgtgtga ccggcggctctagagcctctgctaaccatgttcatgccttcttctttttcctacagctcc tgggcaacgtgctggttattgtgctgtctcatcattttggcaaagaattcgccgccacca tgtacagaatgcagctgctgctgctcattgccctgtctctggccctggtcaccaattctg aggtccagctgcttgagagtggtggtggactggttcagcctggtggcagcctgagactgt cttgtgctgcctctggcttcaccttcagccactatatcatgatgtgggtcagacaggccc ctggcaaaggcctggaatgggtgtcaggcatctacagcagtggtggcatcacagtgtatg ctgactctgtgaagggcagattcaccatcagcagagacaacagcaagaacaccctgtacc tgcagatgaactccctgagagctgaggacacagcagtgtactactgtgcctatagaagaa ttggggtgcccagaagggatgagtttgacatctggggccagggcaccatggttacagtgt cctctgccagcacaaagggcccctctgtttttccactggctcccagcagcaagagcacca gtggtggaacagctgccctgggctgtctggtcaaggattacttccctgagcctgtgactg tgtcctggaactctggggctctgacctctggggtgcacacctttccagctgtgctgcagt cctctggcctgtactctctgtcctctgtggtcacagtgcctagctctagcctgggcacac agacctacatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagagagtgg aacccaagagctgtgacaagacccacacctgtcctccatgtcctgctccagaactgcttg gaggcccttctgtgttcctgtttcctccaaagcctaaggacaccctgatgatcagcagaa cccctgaagtgacctgtgtggtggttgatgtgtcccatgaggacccagaagtgaagttca attggtatgtggatggggttgaagtgcacaatgccaagaccaagcctagagaggaacagt acaacagcacctacagagtggtttctgtgctgacagtgctgcaccaggactggctgaatg gcaaagagtacaagtgcaaggtgtccaacaaggccctgcctgctcctattgagaaaacca tctccaaggccaagggccagccaagagaaccccaggtttacaccctgccacctagcagag

Name/ SEQ ID NO.	Sequence
	aagagatgaccaagaaccaggtgtccctgacctgcctggttaagggcttctacccctctg acattgctgtggaatgggagagcaatggccagcctgaaaacaactacaagacaacccctc ctgtgctggactctgatggctcattcttcctgtacagcaagctgactgtggacaagtcca gatggcagcagggaaatgtgttcagctgctctgtgatgcatgaggccctgcacaaccact acacccagaaaagtctgtctctgtcccctggcagaaagagaagaggatcaggggccccag tgaagcagaccctgaactttgatctgctgaagctggctggggatgttgagagcaaccctg gacctatgtataggatgcaactgctcctcctgattgctctgagcctggctcttgtgacca actctgacatccagatgacacagagcccctccacactgtctgcatctgtgggagacagag tgaccatcacctgtagagccagccagtctatctcttcctggctggcctggtatcagcaaa agcctggcaaggcccctaagctgctgatctacaaggccagcacacttgagtcaggggtgc cctccagattttctggctctggatctggcacagagttcaccctgaccatcagctccctgc agccagatgactttgccacctactactgccagcagtacaatacctactggacctttggcc agggaacaaaggtggaaatcaagagaacagtggctgccccatctgtgttcatcttcccac catctgatgaacagctgaagtctggcactgcctctgttgtgtgcctgctgaacaacttttt accctagagaagccaaggtgcagtggaaagtggataatgccctgcagtctggcaatagcc aagaatctgtgacagagcaggactccaaggattccacctacagcctgagcagcaccctga cactgagcaaggctgactatgagaagcacaaagtgtatgcctgtgaagtgacacaccagg gactgagcagcccagtgaccaagagcttcaacaggggagagtgctgataactcgaggacg gggtgaactacgcctgaggatccgatctttttccctctgccaaaaattatggggacatca tgaagccccttgagcatctgacttctggctaataaaggaaatttattttcattgcaatag tgtgttggaatttttgtgtctctca
CAG.LANv2.T2A (CAG.L02) SEQ ID NO: 437	gacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcc catatatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgccca acgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaataggga ctttccattgacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatc aagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcct ggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtat tagtcatcgctattaccatggtcgaggtgagccccacgttctgcttcactctccccatct ccccccctcccccacccccaattttgtatttatttatttttttaattattttgtgcagcga tgggggcgggggggggggggggcgcgcgccaggcggggcggggcggggcgaggggcggg gcggggcgaggcggagaggtgcggcggcagccaatcagagcggcgcgctccgaaagtttc cttttatggcgaggcggcggcggcggcggccctataaaaagcgaagcgcgcggcgggcgg gagtcgctgcgcgctgccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgc cccggctctgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctc cgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggctgcgtgaaa gccttgaggggctccgggagggccctttgtgcgggggggagcggctcgggggggtgcgtgcg tgtgtgtgtgcgtggggagcgccgcgtgcggctccgcgctgcccggcggctgtgagcgct gcgggcgcggcgcggggctttgtgcgctccgcagtgtgcgcgaggggagcgcggccgggg gcggtgccccgcggtgcgggggggggctgcgaggggaacaaaggctgcgtgcggggtgtgt gcgtgggggggtgagcaggggggtgtgggcgcgtcggtcgggctgcaacccccccctgcacc cccctccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacggggcgtg gcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgccgggcggggcgg ggccgcctcgggccggggagggctcgggggaggggcgcggcggcccccggagcgccggcg gctgtcgaggcgcggcgagccgcagccattgccttttatggtaatcgtgcgagagggcgc agggacttcctttgtcccaaatctgtgcggagccgaaatctgggaggcgccgccgcaccc cctctagcgggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagg gccttcgtgcgtcgccgcgccgccgtcccctttctcccctctccagcctcggggctgtccgc gggggacggctgccttcgggggggacggggcagggcggggttcggcttctggcgtgtga ccggcggctctagagcctctgctaaccatgttcatgccttcttcttttttcctacagctcc tgggcaacgtgctggttattgtgctgtctcatcattttggcaaagaattcgccgccacca

Name/ SEQ ID NO.	Sequence
	tgtacagaatgcagctgctgctgctcattgccctgtctctggccctggtcaccaattctg aggtccagctgcttgagagtggtggtggactggttcagcctggtggcagcctgagactgt cttgtgctgcctctggcttcaccttcagccactatatcatgatgtgggtcagacaggccc ctggcaaaggcctggaatgggtgtcaggcatctacagcagtggtggcatcacagtgtatg ctgactctgtgaagggcagattcaccatcagcagagacaacagcaagaacaccctgtacc tgcagatgaactccctgagagctgaggacacagcagtgtactactgtgcctatagaagaa ttggggtgcccagaagggatgagtttgacatctggggccagggcaccatggttacagtgt cctctgccagcacaaagggcccctctgtttttccactggctcccagcagcaagagcacca gtggtggaacagctgccctgggctgtctggtcaaggattacttccctgagcctgtgactg tgtcctggaactctggggctctgacttctggggtgcacacctttccagctgtgctgcagt cctctggcctgtactctctgtcctctgtggtcacagtgcctagctctagcctgggcacac agacctacatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagagagtgg aacccaagagctgtgacaagacccacacctgtcctccatgtcctgctccagaactgcttg gaggcccttctgtgttcctgtttcctccaaagcctaaggacaccctgatgatcagcagaa cccctgaagtgacctgtgtggtggttgatgtgtcccatgaggacccagaagtgaagttca attggtatgtggatggggttgaagtgcacaatgccaagaccaagcctagagaggaacagt acaacagcacctacagagtggtttctgtgctgacagtgctgcaccaggactggctgaatg gcaaagagtacaagtgcaaggtgtccaacaaggccctgcctgctcctattgagaaaacca tctccaaggccaagggccagccaagagaaccccaggtttacaccctgccacctagcagag aagagatgaccaagaaccaggtgtccctgacctgcctggttaagggcttctacccctctg acattgctgtggaatgggagagcaatggccagcctgaaaacaactacaagacaacccctc ctgtgctggactctgatggctcattcttcctgtacagcaagctgactgtggacaagtcca gatggcagcagggaaatgtgttcagctgctctgtgatgcatgaggccctgcacaaccact acacccagaaaagtctgtctctgtcccctggcagaaagagaagaggctctggagaaggca gaggctccctgctgacatgtggggatgttgaagagaatcctgggcctatgtataggatgc aactgctcctcctgattgctctgagcctggctcttgtgaccaactctgacatccagatga cacagagcccctccacactgtctgcatctgtgggagacagagtgaccatcacctgtagag ccagccagtctatctctagctggctggcctggtatcagcaaaagcctggcaaggccccta agctgctgatctacaaggccagcacacttgagtcaggggtgccctccagattttctggct ctggatctggcacagagttcaccctgaccatcagctccctgcagccagatgactttgcca cctactactgccagcagtacaatacctactggacctttggccagggaacaaaggtggaaa tcaagagaacagtggctgccccatctgtgttcatcttcccaccatctgatgaacagctga agtctggcactgcctctgttgtgtgcctgctgaacaacttttaccccagagaagccaagg tgcagtggaaagtggataatgccctgcagtctggcaatagccaagaatctgtgacagagc aggactccaaggattccacctacagcctgagcagcaccctgacactgagcaaggctgact atgagaagcacaaagtgtatgcctgtgaagtgacacaccagggactgagcagcccagtga ccaagagcttcaacaggggagagtgctgataactcgaggacggggtgaactacgcctgag gatccgatcttttccctctgccaaaaattatggggacatcatgaagccccttgagcatc tgacttctggctaataaaggaaatttattttcattgcaatagtgtgttggaatttttgt gtctctcactcg
TBG.LANv2.T2A (TBG.L02) SEQ ID NO: 438	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactctctc tgtttgctctggttaataatctcaggagcacaaacattccagatccaggttaatttttaa aaagcagtcaaaagtccaagtggcccttggcagcatttactctctctgtttgctctggtt aataatctcaggagcacaaacattccagatccggcgcgccagggctggaagctacctttg acatcatttcctctgcgaatgcatgtataatttctacagaacctattagaaaggatcacc cagcctctgcttttgtacaactttcccttaaaaaactgccaattccactgctgtttggcc caatagtgagaacttttttcctgctgcctcttggtgcttttgcctatggcccctattctgc ctgctgaagacactcttgccagcatggacttaaacccctccagctctgacaatcctcttt ctcttttgttttacatgaagggtctggcagccaaagcaatcactcaaagttcaaacctta tcatttttttgctttgttcctcttggccttggttttgtacatcagctttgaaaataccatc

Name/ SEQ ID NO.	Sequence
	ccagggttaatgctggggttaatttataactaagagtgctctagttttgcaatacaggac atgctataaaaatggaaagatgttgctttctgagagacagctttattgcggtagtttatc acagttaaattgctaacgcagtcagtgcttctgacacaacagtctcgaacttaagctgca gaagttggtcgtgaggcactgggcaggtaagtatcaaggttacaagacaggtttaaggag accaatagaaactgggcttgtcgagacagagaagactcttgcgtttctgataggcaccta ttggtcttactgacatccactttgcctttctctccacaggtgtccactcccagttcaatt acagctcttaaggctagagtacttaatacgactcactataggctagcctcgagaattcac gcgtgccgccaccatgtacagaatgcagctgctgctgctcattgccctgtctctggccct ggtcaccaattctgaggtccagctgcttgagagtggtggtggactggttcagcctggtgg cagcctgagactgtcttgtgctgcctctggcttcaccttcagccactatatcatgatgtg ggtcagacaggcccctggcaaaggcctggaatgggtgtcaggcatctacagcagtggtgg catcacagtgtatgctgactctgtgaagggcagattcaccatcagcagagacaacagcaa gaacaccctgtacctgcagatgaactccctgagagctgaggacacagcagtgtactactg tgcctatagaagaattggggtgcccagaagggatgagtttgacatctggggccagggcac catggttacagtgtcctctgccagcacaaagggcccctctgtttttccactggctcccag cagcaagagcaccagtggtggaacagctgccctgggctgtctggtcaaggattacttccc tgagcctgtgactgtgtcctggaactctggggctctgacttctggggtgcacacctttcc agctgtgctgcagtcctctggcctgtactctctgtcctctgtggtcacagtgcctagctc tagcctgggcacacagacctacatctgcaatgtgaaccacaagcctagcaacaccaaggt ggacaagagagtggaacccaagagctgtgacaagacccacacctgtcctccatgtcctgc tccagaactgcttggaggcccttctgtgttcctgtttcctccaaagcctaaggacaccct gatgatcagcagaacccctgaagtgacctgtgtggtggttgatgtgtcccatgaggaccc agaagtgaagttcaattggtatgtggatggggttgaagtgcacaatgccaagaccaagcc tagagaggaacagtacaacagcacctacagagtggtttctgtgctgacagtgctgcacca ggactggctgaatggcaaagagtacaagtgcaaggtgtccaacaaggccctgcctgctcc tattgagaaaaccatctccaaggccaagggccagccaagagaaccccaggtttacaccct gccacctagcagagaagagatgaccaagaaccaggtgtccctgacctgcctggttaaggg cttctacccctctgacattgctgtggaatgggagagcaatggccagcctgaaaacaacta caagacaacccctcctgtgctggactctgatggctcattcttcctgtacagcaagctgac tgtggacaagtccagatggcagcagggaaatgtgttcagctgctctgtgatgcatgaggc cctgcacaaccactacacccagaaaagtctgtctctgtcccctggcagaaagagaagagg ctctggagaaggcagaggctccctgctgacatgtggggatgttgaagagaatcctgggcc tatgtataggatgcaactgctcctcctgattgctctgagcctggctcttgtgaccaactc tgacatccagatgacacagagcccctccacactgtctgcatctgtgggagacagagtgac catcacctgtagagccagccagtctatctctagctggctggcctggtatcagcaaaagcc tggcaaggcccctaagctgctgatctacaaggccagcacacttgagtcaggggtgccctc cagattttctggctctggatctggcacagagttcaccctgaccatcagctccctgcagcc agatgactttgccacctactactgccagcagtacaatacctactggacctttggccaggg aacaaaggtggaaatcaagagaacagtggctgccccatctgtgttcatcttcccaccatc tgatgaacagctgaagtctggcactgcctctgttgtgtgcctgctgaacaacttttaccc cagagaagccaaggtgcagtggaaagtggataatgccctgcagtctggcaatagccaaga atctgtgacagagcaggactccaaggattccacctacagcctgagcagcaccctgacact gagcaaggctgactatgagaagcacaaagtgtatgcctgtgaagtgacacaccagggact gagcagcccagtgaccaagagcttcaacaggggagagtgctgataagtcgacccgggcgg cctcgaggacggggtgaactacgcctgaggatccgatcttttccctctgccaaaaatta tggggacatcatgaagccccttgagcatctgacttctggctaataaaggaaatttatttt cattgcaatagtgtgttggaatttttgtgtctctca
ApoE.hAAT.LANv2.T2A	ggctcagaggcacacaggagtttctgggctcaccctgccccttccaacccctcagttcc catcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcct actcatgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctcc

Name/ SEQ ID NO.	Sequence
(ApoE.hAAT.L02) SEQ ID NO: 439	ctgcctgctgaccttggagctggggcagaggtcagagacctctctgggcccatgccacct ccaacatccactcgacccctggaatttcggtggagaggagcagaggttgtcctggcgtg gtttaggtagtgtgagaggggtacccggggatcttgctaccagtggaacagccactaagg attctgcagtgagagcagagggccagctaagtggtactctcccagagactgtctgactca cgccacccctccaccttggacacaggacgctgtggtttctgagccaggtacaatgactc ctttcggtaagtgcagtggaagctgtacactgcccaggcaaagcgtccgggcagcgtagg cgggcgactcagatcccagccagtggacttagcccctgtttgctcctccgataactgggg tgaccttggttaatattcaccagcagcctcccccgttgcccctctggatccactgcttaa atacggacgaggacagggccctgtctcctcagcttcaggcaccaccactgacctgggaca gtcaggtaagtatcaaggttacaagacaggtttaaggagaccaatagaaactgggcttgt cgagacagagaagactcttgcgtttctgataggcacctattggtcttactgacatccact ttgcctttctctccacaggttcgaattcgccgccaccatgtacagaatgcagctgctgct gctcattgccctgtctctggccctggtcaccaattctgaggtccagctgcttgagagtgg tggtggactggttcagcctggtggcagcctgagactgtcttgtgctgcctctggcttcac cttcagccactatatcatgatgtgggtcagacaggcccctggcaaaggcctggaatgggt gtcaggcatctacagcagtggtggcatcacagtgtatgctgactctgtgaagggcagatt caccatcagcagagacaacagcaagaacaccctgtacctgcagatgaactccctgagagc tgaggacacagcagtgtactactgtgcctatagaagaattggggtgcccagaagggatga gtttgacatctggggccagggcaccatggttacagtgtcctctgccagcacaaagggccc ctctgtttttccactggctcccagcagcaagagcaccagtggtggaacagctgccctggg ctgtctggtcaaggattacttccctgagcctgtgactgtgtcctggaactctggggctct gacttctggggtgcacacctttccagctgtgctgcagtcctctggcctgtactctctgtc ctctgtggtcacagtgcctagctctagcctgggcacacagacctacatctgcaatgtgaa ccacaagcctagcaacaccaaggtggacaagagagtggaacccaagagctgtgacaagac ccacacctgtcctccatgtcctgctccagaactgcttggaggcccttctgtgttcctgtt tcctccaaagcctaaggacaccctgatgatcagcagaacccctgaagtgacctgtgtggt ggttgatgtgtcccatgaggacccagaagtgaagttcaattggtatgtggatggggttga agtgcacaatgccaagaccaagcctagagaggaacagtacaacagcacctacagagtggt ttctgtgctgacagtgctgcaccaggactggctgaatggcaaagagtacaagtgcaaggt gtccaacaaggccctgcctgctcctattgagaaaaccatctccaaggccaagggccagcc aagagaaccccaggtttacaccctgccacctagcagagaagagatgaccaagaaccaggt gtccctgacctgcctggttaagggcttctacccctctgacattgctgtggaatgggagag caatggccagcctgaaaacaactacaagacaacccctcctgtgctggactctgatggctc attcttcctgtacagcaagctgactgtggacaagtccagatggcagcagggaaatgtgtt cagctgctctgtgatgcatgaggccctgcacaaccactacacccagaaaagtctgtctct gtcccctggcagaaagagaagaggctctggagaaggcagaggctccctgctgacatgtgg ggatgttgaagagaatcctgggcctatgtataggatgcaactgctcctcctgattgctct gagcctggctcttgtgaccaactctgacatccagatgacacagagcccctccacactgtc tgcatctgtgggagacagagtgaccatcacctgtagagccagccagtctatctctagctg gctggcctggtatcagcaaaagcctggcaaggcccctaagctgctgatctacaaggccag cacacttgagtcaggggtgccctccagattttctggctctggatctggcacagagttcac cctgaccatcagctccctgcagccagatgactttgccacctactactgccagcagtacaa tacctactggacctttggccagggaacaaaggtggaaatcaagagaacagtggctgcccc atctgtgttcatcttcccaccatctgatgaacagctgaagtctggcactgcctctgttgt gtgcctgctgaacaacttttaccccagagaagccaaggtgcagtggaaagtggataatgc cctgcagtctggcaatagccaagaatctgtgacagagcaggactccaaggattccaccta cagcctgagcagcaccctgacactgagcaaggctgactatgagaagcacaaagtgtatgc ctgtgaagtgacacaccagggactgagcagcccagtgaccaagagcttcaacaggggaga gtgctgataactcgaggacggggtgaactacgcctgaggatccgatcttttttccctctgc

Name/ SEQ ID NO.	Sequence
	caaaaattatggggacatcatgaagcccttgagcatctgacttctggctaataaaggaa atttattttcattgcaatagtgtgttggaatttttgtgtctctca
LSPX1.LANv2.T2A (LSPX.L02) SEQ ID NO: 440	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactctctc tgtttgctctggttaataatctcaggagcacaaacattccagatccaggttaatttttaa aaagcagtcaaaagtccaagtggcccttggcagcatttactctctctgtttgctctggtt aataatctcaggagcacaaacattccagatccggcgcgccagggctggaagctacctttg tctagaaggctcagaggcacacaggagtttctgggctcaccctgccccttccaacccct cagttcccatcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaact tcagcctactcatgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacaca gccctccctgcctgctgaccttggagctggggcagaggtcagagacctctctgggcccat gccacctccaacatccactcgacccctggaatttcggtggagaggagcagaggttgtcc tggcgtggtttaggtagtgtgagaggggtacccggggatcttgctaccagtggaacagcc actaaggattctgcagtgagagcagagggccagctaagtggtactctcccagagactgtc tgactcacgccacccctccaccttggacacaggacgctgtggtttctgagccaggtaca atgactcctttcggtaagtgcagtggaagctgtacactgcccaggcaaagcgtccgggca gcgtaggcgggcgactcagatcccagccagtggacttagcccctgtttgctcctccgata actggggtgaccttggttaatattcaccagcagcctcccccgttgcccctctggatccac tgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcaccaccactgacc tgggacagtcaggtaagtatcaaggttacaagacaggtttaaggagaccaatagaaactg ggcttgtcgagacagagaagactcttgcgtttctgataggcacctattggtcttactgac atccactttgcctttctctccacaggttgaattcgccgccaccatgtacagaatgcagct gctgctgctcattgccctgtctctggccctggtcaccaattctgaggtccagctgcttga gagtggtggtggactggttcagcctggtggcagcctgagactgtcttgtgctgcctctgg cttcaccttcagccactatatcatgatgtgggtcagacaggcccctggcaaaggcctgga atgggtgtcaggcatctacagcagtggtggcatcacagtgtatgctgactctgtgaaggg cagattcaccatcagcagagacaacagcaagaacaccctgtacctgcagatgaactccct gagagctgaggacacagcagtgtactactgtgcctatagaagaattggggtgcccagaag ggatgagtttgacatctggggccagggcaccatggttacagtgtcctctgccagcacaaa gggcccctctgtttttccactggctcccagcagcaagagcaccagtggtggaacagctgc cctgggctgtctggtcaaggattacttccctgagcctgtgactgtgtcctggaactctgg ggctctgacttctggggtgcacacctttccagctgtgctgcagtcctctggcctgtactc tctgtcctctgtggtcacagtgcctagctctagcctgggcacacagacctacatctgcaa tgtgaaccacaagcctagcaacaccaaggtggacaagagagtggaacccaagagctgtga caagacccacacctgtcctccatgtcctgctccagaactgcttggaggcccttctgtgtt cctgtttcctccaaagcctaaggacaccctgatgatcagcagaaccctgaagtgacctg tgtggtggttgatgtgtcccatgaggacccagaagtgaagttcaattggtatgtggatgg ggttgaagtgcacaatgccaagaccaagcctagagaggaacagtacaacagcacctacag agtggtttctgtgctgacagtgctgcaccaggactggctgaatggcaaagagtacaagtg caaggtgtccaacaaggccctgcctgctcctattgagaaaaccatctccaaggccaaggg ccagccaagagaaccccaggtttacaccctgccacctagcagagaagagatgaccaagaa ccaggtgtccctgacctgcctggttaagggcttctacccctctgacattgctgtggaatg ggagagcaatggccagcctgaaaacaactacaagacaacccctcctgtgctggactctga tggctcattcttcctgtacagcaagctgactgtggacaagtccagatggcagcagggaaa tgtgttcagctgctctgtgatgcatgaggccctgcacaaccactacacccagaaaagtct gtctctgtcccctggcagaaagagaagaggctctggagaaggcagaggctccctgctgac atgtggggatgttgaagagaatcctgggcctatgtataggatgcaactgctcctcctgat tgctctgagcctggctcttgtgaccaactctgacatccagatgacacagagcccctccac actgtctgcatctgtgggagacagagtgaccatcacctgtagagccagccagtctatctc tagctggctggcctggtatcagcaaaagcctggcaaggcccctaagctgctgatctacaa ggccagcacacttgagtcaggggtgccctccagattttctggctctggatctggcacaga

Name/ SEQ ID NO.	Sequence
	gttcaccctgaccatcagctccctgcagccagatgactttgccacctactactgccagca gtacaatacctactggacctttggccagggaacaaaggtggaaatcaagagaacagtggc tgccccatctgtgttcatcttcccaccatctgatgaacagctgaagtctggcactgcctc tgttgtgtgcctgctgaacaacttttaccccagagaagccaaggtgcagtggaaagtgga taatgccctgcagtctggcaatagccaagaatctgtgacagagcaggactccaaggattc cacctacagcctgagcagcaccctgacactgagcaaggctgactatgagaagcacaaagt gtatgcctgtgaagtgacacaccagggactgagcagcccagtgaccaagagcttcaacag gggagagtgctgataactcgaggacggggtgaactacgcctgaggatccgatcttttcc ctctgccaaaaattatggggacatcatgaagccccttgagcatctgacttctggctaata aaggaaatttattttcattgcaatagtgtgttggaatttttgtgtctctca
LSPX2.LANv2. T2A (LSPX2.L02) SEQ ID NO: 441 SEQ ID NO:	aggctcagaggcacacaggagtttctgggctcaccctgccccttccaacccctcagttc ccatcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcc tactcatgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctc cctgcctgctgaccttggagctggggcagaggtcagagacctctctgggcccatgccacc tccaacatccactcgacccttggaatttcggtggagaggagcagaggttgtcctggcgt ggtttaggtagtgtgagagggtctagaaggctcagaggcacacaggagtttctgggctca ccctgccccttccaacccctcagttcccatcctccagcagctgtttgtgtgctgcctct gaagtccacactgaacaaacttcagcctactcatgtccctaaaatgggcaaacattgcaa gcagcaaacagcaaacacacagccctccctgcctgctgaccttggagctggggcagaggt cagagacctctctgggcccatgccacctccaacatccactcgacccttggaatttcggt ggagaggagcagaggttgtcctggcgtggtttaggtagtgtgagaggggtacccggggat cttgctaccagtggaacagccactaaggattctgcagtgagagcagagggccagctaagt ggtactctcccagagactgtctgactcacgccacccctccaccttggacacaggacgct gtggtttctgagccaggtacaatgactcctttcggtaagtgcagtggaagctgtacactg cccaggcaaagcgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttag cccctgtttgctcctccgataactggggtgaccttggttaatattcaccagcagcctccc ccgttgcccctctggatccactgcttaaatacggacgaggacagggccctgtctcctcag cttcaggcaccaccactgacctgggacagtcaggtaagtatcaaggttacaagacaggtt taaggagaccaatagaaactgggcttgtcgagacagagaagactcttgcgtttctgatag gcacctattggtcttactgacatccactttgcctttctctccacaggttgaattcgccgc caccatgtacagaatgcagctgctgctgctcattgccctgtctctggccctggtcaccaa ttctgaggtccagctgcttgagagtggtggtggactggttcagcctggtggcagcctgag actgtcttgtgctgcctctggcttcaccttcagccactatatcatgatgtgggtcagaca ggcccctggcaaaggcctggaatgggtgtcaggcatctacagcagtggtggcatcacagt gtatgctgactctgtgaagggcagattcaccatcagcagagacaacagcaagaacaccct gtacctgcagatgaactccctgagagctgaggacacagcagtgtactactgtgcctatag aagaattggggtgcccagaagggatgagtttgacatctggggccagggcaccatggttac agtgtcctctgccagcacaaagggcccctctgtttttccactggctcccagcagcaagag caccagtggtggaacagctgccctgggctgtctggtcaaggattacttccctgagcctgt gactgtgtcctggaactctggggctctgacttctggggtgcacacctttccagctgtgct gcagtcctctggcctgtactctctgtcctctgtggtcacagtgcctagctctagcctggg cacacagacctacatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagag agtggaacccaagagctgtgacaagacccacacctgtcctccatgtcctgctccagaact gcttggaggcccttctgtgttcctgtttcctccaaagcctaaggacaccctgatgatcag cagaacccctgaagtgacctgtgtggtggttgatgtgtcccatgaggacccagaagtgaa gttcaattggtatgtggatggggttgaagtgcacaatgccaagaccaagcctagagagga acagtacaacagcacctacagagtggtttctgtgctgacagtgctgcaccaggactggct gaatggcaaagagtacaagtgcaaggtgtccaacaaggccctgcctgctcctattgagaa aaccatctccaaggccaagggccagccaagagaaccccaggtttacaccctgccacctag cagagaagagatgaccaagaaccaggtgtccctgacctgcctggttaagggcttctaccc

Name/ SEQ ID NO.	Sequence
	ctctgacattgctgtggaatgggagagcaatggccagcctgaaaacaactacaagacaac ccctcctgtgctggactctgatggctcattcttcctgtacagcaagctgactgtggacaa gtccagatggcagcagggaaatgtgttcagctgctctgtgatgcatgaggccctgcacaa ccactacacccagaaaagtctgtctctgtcccctggcagaaagagaagaggctctggaga aggcagaggctccctgctgacatgtggggatgttgaagagaatcctgggcctatgtatag gatgcaactgctcctcctgattgctctgagcctggctcttgtgaccaactctgacatcca gatgacacagagcccctccacactgtctgcatctgtgggagacagagtgaccatcacctg tagagccagccagtctatctctagctggctggcctggtatcagcaaaagcctggcaaggc ccctaagctgctgatctacaaggccagcacacttgagtcaggggtgccctccagattttc tggctctggatctggcacagagttcaccctgaccatcagctccctgcagccagatgactt tgccacctactactgccagcagtacaatacctactggacctttggccagggaacaaaggt ggaaatcaagagaacagtggctgccccatctgtgttcatcttcccaccatctgatgaaca gctgaagtctggcactgcctctgttgtgtgcctgctgaacaacttttaccccagagaagc caaggtgcagtggaaagtggataatgccctgcagtctggcaatagccaagaatctgtgac agagcaggactccaaggattccacctacagcctgagcagcaccctgacactgagcaaggc tgactatgagaagcacaaagtgtatgcctgtgaagtgacacaccagggactgagcagccc agtgaccaagagcttcaacaggggagagtgctgataactcgaggacggggtgaactacgc ctgaggatccgatcttttccctctgccaaaaattatggggacatcatgaagccccttga gcatctgacttctggctaataaaggaaatttattttcattgcaatagtgtgttggaattt tttgtgtctctca
LTP1.LANv2.T2A (LTP1.L02) SEQ ID NO: 442	aggttaatttttaaaaagcagtcaaaagtccaagtggcccttggcagcatttactctctc tgtttgctctggttaataatctcaggagcacaaacattccagatccaggttaatttttaa aaagcagtcaaaagtccaagtggcccttggcagcatttactctctctgtttgctctggtt aataatctcaggagcacaaacattccagatccggcgcgccagggctggaagctacctttg acatcatttcctctgcgaatgcatgtataatttctacagaacctattagaaaggatcacc cagcctctgcttttgtacaactttcccttaaaaaactgccaattccactgctgtttggcc caatagtgagaacttttttcctgctgcctcttggtgcttttgcctatggcccctattctgc ctgctgaagacactcttgccagcatggacttaaaccccctccagctctgacaatcctcttt ctcttttgttttacatgaagggtctggcagccaaagcaatcactcaaagttcaaacctta tcatttttttgctttgttcctcttggccttggttttgtacatcagctttgaaaataccatc ccagggttaatgctggggttaatttataactaagagtgctctagttttgcaatacaggac atgctataaaaatggaaagatgttgctttctgagaggatcttgctaccagtggaacagcc actaaggattctgcagtgagagcagagggccagctaagtggtactctcccagagactgtc tgactcacgccacccccctccaccttggacacaggacgctgtggtttctgagccaggtaca gtgactcctttcggtaagtgcagtggaagctgtacactgcccaggcaaagcgtccgggca gcgtaggcgggcgactcagatcccagccagtggacttagcccctgtttgctcctccgata actggggtgaccttggttaatattcaccagcagcctcccccgttgcccctctggatccac tgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcaccaccactgacc tgggacagtcaggtaagtatcaaggttacaagacaggtttaaggagaccaatagaaactg ggcttgtcgagacagagaagactcttgcgtttctgataggcacctattggtcttactgac atccactttgcctttctctccacaggttgaattcgccgccaccatgtacagaatgcagct gctgctgctcattgccctgtctctggccctggtcaccaattctgaggtccagctgcttga gagtggtggtggactggttcagcctggtggcagcctgagactgtcttgtgctgcctctgg cttcaccttcagccactatatcatgatgtgggtcagacaggcccctggcaaaggcctgga atgggtgtcaggcatctacagcagtggtggcatcacagtgtatgctgactctgtgaaggg cagattcaccatcagcagagacaacagcaagaacaccctgtacctgcagatgaactccct gagagctgaggacacagcagtgtactactgtgcctatagaagaattggggtgcccagaag ggatgagtttgacatctggggccagggcaccatggttacagtgtcctctgccagcacaaa gggcccctctgtttttccactggctcccagcagcaagagcaccagtggtggaacagctgc cctgggctgtctggtcaaggattacttccctgagcctgtgactgtgtcctggaactctgg

Name/ SEQ ID NO.	Sequence
	ggctctgacttctggggtgcacacctttccagctgtgctgcagtcctctggcctgtactc tctgtcctctgtggtcacagtgcctagctctagcctgggcacacagacctacatctgcaa tgtgaaccacaagcctagcaacaccaaggtggacaagagagtggaacccaagagctgtga caagacccacacctgtcctccatgtcctgctccagaactgcttggaggcccttctgtgtt cctgtttcctccaaagcctaaggacaccctgatgatcagcagaaccctgaagtgacctg tgtggtggttgatgtgtcccatgaggacccagaagtgaagttcaattggtatgtggatgg ggttgaagtgcacaatgccaagaccaagcctagagaggaacagtacaacagcacctacag agtggtttctgtgctgacagtgctgcaccaggactggctgaatggcaaagagtacaagtg caaggtgtccaacaaggccctgcctgctcctattgagaaaaccatctccaaggccaaggg ccagccaagagaaccccaggtttacaccctgccacctagcagagaagagatgaccaagaa ccaggtgtccctgacctgcctggttaagggcttctacccctctgacattgctgtggaatg ggagagcaatggccagcctgaaaacaactacaagacaacccctcctgtgctggactctga tggctcattcttcctgtacagcaagctgactgtggacaagtccagatggcagcagggaaa tgtgttcagctgctctgtgatgcatgaggccctgcacaaccactacacccagaaaagtct gtctctgtcccctggcagaaagagaagaggctctggagaaggcagaggctccctgctgac atgtggggatgttgaagagaatcctgggcctatgtataggatgcaactgctcctcctgat tgctctgagcctggctcttgtgaccaactctgacatccagatgacacagagcccctccac actgtctgcatctgtgggagacagagtgaccatcacctgtagagccagccagtctatctc tagctggctggcctggtatcagcaaaagcctggcaaggcccctaagctgctgatctacaa ggccagcacacttgagtcaggggtgccctccagattttctggctctggatctggcacaga gttcaccctgaccatcagctccctgcagccagatgactttgccacctactactgccagca gtacaatacctactggacctttggccagggaacaaaggtggaaatcaagagaacagtggc tgccccatctgtgttcatcttcccaccatctgatgaacagctgaagtctggcactgcctc tgttgtgtgcctgctgaacaacttttaccccagagaagccaaggtgcagtggaaagtgga taatgccctgcagtctggcaatagccaagaatctgtgacagagcaggactccaaggattc cacctacagcctgagcagcaccctgacactgagcaaggctgactatgagaagcacaaagt gtatgcctgtgaagtgacacaccagggactgagcagcccagtgaccaagagcttcaacag gggagagtgctgataactcgaggacggggtgaactacgcctgaggatccgatcttttcc ctctgccaaaaattatggggacatcatgaagccccttgagcatctgacttctggctaata aaggaaatttatttcattgcaatagtgtgttggaatttttgtgtctctca
LMTP6.LANv2. T2A (LMTP6.L02) SEQ ID NO: 443	aggctcagaggcacacaggagtttctgggctcaccctgccccttccaacccctcagttc ccatcctccagcagctgtttgtgtgctgcctctgaagtccacactgaacaaacttcagcc tactcatgtccctaaaatgggcaaacattgcaagcagcaaacagcaaacacacagccctc cctgcctgctgaccttggagctggggcagaggtcagagacctctctgggcccatgccacc tccaacatccactcgacccctggaatttcggtggagaggagcagaggttgtcctggcgt ggtttaggtagtgtgagagggccactacgggtttaggctgcccatgtaaggaggcaaggc ctggggacacccgagatgcctggttataattaacccagacatgtggctgccccccccccc cccaacacctgctgcctctaaaaataaccctgtccctggtggatcccactacgggtttag gctgcccatgtaaggaggcaaggcctggggacacccgagatgcctggttataattaaccc agacatgtggctgccccccccccccccaacacctgctgcctctaaaaataaccctgtccc tggtggatcccactacgggtttaggctgcccatgtaaggaggcaaggcctggggacaccc gagatgcctggttataattaacccagacatgtggctgccccccccccccccaacacctgc tgcctctaaaaataaccctgtccctggtggatcccctgcatgcgaagatcttcgaacaag gctgtgggggactgagggcaggctgtaacaggcttgggggccagggcttatacgtgcctg ggactcccaaagtattactgttccatgttcccggcgaagggccagctgtcccccgccagc tagactcagcacttagtttaggaaccagtgagcaagtcagcccttggggcagcccataca aggccatggggctgggcaagctgcacgcctgggtccggggtgggcacggtgcccgggcaa cgagctgaaagctcatctgctctcaggggcccctccctggggacagcccctcctggctag tcacaccctgtaggctcctctatataacccaggggcacaggggctgccctcattctacca ccacctccacagcacagacagacactcaggagccagccagcgtcgagatcttgctaccag

Name/ SEQ ID NO.	Sequence
	tggaacagccactaaggattctgcagtgagagcagagggccagctaagtggtactctccc agagactgtctgactcacgccacccctccaccttggacacaggacgctgtggtttctga gccaggtacagtgactcctttcggtaagtgcagtggaagctgtacactgcccaggcaaag cgtccgggcagcgtaggcgggcgactcagatcccagccagtggacttagcccctgtttgc tcctccgataactggggtgaccttggttaatattcaccagcagcctcccccgttgcccct ctggatccactgcttaaatacggacgaggacagggccctgtctcctcagcttcaggcacc accactgacctgggacagtcaggtaagtatcaaggttacaagacaggtttaaggagacca atagaaactgggcttgtcgagacagagaagactcttgcgtttctgataggcacctattgg tcttactgacatccactttgcctttctctccacaggttcgaattcgccgccaccatgtac agaatgcagctgctgctgctcattgccctgtctctggccctggtcaccaattctgaggtc cagctgcttgagagtggtggtggactggttcagcctggtggcagcctgagactgtcttgt gctgcctctggcttcaccttcagccactatatcatgatgtgggtcagacaggcccctggc aaaggcctggaatgggtgtcaggcatctacagcagtggtggcatcacagtgtatgctgac tctgtgaagggcagattcaccatcagcagagacaacagcaagaacaccctgtacctgcag atgaactccctgagagctgaggacacagcagtgtactactgtgcctatagaagaattggg gtgcccagaagggatgagtttgacatctggggccagggcaccatggttacagtgtcctct gccagcacaaagggcccctctgtttttccactggctcccagcagcaagagcaccagtggt ggaacagctgccctgggctgtctggtcaaggattacttccctgagcctgtgactgtgtcc tggaactctggggctctgacttctggggtgcacacctttccagctgtgctgcagtcctct ggcctgtactctctgtcctctgtggtcacagtgcctagctctagcctgggcacacagacc tacatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagagagtggaaccc aagagctgtgacaagacccacacctgtcctccatgtcctgctccagaactgcttggaggc ccttctgtgttcctgtttcctccaaagcctaaggacaccctgatgatcagcagaacccct gaagtgacctgtgtggtggttgatgtgtcccatgaggacccagaagtgaagttcaattgg tatgtggatggggttgaagtgcacaatgccaagaccaagcctagagaggaacagtacaac agcacctacagagtggtttctgtgctgacagtgctgcaccaggactggctgaatggcaaa gagtacaagtgcaaggtgtccaacaaggccctgcctgctcctattgagaaaaccatctcc aaggccaagggccagccaagagaaccccaggtttacaccctgccacctagcagagaagag atgaccaagaaccaggtgtccctgacctgcctggttaagggcttctacccctctgacatt gctgtggaatgggagagcaatggccagcctgaaaacaactacaagacaacccctcctgtg ctggactctgatggctcattcttcctgtacagcaagctgactgtggacaagtccagatgg cagcagggaaatgtgttcagctgctctgtgatgcatgaggccctgcacaaccactacacc cagaaaagtctgtctctgtcccctggcagaaagagaagaggctctggagaaggcagaggc tccctgctgacatgtggggatgttgaagagaatcctgggcctatgtataggatgcaactg ctcctcctgattgctctgagcctggctcttgtgaccaactctgacatccagatgacacag agcccctccacactgtctgcatctgtgggagacagagtgaccatcacctgtagagccagc cagtctatctctagctggctggcctggtatcagcaaaagcctggcaaggcccctaagctg ctgatctacaaggccagcacacttgagtcaggggtgccctccagattttctggctctgga tctggcacagagttcaccctgaccatcagctccctgcagccagatgactttgccacctac tactgccagcagtacaatacctactggacctttggccagggaacaaaggtggaaatcaag agaacagtggctgccccatctgtgttcatcttcccaccatctgatgaacagctgaagtct ggcactgcctctgttgtgtgcctgctgaacaacttttaccccagagaagccaaggtgcag tggaaagtggataatgccctgcagtctggcaatagccaagaatctgtgacagagcaggac tccaaggattccacctacagcctgagcagcaccctgacactgagcaaggctgactatgag aagcacaaagtgtatgcctgtgaagtgacacaccagggactgagcagcccagtgaccaag agcttcaacaggggagagtgctgataactcgaggacggggtgaactacgcctgaggatcc gatctttttccctctgccaaaaattatggggacatcatgaagccccttgagcatctgact tctggctaataaaggaaatttattttcattgcaatagtgtgttggaatttttttgtgtctc tca

[0820] HEK293 cells were plated at a density of $7.5x10^5$ cells/well in each well of a standard 6-well dish containing Dulbecco's modified eagle medium (DMEM) supplied with 10% fetal bovine serum (FBS). The next day, cells were transfected with CAG.L01 (SEQ ID NO: 435), CAG.L02 (SEQ ID NO: 437), and CAG.L03 (SEQ ID NO: 436) AAV constructs using Lifpofectamine 2000 (Invitrogen) according the manufacturer's protocol). Non-transfected cells were used as negative control. Cell culture medium was changed 24 hours post-transfection to opti-mem I reduced serum media (2 mL/well). Cell culture supernatant was harvested at 48 hours post-transfection, and cell lysates were harvested with RIPA buffer (Pierce) supplemented with EDTA-free protease inhibitor tablets (Pierce). Supernatant and lysates samples were stored at -80C.

[0821] Proteins from supernatant or cell lysate samples were separated via the NuPAGE electrophoresis system (Thermo Fisher Scientific). For samples derived from cell lysates, 40 µg of protein was loaded unless indicated otherwise. Purified human IgG or Lanadelumab IgG (produced by Genscript) were used as loading controls (50-100 ng). Samples were heated with LDS sample buffer and NuPAGE reducing agent at 70C for 10 minutes and then loaded into NuPAGE 4-12% Bis-Tris protein gels. Separated proteins were transferred to PVDF membranes using the iBlot2 dry blotting system according to manufacturer's instructions (P3 default setting was used for the protein transfer). Membranes were immediately washed in phosphate buffer saline with 0.1% v/v Tween-20 (PBST). Membranes were then incubated in blocking solution containing PBST and 1% Clear Milk Blocking Buffer (Thermo Scientific) for 1 hour at room temperature. Membranes were then incubated in fresh blocking solution supplemented with goat anti-human kappa light chain-HRP antibody (Bethyl Laboratories; 1:2000 dilution) and goat anti-human IgG Fc-HRP antibody (1:2000 dilution). Following antibody incubation, membranes were washed three times in PBST for 5 minutes per wash. Finally, membranes were incubated in SuperSignal West Pico PLUS chemiluminescent substrate for 5 minutes and imaged on the BioRad Universal Hood II gel doc system for detection of horseradish peroxidase (HRP) signal.

Results

[0822] Expression analysis of reporter transgene (eGFP) following transfection of different plasmid quantities (4 µg-nontransfected) showed a dose dependent increase in eGFP levels (FIG. 24B).

Protein expression analysis of lanadelumab in the cell lysate (FIG. 24C) and in the cell supernatant (FIG. 24D) showed dose-dependent levels of lanadelumab in cell lysates and supernatant. Transfection with the construct containing the L02 transgene (SEQ ID NO: 286, CAG.L02 (SEQ ID NO: 437)), a codon-optimized and depleted of CpG dinucleotide sequences construction, resulted in higher expression levels compared to L01 transgene (SEQ ID NO: 141, CAG.L01 SEQ ID NO: 435). Transfection of CAG.L02 (SEQ ID NO: 437) and CAG.L03 (SEQ ID NO: 436) resulted in similar expression levels.

6.51 EXAMPLE 51: Serum expression of Lanadelumab in mice

Methods

[0823] **A.** Mouse experiments were performed with either AAV8 or AAV9 containing an AAV construct (as depicted in FIG. 24A) comprising the L01 sequence (SEQ ID NO: 141), which contains the Furin and F2A sequence (SEQ ID NO: 231). AAV8 and AAV9 vectors (n=5 mice per group; 2e11 genome copies (gc)) were administered to immunocompromised NSG mice via either intravenous (IV) or intramuscular (IM) routes. IV administrations were into the tail vein and IM administrations were bilateral into the gastrocnemius muscles. Mice injected with vehicle were included as controls. Seven weeks post administration mice were sacrificed and serum human antibody levels were determined by enzyme-linked immunosorbent assay (ELISA).

[0824] Lanadelumab levels in NSG mouse serum was assessed by ELISA. Briefly, mouse serum was obtained before treatment and at 1, 3, 5 and 7 weeks post *in vivo* gene transfection and stored at -80°C. 96-well plate was coated with 1 µg/ml human IgG-Fc fragment antibody (Bethyl, Montgomery, TX) in carbonate bicarbonate buffer (0.05M, pH 9.6, Sigma-Aldrich, St. Louis, MO) and incubated overnight at 4°C. After washing with Tween 20 washing buffer (PBST, 0.05%, Alfa Aesar, Haverhill, MA), plate was incubated with blocking buffer (3% BSA in PBS, ThermoFisher Scientific, Waltham, MA) for 1 h at 37°C followed by washing. Mouse serum samples diluted in sample dilution buffer (0.1% Tween 20 and 3% BSA in PBS) was added to the plate (50µl/well) and incubated for 2 h at 37°C. A standard curve of known lanadelumab concentrations ranging from 360 to 0.001 ng/mL was included in each plate. Plate was washed with PBST for five times after incubation. The levels of lanadelumab was detected by incubation with horseradish peroxidase-

conjugated goat anti-human IgG (H+L) (200 ng/mL; Bethyl, Montgomery, TX) for 1 h at 37°C. The optical density was assessed using KPL TMB Microwell Peroxidase Substrate System (Seracare, Milford, MA) following the manufacturer's specifications. Data analysis was performed with SoftMax Pro version 7.0.2 software (Molecular Devices, Sunnyvale, CA).

Results

[0825] **A.** Results from a representative experiment are shown in FIG. 25. Serum analysis of AAV8-, AAV9-injected and control (vehicle) NSG mice at 7 weeks post gene transfer showed expression and serum accumulation of Lanadelumab following AAV9 delivery ($2E^{11}$ gc). Serum Lanadelumab concentration was 100-fold higher in AAV9-injected mice compared to AAV8-injected mice and slightly higher in IV-AAV9-injected compared to IM-AAV9-injected mice. Serum human antibody levels in control mice were undetectable at 7 week time point.

[0826] **B**. In an analogous experiment, a time course of lanadelumab serum levels in NSG mice post-AAV9 administration (n=5 per group) was performed. AAV9 vectors ($2E^{11}$ gc) were injected either IV or IM (as above, in experiment A), and serum antibody levels were determined by ELISA at day 7 (D7), day 21 (D21), day 35 (D35), and day 49 (D49).

[0827] Serum Lanadelumab expression is detectable as early as 1 week (D7) after AAV9 administration in NSG mice. The expression levels increased at 3 weeks (D2), peaked at 5 weeks (D35) and then sustained up to 7 week post-injection (D49). It was observed that serum lanadelumab concentration is higher in IV vs. IM injected mice over the entire time course. See **FIG. 26**.

[0828] **C.** In an analogous experiment, a time course of lanadelumab serum levels in C/57BL6 mice post AAV8 administration was performed. The optimized expression cassette containing a liver-specific promoter and a codon optimized and CpG depleted transgene with a modified furin-2A processing signal resulted in robust serum antibody concentration when delivered intravenously using an AAV8 vector. Very high (>1mg/ml) and sustained levels of functional anti-kallikrein antibody were achieved in the serum of C57BL/6 mice following IV vector administration at a dose of $1E^{13}$gc/kg.

6.52 EXAMPLE 52: Analysis of *in vitro* Transduction and Expression of Tandem Liver- and Tandem Liver/Muscle-Specific Promoters Driving Expression of Lanadelumab

[0829] Cis plasmids expressing vectorized lanadelumab were packaged in AAV, then rAAV particles evaluated for potency of the transduction by AAV. Each cis plasmid contained lanadelumab (Mab1) antibody light chain and heavy chain which are multicistrons driven by the CAG, ApoE.hAAT (SEQ ID NO: 412) or LMTP6 (SEQ ID NO: 320) promoter. Full-length lanadelumab antibody light chain and antibody heavy chain genes were separated by a furin 2A linker to ensure separate expression of each antibody chain. The entire cassette is flanked by AAV2 ITRs, and the genome is encapsidated in an AAV8 capsid for delivery to C2C12 cells ($1E^{10}$ vg per well). For detection of antibody protein, following transduction, the cells are treated with FITC conjugated anti-Fc (IgG) antibody. The AAV8.CAG.Mab1 and AAV8.LMTP6.Mab1 infected cells show high expression in muscle cells, whereas the AAV8.hAAT.Mab1 infection does not result in expression of the antibody in muscle cells (**FIG. 27**). Cells appeared to be equally confluent and viable in all test wells, as seen by DAPI (DNA) staining (**FIG. 27**).

6.53 EXAMPLE 53: Antibody Expression And Vector Biodistribution In Mouse Treated With AAV8 Lanadelumab Vectors Driven By Various Promoters

[0830] Thyroxine binding globulin (TBG) and alpha-1 antitrypsin (hAAT) promoters have been widely used as liver-specific promoters in previous pre-clinical and clinical gene therapy studies. A panel of designed promoter cassettes derived from multiple promoters and enhancers were generated and tested them in vitro by transfecting Huh7 cells, a human liver cell line. Promoter candidates were selected, which include ApoE.hAAT (SEQ ID NO: 412), LSPX1 (SEQ ID NO: 315), LSPX2 (SEQ ID NO: 316), LTP1 (SEQ ID NO: 317) and LMTP6 (SEQ ID NO: 320). AAV8 vectors encoding vectorized lanadelumab regulated by these promoter candidates were then generated. CAG (SEQ ID NO: 411) and TBG (SEQ ID NO: 423) promoters served as controls for ubiquitous and liver-specific promoters, respectfully. Strength of these promoters and vector biodistribution were tested *in vivo* by measuring lanadelumab protein expression compared to vector genome copy in each wild type mouse.

[0831] Vectors were administered intravenously to C57Bl/6 mice at equivalent doses ($2.5x10^{12}$ vg/kg). Mouse serum was collected biweekly, and lanadelumab protein expression levels were determined by ELISA. Liver samples were harvested at 49 days post vector administration. The

presence of viral genomes in each sample was quantified using Lanadelumab probe and primer by Droplet Digital PCR (ddPCR) (the NAICA™ system from Stilla). The genome copy number of glucagon was also measured simultaneously in each sample, the viral genomes were then normalized and demonstrated as vector genome copy number per cell (assuming 2 glucagon/cell). Statistical analysis was performed using one-way ANOVA in GraphPad Prism 8.

[0832] Among the AAV8 vectors with liver-specific promoters, the vectors driven by the ApoE.hAAT (SEQ ID NO: 412) and LMTP6 (SEQ ID NO: 320) promoters provided the highest amount of protein expression at all time points (**FIG. 28A**). While for the biodistribution data, there was no significant difference of vector genome copy number per cell in liver samples in animals treated with vectors driven by different promoters (**FIG. 28B**).

[0833] All liver-specific promoters outperform the TBG promoter (SEQ ID NO: 423), and the dual-specific LMTP6 promoter (SEQ ID NO: 320) consistently shows the highest expression in the serum (μg/ml) (**FIG. 28**).

6.54 EXAMPLE 54: Lanadelumab expression in rat serum following administration of vectorized antibody

[0834] A high level of Lanadelumab expression was detected in the serum of mice treated with AAV-Lanadelumab via IV administration. In parts of the study, the lanadelumab expression levels in different rat strains treated with different doses of AAV-Lanadelumab vectors and controls were examined.

Experiment 1 (Wistar rats):

[0835] To evaluate the route and the dose of vector administration in rats, a control vector AAV.CAG-LANv2.T2A (CAG.L02; SEQ ID NO: 437) was tested in Wistar rat. Eight to ten weeks old male Wistar rats were assigned into three groups (n=3 per group) to receive vector administration via IM or IV injection at a dose of $1x10^{13}$ vg/kg or $1x10^{14}$ vg/kg. Blood was collected at 7 days before treatment and 7, 10, 14, 17, 21, 28, 35, 42 and 49 days post vector administration and processed into serum.

Table 9. Study details for Lanadelumab expression in rat serum, *Experiment 1.*

Rat group	Male 8-10 week old Wistar Rats (180-200g)			Bleeds – Day sampled (X)									
	Treatment	N	ROA	Day -7	Day 0	Day 7	Day 10	Day 14	Day 17	Day 21	Day 28	Day 35	Day 42	Day 49
1	AAV8.CAG.LANv2.T2A Dose: 1e13 vg/kg	3	IM	X	Administration	X	X	X	X	X	X	X	X	sacrifice
2	AAV8.CAG.LANv2.T2A Dose: 1e13 vg/kg	3	IV	X	Administration	X	X	X	X	X	X	X	X	sacrifice
3	AAV8.CAG.LANv2.T2A Dose: 1e14 vg/kg	3	IV	X	Administration	X	X	X	X	X	X	X	X	sacrifice

[0836] Levels of human IgG antibody in collected rat serum were detected by ELISA. Statistical analysis was done by one-way ANOVA with multiple comparisons at each time point using Prism

Table 10. Results of Lanadelumab expression in Wistar rats, *Experiment 1*

Day sampled	AAV8.CAG.Lanv2.T2A 1e13 vg/kg- IM			AAV8.CAG.Lanv2.T2A 1e13 vg/kg- IV			AAV8.CAG.Lanv2.T2A 1e14 vg/kg- IM		
	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N
D7	4.1	0.96	3	8.43	0.64	3	33.6	13.86	3
D10	7.67	1.91	3	12.3	0.81	3	64.5	30.2	3
D14	9.37	0.73	3	23.13	0.18	3	123.23	69.12	3
D17	4.97	2.23	3	92	53.52	3	245.17	151.09	3
D21	2.04	0.9	3	33.06	5.84	3	252.63	149.41	3
D28	92.08	87.07	3	65.23	41.69	3	117.97	112.47	3
D35	14.46	12.31	3	88.1	56.68	3	122.97	74.94	3
D42	82.29	80.46	3	40.43	26.77	3	108.02	99.26	3
D49	1.66	0.95	3	81.4	39.96	3	216.30	118.18	3

[0837] The levels of antibody in rat serum were detectable at 7 days post treatment. It increased over time and reached the peak level at 17 (lower dose) and 21 (higher dose) days post treatment in IV groups and 28 days in IM group. The antibody levels gradually decreased and sustains up to 48

days post treatment in all groups. For animals treated with lower dose ($1x10^{13}$ vg/kg) vector, the antibody expression levels in IV groups are significantly higher than that in IM group at 7, 14 and 21 days post vector administration. For animals received IV administration, the antibody expression levels were dose-dependent at all time points. The highest level of lanadelumab expression was 252.6±149.4 μg/ml, which was detected in animals treated with higher dose ($1 x10^{14}$ vg/kg) at 21 days post IV administration. See **FIG. 30A**.

Experiment 2 (Wistar and Sprague-Dawley rats):

[0838] The aim of this experiment was to investigate the rat strain and the vector dose that will be used for a rat efficacy study. Eight to ten weeks old male Wistar and Sprague-Dawley (SD) rats were assigned into four groups (n=3 per group) to receive treatment of AAV8 vector carrying genome encoding lanadelumab driven by a universal promoter, CAG.L02 (SEQ ID NO: 437), or a liver-specific promoter, ApoE.hAAT.L02 (SEQ ID NO: 439). Vectors were administered via IV injection at a dose of $5x10^{13}$ vg/kg. Blood was collected at 7 days before treatment and 7, 10, 14, 17, 21, 28, 35, 42 and 49 days post vector administration and processed into the serum (**Table 11**). Levels of human IgG antibody in collected rat serum were detected by ELISA. Statistical analysis was done by one-way ANOVA with multiple comparisons at each time point using Prism.

Table 11. Study details for lanadelumab expression in rat serum, *Experiment 2*.

Rat group	Male 8-10 week old Wistar or Sprague Dawley (SD) Rats (180-200g)			→ Bleeds—Day sampled (X)									
	Treatment Dose: 5e13 vg/kg	N	ROA	Day -1	Day 0	Day 7	Day 14	Day 17	Day 21	Day 28	Day 35	Day 42	Day 49
1	CAG.L02 Wistar	3	IV	X	Administration	X	X	X	X	X	X	X	sacrifice
2	ApoE.hAAT.L02 Wistar	3	IV	X	Administration	X	X	X	X	X	X	X	sacrifice
3	CAG.L02 Sprague Dawley (SD)	3	IV	X	Administration	X	X	X	X	X	X	X	sacrifice
4	ApoE.hAAT.L02 Sprague Dawley (SD)	3	IV	X	Administration	X	X	X	X	X	X	X	sacrifice

[0839] In this experiment, a control vector (CAG.L02, SEQ ID NO: 437) and vector ApoE.hAAT.L02 (SEQ ID NO: 439) were tested in Wistar and SD rats, respectively. Lanadelumab expression levels were higher in Wistar rat than SD rat in both vector groups at all time points. At the early time points, animals treated with control vector showed significant higher serum antibody levels than those treated with the liver-specific promoter containing vector. This was observed in Wistar rat at 7 days post treatment, and in SD rat at 7, 14 and 17 days post treatment. In Wistar rats, the concentrations of antibody gradually increased over time in both vectors group. The highest antibody levels were 173.1±78.8 µg/ml and 109.57±18.9 µg/ml at 35 and 49 days respectively in control CAG-Lanadelumab and hAAT-Lanadelumab vector-treated animals. In SD rats, however, the levels of antibody reached peaks at 14 and 21 days in control and lead vector-treated animals, respectively, and decreased gradually afterward in both groups. The highest antibody concentrations were 48.23 ± 3.1 µg/ml and 22.33 ± 8.98 µg/ml in CAG.L02 (SEQ ID NO: 437) and ApoE.hAAT.L02 (SEQ ID NO: 439) vector groups, respectively. See **Table 12** and **FIG. 30B**.

Table 12. Results of Lanadelumab expression in Wistar rats, *Experiment 2*:

Day sampled	CAG-Wistar 5e13 vg/kg- IV			ApoE.hAAT- Wistar 5e13 vg/kg- IV		
	Mean	SEM	N	Mean	SEM	N
D7	25.04	5.26	3	5.80	0.61	3
D14	91.50	39.90	3	29.73	6.36	3
D17	111.30	51.29	3	55.10	18.60	3
D21	132.03	58.76	3	75.80	17.94	3
D28	159.90	69.08	3	74.27	21.84	3
D35	173.10	78.76	3	97.67	33.89	3
D42	173.00	57.73	3	83.10	27.67	3
D49	163.57	39.45	3	109.57	18.87	3

6.55 EXAMPLE 55: Characterization of vectorized Lanadelumab regulated by tissue-specific promoters following intramuscular administration

[0840] In a previous study, high liver-driven expression of vectorized lanadelumab with AAV8 regulated by the ApoE.hAAT or LMTP6 promoters was identified. The goal of this study was to characterize muscle-driven expression of the LMTP6 promoter following direct injection of lanadelumab vectors into the gastrocnemius (GA) muscle. Animals received bilateral injections of

$5x10^{10}$ vg into the GA muscle. Serum was collected biweekly to measure systemic lanadelumab concentration (**FIG. 31A**). Animals were harvested at 49 days post-injection, and relevant tissues (liver, GA muscle, heart) were analyzed for vector biodistribution and transgene expression.

[0841] Vectors regulated by the hAAT and LMTP6 promoters demonstrated significantly increased antibody concentrations in serum compared to CAG at all time points (**FIG. 31A**). The hAAT and LMTP6 were not significantly different from each other in this experiment. Vector genome copies per cell of vectorized lanadelumab was detected and quantified in GA, liver and heart (**FIG. 31B**) with a notable difference of higher quantity of genome detected in heart for the dual muscle/liver promoter, LMTP6 vector. Increased liver RNA expression was also detected for all test vectors directly injected into GA muscle at 49 days (relative fold gene expression compared to a reference gene) (**FIG. 31C**). Gene expression (mRNA μg/mL) data from each of liver, GA muscle, and heart (**FIG. 31D**) indicates the dual specificity of LMPT6 in liver and muscle tissues following IM administration, whereas the hAAT-driven samples were reduced in muscle compared to LMTP6 and CAG. Significant differences were also seen between the hAAT and LMTP6 groups.

6.56 EXAMPLE 56: Comparison of lanadelumab protein levels in mouse serum derived from mice treated with AAV-Lanadelumab vectors produced with different production systems

[0842] Different AAV production protocols were developed to identify methods that can increase AAV titer and scalability, as well as assess the quality of vector product. Cis and trans plasmids to generate AAV8.Lanadelumab rAAV vectors (all having the same transgene driven by a CAG promoter) were constructed by well-known methods suitable for HEK293-transfected cell and also baculovirus (BV)/Sf9 insect cell production methods. Three different BV/Sf9 vector systems, BV1, BV2 and BV3, were provided as well as rAAV vector produced by an HEK293 method as a control. Purified rAAV product was injected into wild-type mice for this protein expression study (**Table 13**).

[0843] Young adult C57BL/6 mice (aged 8-10 weeks) were administered with above-mentioned vectors at $2.5E^{12}$ vg/kg via tail vein injection (n=5 per group). Serum was collected from each animal at 7, 21, 35, and 49 days post vector administration. Serum collected two days before injection (Day 0) served as baseline control. Levels of antibody (lanadelumab) expression were

detected via ELISA. Data analysis was done by one-way ANOVA with multiple comparisons at each time point using Prism.

Table 13. Production system expression study design

Mouse Group	AAV8.Lanadelumab 5e10 vg (2.5e12 vg/kg)			Bleeds sampled (X)						
	rAAV Production method	N	ROA	Day -2	Day 0 (Week 0)	Day 7 (Week 1)	Day 21 (Week 3)	Day 35 (Week 5)	Day 49 (Week 7)	Day 50
1	HEK cells	5	IV	X	Injection	X	X	X	X	Serum
2	BV1	5	IV	X	Injection	X	X	X	X	Serum
Werum 3	BV2	5	IV	X	Injection	X	X	X	X	Serum
4	BV3	5	IV	X	Injection	X	X	X	X	Serum

[0844] All production methods tested are viable based on this study, with greater yields from the HEK cell production method at the time points tested (see **FIG. 32.**). Antibody expression in serum is detectable as early as 7 days post administration in all groups. The average of antibody concentration at Day 7 in the HEK production group is 386 µg/ml, which is significantly higher than other groups (61-102 µg/ml). The levels of antibody expression increase at day 21 by 1-, 6-, 7-, and 4-fold in BV1, BV2 and BV3 groups, respectively. Antibody expression levels sustained at 35 and 49 days post administration. There is no significant difference in between HEK produced vector and BV3 produced vectors at day 21, 35 and 49 time points.

6.57 EXAMPLE 57: Vectorized human anti-pKal antibody, Lanadelumab, derived from mouse serum suppressed human pKal function

[0845] In order to measure pKal function of lanadelumab derived from mouse serum following AAV-lanadelumab administration, we developed a fluorescence-based kinetic enzymatic functional assay. First, activated human plasma kallikrein (Enzyme Research Laboratories) was diluted in sample dilution buffer (SDB; 1X PBS, 3% BSA, 0.1% Tween-20) to top concentration of 100 nM. This pKal was two-fold serially diluted for a total of 12 concentrations in the dilution series (100nM-0.05nM).

From each dilution, and in duplicate, 25µL was placed in one well of a 96-well, opaque flat-bottomed plate along with 25µL of SDB. Then, 50µL of the fluorogenic substrate Pro-Phe-Arg-7-Amino-4-Methylcoumarin (PFR-AMC) (Bachem) prepared at 100µM in assay buffer (50 mM Tris, 250 mM NaCl, pH 7.5) was added to each well. The samples were immediately run in kinetic mode for AMC fluorescence at excitation/ emission wavelengths of 380/460 nm, respectively, for 3 hours using a SpectraMax 3 fluorescent plate reader.

[0846] The signal-to-noise ratio for each pKal concentration RFU (last RFU fluorescent value chosen) was calculated by dividing its RFU by background PFR-AMC substrate fluorescence. The two lowest pKal concentrations with a signal-to-noise ratio $\geq$ 2 (6.25nM and 12.5nM) were then chosen to evaluate the suppressive effect and range of lanadelumab antibody of pKal function in a lanadelumab dose response. Lanadelumab (GenScript) or human IgG control antibody was diluted in SDB to top concentration of 200nM and two-fold serially diluted to 0.39nM. Next, 25µL pKal (each of two chosen concentrations) was incubated with 25 µL lanadelumab or human IgG at 30°C for 1 hour. Antibody-pKal mixture was then given PFR-AMC and immediately run in kinetic mode for AMC fluorescence at excitation/ emission wavelengths of 380/460 nm, respectively, for 3 hours using a SpectraMax fluorescent plate reader.

[0847] *In vitro pKal functional assay*. When used, mouse serum was diluted in sample dilution buffer and incubated 1:1 with 6.25nM (1.56nM in-well) pKal for 30°C/1 hour. For total IgG purification from mouse serum, antibody was purified using the Protein A Spin Antibody Purification Kit (BioVision) according to manufacturer's protocol. Total antibody concentration was measured using a Nanodrop spectrophotometer, with OD absorbance = 280nM. AMC standard curve was generated by a two-fold downward dilution series of AMC (500nM, eleven dilutions and blank subtracted) diluted in assay buffer. AMC was read as end point fluorescence at excitation/ emission wavelengths of 380/460 nm, respectively. Specific plasma kallikrein activity was calculated as: (adjusted experimental sample Vmax, RFU/sec) x (Conversion factor, AMC standard curve µM/RFU)/ (pKal concentration, nM). Percent reduction in pKal activity was derived from calculating day 49 by day -7 pKal activity.

[0848] To determine whether AAV-derived lanadelumab can suppress plasma kallikrein function, we developed the *in vitro* AMC substrate-based functional assay to address this in a proof-of-concept study (**FIGS. 33A** and **33B**). In this assay, antibody-containing medium is incubated with activated human pKal, as described above. Antibody-bound pKal is then given the synthetic peptide substrate Pro-Phe-Arg conjugated to AMC (PFR-AMC) and amount of released AMC is measured over time at excitation/ emission wavelengths of 380/460 nm, respectively, for 3 hours. The assay showed noticeable lanadelumab-mediated suppression of pKal activity down to 0.1 nM (in-well concentration) (**FIG. 33C**) at a defined enzyme concentration. We first sought to determine whether serum from mice administered lanadelumab-encoded AAV could suppress pKal activity. Serum from mice 49 days post-administration was diluted 1:25 (in range predicted to be suppressive), incubated with pKal in vitro, and pKal activity was assayed. Serum from mice post-vector administration, as opposed to 7 days pre-administration, suppressed pKal activity, as reflected in a significant reduction of enzyme activity and a ~50% percent reduction in pKal activity between the two time points (**FIGS. 33D and 33E**).

[0849] Further experiments show that suppression was due to the lanadelumab within the serum. Reasoning that the human IgG, namely lanadelumab, would only be found in the day 49 post-administration IgG fraction, but not the day -7 pre-administration samples, purified and total IgG antibody was used from the aforementioned day -7 and day 49 mouse serum samples to test pKal suppression. Indeed, only lanadelumab-containing purified IgG from day 49 post-administration serum, but not IgG from the pre-administration time point, suppressed human pKal function (**FIG. 33F**).

6.58 EXAMPLE 58: Effects of AAV-Lanadelumab in Carrageenan Animal Models

6.58.1 Example 58A: Effects of AAV-Lanadelumab in the carrageenan paw edema model in mice

[0850] Inflammation models induced by carrageenan are frequently used acute inflammation models. Carrageenan (Cg) is a strong chemical agent that functions in stimulating the release of inflammatory and proinflammatory mediators, including bradykinin, histamine, tachykinins, reactive oxygen, and nitrogen species. Typical signs of inflammation include edema, hyperalgesia, and erythema, which develop immediately following the treatment of carrageenan. This example evaluated

the effect of AAV-mediated gene delivery of Lanadelumab on carrageenan-induced paw edema in mice.

[0851] In total eighty young adult (8-9 weeks old) male C57BL/6 mice were used for this study. Animals were divided into eight groups as listed in Table 14. Paw edema was induced by a single subcutaneous (s.c.) injection of 30 µL of 0.7% or 1% carrageenan solution. Test vectors and positive control Diclofenac were administered at 21 days and 30 minutes prior to carrageenan treatment. Blood was collected before vectors injection and at 7 and 21 days post injection from mice in groups 1, 3, 4, 5, 7 and 8. Paw volume was measured using a digital Plethysmometer prior to carrageenan injection, and at 2, 4, 6, 8, 24 and 48 hours after injection. All animals were sacrificed 48 hours after carrageenan injection. Liver and paw specimens were also collected at the necropsy.

Table 14. Carrageenan (Cg) Paw Edema Mouse Study design

*Gr.	Group/treatment	Test Items Dose level	Route, Dose volume	Pre-treatment time	N
1	Cg (0.7%) / Vehicle of diclofenac	0	I.P., 10mL/kg	30 min before Cg	10
2	Cg (0.7%) /Diclofenac	60 mg/kg	I.P., 10mL/kg	30 min before Cg	10
3	Cg (0.7%) / Vector 1	1e13 vg/kg	I.V., 3.333 mL/kg	3 weeks before Cg	10
4	Cg (0.7%) / AAV8.ApoE.hAAT.Lan	1e13 vg/kg	I.V., 3.333 mL/kg	3 weeks before Cg	10
5	Cg (1.0%)/ Vehicle of diclofenac	0	I.P., 10mL/kg	30 min before Cg	10
6	Cg (1.0%)/ Diclofenac	60 mg/kg	I.P., 10mL/kg	30 min before Cg	10
7	Cg (1.0%)/ Vector 1	1e13 vg/kg	I.V., 3.333 mL/kg	3 weeks before Cg	10
8	Cg (1.0%)/ AAV8.ApoE.hAAT.Lan	1e13 vg/kg	I.V., 3.333 mL/kg	3 weeks before Cg	10

Vector 1: AAV8-GFP

[0852] Both 0.7% and 1.0% carrageenan induced swelling in the injected paw; however, swelling was more pronounced with 1.0% carrageenan injection (**FIGS. 34, A-L).** In the positive control groups (Group 2 and 6), diclofenac treatment significantly decreased the paw volume at 2, 4,

6, 8 and 24 hours post carrageenan injection in 1.0% Cg model (group 2), while a significant decrease on paw volume was observed only at 4 and 24 hours post injection in 0.7% Cg model (group 6).

[0853] ApoE.hAAT.L02 (SEQ ID NO: 439) treatment significantly reduced the paw volume at 2, 4, 6 and 8 hours post carrageenan injection in 1.0% Cg model when compared with the vehicle control group (group 1, vector formulation buffer) (**FIG. 35A** and **35B**). However, no effect of ApoE.hAAT.L02 treatment was observed in 0.7% Cg model at any time points (**FIG. 35A** and **35 B**). There is no significant difference in between groups treated with vehicle (groups 1 and 4) or control vector (AAV-GFP, groups 3 and 7) in both 1.0% and 0.7% Cg models (**FIGs. 33A-L**). All data was analyzed with One-way ANOVA with Dunnett's post-hoc test for multiple comparisons.

[0854] These data indicate that acute inflammation can be successfully induced in mouse paw with a single subcutaneous injection of 1% carrageenan solution. Lanadelumab, a human IgG antibody produced in mouse serum via AAV-mediated gene delivery significantly reduces the severity of inflammation in mouse 1% carrageenan model.

6.58.2 Example 58B: Efficacy study of AAV-Lanadelumab on carrageenan-induced paw edema in Wistar rats

[0855] This project aims to evaluate the efficacy of AAV-mediated antibody (Lanadelumab) therapy on Carrageenan-induced paw edema in Wistar rats. The experiment involves 50 male Wistar rats in total, divided into 5 groups (see **Table. 15**). Paw edema will be induced by a single subcutaneous (s.c.) injection of 100 µL of 1% carrageenan solution. Test articles will be administered at different time points (30 minutes, 21 days, 24 hours, or 1 hour) prior to carrageenan treatment.

Table 15. Grouping and Treatment for Wistar Rat Study

Group	N	Carrageenan	Treatment	R.O.A	Dosing Time	Conc.	Dosage	
							mL/kg	mg/kg / vg/kg
1	10	Yes	Vehicle[a]	IV	30 min prior to Carrageenan injection	N/A	1.6	N/A
2	10	Yes	ApoE.hAAT.L02	IV	21 days prior to Carrageenan injection	6.25E+13 vg/mL	1.6	1e14 vg/kg
3	10	Yes	Control AAV (irrelevant transgene)	IV	21 days prior to Carrageenan injection	6.25E+13 vg/ml	1.6	1e14 vg/kg
4	10	Yes	Lanadelumab	SC	24 hours prior to Carrageenan injection	4.81 mg/ml	6.237	30 mg/kg
5	10	Yes	Dexamethasone[b]	PO	1 hour prior to and 6 hours after Carrageenan injection	1 mg/mL	10	10 mg/kg

a: Formulation buffer
b: Normal saline

[0856] Body weight will be measured twice a week. On 7 days before vectors administration, and 7 and 14 days post-vector injection, 0.3 mL of blood will be collected by retroorbital/submandibular bleeding in all rats, and then processed into serum. Paw volume will be measured prior to carrageenan injection, and at 2, 4, 6, 8, 24 hours post carrageenan injection. All animals will be sacrificed 24 hours after carrageenan injection. At necropsy, blood will be collected for serum preparation by intracardiac puncture. Then, three pieces of liver (approximately 50 mg per unit) from the same lobe of each animal will be collected and cryopreserved in three separate tubes, respectively. The right paw from all rats will be resected, formalin-fixed, and embedded in paraffin (FFPE). See **Table 16.**

Table 16. Measurement and Sampling Regime for Wistar Rat Study

	Bleed	Treatment	Bleed	Bleed	Treatment	Treatment	Carageenan	Paw edema measurement (hr post carrageenan)						Bleed and end of study
Group	Day -7	Day 0	Day 7	Day 14	Day 20	Day 21	Day 21	0 h	2h	4h	6h	8h	24h	Day 22
1	√	x	√	√	x	Vehicle	√	√	√	√	√	√	√	√
2	√	AAV8.Lan	√	√	x	x	√	√	√	√	√	√	√	√
3	√	Control AAV	√	√	x	x	√	√	√	√	√	√	√	√

	Bleed	Treatment	Bleed	Bleed	Treatment	Treatment	Carageenan	Paw edema measurement (hr post carrageenan)						Bleed and end of study
4	√	x	√	√	Antibody	x	√	√	√	√	√	√	√	√
5	√	x	√	√	x	Dexamethasone	√	√	√	√	√	√	√	√

Data will be presented as mean ± SEM. Statistical analysis including t-test or ANOVA will be performed using Graphpad, prism 6.0 with the significance level alpha of 0.05.

6.59 EXAMPLE 59: AAV-mediated anti-plasma kallikrein antibody treatment for diabetic retinopathy

[0857] Diabetic retinopathy (DR) and diabetic macular edema (DME) are the most common complications of diabetes and the leading causes of blindness among working-age adults. Chronic hyperglycemia leads to retinal microvasculature damage and promote an increase in microvascular permeability, upregulation of inflammatory response, and fluid accumulation into the neural retina, which ultimately result in visual loss. Intravitreal administration of anti-VEGFs is the first-line treatment for DME. However, DME response to anti-VEGF is highly variable. Only 54% of DME patients treated with consecutive, monthly anti-VEGF gain vision (Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117:1064–1077; Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: The 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 2013;120:2013–2022). Recent studies suggested that plasma kallikrein, a mediator of vascular leakage and inflammation, may play an important role in the pathogenesis of DR and DME independent of VEGF (Gao -B-B, Clermont A, Rook S, et al. Extracellular carbonic anhydrase mediates hemorrhagic retinal and cerebral vascular permeability through prekallikrein activation. Nature Medicine 2007;13:181; Clermont A, Chilcote TJ, Kita T, et al. Plasma kallikrein mediates retinal vascular dysfunction and induces retinal thickening in diabetic rats. Diabetes 2011;60:1590–1598; and Kita T, Clermont AC, Murugesan N, et al. Plasma kallikrein-kinin system as a VEGF-independent mediator of diabetic macular edema. Diabetes 2015;64:3588–3599). Plasma kallikrein inhibitors could be the potential alternative therapies for DR and DME patients who are not response to anti-VEGF therapies. This study aims to test the

possibility of therapy for DR/DME using ocular vectorized antibody delivery with adeno-associated virus (AAV) gene transfer.

[0858] Vectorized anti-plasma kallikrein antibody (anti-pKal Ab such as Lanadelumab) sequence has been constructed and tested for its use in treatment of hereditary angioedema (HAE), as described above. In this study AAV8.CAG.LAN Ab and AAV8.CAG.GFP will be used as test vectors. AAV8.NUL will serve as a control vector.

[0859] First, the transduction efficiency and cell type specificity is evaluated in wild type rats. Adult Wistar rats (3-4 months old) will be used for this study. Vectors including AAV8.CAG.LAN Ab, AAV8.CAG.GFP and AAV8.NUL, will be delivered in rat eyes via subretinal (SR) injection at different doses ($5x10^8$ vg/eye and $5x10^9$ vg/eye) in 3µl of formulation buffer. Fundus and OCT imaging will be performed at 2, 4 and 8 weeks after SR injection. Ocular tissue specimens will be collected at 8 weeks post administration. Levels of antibody expression in individual ocular tissues including retina and retinal pigment epithelium (RPE) will be quantified by ELISA. Cell type specificity will be determined by immunofluorescent staining with various retinal cell markers.

[0860] Streptozotocin (STZ)-induced diabetic Wistar rats will be used as the animal model for efficacy studies. Diabetes will be induced by intravenous injection of STZ at the dose of 60 mg/kg of the body weight in young adult Wistar rats (8-10 weeks old). Significant and progressive loss of visual acuity generally starts at 8 weeks following induction in this model. AAV8.CAG.pKal Ab vector will be injected subretinally at 4 or 8 weeks after the induction of Diabetes. Contralateral eye will be injected with AAV.NUL vector and serve as a control. Fundus, fluorescein angiography (FA) and OCT imaging, electroretinography (ERG) and Optokinetic nystagmus (OKN) will be tested at 8, 12 and 16 weeks following induction of Diabetes. Ocular tissues or the whole eyeballs will be collected at 16-17 weeks post Diabetes induction. Antibody expression in ocular tissues will be quantified by ELISA. Retina structure changes and neuron survival will be evaluated by histology and immunofluorescent staining.

6.60 EXAMPLE 60: Characterization of tissue-restricted transgene immunogenicity

[0861] The goal of this study is to understand transgene immunogenicity and/or tolerance induction in the context of ubiquitous, tissue-specific, or tandem promoters. *Hypothesis:* Vectors

driven by liver-specific and liver-muscle tandem promoters will demonstrate reduced immunogenicity compared to vectors driven by a ubiquitous promoter. To test this hypothesis, four AAV vectors that drive expression of a highly immunogenic membrane-bound ovalbumin (mOVA) were constructed. These vectors differ in their promoter sequences which includes: a) a ubiquitous CAG promoter (SEQ ID NO: 411) b) the liver-specific hAAT promoter with upstream ApoE enhancer (SEQ ID NO: 412) c) the muscle-specific CK8 promoter cassette composed of the CK core promoter and three copies of a modified MCK enhancer (SEQ ID NO: 413) and d) liver-muscle tandem promoter 6 (LMTP6, SEQ ID NO: 320) that contains sequence elements derived from hAAT and CK8. Initial experiments will measure the immune response following intravenous (IV) vector administration within mice. Study endpoints will include characterization of humoral and cell-mediated immune responses against the mOVA transgene product. In addition, tissues will be harvested for vector biodistribution and transgene expression analysis.

6.61 EXAMPLE 61: Plasma expression of Vectorized Lanadelumab in Cynomolgus Monkeys

[0862] Plasma kinetics of lanadelumab expression in non-human primates administered AAV vectors encoding lanadelumab antibodies will be assessed. The goal is to assess and select the dose of AAV8.ApoE.hAAT.Lan vector that results in sustained lanadelumab expression of at least 200 μg/ml lanadelumab by three months or more. The cynomolgus monkey is chosen as the test system because of its established usefulness and acceptance as a model for AAV biodistribution studies in a large animal species and for further translation to human. All animals on this study are naïve with respect to prior treatment.

[0863] Nine cynomolgus animals will be used. Animals judged suitable for experimentation based on clinical sign data and prescreening antibody titers will be placed in three study groups, each receiving a different dosage of AAV vector, by body weight using computer-generated random numbers. Each set of three animals will be administered a single i.v. dose of the vector AAV8.ApoE.hAAT.Lan vector (described above) at the dose of 1e12 gc/kg (Group 1), 1e13 gc/kg (Group 2), and 1e14 gc/kg (Group 3).

[0864] Clinical signs will be recorded at least once daily beginning approximately two weeks prior to initiation of dosing and continuing throughout the study period. The animals will be observed for signs of clinical effects, illness, and/or death. Additional observations may be recorded based upon the condition of the animal at the discretion of the Study Director and/or technicians.

[0865] Blood samples will be collected from a peripheral vein for bioanalytical analysis prior to dose administration and then at weekly intervals for at least 3 months (9 weeks). The samples will be collected in clot tubes and the times recorded. The tubes will be maintained at room temperature until fully clotted, then centrifuged at approximately 2400 rpm at room temperature for 15 minutes. The serum will be harvested, placed in labeled vials, frozen in liquid nitrogen, and stored at -60°C or below.

[0866] A gross necropsy will be performed on any animal found dead or sacrificed moribund, and at the end of the study period, at least three months after vector administration. All animals, except those found dead, will be sedated with 8 mg/kg of ketamine HCl IM, maintained on an isoflurane/oxygen mixture and provided with an intravenous bolus of heparin sodium, 200 IU/kg. The animals will be perfused via the left cardiac ventricle with 0.001% sodium nitrite in saline. Animals found dead will be necropsied but will not be perfused.

[0867] As primary endpoint analysis, plasma samples will be assayed for lanadelumab concentration by ELISA and/or western blot, to be reported at least as μg lanadelumab per ml plasma; and lanadelumab activity, for example, kallikrein inhibition, by fluorogenic assay.

[0868] The presence of antibodies against lanadelumab (ADAs) in the serum will be evaluated by ELISA and lanadelumab binding assays. Biodistribution of the vector and lanadelumab coding transcripts will be assessed in necroscopy samples by quantitative PCR and NGS methods. Tissues to be assayed include liver, muscle, and heart. Toxicity assessment will be done by full pathology, including assaying liver enzymes, urinalysis, cardiovascular health, and more.

6.62 EXAMPLE 62: Vectorized adalimumab IgG and Fab cassettes: design and characterization

[0869] An AAV transgene cassette was constructed (SEQ ID NO: 451) that drives ubiquitous expression of vectorized adalimumab IgG (TNF001, SEQ ID NO: 452). The protein coding sequence

is composed of the heavy and light chains of adalimumab separated by a Furin cleavage site, Gly-Ser-Gly (GSG) linker (SEQ ID NO: 427), and T2A self-processing peptide sequence (SEQ ID NO: 429). 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: 411). Similarly, an additional cassette was developed (SEQ ID NO: 453) that drives expression of a Fab containing the adalimumab variable regions (TNF002, SEQ ID NO: 454). Constructs are outlined in **FIG 1**, and **FIG 12A** and sequences are provided in Table. 17.

Table 17.

Name/ SEQ ID NO.	Sequence
TNF001 SEQ ID NO: 451	gacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcc catatatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgccca acgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaatagggа ctttccattgacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatc aagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcct ggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtat tagtcatcgctattaccatggtcgaggtgagccccacgttctgcttcactctccccatct ccccccccctccccacccccaattttgtatttatttatttttttaattattttgtgcagcga tgggggcgggggggggggggggcgcgcgccaggcggggcggggcggggcgaggggcggg gcggggcgaggcggagaggtgcggcggcagccaatcagagcggcgcgctccgaaagtttc cttttatggcgaggcggcggcggcggcggccctataaaaagcgaagcgcgcggcgggcgg gagtcgctgcgcgctgccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgc cccggctctgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctc cgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggctgcgtgaaa gccttgaggggctccgggagggccctttgtgcgggggggagcggctcgggggggtgcgtgcg tgtgtgtgtgcgtggggagcgccgcgtgcggctccgcgctgcccggcggctgtgagcgct gcgggcgcggcgcggggctttgtgcgctccgcagtgtgcgcgaggggagcgcggccgggg gcggtgccccgcggtgcgggggggggctgcgaggggaacaaaggctgcgtgcggggtgtgt gcgtgggggggtgagcaggggggtgtgggcgcgtcggtcgggctgcaacccccccctgcacc cccctccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacgggggcgtg gcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgccgggcgggggcgg ggccgcctcgggccggggagggctcgggggagggggcgcggcggcccccggagcgccggcg gctgtcgaggcgcggcgagccgcagccattgccttttatggtaatcgtgcgagagggcgc agggacttcctttgtcccaaatctgtgcggagccgaaatctgggaggcgccgccgcaccc cctctagcgggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagg gccttcgtgcgtcgccgcgccgccgtcccctctccctctccagcctcggggctgtccgc gggggacggctgccttcgggggggacggggcagggcggggttcggcttctggcgtgtga ccggcggctctagagcctctgctaaccatgttcatgccttcttctttttcctacagctcc tgggcaacgtgctggttattgtgctgtctcatcattttggcaaagaattcgccaccatgt acagaatgcagctgctgctgctcattgccctgtctctggccctggtcaccaattctgaag tgcagctggtggaaagtggtggtggactggtgcagcctggcagaagcctgagactgtctt gtgctgcctctggcttcacctttgatgactatgccatgcactgggtcagacaggccctg gcaaaggactggaatgggtgtcagccatcacctggaactctggccacattgactatgctg actctgtggaaggcagattcaccatcagcagagacaatgccaagaacagcctgtacctgc agatgaactccctgagagctgaggacacagcagtgtactactgtgccaaggtgtcctacc

Name/ SEQ ID NO.	Sequence
	tgagcacagccagcagcctggattattggggccagggcacactggttacagtgtcctctg ccagcacaaagggcccctctgtttttccactggctcccagcagcaagagcaccagtggtg gaacagctgccctgggctgtctggtcaaggattacttccctgagcctgtgacagtgtctt ggaactcaggggctctgacctctggggtgcacacatttccagctgtgctgcagtcctctg gcctgtactctctgtcctctgtggtcacagtgcctagctctagcctgggcacccagacct acatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagaaggtggaaccca agagctgtgacaagacccacacctgtcctccatgtcctgctccagaactgcttggaggcc cttctgtgttcctgtttcctccaaagcctaaggacaccctgatgatcagcagaaccctg aagtgacctgtgtggtggttgatgtgtcccatgaggacccagaagtgaagttcaattggt atgtggatggggttgaagtgcacaatgctaagaccaagcctagagaggaacagtacaaca gcacctacagagtggtgtctgtgctgacagtgctgcatcaggactggctgaatggcaaag agtacaagtgcaaagtgtccaacaaggccctgcctgctcctattgagaaaaccatctcca aggccaagggccagccaagagaaccccaggtttacacactgccacctagcagagatgagc tgaccaagaaccaggtgtccctgacctgcctggttaagggcttctacccctctgacattg ctgtggaatgggagagcaatggccagcctgagaacaactacaagacaacccctcctgtgc tggactctgatggctcattcttcctgtacagcaagctgactgtggacaagtccagatggc agcaggggaatgtgttcagctgctctgtgatgcatgaggccctgcacaaccactacaccc agaaaagtctgagtctgagccctggcaagagaaagagaagaggctctggagaaggcagag gctccctgctgacatgtggggatgttgaagagaatcctgggcctatgtataggatgcaac tgctcctcctgattgctctgagcctggctcttgtgaccaactctgacatccagatgacac agagccctagcagcctgtctgcttctgtgggagacagagtgaccatcacatgcagagcca gccagggaatcagaaactacctggcctggtatcagcaaaagcctggcaaggcccctaagc tgctgatctatgcagccagcacactgcagtcaggggtgccaagcagattttcaggctctg gctctggcacagacttcaccctgaccatttctagcctgcagcctgaggatgtggccacct actactgccagagatacaacagagccccatacacctttggacagggcacaaaggtggaaa tcaagagaacagtggctgccccatctgtgttcatcttcccaccatctgatgaaacagctga agtctggcactgcctctgttgtgtgcctgctgaacaacttctaccctagagaagccaagg tgcagtggaaggttgacaatgccctgcagtctggcaatagccaagaatctgtgacagagc aggactccaaggattccacctacagcctgagcagcaccctgacactgagcaaggctgact atgagaagcacaaagtgtatgcctgtgaagtgacacaccagggactgagcagcccagtga ccaagagcttcaacaggggagagtgctgataactcgaggacggggtgaactacgcctgag gatccgatcttttccctctgccaaaaattatggggacatcatgaagccccttgagcatc tgacttctggctaataaaggaaatttattttcattgcaatagtgtgttggaatttttgt gtctctcactcg
Adalimumab Full-length mAb single chain construct transgene (TNF001) (HC-*Furin-linker-T2A*-LC) SEQ ID NO: 452	atgtacagaatgcagctgctgctgctcattgccctgtctctggccctggtcaccaattct gaagtgcagctggtggaaagtggtggtggactggtgcagcctggcagaagcctgagactg tcttgtgctgcctctggcttcacctttgatgactatgccatgcactgggtcagacaggcc cctggcaaaggactggaatgggtgtcagccatcacctggaactctggccacattgactat gctgactctgtggaaggcagattcaccatcagcagagacaatgccaagaacagcctgtac ctgcagatgaactccctgagagctgaggacacagcagtgtactactgtgccaaggtgtcc tacctgagcacagccagcagcctggattattggggccagggcacactggttacagtgtcc tctgccagcacaaagggcccctctgtttttccactggctcccagcagcaagagcaccagt ggtggaacagctgccctgggctgtctggtcaaggattacttccctgagcctgtgacagtg tcttggaactcaggggctctgacctctggggtgcacacatttccagctgtgctgcagtcc tctggcctgtactctctgtcctctgtggtcacagtgcctagctctagcctgggcacccag acctacatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagaaggtggaa cccaagagctgtgacaagacccacacctgtcctccatgtcctgctccagaactgcttgga ggcccttctgtgttcctgtttcctccaaagcctaaggacaccctgatgatcagcagaacc cctgaagtgacctgtgtggtggttgatgtgtcccatgaggacccagaagtgaagttcaat tggtatgtggatggggttgaagtgcacaatgctaagaccaagcctagagaggaacagtac

Name/ SEQ ID NO.	Sequence
	aacagcacctacagagtggtgtctgtgctgacagtgctgcatcaggactggctgaatggc aaagagtacaagtgcaaagtgtccaacaaggccctgcctgctcctattgagaaaaccatc tccaaggccaagggccagccaagagaaccccaggtttacacactgccacctagcagagat gagctgaccaagaaccaggtgtccctgacctgcctggttaagggcttctacccctctgac attgctgtggaatgggagagcaatggccagcctgagaacaactacaagacaacccctcct gtgctggactctgatggctcattcttcctgtacagcaagctgactgtggacaagtccaga tggcagcaggggaatgtgttcagctgctctgtgatgcatgaggccctgcacaaccactac acccagaaaagtctgagtctgagccctggcaagagaaagagaagaggctctggagaaggc agaggctccctgctgacatgtggggatgttgaagagaatcctgggcctatgtataggatg caactgctcctcctgattgctctgagcctggctcttgtgaccaactctgacatccagatg acacagagccctagcagcctgtctgcttctgtgggagacagagtgaccatcacatgcaga gccagccagggaatcagaaactacctggcctggtatcagcaaaagcctggcaaggccccct aagctgctgatctatgcagccagcacactgcagtcaggggtgccaagcagattttcaggc tctggctctggcacagacttcaccctgaccatttctagcctgcagcctgaggatgtggcc acctactactgccagagatacaacagagccccatacacctttggacagggcacaaaggtg gaaatcaagagaacagtggctgccccatctgtgttcatcttcccaccatctgatgaacag ctgaagtctggcactgcctctgttgtgtgcctgctgaacaacttctaccctagagaagcc aaggtgcagtggaaggttgacaatgccctgcagtctggcaatagccaagaatctgtgaca gagcaggactccaaggattccacctacagcctgagcagcaccctgacactgagcaaggct gactatgagaagcacaaagtgtatgcctgtgaagtgacacaccagggactgagcagccca gtgaccaagagcttcaacaggggagagtgctga
TNF002 SEQ ID NO: 453	gacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcc catatatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgccca acgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaataggga ctttccattgacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatc aagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcct ggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtat tagtcatcgctattaccatggtcgaggtgagccccacgttctgcttcactctccccatct ccccccctcccccacccccaattttgtatttatttatttttttaattattttgtgcagcga tgggggcgggggggggggggggcgcgcgccaggcggggcggggcggggcgaggggcggg gcggggcgaggcggagaggtgcggcggcagccaatcagagcggcgcgctccgaaagtttc cttttatggcgaggcggcggcggcggcggccctataaaaagcgaagcgcgcggcgggcgg gagtcgctgcgcgctgccttcgccccgtgccccgctccgccgccgcctcgcgccgcccgc cccggctctgactgaccgcgttactcccacaggtgagcgggcgggacggcccttctcctc cgggctgtaattagcgcttggtttaatgacggcttgtttcttttctgtggctgcgtgaaa gccttgaggggctccgggagggccctttgtgcgggggggagcggctcgggggggtgcgtgcg tgtgtgtgtgcgtggggagcgccgcgtgcggctccgcgctgcccggcggctgtgagcgct gcgggcgcggcgcggggctttgtgcgctccgcagtgtgcgcgaggggagcgcggccgggg gcggtgccccgcggtgcgggggggggctgcgaggggaacaaaggctgcgtgcggggtgtgt gcgtgggggggtgagcaggggggtgtgggcgcgtcggtcgggctgcaacccccccctgcacc cccctccccgagttgctgagcacggcccggcttcgggtgcggggctccgtacggggcgtg gcgcggggctcgccgtgccgggcgggggggtggcggcaggtgggggtgccgggcggggcgg ggccgcctcgggccggggagggctcgggggaggggcgcggcggcccccggagcgccggcg gctgtcgaggcgcggcgagccgcagccattgccttttatggtaatcgtgcgagagggcgc agggacttcctttgtcccaaatctgtgcggagccgaaatctgggaggcgccgccgcaccc cctctagcgggcgcggggcgaagcggtgcggcgccggcaggaaggaaatgggcggggagg gccttcgtgcgtcgccgcgccgccgtcccctttctcccctctccagcctcggggctgtccgc gggggacggctgccttcgggggggacggggcagggcggggttcggcttctggcgtgtga ccggcggctctagagcctctgctaaccatgttcatgccttcttcttttttcctacagctcc tgggcaacgtgctggttattgtgctgtctcatcattttggcaaagaattcgccaccatgt

Name/ SEQ ID NO.	Sequence
	acagaatgcagctgctgctgctcattgccctgtctctggccctggtcaccaattctgaag tgcagctggtggaaagtggtggtggactggtgcagcctggcagaagcctgagactgtctt gtgctgcctctggcttcacctttgatgactatgccatgcactgggtcagacaggcccctg gcaaaggactggaatgggtgtcagccatcacctggaactctggccacattgactatgctg actctgtggaaggcagattcaccatcagcagagacaatgccaagaacagcctgtacctgc agatgaactccctgagagctgaggacacagcagtgtactactgtgccaaggtgtcctacc tgagcacagccagcagcctggattattggggccagggcacactggttacagtgtcctctg ccagcacaaagggcccctctgtttttccactggctcccagcagcaagagcaccagtggtg gaacagctgccctgggctgtctggtcaaggattacttccctgagcctgtgacagtgtctt ggaactcaggggctctgacctctggggtgcacacatttccagctgtgctgcagtcctctg gcctgtactctctgtcctctgtggtcacagtgcctagctctagcctgggcacccagacct acatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagaaggtggaaccca agagctgtgacaagacccacagaaagagaagaggctctggagaaggcagaggctccctgc tgacatgtggggatgttgaagagaatcctgggcctatgtataggatgcaactgctcctcc tgattgctctgagcctggctcttgtgaccaactctgacatccagatgacacagagcccta gcagcctgtctgcttctgtgggagacagagtgaccatcacatgcagagccagccagggca tcagaaactacctggcctggtatcagcagaagccaggcaaggcccctaagctgctgatct atgcagccagcacactgcagagtggggtgccaagcagattttcaggctctggctctggca cagacttcaccctgaccatttctagcctgcagcctgaggatgtggccacctactactgcc agagatacaacagagccccatacacctttggacagggcacaaaggtggaaatcaagagaa cagttgcagcaccctcagttttcatcttcccccctcagatgaacagctgaagtctggca ctgcctctgttgtgtgcctgctgaacaacttctaccccagagaagccaaggtgcagtgga aggttgacaatgccctgcagtcaggcaacagccaagaatctgtgactgaacaggattcca aggatagcacctacagcctgagcagcaccctgacactgagcaaggctgactatgagaagc acaaagtgtatgcctgtgaagtgacccaccagggactgagcagcccagtgaccaagagct tcaacaggggagagtgctgataactcgaggacggggtgaactacgcctgaggatccgatc tttttccctctgccaaaaattatggggacatcatgaagccccttgagcatctgacttctg gctaataaaggaaatttatttcattgcaatagtgtgttggaatttttgtgtctctcac tcg
Adalimumab Fab single chain construct transgene (TNF002) (HC-Furin-linker-T2A-LC) SEQ ID NO: 453	atgtacagaatgcagctgctgctgctcattgccctgtctctggccctggtcaccaattct gaagtgcagctggtggaaagtggtggtggactggtgcagcctggcagaagcctgagactg tcttgtgctgcctctggcttcacctttgatgactatgccatgcactgggtcagacaggcc cctggcaaaggactggaatgggtgtcagccatcacctggaactctggccacattgactat gctgactctgtggaaggcagattcaccatcagcagagacaatgccaagaacagcctgtac ctgcagatgaactccctgagagctgaggacacagcagtgtactactgtgccaaggtgtcc tacctgagcacagccagcagcctggattattggggccagggcacactggttacagtgtcc tctgccagcacaaagggcccctctgtttttccactggctcccagcagcaagagcaccagt ggtggaacagctgccctgggctgtctggtcaaggattacttccctgagcctgtgacagtg tcttggaactcaggggctctgacctctggggtgcacacatttccagctgtgctgcagtcc tctggcctgtactctctgtcctctgtggtcacagtgcctagctctagcctgggcacccag acctacatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagaaggtggaa cccaagagctgtgacaagacccacagaaagagaagaggctctggagaaggcagaggctcc ctgctgacatgtggggatgttgaagagaatcctgggcctatgtataggatgcaactgctc ctcctgattgctctgagcctggctcttgtgaccaactctgacatccagatgacacagagc cctagcagcctgtctgcttctgtgggagacagagtgaccatcacatgcagagccagccag ggcatcagaaactacctggcctggtatcagcagaagccaggcaaggcccctaagctgctg atctatgcagccagcacactgcagagtggggtgccaagcagattttcaggctctggctct ggcacagacttcaccctgaccatttctagcctgcagcctgaggatgtggccacctactac tgccagagatacaacagagccccatacacctttggacagggcacaaaggtggaaatcaag agaacagttgcagcaccctcagttttcatcttcccccctcagatgaacagctgaagtct

Name/ SEQ ID NO.	Sequence
	ggcactgcctctgttgtgtgcctgctgaacaacttctaccccagagaagccaaggtgcag tggaaggttgacaatgccctgcagtcaggcaacagccaagaatctgtgactgaacaggat tccaaggatagcacctacagcctgagcagcaccctgacactgagcaaggctgactatgag aagcacaaagtgtatgcctgtgaagtgacccaccagggactgagcagcccagtgaccaag agcttcaacaggggagagtgctga
Adalimumab Heavy Chain (HC) IgG1 SEQ ID NO: 444	gaagtgcagctggtggaaagtggtggtggactggtgcagcctggcagaagcctgagactg tcttgtgctgcctctggcttcacctttgatgactatgccatgcactgggtcagacaggcc cctggcaaaggactggaatgggtgtcagccatcacctggaactctggccacattgactat gctgactctgtggaaggcagattcaccatcagcagagacaatgccaagaacagcctgtac ctgcagatgaactccctgagagctgaggacacagcagtgtactactgtgccaaggtgtcc tacctgagcacagccagcagcctggattattggggccagggcacactggttacagtgtcc tct**gccagcacaaagggcccctctgtttttccactggctcccagcagcaagagcaccagt** **ggtggaacagctgccctgggctgtctggtcaaggattacttccctgagcctgtgacagtg** **tcttggaactcaggggctctgacctctggggtgcacacatttccagctgtgctgcagtcc** **tctggcctgtactctctgtcctctgtggtcacagtgcctagctctagcctgggcacccag** **acctacatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagaaggtg***gaa* *cccaagagctgtgacaagacccacacctgtcctccatgtcct***gctccagaactgcttgga** **ggcccttctgtgttcctgtttcctccaaagcctaaggacaccctgatgatcagcagaacc** **cctgaagtgacctgtgtggtggttgatgtgtcccatgaggacccagaagtgaagttcaat** **tggtatgtggatggggttgaagtgcacaatgctaagaccaagcctagagaggaacagtac** **aacagcacctacagagtggtgtctgtgctgacagtgctgcatcaggactggctgaatggc** **aaagagtacaagtgcaaagtgtccaacaaggccctgcctgctcctattgagaaaaccatc** **tccaaggccaagggccagccaagagaaccccaggtttacacactgccacctagcagagat** **gagctgaccaagaaccaggtgtccctgacctgcctggttaagggcttctacccctctgac** **attgctgtggaatgggagagcaatggccagcctgagaacaactacaagacaacccctcct** **gtgctggactctgatggctcattcttcctgtacagcaagctgactgtggacaagtccaga** **tggcagcaggggaatgtgttcagctgctctgtgatgcatgaggccctgcacaaccactac** **acccagaaaagtctgagtctgagccctggcaag** *IgG1 CH1 and CH2 are shown bold; hinge region is shown in italic.*
Adalimumab VH SEQ ID NO: 445	Gaagtgcagctggtggaaagtggtggtggactggtgcagcctggcagaagcctgagactg tcttgtgctgcctctggcttcacctttgatgactatgccatgcactgggtcagacaggcc cctggcaaaggactggaatgggtgtcagccatcacctggaactctggccacattgactat gctgactctgtggaaggcagattcaccatcagcagagacaatgccaagaacagcctgtac ctgcagatgaactccctgagagctgaggacacagcagtgtactactgtgccaaggtgtcc tacctgagcacagccagcagcctggattattggggccagggcacactggttacagtgtcc tct *CDRs are underlined.*
IgG1 CH1 SEQ ID NO: 446	gccagcacaaagggcccctctgtttttccactggctcccagcagcaagagcaccagtggt ggaacagctgccctgggctgtctggtcaaggattacttccctgagcctgtgacagtgtct tggaactcaggggctctgacctctggggtgcacacatttccagctgtgctgcagtcctct ggcctgtactctctgtcctctgtggtcacagtgcctagctctagcctgggcacccagacc tacatctgcaatgtgaaccacaagcctagcaacaccaaggtggacaagaaggtg
IgG1 CH2 SEQ ID NO: 447	gctccagaactgcttggaggcccttctgtgttcctgtttcctccaaagcctaaggacacc ctgatgatcagcagaacccctgaagtgacctgtgtggtggttgatgtgtcccatgaggac ccagaagtgaagttcaattggtatgtggatggggttgaagtgcacaatgctaagaccaag cctagagaggaacagtacaacagcacctacagagtggtgtctgtgctgacagtgctgcat caggactggctgaatggcaaagagtacaagtgcaaagtgtccaacaaggccctgcctgct cctattgagaaaaccatctccaaggccaagggccagccaagagaaccccaggtttacaca ctgccacctagcagagatgagctgaccaagaaccaggtgtccctgacctgcctggttaag

Name/ SEQ ID NO.	Sequence
	ggcttctacccctctgacattgctgtggaatgggagagcaatggccagcctgagaacaac tacaagacaacccctcctgtgctggactctgatggctcattcttcctgtacagcaagctg actgtggacaagtccagatggcagcaggggaatgtgttcagctgctctgtgatgcatgag gccctgcacaaccactacacccagaaaagtctgagtctgagccctggcaag
Adalimumab Light Chain (kappa) SEQ ID NO: 448	gctccagaactgcttggaggcccttctgtgttcctgtttcctccaaagcctaaggacacc ctgatgatcagcagaaccctgaagtgacctgtgtggtggttgatgtgtcccatgaggac ccagaagtgaagttcaattggtatgtggatggggttgaagtgcacaatgctaagaccaag cctagagaggaacagtacaacagcacctacagagtggtgtctgtgctgacagtgctgcat caggactggctgaatggcaaagagtacaagtgcaaagtgtccaacaaggccctgcctgct cctattgagaaaaccatctccaaggccaagggccagccaagagaaccccaggtttacaca ctgccacctagcagagatgagctgaccaagaaccaggtgtccctgacctgcctggttaag ggcttctacccctctgacattgctgtggaatgggagagcaatggccagcctgagaacaac tacaagacaacccctcctgtgctggactctgatggctcattcttcctgtacagcaagctg actgtggacaagtccagatggcagcaggggaatgtgttcagctgctctgtgatgcatgag gccctgcacaaccactacacccagaaaagtctgagtctgagccctggcaag
Adalimumab VL SEQ ID NO: 449	Gacatccagatgacacagagccctagcagcctgtctgcttctgtgggagacagagtgacc atcacatgcagagccagccagggaatcagaaactacctggcctggtatcagcaaaagcct ggcaaggcccctaagctgctgatctatgcagccagcacactgcagtcaggggtgccaagc agattttcaggctctggctctggcacagacttcaccctgaccatttctagcctgcagcct gaggatgtggccacctactactgccagagatacaacagagccccatacacctttggacag ggcacaaaggtggaaatcaag *CDRs are underlined.*
Adalimumab Light chain C-Domain (CL) SEQ ID NO: 450	agaacagttgcagcaccctcagttttcatcttcccccctcagatgaacagctgaagtct ggcactgcctctgttgtgtgcctgctgaacaacttctaccccagagaagccaaggtgcag tggaaggttgacaatgccctgcagtcaggcaacagccaagaatctgtgactgaacaggat tccaaggatagcacctacagcctgagcagcaccctgacactgagcaaggctgactatgag aagcacaaagtgtatgcctgtgaagtgacccaccagggactgagcagcccagtgaccaag agcttcaacaggggagagtgctga

[0870] Plasmid expression was characterized via western blot following transfection into 293T cells (**FIG. 36A**). In addition, plasmid-expressed antibody activity was assessed via ELISA for binding of recombinant human TNFα (**FIG. 36B**). In addition, this plasmid was used to produce recombinant AAV8 vectors. Expression and activity of adalimumab produced from AAV8 was evaluated with the aforementioned assays (**FIGS. 37A-37C**).

6.63 EXAMPLE 63: Self-complementary adalimumab Fab transgene cassettes: design and characterization

[0871] Two self-complementary AAV (scAAV) transgene cassettes encoding vectorized adalimumab Fab were generated. The transgenes are driven by the ubiquitous mU1a (SEQ ID NO: 414) or EF-1α (SEQ ID NO: 415) core promoters. These plasmids were compared for Fab expression

via transfection into 293T cells (**FIG. 38**). The mU1a-driven vector displayed a higher absorbance values suggesting higher Fab concentration within the cell supernatant.

6.64 EXAMPLE 64: TNFα binding across model species with vectorized adalimumab IgG and Fab

[0872] Vectorized adalimumab candidates for TNFα isolated from model species including human, mouse, and rat were tested for their binding capacity. Vectorized antibodies were expressed and secreted into cell supernatant following cis plasmid transfection into 293T cells. The cell supernatant was tested in an ELISA where the plates were coated with recombinant TNFα derived from the aforementioned species (**FIG. 39**). Adalimumab IgG effectively bound human and mouse derived TNFα. The Fab demonstrates a similar binding profile to human TNFα as the IgG. However, the Fab displays poor binding to mouse TNFα compared to adalimumab IgG. Both IgG and Fab display far reduced binding to rat TNFα.

6.65 EXAMPLE 65: AAV-mediated Ocular Gene Therapy for Non-infectious Posterior Uveitis

[0873] Non-infectious posterior uveitis is a form of ocular inflammation that affects the retina and choroid of the eye and leads to blindness. It afflicts approximately 38,000 Americans per year. Patients are usually treated with systemic steroids or corticosteroids therapy, which results in high risks of systemic complications. In 2016, Humira (adalimumab), a human monoclonal antibody that targets tumor necrosis factor-alpha (TNFα), was approved by FDA and became the only systemic noncorticosteroid agent for the treatment of non-infectious uveitis (NIU) and has been widely used since then. In this study, full length or Fab adalimumab antibody in an adeno-associated virus (AAV) vector, such as AAV8.CAG.adalimumab.IgG, orAAV8.CAG.adalimumab.Fab, as well as AAV8.CAG.GFP, will be evaluated for AAV-mediated antibody expression *in vivo* in mouse ocular tissues via local administration. AAV8.NUL will serve as a control vector. Efficacy studies in rodent EAU model will also be performed to investigate therapeutic potential of AAV-mediated anti-TNFα treatment for NIU.

[0874] Vectorized adalimumab sequence have been constructed and tested in vitro. The transduction efficiency and cell type specificity in wild type mouse will further be evaluated. Young

adult C57BL/6 and B10.RIII mice (8-10 weeks old) will be used for this study. Vectors including AAV8.CAG.adalimumab.IgG, AAV8.CAG.adalimumab.Fab, AAV8.CAG.GFP and AAV8.NUL will be delivered in mouse eyes via subretinal (SR) injection at different doses ($1x10^7$, $1x10^8$ and $1x10^9$ vg/eye) in 1µl of formulation buffer. Fundus and OCT imaging will be performed at 1, 2 and 4 weeks after SR injection. Ocular samples will be collected at 5 weeks post administration. Levels of antibody or fusion protein expression in ocular tissues will be quantified by ELISA. Cell type specificity will be determined by immunofluorescent staining with various retinal cell markers. Test vector(s) will be selected for efficacy study. Different routes of administration (ROA) including suprachoroidal, intracameral and intravitreal injections will also be explored. The preferred ROA will be used for efficacy study.

[0875] Efficacy studies will be conducted by inducing experimental autoimmune uveitis (EAU) in B10.RIII mice by immunization with the human IRBP peptide. T-cell mediated ocular autoimmune response will occur in this model with a peak from approximately 11 to 18 days post-induction. Test vector will be administrated in mouse eye via preferred ROA at 2 weeks before or 1 week after induction of EAU. Contralateral eye will be delivered with AAV.NUL vector and serve as a control. Fundus and OCT imaging, electroretinography (ERG) and Optokinetic nystagmus (OKN) will be tested at 10, 17 and 30 days following induction of EAU to monitor the progress of the disease. Ocular tissues or whole eyeballs will be collected at 5 weeks post EAU induction. Levels of antibody or fusion protein expression in ocular tissues will be detected and quantified by ELISA. Retina structure changes and neuron survival will be evaluated by histology and immunofluorescent staining.

EQUIVALENTS

[0876] 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.

[0877] 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 angioedema including hereditary angioedema in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of AAV8 capsid (SEQ ID NO: 143); AAVrh10 capsid (SEQ ID NO: 145); or AAV9 capsid (SEQ ID NO: 144); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a full-length or substantially full-length anti-kallikrein (anti-pKal) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for administration to the subject, optionally wherein administration is intravenous, subcutaneous, intranasal, or intramuscular.

2. The pharmaceutical composition of claim 2, wherein the anti-pKal mAb is lanadelumab.

3. A pharmaceutical composition for delivering lanadelumab to the bloodstream to treat hereditary angioedema in a human subject in need thereof, said composition comprising a recombinant AAV comprising a transgene encoding lanadelumab operably linked to one or more regulatory sequences that control expression of the transgene in muscle and/or liver cells, wherein said recombinant AAV is administered to said human subject at a dose sufficient to result in expression from the transgene and secretion of lanadelumab into the bloodstream of the human subject to produce lanadelumab plasma levels of at least 5 μg/ml to at least 35 μg/ml lanadelumab in said subject.

4. The method of claim 3, wherein the lanadelumab plasma levels are 20 μg/ml to 35 μg/ml and the lanadelumab plasma levels are maintained for at least three months.

5. The method of claim 3 or 4 wherein the lanadelumab antibody secreted into the plasma exhibits greater a greater than at least 40%, 45%, 50%, 55%, 60%, 65% or 70 reduction in pKal activity as measured by a kinetic enzymatic functional assay wherein the activity of the lanadelumab antibody

is measured at 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks or 12 weeks after said administration.

6. A pharmaceutical composition for delivery of an antibody or antigen binding fragment thereof to the bloodstream of a human subject in need thereof, comprising an AAV vector comprising:

(a) An AAV viral capsid that infects liver and/or muscle cells; and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a full-length antibody or an antigen-binding fragment thereof, operably linked to a chimeric promoter that directs expression in muscle and liver cells;

wherein said AAV vector is formulated for intramuscular administration.

7. The pharmaceutical composition of claim 6 wherein the chimeric promoter is LMTP6 (SEQ ID NO: 320), LMTP13 (SEQ ID NO: 321), LMTP14 (SEQ ID NO: 322), LMTP15 (SEQ ID NO: 323), LMTP18 (SEQ ID NO: 324), LMTP19 (SEQ ID NO: 325), or LMTP20 (SEQ ID NO: 326).

8. A pharmaceutical composition for treating non-infectious uveitis in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV2.7m8 (SEQ ID NO: 142), an AAV8 capsid (SEQ ID NO: 143), or AAV9 capsid (SEQ ID NO: 144); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or full-length anti-tumor necrosis factor-alpha (anti-TNFα) mAb or an antigen-binding fragment thereof, a substantially full-length or full-length anti-complement component 5 (C5) mAb or an antigen-binding fragment thereof, a substantially full-length or full-length anti-interleukin-6 (IL-6) mAb or an antigen-binding fragment thereof, or a substantially full-length or full-length anti-interleukin-6 receptor (IL-6R) mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human retina cells;

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

9. The pharmaceutical composition of claim 8 wherein the anti-TNFα mAb is adalimumab, infliximab or golimumab; the anti-C5 mAb is tesidolumab or ravulizumab; the anti-IL-6 mAb is siltuximab, clazakimzumab, sirukumab, olokizumab or gerilimzumab; or the anti-IL-6R mAb is satralizumab, sarilumab or tocilizumab.

10. A pharmaceutical composition for treating Alzheimer's disease, frontotemporal dementia (FD), tauopathies, progressive supranuclear palsy, chronic traumatic encephalopathy, Pick's Complex, and primary age-related tauopathy, Huntington's disease, juvenile Huntington's disease, Parkinson's disease, synucleinopathies, ALS, migraines, or cluster headaches in a human subject in need thereof, comprising an adeno-associated virus (AAV) vector having:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), AAV9 capsid (SEQ ID NO: 144), AAVrh10 capsid (SEQ ID NO: 145), an AAVrh20 capsid, an AAVrh39 capsid or an AAVcy5 capsid; 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 full-length or substantially full-length anti-amyloid beta (anti-Aβ), anti-sortilin, anti-Tau protein (anti-Tau), anti-semaphorin 4D (anti-SEMA4D), anti-alpha synuclein (anti-SNCA), anti-superoxide dismutase-1 (anti-SOD1) or anti-calcitonin gene-related peptide receptor (anti-CGRPR) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human CNS, muscle, or liver cells;

wherein said AAV vector is formulated for administration to the subject, optionally wherein administration is intrathecal, intravenous, subcutaneous, intranasal, or intramuscular.

11. The pharmaceutical composition of claim 10, wherein the anti-Aβ mAb is solanezumab, lecanemab, or GSK933776; the anti-sortilin mAb is AL-001; the anti-Tau mAb is ABBV-8E12, UCB-0107, or NI-105 (BIIB076); the anti-SEMA4D mAb is VX15/2503; the anti-SNCA mAb is

prasinezumab, NI-202 (BIIB054), or MED-1341; the anti-SOD1 mAb is NI-2041.10D12 or NI-204.12G7; and the anti-CGRPR mAb is eptinezumab, fremanezumab, or galcanezumab.

12. A pharmaceutical composition for treating retinal disorders including diabetic retinopathy, myopic choroidal neovascularization (mCNV), macular degeneration (e.g., neovascular (wet) or dry age-related macular degeneration (nAMD)), macular edema (e.g., macular edema following a retinal vein occlusion (RVO) or diabetic macular edema (DME)), retinal vein occlusion, diabetic retinopathy (DR), non-infectious uveitis, or glaucoma, or abnormal vascularization of the retina in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV2.7m8 capsid (142), an AAV8 capsid (SEQ ID NO: 143), or an AAV9 capsid (SEQ ID NO: 144); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a full-length or substantially full-length anti-vascular endothelial growth factor (anti-VEGF), anti-erythropoietin receptor (anti-EPOR), anti-Aβ, anti-activin receptor like kinase 1 (anti-ALK1), anti-complement component 5 (anti-C5), anti-endoglin (anti-ENG), anti-complement component 1Q (anti-CC1Q), anti-tumor necrosis factor-alpha (anti-TNFα), or anti-pKal mAb or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human retinal cells;

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

13. The pharmaceutical composition of claim 12 wherein the anti-VEGF mAb is sevacizumab; anti-EPOR mAb is LKA-651 (NSV2) or LKA-651 (NSV3); anti- Aβ mAb is solanezumab, lecanemab, or GSK933776; anti-ALK1 mAb is ascrinvacumab; anti-C5 mAb is tesidolumab or ravulizumab; anti-ENG mAb is carotuximab; the anti-CC1Q mAb is ANX-007; wherein anti-TNFα mAb is adalimumab, infliximab or golimumab; and the anti-pKal mAb is lanadelumab.

14. A pharmaceutical composition for treating multiple sclerosis in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), AAV9 capsid (SEQ ID NO: 144), AAVrh10 capsid (SEQ ID NO: 145), an AAVrh20 capsid, an AAVrh39 capsid or an AAVcy5 capsid; and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a full-length or substantially full-length anti-repulsive guidance molecule-A (anti-RGMa) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human CNS, liver, or muscle cells;

wherein said AAV vector is formulated for administration to the subject, optionally wherein administration is intrathecal, intravenous, subcutaneous, intranasal, or intramuscular.

15. The pharmaceutical composition of claim 14, wherein the anti-RGMa mAb is elezanumab.

16. A pharmaceutical composition for treating amyloidosis (ATTR), familial amyloid cardiomyopathy (FAC), or familial amyloid polyneuropathy (FAP) in a human subject in need thereof, comprising AAV vector comprising:

(c) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), an AAVrh10 capsid (SEQ ID NO: 145), an AAVrh20 capsid, an AAVrh39 capsid, or an AAVcy5 capsid; and

(a) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a full-length or substantially full-length anti-TTR mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for administration to the subject, optionally wherein administration is intravenous, subcutaneous, intranasal, or intramuscular.

17. The pharmaceutical composition of claim 16, wherein the anti-TTR mAb is NI-301 or PRX-004.

18. A pharmaceutical composition for treating fibrotic disorders, pulmonary fibrosis, cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), liver cirrhosis, atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, arthrofibrosis, Crohn's disease, ulcerative colitis, mediastinal fibrosis, myelofibrosis (MF), nephrogenic systemic fibrosis (NSF), progressive massive fibrosis (PMF), and retroperitoneal fibrosis (RPF) in a human subject in need thereof, comprising an AAV vector comprising:

(c) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), or AAVrh10 (SEQ ID NO: 145); and

(d) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a full-length or substantially full-length anti-connective tissue growth factor (anti-CTGF) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for administration to said subject, optionally wherein administration is intravenous, subcutaneous, intranasal, or intramuscular.

19. The pharmaceutical composition of claim 18, wherein the anti-CTGF mAb is pamrevlumab.

20. A pharmaceutical composition for treating non-infectious uveitis, neuromyelitis optica (NMO), diabetic retinopathy (DR), or diabetic macular edema (DME) in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV2.7m8 capsid (SEQ ID NO: 142) or an AAV9 capsid (SEQ ID NO: 144); 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 full-length or substantially full-length anti-interleukin-6 receptor (anti-IL6R), anti-interleukin 6 (IL6), or anti-cluster of differentiation 19 (anti-CD19) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human retinal cells;

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

21. The pharmaceutical composition of claim 20, wherein the anti-IL6R mAb is satralizumab, sarilumab, or tocilizumab, or the anti-IL6 mAb is siltuximab, clazakizumab, sirukumab, olokizumab, or gerilimzumab, or the anti-CD19 mAb is inebilizumab.

22. A pharmaceutical composition for reducing, inhibiting or ameliorating a detrimental immune response in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143), an AAV9 capsid (SEQ ID NO: 144), an AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a substantially full-length or full-length mAb of an anti-interleukin-6 receptor (anti-IL6R) or anti-interleukin-6 (IL6), or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or muscle cells;

wherein said AAV vector is formulated for subcutaneous, intramuscular, intravenous or pulmonary administration to the subject.

23. The pharmaceutical composition of claim 22, wherein the anti-IL6R mAb is satralizumab, sarilumab, or tocilizumab, or the anti-IL6 mAb is siltuximab, clazakizumab, sirukumab, olokizumab, or gerilimzumab.

24. A pharmaceutical composition for treating inflammatory bowel disease (IBD) including UC and CD in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of AAV8 capsid (SEQ ID NO: 143); AAV9 capsid (SEQ ID NO: 144); or AAVrh10 capsid (SEQ ID NO: 145); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a full-length or substantially full-length anti-integrin β7 subunit (anti-ITGB7) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for administration to the subject, optionally wherein administration is intravenous, subcutaneous, intranasal, or intramuscular.

25. The pharmaceutical composition of claim 24, wherein the anti-ITGB7 mAb is etrolizumab.

26. A pharmaceutical composition for treating osteoporosis or abnormal bone loss or weakness (e.g., treating giant cell tumor of bone, treating treatment-induced bone loss, slowing the loss of (or increasing) bone mass in breast and prostate cancer patients, preventing skeletal-related events due to bone metastasis, or for decreasing bone resorption and turnover in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143); AAVrh10 capsid (SEQ ID NO: 145); or an AAV9 capsid (SEQ ID NO: 144);

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding a full-length or substantially full-length anti-sclerostin (anti-SOST) mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for administration to the subject, optionally wherein administration is intravenous, subcutaneous, intranasal, or intramuscular.

27. The pharmaceutical composition of claim 26, wherein the anti-SOST mAb is romosozumab.

28. A pharmaceutical composition for treating atopic dermatitis in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143) or AAV9 capsid (SEQ ID NO: 144); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding an anti-IL13 mAb or anti-IL31RA, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous administration to the liver or muscle of said subject.

29. The pharmaceutical composition of claim 28 wherein the anti-IL13 or the IL31RA is tralokinumab or nemolizumab.

30. A pharmaceutical composition for treating eosinophilic asthma in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143) or an AAV9 capsid (SEQ ID NO: 144); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding an anti-IL5R mAb or anti-IgE mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous administration to the liver or muscle of said subject.

31. The pharmaceutical composition of claim 30 wherein the anti-IL5R or anti-IgE mAb is reslizumab or omalizumab.

32. A pharmaceutical composition for treating asthma or chronic obstructive pulmonary disease (COPD) in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143) or an AAV9 capsid (SEQ ID NO: 144); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding an anti-IL5, anti-IL-5R, anti-IgE, or anti-TSLP mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous administration to the liver or muscle of said subject.

33. The pharmaceutical composition of claim 32 wherein the anti-IL-5, anit-IL5R, anti-IgE, or anti-TSLP mAb is benralizumab, reslizumab, omalizumab, or tezepelumab. .

34. A pharmaceutical composition for treating chronic idiopathic urticaria in a human subject in need thereof, comprising an AAV vector comprising:

(a) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO:143) or an AAV9 capsid (SEQ ID NO: 144); and

(b) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding an anti-IgE mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous administration to the liver or muscle of said subject.

35. The pharmaceutical composition of claim 34, wherein the anti-IgE mAb is omalizumab.

36. A pharmaceutical composition for treating myasthenia gravis in a human subject in need thereof, comprising an AAV vector comprising:

(c) a viral capsid that is at least 95% identical to the amino acid sequence of an AAV8 capsid (SEQ ID NO: 143) or AAV9 capsid (SEQ ID NO: 144); and

(d) an artificial genome comprising an expression cassette flanked by AAV ITRs wherein the expression cassette comprises a transgene encoding an anti-C5 mAb, or an antigen-binding fragment thereof, operably linked to one or more regulatory sequences that control expression of the transgene in human liver cells or human muscle cells;

wherein said AAV vector is formulated for intravenous administration to the liver or muscle of said subject.

37. The pharmaceutical composition of claim 36 wherein the anti-C5 is ravulizumab.

38. A method of determining human anti-pKal antibody activity in a sample, said method comprising

a. Incubating the sample with activated human pKal;

b. Subsequently incubating the sample having been incubated with the activated human pKal with the synthetic substrate Pro-Phe-Arg-AMC

c. Measure the relase of AMC over three hours as compared to a control sample.

FIG. 1

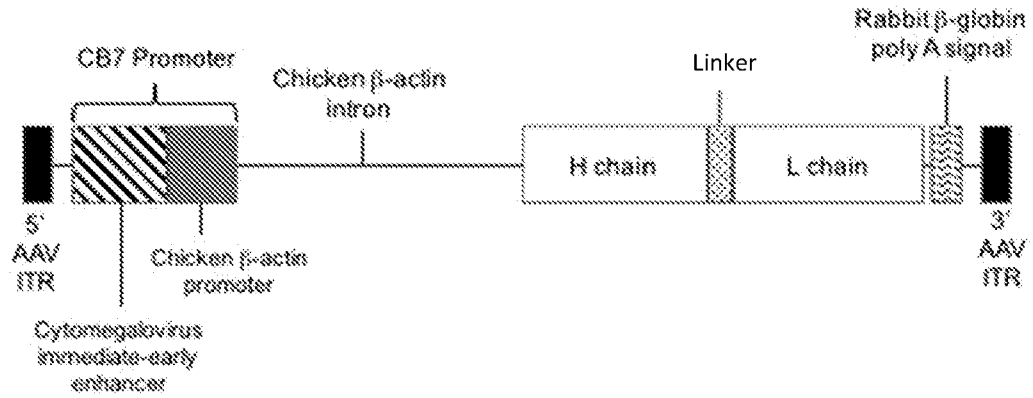


FIG. 2A SOLANEZUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Solanezumab Heavy Chain (SEQ ID NO: 1)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYSMSWVRQAPGKGLELVAQINSVGNSTYY
PDTVKGRFTISRDNAKNTLYLQMNSLRA*EDTAVYY*CASGDYWGQGTLVTVSSASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT(or KTHL) +/-*
*CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Solanezumab Light Chain (SEQ ID NO: 2)
DVVMTQSPLSLPVTLGQPASISCRSSQSLIYSDGNAYLHWFLQKPGQSPRLLIYKVSNRF
SGVPDRFSGSGSGTDFTLKISRVEA*EDVGVYY*CSQSTHVPWTFGQGTKVEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Heavy Chain Legend:
CDRs are underscored
EDTAVYY and *YCASGDYW* = Y-sulfation sites (SEQ ID NO: 236 and 237)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
NX(S/T) = Consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDVGVYY= Y-sulfation sites (SEQ ID NO: 238)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 2B GSK933776 IgG1 FAB CONSTRUCT:
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
GSK933776 Heavy Chain (SEQ ID NO: 3)
EVQLVESGGGLVQPGGSLRLSCAASGFTF**SDN**GMAWVRQAPGKGLEWVSFISNLAYSIDY
ADTVTGRFTISRDNAKNSLYLQMNSLRA*EDTAVYY*CVSGTWFAYWG**QGT**LVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or KTHL)*
*+/- CPPCPA +/- PELAGA*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
GSK933776 Light Chain (SEQ ID NO: 4)
DIVMTQSPLSLPVTPGEPASISCRVSQSLLHSNGYTYLHWYLQKPGQSPQLLIYKVSNRF
SGVPDRFSGSGSGTDFTLKISRVEA*EDVGVYY*CSQTRHVPYTFGGGTKVEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELAGA = Hinge Region (SEQ ID NO: 202)
Or
EPKSCDKTHLCPPCPAPELAGA = Hinge Region (SEQ ID NO: 203)
24 can be substituted for V

Light Chain Legend:
CDRs are underscored
EDVGVYY= Y-sulfation sites (SEQ ID NO: 238)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 2C LECANEMAB IgG1 FAB CONSTRUCT:
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Lecanemab Heavy Chain (SEQ ID NO: 360)
EVQLVESGGGLVQPGGSLRLSCSASGFTFSSFGMHWVRQAPGKGLEWVAYISSGSSTIYY
GDTVKGRFTISRDNAKNSLFLQMSSLRA*EDTAVYY*CAREGGYYYGRSYYTMDYWG**QGT**TV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT(or*
*KTHL) +/-CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Lecanemab Light Chain (SEQ ID NO: 361)
DVVMTQSPLSLPVTPGAPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKVSNRF
SGVPDRFSGSGSGTDFTLRISRVEA*EDVGIYY*CFQGSHVPPTFGPGTKLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC
Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDVGIVYY= Y-sulfation sites (SEQ ID NO: 409)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 3 AL-001 IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
AL-001 Heavy Chain (SEQ ID NO: 5)
QVQLVQSGAEVKKPGASVKVSCKASGYTFTKYYMSWVRQAPGQGLEWMGIINPIGGSTSY
AQKFQGRVTMTRDTSTSTVYMELSSLRS*EDTAVYY*CARDPSGIALAGPASRGYQGMDVWG
QGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT*
*(or KTHL) +/-CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
AL-001 Light Chain (SEQ ID NO: 6)
EIVMTQSPATLSVSPGERATLSCRASQSV**SSN**LAWYQQKPGQAPRLLIYGASTRATGIPA
RFSGSGSGTEFTLTISSLQS*EDFAVYY*CQQARLGPWTFGGGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDFAVYY = Y-sulfation sites (SEQ ID NO: 239)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 4A ABBV-8E12 IgG4 FAB CONSTRUCT:

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
ABBV-8E12 Heavy Chain (SEQ ID NO: 7)
EVKVVESGGGLVQPGGSMKLSCVVSGFTFSNYWVNWVRQAPGKGLEWVAQIRLKSDNYAT
HYEESVKGRFTISRDDSKSSVYLQMNNLRAEDSGIYYCTNWEDYWGQGTTVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY+/- GPPCPPCPA (or GPPCP
SCPA) +/- PEFLGGPSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
ABBV-8E12 Light Chain (SEQ ID NO: 8)
DIVLTQSPDSLAVSLGERATISCRASQSVSTSRYSYIHWYQQKPGQFPKLLIKYASNLES
GVPSRFSGSGSGTDFTLNIHPLEPEDFATYYCHHSWEIPLTFGQGTKLEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Heavy Chain Legend:
CDRs are underscored
EDSGIYY and *NWEDYW* = Y-sulfation site (SEQ ID NOs: 240 and 241)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
ESKYGPPCPPCPAPEFLGG = Hinge region (SEQ ID NO: 214)
Or
ESKYGPPCPSCPAPEFLGG = Hinge region (SEQ ID NO: 215)

Light Chain Legend:
CDRs are underscored
EDFATYY = Y-sulfation site (SEQ ID NO: 242)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 4B UCB-0107 IgG4 FAB CONSTRUCT:

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
UCB-0107 Heavy Chain (SEQ ID NO: 9)
EVQLQESGPGLVKPSETLSLTCTVSGFSL**TSN**DIAWIRQPPGKGLEWMGTIWTDG**STN**YN
XAVQSRVTISVDT**SKN**QFSLKLSSVTAA*DTAVYY*CARHRL*YYGAFD*YWG**QGT**MVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTKTY**TCN**VDHKPSNTKVDKRV*ESKY+/- GPPCPPCPA (or GP*
*PCPSCPA) +/- PEFLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
UCB-0107 Light Chain (SEQ ID NO: 10)
DIVMTQTPLSLSVTPGQPASISCRSSQSLEYSDGYTYLEWYLQKPGQSPQLLIYEVSNRF
SGVPDRFSGSGSGTDFTLKISRVEA*EDVGVYY*CFQA**THN**PYTFGQGTKLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored (predicted for aTAU)
DTAVYY and *YYGAFD* = Y-sulfation sites (SEQ ID NOs: 243 and 244)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
ESKYGPPCPPCPAPEFLGG = Hinge region (SEQ ID NO: 214)
Or
ESKYGPPCPSCPAPEFLGG = Hinge region (SEQ ID NO: 215)
X61 can be substituted for T

Light Chain Legend:
CDRs are underscored (predicted for aTAU)
EDVGVYY = Y-sulfation site (SEQ ID NO: 238)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 4C NI-105 IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
NI-105 Heavy Chain (SEQ ID NO: 11)
QVQLVESGGGVVQPGRSLRVSCAASGFTFSSYDMHWVRQAPGKGLEWVAVIWFDGSNEFY
ADSVKGRFTISRDN**SKN**TLFQMNSLRA*EDTAVYY*CARDLGASVT**TSN**AENFHHWG**QGT**LV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT*
*(or KTHL)+/- CPPCPA +/- PELAGA*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
NI-105 Light Chain (SEQ ID NO: 12)
SYELTQPPSVSVSPGQTARITCSGDALPKRYVYWYQQKSGQAPVLVIYEDSKRPSGIPET
FSGSSSGTMATLTISGAQV*EDEADYY*CYSTDSNGHHWVFGGGTKLTVLGQPKAAPSVTLF
PPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ**SNN**KYAASSYL
SLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTCS

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
f = Hinge Region (SEQ ID NO: 202)
EPKSCDKTHTCPPCPAPELAGA = Hinge Region (SEQ ID NO: 202)
Or
EPKSCDKTHLCPPCPAPELAGA = Hinge Region (SEQ ID NO: 203)

Light Chain Legend:
CDRs are underscored
EDEADYY = Y-sulfation site (SEQ ID NO: 245)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG.5 VX15/2503 IgG4 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
VX15/2503 Heavy Chain (SEQ ID NO: 13)
QVQLVQSGAEVKKPGSSVKVSCKASGYSFSDYYMHWVRQAPGQGLEWMGQINPTTGGA**SY**
NQKFKGKATITVDKSTSTAYMELSSLRS*EDTAVYY*CAR*YYYGRHFD*VWG**QGT**TVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVTVSSVL
QSSGLYSLSSVVTVPSSSLGTKTY**TCN**VDHKPSNTKVDKRV*ESKY+/- GPPCPPCPA*
*(or GPPCPSCPA)+/- PEFLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
VX15/2503 Light Chain (SEQ ID NO: 14)
DIVMTQSPDSLAVSLGERA**TIN**CK*ASQSVDYDGDSY*MNWYQQKPGQPPKLLIYAASNLES
GVPDRFSGSGSGTDFTLTISSLQA*EDVAVYY*CQQSNEDPYTFG**QGT**KLEIKFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLTLSKA
DYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY and YYYGRHFD= Y-sulfation sites (SEQ ID NO: 236 and 246)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
ESKYGPPCPPCPAPEFLGG = Hinge region (SEQ ID NO: 214)
Or
ESKYGPPCPSCPAPEFLGG = Hinge region (SEQ ID NO: 215)

Light Chain Legend:
CDRs are underscored
SQSVDYDGDSY and EDVAVYY = Y-sulfation sites (SEQ ID NO: 247 and 248)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 6A PRASINEZUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Prasinezumab Heavy Chain (SEQ ID NO: 15)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVASISSGGGSTYY
PDNVKGRFTISRDDAKNSLYLQMNSLRA*EDTAVYY*CARGGAGIDYWG**QGT**LVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT(or KTHL)*
*+/-CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Prasinezumab Light Chain (SEQ ID NO: 16)
DIQMTQSPSSLSASVGDRVTITCKSIQTLLY**SSN**QKNYLAWFQQKPGKAPKLLIYWASIR
KSGVPSRFSGSGSGTDFTLTISSLQP*EDLATYY*CQQYYSYPLTFGGGTKLEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation sites (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDLATYY = Y-sulfation sites (SEQ ID NO: 249)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 6B NI-202 IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
NI-202 Heavy Chain (SEQ ID NO: 17)
EVQLVESGAEVKKPGASVKVSCKASGYTFTNYAMHWVRQAPGQRLEWMGWINAGNGKRKY
SQKFQDRVTINRDTSASTIYMELSSLGS*EDTAVYY*CAREEDHAGSGSYLSMDVWGQGTLV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT(or*
*KTHL) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
NI-202 Light Chain (SEQ ID NO: 18)
DIQMTQSPSSLSASVGDRVTITCKSIQTLLYSSNQKNYLAWFQQKPGKAPKLLIYWASIR
KSGVPSRFSGSGSGTDFTLTISSLQP*EDLATYY*CQQYYSYPLTFGGGTKLEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation sites (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDLATYY = Y-sulfation sites (SEQ ID NO: 249)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 6C MEDI-1341/TAK 341 IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
MEDI-1341/TAK 341 Heavy Chain (SEQ ID NO: 19)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISHLGGSTYY
ADSVKGRFTISRDN**SKN**TLYLQMNSLRA*EDTAVYY*CAGGANHGKYYYGMDKWG**QGT**TVTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT (or KTHL)*
*+/- CPPCPA +/- PEFEGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
MEDI-1341/TAK 341 Light Chain (SEQ ID NO: 20)
QAVLTQPASLSASPGASASLTCTLRSGAPLPKYRIYWYQQKPGSPPQYLLRYKSDADKHQ
GSGVPSRFSGSKDA**SAN**AGILLISGLQS*EDEADYY*CMVWDHGVWYFGGGTKLTVLGQPKA
APSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ**SNN**K
YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation sites (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPEFEGG = Hinge Region (SEQ ID NO: 206)
Or
EPKSCDKTHLCPPCPAPEFEGG = Hinge Region (SEQ ID NO: 207)

Light Chain Legend:
CDRs are underscored
EDEADYY = Y-sulfation site (SEQ ID NO: 245)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG.7A NI-204.10D12 IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
NI-204.10D12 Heavy Chain (SEQ ID NO: 21)
EVQLVESGGDLVRPGGSLRLSCVASGFTFSNYWMHWVRQAPGQRPVWVSRTNTDGRNTAY
ADYAKGRFTISRDNAKSTLYLQLNSLRA*EDTAVY*FCARLRRNVADQI**THN**YYMDVWGKGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT*
*(or KTHL) +/- CPPCPA +/- PEAAGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
NI-204.10D12 Light Chain (SEQ ID NO: 22)
DIQMTQSPSSLSASVGDRVTACRASQSVGTYLNWYQQKRGKAPKLLIFAASSLQSGVPSR
FSGSGSGTDFTLTISSLQP*EDFATYY*CQQSYSSPPTFG**QGT**KVEIKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLTL
SKADY*EKHKVY*ACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVY = Y-sulfation site (SEQ ID NO: 250)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPEAAGG = Hinge Region (SEQ ID NO: 210)
Or
EPKSCDKTHLCPPCPAPEAAGG = Hinge Region (SEQ ID NO: 211)

Light Chain Legend:
CDRs are underscored
EDFATYY = Y-sulfation sites (SEQ ID NO: 242)
EKHKVY = Y-sulfation sites)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG.7B NI-204.12G7 IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
NI-204.12G7 Heavy Chain (SEQ ID NO: 23)
QVQLVQSGAEVKKPGASVTLSCKASGYTFTAYYIHWVRQAREQGLEWMGVINPSTGTTFY
AQNFPDRVSVTRDTSTSTVFMELHNLKS*EDTAVYY*CARAISEHGSGSYSPYYWG**QGT**LVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or*
*KTHL)+/-CPPCPA +/- PEAAGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
NI-204.12G7 Light Chain (SEQ ID NO: 24)
SYELTQPPSVSVSLGQMAAITCSGEALPKKYGYWYQQKPGQVPVLLIYRDVERPSGVPDR
FSGSSSGTMVTLTISGVQA*EDEADYY*CLSADSSGTWVFGGGTKLTVLGQPKANPTVTLFP
PSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQ**SNN**KYAASSYLS
LTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPEAAGG = Hinge Region (SEQ ID NO: 210)
Or
EPKSCDKTHLCPPCPAPEAAGG = Hinge Region (SEQ ID NO: 211)

Light Chain Legend:
CDRs are underscored
EDEADYY = Y-sulfation sites (SEQ ID NO: 245)

FIG. 8A EPTINEZUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Eptinezumab Heavy Chain (SEQ ID NO: 25)
EVQLVESGGGLVQPGGSLRLSCAVSGI*DLSGYY*MNWVRQAPGKGLEWVGVIGINGATYYA
SWAKGRFTISRDNSKTTVYLQMNSLRA*EDTAVY*FCARGDIWG**QGT**LVTVSSASTKGPSVF
PLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDARV*EPKSCD +/- KTHT (or KTHL) +/-*
*CPPCPA +/- PELLGG*PSVTL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Eptinezumab Light Chain (SEQ ID NO: 26)
QVLTQSPSSLSASVGDRV**TIN**CQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVP
SRFSGSGSGTDFTLTISSLQP*EDVATYY*CLGSYDCTNGDCFVFGGGTKVEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSL
SSTLTLSKADY*EKHKVY*ACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
DLSGYY and *EDTAVY* = Y-sulfation sites (SEQ ID NO: 252 and 250)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDVATYY = Y-sulfation site (SEQ ID NO: 253)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 8B FREMANEZUMAB IgG2 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Fremanezumab Heavy Chain (SEQ ID NO: 27)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWISWVRQAPGKGLEWVAEIRSESDASAT
HYAEAVKGRFTISRDNAKNSLYLQMNSLRA*EDTAVYY*CLAYFDYGLAIQNYWGQGTLVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSNFGTQTY*TCN*V*D*HKPSNTKVDKTV*ERKCCVE +/- CPPCPA +/-*
PPVAG
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Fremanezumab Light Chain (SEQ ID NO: 28)
EIVLTQSPATLSLSPGERATLSCKASKRVTTYVSWYQQKPGQAPRLLIYGASNRYLGIPA
RFSGSGSGTDFTLTISSLEP*EDFAVYY*CSQSYNYPYTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY= Y-sulfation sites (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
ERKCCVECPPCPAPPVAG = Hinge region (SEQ ID NO: 220)

Light Chain Legend:
CDRs are underscored
EDFAVYY = Y-sulfation site (SEQ ID NO: 239)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 8C GALCANEZUMAB IgG4 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Galcanezumab Heavy Chain (SEQ ID NO: 29)
QVQLVQSGAEVKKPGSSVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAIYEGTGKTVY
IQKFADRVTITADKSTSTAYMELSSLRS*EDTAVYY*CARLSDYVSGFGYWGQGTTVTVSSA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV*ESKY+/-GPPCPPCPA (or GP*
*PCPSCPA) +/- PEAAGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Galcanezumab Light Chain (SEQ ID NO: 30)
DIQMTQSPSSLSASVGDRVTITCRASKDISKYLNWYQQKPGKAPKLLIYYTSGYHSGVPS
RFSGSGSGTDFTLTISSLQP*EDFATYY*CQQGDALPPTFGGGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
ESKYGPPCPPCPAPEAAGG = Hinge region (SEQ ID NO: 431)
Or
ESKYGPPCPSCPAPEAAGG = Hinge region (SEQ ID NO: 432)

Light Chain Legend:
CDRs are underscored
EDFATYY = Y-sulfation site (SEQ ID NO: 242)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 9A SEVACIZUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Sevacizumab Heavy Chain (SEQ ID NO: 31)
EVQLVESGGGLVKPGGSLRLSCAASGFSF**SNN**DVMCWVRQAPGKGLEWIGCIMTTDVVTE
YANWAKSRFTVSRDSAKNSVYLQMNSLRA*EDTAVY*FCARDSVGSPLMSFDLWGPGTLVTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or*
*KTHL) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Sevacizumab Light Chain (SEQ ID NO: 32)
DIQMTQSPSSLSASVGDRV**TIN**CQASQSIYNNNELSWYQQKPGKPPKLLIYRASTLASGVP
SRFSGSGSGTDFTLTISSLQP*EDVATYY*CGGYKSYSNDGNGFGGGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSST
LTLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVY = Y-sulfation site (SEQ ID NO: 250)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDVATYY = Y-sulfation site (SEQ ID NO: 253)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 9B LKA-651 NVS2 IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
LKA-651 NVS2 Heavy Chain (SEQ ID NO: 33)
EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGWIDPYRSEIRY
SPSFQGQVTISADKSISTAYLQWSSLKAS*DTAMYY*CARVSSEPFDSWG**QGT**LVTVSSAST
KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT (or KTHL)*
*CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
LKA-651 NVS2 Light Chain (SEQ ID NO: 34)
SYVLTQPPSVSVAPGKTARITCSGDKLGDHYAYWYQQKPGQAPVLVIYDDSKRPSGIPERF
SGSN**SGN**TATLTISRVEAG*DEADYY*C*ATW**TFEGDYVF*GGGTKLTVLGQPKAAPSVTLFPPS
SEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ**SNN**KYAASSYLSLTP
EQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Heavy Chain Legend:
CDRs are underscored
DTAMYY = Y-sulfation site (SEQ ID NO: 254)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)
Light Chain Legend:
CDRs are underscored
DEADYY and TFEGDYVF= Y-sulfation site (SEQ ID NO: 255 and 256)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 9C LKA-651 NVS3 IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
LKA-651 NVS3 Heavy Chain (SEQ ID NO: 35)
QVQLQQSGPGLVKPSQTLSLTCAISGDSV**SSN**TAAWNWIRQSPSRGLEWLGVIYYRSKWY
NDYAVSVKSRITINPDT**SKN**QFSLQLNSVTPEDTAVYYCARSVPGGDPGLEHAFAYWGRG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT*
*(or KTHL) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
LKA-651 NVS3 Light Chain (SEQ ID NO: 36)
SYVLTQPPSVSVAPGKTARITC*SG**DNLGTYYVE***WYQQKPGQAPVLVIY*DDSDRPS*GIPERF
SGSN**SGN**TATLTISRVEA*GDEADYY*C*ASFASWSDSV*FGGGTKLTVLGQPKAAPSVTLFPPS
SEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ**SNN**KYAASSYLSLTP
EQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
DNLGTYYVE and DEADYY = Y-sulfation sites (SEQ ID NO: 257 and 255)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 10A ASCRINVACUMAB IgG2 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Ascrinvacumab Heavy Chain (SEQ ID NO: 37)
QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGEYYWNWIRQHPGKGLEWIGYIYYSGSTY
Y**NPS**LKSRVTISVDT**SKN**QFSLKLSSVTAA*DTAVYY*CARESVAGFDYWG**QGT**LVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGL
YSLSSVVTVP**SSN**FGTQTY**TCN**VDHKPSNTKVDKTV*ERKCCVE +/- CPPCPA +/- P*
PVAG
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Ascrinvacumab Light Chain (SEQ ID NO: 38)
EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGTSSRATGIP
DRFSGSGSGTDFTLTISRLEP*EDFAVYY*CQQYGSSPITFG**QGT**RLEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
DTAVYY= Y-sulfation sites (SEQ ID NO: 243)
QGT = Glutamine (Q) glycosylation site
NX(S/T) = Consensus Asparaginal (N) glycosylation
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
ERKCCVECPPCPAPPVAG = Hinge region (SEQ ID NO: 220)

Light Chain Legend:
CDRs are underscored
EDFAVYY= Y-sulfation site (SEQ ID NO: 239)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 10B TESIDOLUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Tesidolumab Heavy Chain (SEQ ID NO: 39)
EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIGPFFGTANY
AQKFQGRVTITADESTSTAYMELSSLRS*EDTAVYY*CARDTPYFDYWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT (or KTHL)*
*+/- CPPCPA +/- PEAAGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Tesidolumab Light Chain (SEQ ID NO: 40)
SYELTQPLSVSVALGQTARITCSG*DSIPNYYVY*WYQQKPGQAPVLVIYDDSNRPSGIPER
FSGSN**SGN**TATLTISRAQAG*DEADYYCQSFDS***SLN**AEVFGGGTKLTVLGQPKAAPSVTLF
PPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ**SNN**KYAASSYL
SLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPEAAGG = Hinge Region (SEQ ID NO: 210)
Or
EPKSCDKTHLCPPCPAPEAAGG = Hinge Region (SEQ ID NO: 211)

Light Chain Legend:
CDRs are underscored
DSIPNY and *YCQSFD and DEADYY*= Y-sulfation sites (SEQ ID NO: 259, 260, and 255)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 10C CAROTUXIMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Carotuximab Heavy Chain (SEQ ID NO: 41)
EVKLEESGGGLVQPGGSMKLSCAASGFTFSDAWMDWVRQSPEKGLEWVAEIRSKASNHAT
YYAESVKGRFTISRDDSKSSVYLQMNSLRA*EDTGIYY*CTRWRRFFDSWG**QGT**TLTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or KTHL)*
*+/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Carotuximab Light Chain (SEQ ID NO: 42)
QIVLSQSPAILSASPGEKVTMTCRASSSVSYMHWYQQKPGSSPKPWIYA**TSN**LASGVPVR
FSGSGSGTSYSLTISRVEA*EDAATYY*C**QQW**SSNPLTFGAGTKLELKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTGIYY = Y-sulfation site (SEQ ID NO: 261)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDAATYY = Y-sulfation sites (SEQ ID NO: 262)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 10D Ravulizumab IgG2 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Ravulizumab Heavy Chain (SEQ ID NO: 362)
QVQLVQSGAEVKKPGASVKVSCKASGHIFSNYWIQWVRQAPGQGLEWMGEILPGSGHTEY
TENFKDRVTMTRDTSTSTVYMELSSLRS*EDTAVYY*CARYFFGS**SPN**WYFDVWG**QGT**LVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQ
SSGLYSLSSVVTVP**SSN**FGTQTY**TCN**VDHKPSNTKVDKTV*ERKCCVE +/- CPPCPA +/-*
PPVAG
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Ravulizumab Light Chain (SEQ ID NO: 363)
DIQMTQSPSSLSASVGDRVTITCGA**SEN**IYGALNWYQQKPGKAPKLLIYGATNLADGVPS
RFSGSGSGTDFTLTISSLQP*EDFATYYC*QNVLNTPLTFG**QGT**KVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
ERKCCVECPPCPAPPVAG = Hinge region (SEQ ID NO: 220)

Light Chain Legend:
CDRs are underscored
EDFATYY = Y-sulfation sites (SEQ ID NO: 242)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 11 ANX-007 IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
ANX-007 Heavy Chain (SEQ ID NO: 43)
QVQLVQSGAELKKPGASVKVSCKSSGYHFTSYWMHWVKQAPGQGLEWIGVIHPNSG**SIN**Y
*NEKFE*SRVTITVDKSTSTAYMELSSLRS*EDTAVYY*CAGERDSTEVLPMDYWG**QGT**TVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT (or K*
*THL) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
ANX-007 Light Chain (SEQ ID NO: 44)
DVQITQSPSSLSASLGERA**TIN**CRASK**SIN**KYLAWYQQKPGKAPKLLIYSGSTLQSGIPA
RFSGSGSGTDFTLTISSLEP*EDFAMYY*CQQHNEYPLTFG**QGT**KLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
YNEKFE and *EDTAVYY* = Y-sulfation sites (SEQ ID NO: 263 and 236)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDFAMYY = Y-sulfation sites (SEQ ID NO: 264)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 12A ADALIMUMAB IgG1 Fab Construct

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Adalimumab Heavy Chain (SEQ ID NO: 45):
EVQLVESGGGLVQPGRSLRLSCAASG*FTFDDYA*MHWVRQAPGKGLEWVSAI**TWN**SGHIDY
ADSVEGRFTISRDNAKNSLYLQMNSLRA*EDTAVYY*CAKVSYLSTASSLDYWG**QGT**LVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or KTHL) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP) (SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Adalimumab Light Chain (SEQ ID NO: 46)
DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQKPGKAPKLLIYAASTLQSGVPS
RFSGSGSGTDFTLTISSLQP*EDVATYY*C**QRYNRAPYT**FG**QGT**KVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored (predicted for Adalimumab)
FTFDDYA and *EDTAVYY* = Y-sulfation sites (SEQ ID NOs: 265 and 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored (predicted for Adalimumab)
EDVATYY = Y-sulfation site (SEQ ID NO: 253)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 12B INFLIXIMAB IgG1 Fab Construct

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Infliximab Heavy Chain (SEQ ID NO: 47):
EVKLEESGGGLVQPGGSMKLSCVASGFIFSNHWMNWVRQSPEKGLEWVAEIRSK**SIN**SAT
HYAESVKGRFTISRDDSKSAVYLQMTDLRT*EDTGVYY*C**SRN**YYGSTYDYWG**QGT**TLTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or KT
HL)+/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Infliximab Light Chain (SEQ ID NO: 48)
DILLTQSPAILSVSPGERVSFSCRASQFVGSSIHWYQQRT**NGS**PRLLIKYASESMSGIPS
RFSGSGSGTDFTL**SIN**TVES*EDIADYY*CQQSHSWPFTFGSGTNLEVKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored (predicted for Infliximab)
EDTGVYY = Y-sulfation site (SEQ ID NO: 266)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored (predicted for Infliximab)
EDIADYY = Y-sulfation site (SEQ ID NO: 267)
NX(S/T) = Consensus glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 12C GOLIMUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Golimumab Heavy Chain (SEQ ID NO: 49)
SKLQVQLVESGGGVVQPGRSLRLSCAASGFIFSSYAMHWVRQAPGNGLEWVAFMSYDGSN
KKYADSVKGRFTISRDN**SKN**TLYLQMNSLRA*EDTAVYY*CARDRGIAAGGNY*YYYGMDV*WG
QGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KT*
*HT (or KTHL) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Golimumab Light Chain (SEQ ID NO: 50)
AGSEIVLTQSPATLSLSPGERATLSCRASQSVYSYLAWYQQKPGQAPRLLIYDASNRATG
IPARFSGSGSGTDFTLTISSLEP*EDFAVYY*CQQRSNWPPFTFGPGTKVDIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
YYYGMD and *EDTAVYY*= Y-sulfation site (SEQ ID NOs: 268 and 236)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDFAVYY= Y-sulfation site (SEQ ID NO: 239)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 13 ELEZANUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Elezanumab Heavy Chain (SEQ ID NO: 51)
EVQLVQSGAEVKKPGASVKVSCKASGYTFTSHGISWVRQAPGQGLDWMGWISPY**SGN**TNY
AQKLQGRVTMTTDTSTSTAYMELSSLRS*EDTAVYY*CARVGSGPYYYMDVWG**QGT**LVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or KT*
*HL)+/- CPPCPA +/- PEAAGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Elezanumab Light Chain (SEQ ID NO: 52)
QSALTQPRSVSGSPGQSVTISCTGTSSSVGDSIYVSWYQQHPGKAPKLMLYDVTKRPSGV
PDRFSGSK**SGN**TASLTISGLQA*EDEADYY*CYSYAGTDTLFGGGTKVTVLGQPKAAPSVTL
FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ**SNN**KYAASSY
LSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPEAAGG = Hinge Region (SEQ ID NO: 210)
Or
EPKSCDKTHLCPPCPAPEAAGG = Hinge Region (SEQ ID NO: 211)

Light Chain Legend:
CDRs are underscored
EDEADYY = Y-sulfation sites (SEQ ID NO: 245)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 14A NI-301 IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
NI-301 Heavy Chain (SEQ ID NO: 53)
QVQLQESGPGLVKPSETLSLTCSVSGGSIISRSSYWGWIRQPPGKGLEWIGGIYH**SGN**TY
DNPSLKSRLTMSVDT**SKN**QF**SLN**LRSVTA*ADTAVYY*CARIVPGGDAFDIWG**QGT**MVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT (or KT*
*HL)+/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
NI-301 Light Chain (SEQ ID NO: 54)
DIQMTQSPSSLSASVGDRVTACRASQSVGTYLNWYQQKRGKAPKLLIFAASSLQSGVPSR
FSGSGSGTDFTLTISSLQP*EDFATYY*CQQSYSSPPTFG**QGT**KVEIKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
DTAVYY = Y-sulfation site (SEQ ID NO: 243)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDFATYY = Y-sulfation sites (SEQ ID NO: 242)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 14B PRX-004 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
PRX-004 Heavy Chain (SEQ ID NO: 55)
EVQLVESGGGLIQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSSISSGGST
YYPDSVKGRFTISRDN**SKN**TLYLQMNSLRA*EDTAVYY*CARYYYGQYFDFWG**QGT**LVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KT*
*HT (or KTHL) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
PRX-004 Light Chain (SEQ ID NO: 56)
DIVMTQSPSSLSASVGDRVTITCKASQDVSTTVAWYQQKPGKAPKLLIYSASYRSTG
VPSRFSGSGSGTDFTLTISSLQP*EDFAVYY*CQQHYSTPLTFGGGTKVEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDFAVYY = Y-sulfation sites (SEQ ID NO: 239)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 15 PAMREVLUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Pamrevlumab Heavy Chain (SEQ ID NO: 57)
EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIGPFFGTANY
AQKFQGRVTITADESTSTAYMELSSLRS*EDTAVYY*CARDTPYFDYWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT (or KTHL)+*
*/- CPPCPA +/- PEAAGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Pamrevlumab Light Chain (SEQ ID NO: 58)
SYELTQPLSVSVALGQTARITCSG*DSIPNYYVY*WYQQKPGQAPVLVIYDDSNRPSGIPER
FSGSNSGNTATLTISRAQAG*DEADYYCQSFDS*SLNAEVFGGGTKLTVLGQPKAAPSVTLF
PPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYL
SLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPEAAGG = Hinge Region (SEQ ID NO: 210)
Or
EPKSCDKTHLCPPCPAPEAAGG = Hinge Region (SEQ ID NO: 211)

Light Chain Legend:
CDRs are underscored
DSIPNY and *DEADYY* and *YCQSFD*= Y-sulfation sites (SEQ ID NO: 259, 255, and 260)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 16A SATRALIZUMAB IgG2 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Satralizumab Heavy Chain (SEQ ID NO: 59)
QVQLQESGPGLVKPSETLSLTCAVSGHSISHDHAWSWVRQPPGEGLEWIGFISYSGITNY
NPSLQGRVTISRDN**SKN**TLYLQMNSLRA*EDTAVYY*CARSLARTTAMDYWGEGTLVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSG
LYSLSSVVTVP**SSN**FGTQTY**TCN**VDHKPSNTKVDKTV*ERKSCVE +/- CPPCPA +/- P*
PVAG
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Satralizumab Light Chain (SEQ ID NO: 60)
DIQMTQSPSSLSASVGDSVTITCQASTDISSHLNWYQQKPGKAP*ELLIYY*GSHLLSGVPS
RFSGSGSGTDFTFTISSLEA*EDAATYY*CGQGNRLPYTFG**QGT**KVEIERTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY and *YTCNVD* = Y-sulfation sites (SEQ ID NOs: 236)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
ERKSCVECPPCPAPPVAG = Hinge region (SEQ ID NO: 433)

Light Chain Legend:
CDRs are underscored
ELLIYY and *EDAATYY* = Y-sulfation sites (SEQ ID NO: 269 and 262)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 16B SARILUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Sarilumab Heavy Chain (SEQ ID NO: 61)
EVQLVESGGGLVQPGRSLRLSCAASR*FTFDDYA*MHWVRQAPGKGLEWVSGI**SWN**SGRIGY
ADSVKGRFTISRDNAENSLFLQMNGLRA*EDTALYY*CAKGRDSFDIWG**QGT**MVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or KTHL)+*
*/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Sarilumab Light Chain (SEQ ID NO: 62)
DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYGASSLESGVPS
RFSGSGSGTDFTLTISSLQP*EDFASYY*CQQANSFPYTFG**QGT**KLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
FTFDDYA and EDTALYY = Y-sulfation sites (SEQ ID NO: 265 and 270)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDFASYY = Y-sulfation sites (SEQ ID NO: 271)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 16C SILTUXIMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Siltuximab Heavy Chain (SEQ ID NO: 331)
EVQLVESGGKLLKPGGSLKLSCAASGFTFSSFAMSWFRQSPEKRLEWVAEISSGGSYTYY
PDTVTGRFTISRDNAKNTLYLEMSSLRS*EDTAMYY*CARGLWGYYALDYWG**QGT**SVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or KTH*
*L) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Siltuximab Light Chain (SEQ ID NO: 332)
QIVLIQSPAIMSASPGEKVTMTCSASSSVSYMYWYQQKPGSSPRLLIYD**TSN**LASGVPVR
FSGSGSGTSYSLTISRMEA*EDAATYY*CQQWSGYPYTFGGGTKLEIKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAMYY = Y-sulfation site (SEQ ID NO: 402)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDAATYY = Y-sulfation sites (SEQ ID NO: 262)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 16D Clazakizumab IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Clazakizumab Heavy Chain (SEQ ID NO: 333)
EVQLVESGGGLVQPGGSLRLSCAASGFSLSNYYVTWVRQAPGKGLEWVGIIYGSDETAYA
TSAIGRFTISRDNSKNTLYLQMNSLRA*EDTAVYY*CARDDSSDWDAKFNLWGQGTLVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT (or KT*
*HL) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Clazakizumab Light Chain (SEQ ID NO: 334)
AIQMTQSPSSLSASVGDRVTITCQASQSINNELSWYQQKPGKAPKLLIYRASTLASGVPS
RFSGSGSGTDFTLTISSLQP*DDFATYY*CQQGYSLRNIDNAFGGGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS
TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
DDFATYY = Y-sulfation sites (SEQ ID NO: 251)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 16E Sirukumab IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Sirukumab Heavy Chain (SEQ ID NO: 335)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSPFAMSWVRQAPGKGLEWVAKISPGGSWTYY
SDTVTGRFTISRDNAKNSLYLQMNSLRA*EDTAVYY*CARQLWGYYALDIWG**QGT**TVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +-/ KTHT (or KTH*
*L) +/- CPPCPA +-/ PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Sirukumab Light Chain (SEQ ID NO: 336)
EIVLTQSPATLSLSPGERATLSCSASISVSYMYWYQQKPGQAPRLLIYDMSNLASGIPAR
FSGSGSGTDFTLTISSLEP*EDFAVYY*CMQWSGYPYTFGGGTKVEIKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDFAVYY = Y-sulfation sites (SEQ ID NO: 239)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 16F Olokizumab IgG4 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Olokizumab Heavy Chain (SEQ ID NO: 337)
EVQLVESGGGLVQPGGSLRLSCAASGFNFNDYFMNWVRQAPGKGLEWVAQMRNKNYQY
GTYYAESLEGRFTISRDD**SKN**SLYLQMNSLKT*EDTAVYY*CARESYYGFTSYWGQ**GT**LV
TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSSLGTKTY**TCN**VDHKPSNTKVDKRV*ESKY +/- GPPCP*
PCPA (or GPPCPSCPA) +/- *PEFLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Olokizumab Light Chain (SEQ ID NO: 338)
DIQMTQSPSSLSASVGDRVTITCQASQDIGISLSWYQQKPGKAPKLLIYNANNLADGV
PSRFSGSGSGTDFTLTISSLQP*EDFATYY*CLQHNSAPYTFG**QGT**KLEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
ESKYGPPCPPCPAPEFLGG = Hinge region (SEQ ID NO: 214)
Or
ESKYGPPCPSCPAPEFLGG = Hinge region (SEQ ID NO: 215)

Light Chain Legend:
CDRs are underscored
EDFATYY = Y-sulfation sites (SEQ ID NO: 242)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 16G Gerilimzumab IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Gerilimzumab Heavy Chain (SEQ ID NO: 339)
EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWIRQPPGKGLEWIGVIDYDG
DTYYSPSLKSRVSISWDT**SKN**QFSLKLSSVTPA*DTAVYY*CARDPDVVTGFHYDYWG**Q**
GTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD*
*+/- KTHT (or KTHL) +/- CPPCPA +-/ PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Gerilimzumab Light Chain (SEQ ID NO: 340)
QSALTQPPSVSGTPGQSVTISCAGANNDIGTYAYVSWYQQLPGTAPKLMIYKVTTRA
SGIPDRFSGSK**SGN**TASLTISGLQA*EDEADYY*CASYRNFNNAVFGTGTKLTVLGQPK
AAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ
SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Heavy Chain Legend:
CDRs are underscored
DTAVYY = Y-sulfation site (SEQ ID NO: 243)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDEADYY = Y-sulfation sites (SEQ ID NO: 245)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 16H Tocilizumab IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Tocilizumab Heavy Chain (SEQ ID NO: 341)
QVQLQESGPGLVRPSQTLSLTCTVSGYSITSDHAWSWVRQPPGRGLEWIGYISYSGITT
YNPSLKSRVTMLRDTSKNQFSLRLSSVTAA*DTAVYY*CARSLARTTAMDYWGQGSLVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or
KTHL) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Tocilizumab Light Chain (SEQ ID NO: 342)
DIQMTQSPSSLSASVGDRVTITCRASQDISSYLNWYQQKPGKAPKLLIYYTSRLHSGVP
SRFSGSGSGTDFTFTISSLQP*EDIATYY*CQQGNTLPYTFGQGTKVEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS
TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Heavy Chain Legend:
CDRs are underscored
DTAVYY = Y-sulfation site (SEQ ID NO: 243)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDIATYY = Y-sulfation sites (SEQ ID NO: 403)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 16I INEBILIZUMAB (MEDI-551) IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Inebilizumab Heavy Chain (SEQ ID NO: 63)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSSWMNWVRQAPGKGLEWVGRIYPGDGDTNY
NVKFKGRFTISRDD**SKN**SLYLQMNSLKT*EDTAVYY*CARSGFITTVRDFDYWG**QGT**LVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD +/- KTHT (or K*
*THL)+/- CPPCPA+/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Inebilizumab Light Chain (SEQ ID NO: 64)
EIVLTQSPDFQSVTPKEKVTITCRASESVDTFGISFMNWFQQKPDQSPKLLIHEASNQGS
GVPSRFSGSGSGTDFTL**TIN**SLEA*EDAATYY*CQQSKEVPFTFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY = Y-sulfation site (SEQ ID NO: 236)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
EDAATYY = Y-sulfation sites (SEQ ID NO: 262)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 17 ETROLIZUMAB FAB IgG1 CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Etrolizumab Heavy Chain (SEQ ID NO: 65)
EVQLVESGGGLVQPGGSLRLSCAASGFFITNNYWGWVRQAPGKGLEWVGYISYSGST**SYN**
PSLKSRFTISRDT**SKN**TFYLQMNSLRA*EDTAVYY*CARTGSSGYFDFWG**QGT**LVTVSSAST
KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or KTHL)*
*+/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Etrolizumab Light Chain (SEQ ID NO: 66)
DIQMTQSPSSLSASVGDRVTITCRASESVD*DLLHWY*QQKPGKAPKLLIKYASQSISGVPS
RFSGSGSGTDFTLTISSLQP*EDFATYY*CQQGNSLPNTFG**QGT**KVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
EDTAVYY= Y-sulfation sites (SEQ ID NO: 236)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored
DLLHWY and EDFATYY = Y-sulfation sites (SEQ ID NOs: 272 and 242)
QGT = Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 18 ROMOSOZUMAB IgG2 FAB CONSTRUCT:

Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Romosozumab Heavy Chain (SEQ ID NO: 67)
EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNMHWVRQAPGQGLEWMGEINPNSGGAGY
NQKFKGRVTMTTDTSTSTAYMELRSLRS*DDTAVYY*CARLGYDDIYDDWYFDVWG**QGT**TVT
VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVL
QSSGLYSLSSVVTVP**SSN**FGTQTY**TCN**VDHKPSNTKVDKTV*ERKCCVE +/- CPPCPA*
+/- PPVAG
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146)
MYRMQLLLLIALSLALVTNS
Romosozumab Light Chain (SEQ ID NO: 68)
DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAPKLLIYYTSRLLSGVPS
RFSGSGSGTDFTLTISSLQP*EDFATYY*CQQGDTLPYTFGGGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored
DDTAVYY= Y-sulfation sites (SEQ ID NO: 273)
QGT= Glutamine (Q) glycosylation site
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site
ERKCCVECPPCPAPPVAG = Hinge region (SEQ ID NO: 220)

Light Chain Legend:
CDRs are underscored
EDFATYY = Y-sulfation sites (SEQ ID NO: 242)
(S/T)XN = Non-consensus Asparaginal (N) glycosylation site

FIG. 19 LANADELUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Lanadelumab Heavy Chain (SEQ ID NO: 69):
EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYIMMWVRQAPGKGLEWVSGIYSSGGITVY
ADSVKGRFTISRDN**SKN**TLYLQMNSLRA*EDTAVYY*CAYRRIGVPRRDEFDIWG**QGT**MVTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV *EPKSCD +/- KTHT*
(or KTHL) +/- CPPCPA +/- PELLGGPSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Lanadelumab Light Chain (SEQ ID NO: 70):
DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASTLESGVPS
RFSGSGSGTEFTLTISSLQP*DDFATYY*CQQYNTYWTFG**QGT**KVEIKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored.
EDTAVYY = Y-sulfation site (SEQ ID NO: 236).
QGT= Glutamine (Q) glycosylation site.
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored.
DDFATYY = Y-sulfation site (SEQ ID NO: 251)
QGT = Glutamine (Q) glycosylation site.
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site.

FIGS.20A-20B

FIG. 20A CLUSTAL O(1.2.4) ALIGNMENT OF THERAPEUTIC Fab HEAVY CHAIN

```
Solanezumab ---EVQLVESGGGLVQPGGSLRLSCAASGFTFSRY--SMSWVRQAPGKGLELVAQINSV-  54
GSK933776   ---EVQLVESGGGLVQPGGSLRLSCAASGFTFSDN--GMAWVRQAPGKGLEWVSFISNL-  54
AL-001      ---QVQLVQSGAEVKKPGASVKVSCKASGYTFTKY--YMSWVRQAPGQGLEWMGIINPI-  54
ABBV-8E12   ---EVKVVESGGGLVQPGGSMKLSCVVSGFTFSNY--WVNWVRQAPGKGLEWVAQIRLKS  55
UCB-0107    ---EVQLQESGPGLVKPSETLSLTCTVSGFSLTSND--IAWIRQPPGKGLEWMGTIWTDG  55
NI-105      ---QVQLVESGGGVVQPGRSLRVSCAASGFTFSSY--DMHWVRQAPGKGLEWVAVIWFD-  54
VX15/2503   ---QVQLVQSGAEVKKPGSSVKVSCKASGYSFSDY--YMHWVRQAPGQGLEWMGQINPT-  54
Prasinezumab---EVQLVESGGGLVQPGGSLRLSCAASGFTFSNY--GMSWVRQAPGKGLEWVASISSG-  54
NI-202      ---EVQLVESGAEVKKPGASVKVSCKASGYTFTNY--AMHWVRQAPGQRLEWMGWINAG-  54
MEDI-1341   ---EVQLLESGGGLVQPGGSLRLSCAASGFTFSSY--AMSWVRQAPGKGLEWVSSISHL-  54
NI-204.10D12---EVQLVESGGDLVRPGGSLRLSCVASGFTFSNY--WMHWVRQAPGQRPVWVSRTNTD-  54
NI-204.12G7 ---QVQLVQSGAEVKKPGASVTLSCKASGYTFTAY--YIHWVRQAREQGLEWMGVINPS-  54
Eptinezumab ---EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGY--YMNWVRQAPGKGLEWVGVIGIN-  54
Fremanezumab---EVQLVESGGGLVQPGGSLRLSCAASGFTFSNY--WISWVRQAPGKGLEWVAEIRSES  55
Galcanezumab---QVQLVQSGAEVKKPGSSVKVSCKASGYTFGNY--WMQWVRQAPGQGLEWMGAIYEG-  54
Sevacizumab ---EVQLVESGGGLVKPGGSLRLSCAASGFSFSNN-DVMCWVRQAPGKGLEWIGCIMTT-  55
LKA-651.NVS2---EVQLVQSGAEVKKPGESLKISCKGSGYSFTSY--WIGWVRQMPGKGLEWMGWIDPY-  54
LKA-651.NVS3---QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNTAAWNWIRQSPSRGLEWLGVIYYRS  57
Ascrinvacuma---QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGEYYWNWIRQHPGKGLEWIGYIYYSG  57
Tesidolumab ---EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSY--AISWVRQAPGQGLEWMGGIGPF-  54
Carotuximab ---EVKLEESGGGLVQPGGSMKLSCAASGFTFSDA--WMDWVRQSPEKGLEWVAEIRSKA  55
ANX-007     ---QVQLVQSGAELKKPGASVKVSCKSSGYHFTSY--WMHWVKQAPGQGLEWIGVIHPN-  54
Adalimumab  ---EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY--AMHWVRQAPGKGLEWVSAITWN-  54
Infliximab  ---EVKLEESGGGLVQPGGSMKLSCVASGFIFSNH--WMNWVRQSPEKGLEWVAEIRSKS  55
Golimumab   SKLQVQLVESGGGVVQPGRSLRLSCAASGFIFSSY--AMHWVRQAPGNGLEWVAFMSYD-  57
Elezanumab  ---EVQLVQSGAEVKKPGASVKVSCKASGYTFTSH--GISWVRQAPGQGLDWMGWISPY-  54
NI-301      ---QVQLQESGPGLVKPSETLSLTCSVSGGSIISRSSYWGWIRQPPGKGLEWIGGIYHSG  57
PRX-004     ---EVQLVESGGGLIQPGGSLRLSCAASGFTFSNY--AMSWVRQAPGKGLEWVSSISS--  53
Pamrevlumab ---EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSY--AISWVRQAPGQGLEWMGGIGPF-  54
Satralizumab---QVQLQESGPGLVKPSETLSLTCAVSGHSISH-DHAWSWVRQPPGEGLEWIGFISYSG  56
Sarilumab   ---EVQLVESGGGLVQPGRSLRLSCAASRFTFDDY--AMHWVRQAPGKGLEWVSGISWN-  54
Inebilizumab---EVQLVESGGGLVQPGGSLRLSCAASGFTFSSS--WMNWVRQAPGKGLEWVGRIYPG-  54
Etrolizumab ---EVQLVESGGGLVQPGGSLRLSCAASGFFITNN--YWGWVRQAPGKGLEWVGYISYS-  54
Romosozumab ---EVQLVQSGAEVKKPGASVKVSCKASGYTFTDY--NMHWVRQAPGQGLEWMGEINPN-  54
Lanadelumab ---EVQLLESGGGLVQPGGSLRLSCAASGFTFSHY--IMMWVRQAPGKGLEWVSGIYSS-  54
Siltuximab    ---EVQLVESGGKLLKPGGSLKLSCAASGFTFSSF--AMSWFRQSPEKRLEWVAEISSG-54
Clazakizumab --EVQLVESGGGLVQPGGSLRLSCAASGFSLSNY--YVTWVRQAPGKGLEWVGIIYGS- 54
Sirukumab   ---EVQLVESGGGLVQPGGSLRLSCAASGFTFSPF--AMSWVRQAPGKGLEWVAKISPG- 54
Olokizumab  ---EVQLVESGGGLVQPGGSLRLSCAASGFNFNDY--FMNWVRQAPGKGLEWVAQMRNKN 55
Gerilizumab ---EVQLQESGPGLVKPSQTLSLTCTVSGGSITSRYYAWSWIRQPPGKGLEWIGVIDY-- 55
Tocilizumab ---QVQLQESGPGLVRPSQTLSLTCTVSGYSITS-DHAWSWVRQPPGRGLEWIGYISYSG 57
Lecanemab   ---EVQLVESGGGLVQPGGSLRLSCSASGFTFSSF--GMHWVRQAPGKGLEWVAYISSGS 55
Ravulizumab ---QVQLVQSGAEVKKPGASVKVSCKASGHIFSNY--WIQWVRQAPGQGLEWMGEILPGS 55
Benralizumab---EVQLVQSGAEVKKPGASVKVSCKASGYTFTSY--VIHWVRQRPGQGLAWMGYINPYN 55
Reslizumab  ---EVQLVESGGGLVQPGGSLRLSCAVSGLSLTSN--SVNWIRQAPGKGLEWVGLIWSNG 55
Tralokinumab---QVQLVQSGAEVKKPGASVKVSCKASGYTFTNY--GLSWVRQAPGQGLEWMGWISANN 55
Nemolizumab ---QVQLVQSGAEVKKPGASVKVSCKASGYTFTGY--IMNWVRQAPGQGLEWMGLINPYN 55
Omalizumab  ---EVQLVESGGGLVQPGGSLRLSCAVSGYSITSGY-SWNWIRQAPGKGLEWVASITYDG 56
Tezepelumab ---QMQLVESGGGVVQPGRSLRLSCAASGFTFRTY--GMHWVRQAPGKGLEWVAVIWYDG 55
```

```
Solanezumab    -GNSTYYPDTVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCASG-------------      99
GSK933776      -AYSIDYADTVTGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCVSGTW------------      101
AL-001         -GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDPSGIALAGPASRGY      113
ABBV-8E12      DNYATHYEESVKGRFTISRDDSKSSVYLQMNNLRAEDSGIYYCTN---------------      100
UCB-0107       S-TN--YNAAVQSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARHRLYY---G------      103
NI-105         -GSNEFYADSVKGRFTISRDNSKNTLF-QMNSLRAEDTAVYYCARDLGAS---VT-TSNA      108
VX15/2503      TGGASYNQKFKGKATITVDKSTSTAYMELSSLRSEDTAVYYCARY-YY----------G       102
Prasinezumab   -GGSTYYPDNVKGRFTISRDDAKNSLYLQMNSLRAEDTAVYYCARG-------------G      100
NI-202         -NGKRKYSQKFQDRVTINRDTSASTIYMELSSLGSEDTAVYYCAREEDHA-----GSGSY      108
MEDI-1341      -GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGGANH-------GKYY      106
NI-204.10D12   -GRNTAYADYAKGRFTISRDNAKSTLYLQLNSLRAEDTAVYFCARLRRNV---ADQITHN      110
NI-204.12G7    -TGTTFYAQNFPDRVSVTRDTSTSTVFMELHNLKSEDTAVYYCARAISEH-----GSGSY      108
Eptinezumab    --GATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARG--------------      98
Fremanezumab   DASATHYAEAVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCLAYFDY---------GL      106
Galcanezumab   -TGKTVYIQKFADRVTITADKSTSTAYMELSSLRSEDTAVYYCARLSDY----------V      103
Sevacizumab    -DVVTEYANWAKSRFTVSRDSAKNSVYLQMNSLRAEDTAVYFCARDSVGS--------PL      106
LKA-651.NVS2   -RSEIRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARVSSE----------      102
LKA-651.NVS3   K-WYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARSVPGG---DPGL--E      111
Ascrinvacumab  S-TY--YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARESV-----A------      103
Tesidolumab    -FGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDTP------------      101
Carotuximab    SNHATYYAESVKGRFTISRDDSKSSVYLQMNSLRAEDTGIYYCTR--WR----------      102
ANX-007        -SGSINYNEKFESRVTITVDKSTSTAYMELSSLRSEDTAVYYCAGERDST--------EV      105
Adalimumab     -SGHIDYADSVEGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKVSYLS---TA-----      105
Infliximab     INSATHYAESVKGRFTISRDDSKSAVYLQMTDLRTEDTGVYYCSRNYYG----------      104
Golimumab      -GSNKKYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGIA---AGGNYYY      113
Elezanumab     -SGNTNYAQKLQGRVTMTTDTSTSTAYMELSSLRSEDTAVYYCARVGSG---------PY      104
NI-301         N-TY--DNPSLKSRLTMSVDTSKNQFSLNLRSVTAADTAVYYCARIVPGG---D------      105
PRX-004        -GGSTYYPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYYY----------G      101
Pamrevlumab    -FGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDTP------------      101
Satralizumab   I-TN--YNPSLQGRVTISRDNSKNTLYLQMNSLRAEDTAVYYCARSLART---T------      104
Sarilumab      -SGRIGYADSVKGRFTISRDNAENSLFLQMNGLRAEDTALYYCAKG--------R-----      100
Inebilizumab   -DGDTNYNVKFKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARSGFI-------TTV-      105
Etrolizumab    --GSTSYNPSLKSRFTISRDTSKNTFYLQMNSLRAEDTAVYYCARTGSS-------G---      102
Romosozumab    -SGGAGYNQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARLGYDDIY------DD      107
Lanadelumab     GGITVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAYRRIG-------VPRR      106
Siltuximab       -GSYTYYPDTVTGRFTISRDNAKNTLYLEMSSLRSEDTAMYYCARGLWGY----------      103
Clazakizumab   --DETAYATSAIGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDDSSDWD--------      104
Sirukumab      -GSWTYYSDTVTGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQLWGY----------      103
Olokizumab     YQYGTYYAESLEGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARESYY----------      104
Gerilizumab    -DGDTYYSPSLKSRVSISWDTSKNQFSLKLSSVTPADTAVYYCARDPDVVTG--------      106
Tocilizumab    ---ITTYNPSLKSRVTMLRDTSKNQFSLRLSSVTAADTAVYYCARSLART----------      104
Lecanemab      --STIYYGDTVKGRFTISRDNAKNSLFLQMSSLRAEDTAVYYCAREGGYYYGRSYY----      109
Ravulizumab    --GHTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPN------      106
Benralizumab   --DGTKYNERFKGKVTITSDRSTSTVYMELSSLRSEDTAVYLCGREGIRYYG--------      105
Reslizumab    --DT-TYNSAIKSRFTISRDTSKSTVYLQMNSLRAEDTAVYYCARE--Y-YG--Y-----      102
Tralokinumab   -GDT-NYGQEFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDSSSSWA--R-----      106
Nemolizumab    -GGTD-YNPQFQDRVTITADKSTSTAYMELSSLRSEDTAVYYCARDGYDDG---P-----      105
Omalizumab     --ST-NYADSVKGRFTISRDDSKNTFYLQMNSLRAEDTAVYYCARGSHY-FG--H-----      105
Tezepelumab    --SNKHYADSVKGRFTITRDNSKNTLNLQMNSLRAEDTAVYYCARAPQWELV--H-----      106
                          .: ::. * : .    :  .:   *:.:*:*
```

```
                    N
Solanezumab     ---DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     156
GSK933776       --FAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     159
AL-001          QGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     173
ABBV-8E12       -WEDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     159
UCB-0107        -AFDYWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     162
NI-105          ENFHHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     168
VX15/2503       RHFDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     162
Prasinezumab    AGIDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     160
NI-202          LSMDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     168
MEDI-1341       YGMDKWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     166
NI-204.10D12    YYMDVWGKGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     170
NI-204.12G7     -SPYYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     167
Eptinezumab     ---DIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     155
Fremanezumab    AIQNYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     166
Galcanezumab    SGFGYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     163
Sevacizumab     MSFDLWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     166
LKA-651.NVS2    -PFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     161
LKA-651.NVS3    HAFAYWGRGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     171
Ascrinvacumab   -GFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     162
Tesidolumab     -YFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     160
Carotuximab     RFFDSWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     162
ANX-007         LPMDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     165
Adalimumab      SSLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     165
Infliximab      STYDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     164
Golimumab       YGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     173
Elezanumab      YYMDVWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     164
NI-301          -AFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     164
PRX-004         QYFDFWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     161
Pamrevlumab     -YFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     160
Satralizumab    -AMDYWGEGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     163
Sarilumab       DSFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     160
Inebilizumab    RDFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     165
Etrolizumab     -YFDFWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     161
Romosozumab     WYFDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     167
Lanadelumab     DEFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     166
Siltuximab      YALDYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     163
Clazakizumab    AKFNLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     164
Sirukumab       YALDIWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     163
Olokizumab      GFTSYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     164
Gerilizumab     FHYDYWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     166
Tocilizumab     TAMDYWGQGSLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     164
Lecanemab       -TMDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     168
Ravulizumab     WYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     166
Benralizumab    LLGDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     165
Reslizumab      --FDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     160
Tralokinumab    WFFDLWGRGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG   166
Nemolizumab     YTLETWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     165
Omalizumab      WHFAVWGQGTLVTVS----SGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG     161
Tezepelumab     EAFDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG     166
                     ** ** :*****************.*:*** .**********************
```

```
Solanezumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      211
GSK933776      ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      214
AL-001         ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      228
ABBV-8E12      ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE      214
UCB-0107       ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE      217
NI-105         ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      223
VX15/2503      ALTSGVHTFPAVTVSSVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE      222
Prasinezumab   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      215
NI-202         ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      223
MEDI-1341      ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      221
NI-204.10D12   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      225
NI-204.12G7    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      222
Eptinezumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVE      210
Fremanezumab   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE      221
Galcanezumab   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE      218
Sevacizumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      221
LKA-651.NVS2   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      216
LKA-651.NVS3   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      226
Ascrinvacumab  ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE      217
Tesidolumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      215
Carotuximab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      217
ANX-007        ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      220
Adalimumab     ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      220
Infliximab     ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      219
Golimumab      ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      228
Elezanumab     ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      219
NI-301         ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      219
PRX-004        ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      216
Pamrevlumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      215
Satralizumab   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE      218
Sarilumab      ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      215
Inebilizumab   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      220
Etrolizumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      216
Romosozumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE      222
Lanadelumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      221
Siltuximab     ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      218
Clazakizumab   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      219
Sirukumab      ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE     218
Olokizumab     ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE      219
Gerilizumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      221
Tocilizumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      219
Lecanemab      ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE      223
Ravulizumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE      221
Benralizumab   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE      220
Reslizumab     ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE     215
Tralokinumab   ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE      220
Nemolizumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE      220
Omalizumab     ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKAE      216
Tezepelumab    ALTSGVHTFPAV-----LQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE      221
               ************     ******************.:**:** ***:*********  **
```

Solanezumab	PKSCDKTHT	220
GSK933776	PKSCDKTHT	223
AL-001	PKSCDKTHT	237
ABBV-8E12	SKYGPP---	220
UCB-0107	SKYGPP---	223
NI-105	PKSCDKTHT	232
VX15/2503	SKYGPP---	228
Prasinezumab	PKSCDKTHT	224
NI-202	PKSCDKTHT	232
MEDI-1341	PKSCDKTHT	230
NI-204.10D12	PKSCDKTHT	234
NI-204.12G7	PKSCDKTHT	231
Eptinezumab	PKSCDKTHT	219
Fremanezumab	RKCCVE---	227
Galcanezumab	SKYGPP---	224
Sevacizumab	PKSCDKTHT	230
LKA-651.NVS2	PKSCDKTHT	225
LKA-651.NVS3	PKSCDKTHT	235
Ascrinvacumab	RKCCVE---	223
Tesidolumab	PKSCDKTHT	224
Carotuximab	PKSCDKTHT	226
ANX-007	PKSCDKTHT	229
Adalimumab	PKSCDKTHT	229
Infliximab	PKSCDKTHT	228
Golimumab	PKSCDKTHT	237
Elezanumab	PKSCDKTHT	228
NI-301	PKSCDKTHT	228
PRX-004	PKSCDKTHT	225
Pamrevlumab	PKSCDKTHT	224
Satralizumab	RKSCVE---	224
Sarilumab	PKSCDKTHT	224
Inebilizumab	PKSCDKTHT	229
Etrolizumab	PKSCDKTHT	225
Romosozumab	RKCCVE---	228
Lanadelumab	PKSCDKTHT	230
Siltuximab	PKSCDKTHT	227
Clazakizuma	PKSCDKTHT	228
Sirukumab	PKSCDKTHT	227
Olokizumab	SKYGPP---	224
Gerilizumab	PKSCDKTHT	230
Tocilizumab	PKSCDKTHT	228
Lecanemab	PKSCDKTHT	232
Ravulizumab	RKCCVE---	227
Benralizumab	PKSCDKTHT	229
Reslizumab	SKYGPP---	221
Tralokinumab	SKYGPP---	226
Nemolizumab	RKSCVE---	226
Omalizumab	PKSCDKTHT	225
Tezepelumab	RKCCVE---	227
	*	

FIG. 20B CLUSTAL O(1.2.4) ALIGNMENT OF THERAPEUTIC Fab LIGHT CHAIN

```
Solanezumab    ---DVVMTQSPLSLPVTLGQPASISCRSSQSLIYSD-GNAYLHWFLQKPGQSPRLLIYK-      55
GSK933776      ---DIVMTQSPLSLPVTPGEPASISCRVSQSLLHSN-GYTYLHWYLQKPGQSPQLLIYK-      55
AL-001         ---EIVMTQSPATLSVSPGERATLSCRASQSV------SSNLAWYQQKPGQAPRLLIYG-      50
ABBV-8E12      ---DIVLTQSPDSLAVSLGERATISCRASQSVSTS--RYSYIHWYQQKPGQFPKLLIKY-      54
UCB-0107       ---DIVMTQTPLSLSVTPGQPASISCRSSQSLEYSD-GYTYLEWYLQKPGQSPQLLIYE-      55
NI-105         ---SYELT-QPPSVSVSPGQTARITCSGDAL------PKRYVYWYQQKSGQAPVLVIYE-      49
VX15/2503      ---DIVMTQSPDSLAVSLGERATINCKASQSVDYD--GDSYMNWYQQKPGQPPKLLIYA-      54
Prasinezumab   ---DIQMTQSPSSLSASVGDRVTITCKSIQTLLYSSNQKNYLAWFQQKPGKAPKLLIYW-      56
NI-202         ---DIQMTQSPSSLSASVGDRVTITCKSIQTLLYSSNQKNYLAWFQQKPGKAPKLLIYW-      56
MEDI-1341      ---QAVLT-QPASLSASPGASASLTCTLRSGAPL---PKYRIYWYQQKPGSPPQYLLRYK      53
NI-204.10D12   ---DIQMTQSPSSLSASVGDRVT-ACRASQS------VGTYLNWYQQKRGKAPKLLIFA-      49
NI-204.12G7    ---SYELT-QPPSVSVSLGQMAAITCSGEAL------PKKYGYWYQQKPGQVPVLLIYR-      49
Eptinezumab    ----QVLTQSPSSLSASVGDRVTINCQASQSVY----HNTYLAWYQQKPGKVPKQLIYD-      51
Fremanezumab   ---EIVLTQSPATLSLSPGERATLSCKASKRV------TTYVSWYQQKPGQAPRLLIYG-      50
Galcanezumab   ---DIQMTQSPSSLSASVGDRVTITCRASKD------ISKYLNWYQQKPGKAPKLLIYY-      50
Sevacizumab    ---DIQMTQSPSSLSASVGDRVTINCQASQSIY----NNNELSWYQQKPGKPPKLLIYR-      52
LKA-651.NVS2   ---SYVLT-QPPSVSVAPGKTARITCSGDKL------GDHYAYWYQQKPGQAPVLVIYD-      49
LKA-651.NVS3   ---SYVLT-QPPSVSVAPGKTARITCSGDNL------GTYYVEWYQQKPGQAPVLVIYD-      49
Ascrinvacumab  ---EIVLTQSPGTLSLSPGERATLSCRASQSVS-----SSYLAWYQQKPGQAPRLLIYG-      51
Tesidolumab    ---SYELT-QPLSVSVALGQTARITCSGDSI------PNYYVYWYQQKPGQAPVLVIYD-      49
Carotuximab    ---QIVLSQSPAILSASPGEKVTMTCRASSS-------VSYMHWYQQKPGSSPKPWIYA-      49
ANX-007        ---DVQITQSPSSLSASLGERATINCRASKS------INKYLAWYQQKPGKAPKLLIYS-      50
Adalimumab     ---DIQMTQSPSSLSASVGDRVTITCRASQG------IRNYLAWYQQKPGKAPKLLIYA-      50
Infliximab     ---DILLTQSPAILSVSPGERVSFSCRASQFVG------SSIHWYQQRTNGSPRLLIKY-      50
Golimumab      AGSEIVLTQSPATLSLSPGERATLSCRASQSV------YSYLAWYQQKPGQAPRLLIYD-      53
Elezanumab     ---QSALT-QPRSVSGSPGQSVTISCTGTSSSVG---DSIYVSWYQQHPGKAPKLMLYD-      52
NI-301         ---DIQMTQSPSSLSASVGDRVT-ACRASQS------VGTYLNWYQQKRGKAPKLLIFA-      49
PRX-004        ---DIVMTQSPSSLSASVGDRVTITCKASQDV------STTVAWYQQKPGKAPKLLIYS-      50
Pamrevlumab    ---SYELT-QPLSVSVALGQTARITCSGDSI------PNYYVYWYQQKPGQAPVLVIYD-      49
Satralizumab   ---DIQMTQSPSSLSASVGDSVTITCQASTD------ISSHLNWYQQKPGKAPELLIYY-      50
Sarilumab      ---DIQMTQSPSSVSASVGDRVTITCRASQG------ISSWLAWYQQKPGKAPKLLIYG-      50
Inebilizumab   ---EIVLTQSPDFQSVTPKEKVTITCRASESVDTF--GISFMNWFQQKPDQSPKLLIHE-      54
Etrolizumab    ---DIQMTQSPSSLSASVGDRVTITCRASES------VDDLLHWYQQKPGKAPKLLIKY-      50
Romosozumab    ---DIQMTQSPSSLSASVGDRVTITCRASQD------ISNYLNWYQQKPGKAPKLLIYY-      50
Lanadelumab    ---DIQMTQSPSTLSASVGDRVTITCRASQS------ISSWLAWYQQKPGKAPKLLIYK-      50
Siltuximab     ---QIVLIQSPAIMSASPGEKVTMTCSASSSVS-------YMYWYQQKPGSSPRLLIYD-      49
Clazakizumab   ---AIQMTQSPSSLSASVGDRVTITCQASQSI------NNELSWYQQKPGKAPKLLIYR-      50
Sirukumab      ---EIVLTQSPATLSLSPGERATLSCSASISVS-------YMYWYQQKPGQAPRLLIYD-      49
Olokizumab     ---DIQMTQSPSSLSASVGDRVTITCQASQDIG----IS--LSWYQQKPGKAPKLLIYN-      50
Gerilizumab    ---QSALT-QPPSVSGTPGQSVTISCAGANNDIG---TYAYVSWYQQLPGTAPKL-MI--      50
Tocilizumab    ---DIQMTQSPSSLSASVGDRVTITCRASQDI------SSYLNWYQQKPGKAPKLLIYY-      50
Lecanemab      ---DVVMTQSPLSLPVTPGAPASISCRSSQSIVH-SNGNTYLEWYLQKPGQSPKLLIYK-      54
Ravulizumab    ---DIQMTQSPSSLSASVGDRVTITCGASENIYG------ALNWYQQKPGKAPKLLIYG-      50
Benralizumab   ---DIQMTQSPSSLSASVGDRVTITCGTSEDII------NYLNWYQQKPGKAPKLLIYH-      50
Reslizumab     ---DIQMTQSPSSLSASVGDRVTITCLASEGIS------SYLAWYQQKPGKAPKLLIYG-      50
Tralokinumab   ----SYVLTQPPSVSVAPGKTARITCGGNIIGS------KLVHWYQQKPGQAPVLVIYD-      49
Nemolizumab    ---DIQMTQSPSSLSASVGDRVTITCQASEDIY------SFVAWYQQKPGKAPKLLIYN-      50
Omalizumab     ---DIQLTQSPSSLSASVGDRVTITCRASQSVD--YDGDSYMNWYQQKPGKAPKLLIYA-      54
Tezepelumab    ----SYVLTQPPSVSVAPGQTARITCGGNNLGS------KSVHWYQQKPGQAPVLVVYD-      49
                     ::  *     :    .   *                *: *: .  *   :
```

```
Solanezumab    ---VSNRFSGVPDRFSGSGS--GTDFTLKISRVEAEDVGVYYCSQSTH----VPWTFGQG      106
GSK933776      ---VSNRFSGVPDRFSGSGS--GTDFTLKISRVEAEDVGVYYCSQTRH----VPYTFGGG      106
AL-001         ---ASTRATGIPARFSGSGS--GTEFTLTISSLQSEDFAVYYCQQA-RL---GPWTFGGG      101
ABBV-8E12      ---ASNLESGVPSRFSGSGS--GTDFTLNIHPLEPEDFATYYCHHSWE----IPLTFGQG      105
UCB-0107       ---VSNRFSGVPDRFSGSGS--GTDFTLKISRVEAEDVGVYYCFQATH----NPYTFGQG      106
NI-105         ---DSKRPSGIPETFSGSSS--GTMATLTISGAQVEDEADYYCYSTDS--NGHHWVFGGG      102
VX15/2503      ---ASNLESGVPDRFSGSGS--GTDFTLTISSLQAEDVAVYYCQQSNE----DPYTFGQG      105
Prasinezumab   ---ASIRKSGVPSRFSGSGS--GTDFTLTISSLQPEDLATYYCQQY-YS---YPLTFGGG      107
NI-202         ---ASIRKSGVPSRFSGSGS--GTDFTLTISSLQPEDLATYYCQQY-YS---YPLTFGGG      107
MEDI-1341      SDADKHQGSGVPSRFSGSKDASANAGILLISGLQSEDEADYYCMVWD----HGVWYFGGG      109
NI-204.10D12   ---ASSLQSGVPSRFSGSGS--GTDFTLTISSLQPEDFATYYCQQS-YS---SPPTFGQG      100
NI-204.12G7    ---DVERPSGVPDRFSGSSS--GTMVTLTISGVQAEDEADYYCLSADS--S-GTWVFGGG      101
Eptinezumab    ---ASTLASGVPSRFSGSGS--GTDFTLTISSLQPEDVATYYCLGSYDCTNGDCFVFGGG      106
Fremanezumab   ---ASNRYLGIPARFSGSGS--GTDFTLTISSLEPEDFAVYYCSQSYNY----PYTFGQG      101
Galcanezumab   ---TSGYHSGVPSRFSGSGS--GTDFTLTISSLQPEDFATYYCQQG-DA---LPPTFGGG      101
Sevacizumab    ---ASTLASGVPSRFSGSGS--GTDFTLTISSLQPEDVATYYCGG-YKSYSNDGNGFGGG      106
LKA-651.NVS2   ---DSKRPSGIPERFSGSNS--GNTATLTISRVEAGDEADYYCATWTF--E-GDYVFGGG      101
LKA-651.NVS3   ---DSDRPSGIPERFSGSNS--GNTATLTISRVEAGDEADYYCASFAS--W-SDSVFGGG      101
Ascrinvacumab  ---TSSRATGIPDRFSGSGS--GTDFTLTISRLEPEDFAVYYCQQ-YGS---SPITFGQG      102
Tesidolumab    ---DSNRPSGIPERFSGSNS--GNTATLTISRAQAGDEADYYCQSFDS--SLNAEVFGGG      102
Carotuximab    ---TSNLASGVPVRFSGSGS--GTSYSLTISRVEAEDAATYYCQQWSS----NPLTFGAG      100
ANX-007        ---GSTLQSGIPARFSGSGS--GTDFTLTISSLEPEDFAMYYCQQH-NE---YPLTFGQG      101
Adalimumab     ---ASTLQSGVPSRFSGSGS--GTDFTLTISSLQPEDVATYYCQRY-NR---APYTFGQG      101
Infliximab     ---ASESMSGIPSRFSGSGS--GTDFTLSINTVESEDIADYYCQQSHS----WPFTFGSG      101
Golimumab      ---ASNRATGIPARFSGSGS--GTDFTLTISSLEPEDFAVYYCQQRSNW---PPFTFGPG      105
Elezanumab     ---VTKRPSGVPDRFSGSKS--GNTASLTISGLQAEDEADYYCYSYA----GTDTLFGGG      103
NI-301         ---ASSLQSGVPSRFSGSGS--GTDFTLTISSLQPEDFATYYCQQS-YS---SPPTFGQG      100
PRX-004        ---ASYRSTGVPSRFSGSGS--GTDFTLTISSLQPEDFAVYYCQQHYS----TPLTFGGG      101
Pamrevlumab    ---DSNRPSGIPERFSGSNS--GNTATLTISRAQAGDEADYYCQSFDS--SLNAEVFGGG      102
Satralizumab   ---GSHLLSGVPSRFSGSGS--GTDFTFTISSLEAEDAATYYCGQG-NR---LPYTFGQG      101
Sarilumab      ---ASSLESGVPSRFSGSGS--GTDFTLTISSLQPEDFASYYCQQA-NS---FPYTFGQG      101
Inebilizumab   ---ASNQGSGVPSRFSGSGS--GTDFTLTINSLEAEDAATYYCQQSKE----VPFTFGGG      105
Etrolizumab    ---ASQSISGVPSRFSGSGS--GTDFTLTISSLQPEDFATYYCQQG-NS---LPNTFGQG      101
Romosozumab    ---TSRLLSGVPSRFSGSGS--GTDFTLTISSLQPEDFATYYCQQG-DT---LPYTFGGG      101
Lanadelumab    ---ASTLESGVPSRFSGSGS--GTEFTLTISSLQPDDFATYYCQQY-NT---Y-WTFGQG      100
Siltuximab     ---TSNLASGVPVRFSGSGS--GTSYSLTISRMEAEDAATYYCQQWSG----YPYTFGGG      100
Clazakizumab   ---ASTLASGVPSRFSGSGS--GTDFTLTISSLQPDDFATYYCQQGYSLR-NIDNAFGGG      104
Sirukumab      ---MSNLASGIPARFSGSGS--GTDFTLTISSLEPEDFAVYYCMQWSG----YPYTFGGG      100
Olokizumab     ---ANNLADGVPSRFSGSGS--GTDFTLTISSLQP*EDFATYY*CLQH-NS---APYTFGQG      101
Gerilizumab    ---YKVTTRASGIPDRFSGSKSGNTASLTISGLQAEDEADYYCASYRNF---NNAVFGTG      104
Tocilizumab    ---TSRLHSGVPSRFSGSGS--GTDFTFTISSLQPEDIATYYCQQG-NT---LPYTFGQG      101
Lecanemab      ---VSNRFSGVPDRFSGSGS--GTDFTLRISRVEAEDVGIYYCFQGSH----VPPTFGPG      105
Ravulizumab    ---ATNLADGVPSRFSGSGS--GTDFTLTISSLQPEDFATYYCQNVLN---T-PLTFGQG      101
Benralizumab   ---TSRLQSGVPSRFSGSGS--GTDFTLTISSLQPEDFATYYCQQGY----TLPYTFGQG      101
Reslizumab     ---ANSLQTGVPSRFSGSGS--ATDYTLTISSLQPEDFATYYCQQS----YKFPNTFGQG      101
Tralokinumab   ---DGDRPSGIPERFSGSNS--GNTATLTISRVEAGDEADYYCQVW-DT-GSDPVVFGGG      102
Nemolizumab    ---AQTEAQGVPSRFSGSGS--GTDFTLTISSLQPEDFATYYCQHH----Y-DSPLTFGG      100
Omalizumab     ---ASYLESGVPSRFSGSGS--GTDFTLTISSLQPEDFATYYCQQSHE----DPYTFGQG      105
Tezepelumab    ---DSDRPSWIPERFSGSNS--GNTATLTISRGEAGDEADYYCQVWDSSS--DHVVFGGG      102
                        *:*  **** .  ..   : *   :  * . ***            ** *
```

		S/N
Solanezumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	165
GSK933776	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	165
AL-001	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
ABBV-8E12	TKLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	164
UCB-0107	TKLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	165
NI-105	TKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV-	161
VX15/2503	TKLEIK---------FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	156
Prasinezumab	TKLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	166
NI-202	TKLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	166
MEDI-1341	TKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV-	168
NI-204.10D12	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	159
NI-204.12G7	TKLTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGV-	160
Eptinezumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	165
Fremanezumab	TKLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Galcanezumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Sevacizumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	165
LKA-651.NVS2	TKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV-	160
LKA-651.NVS3	TKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV-	160
Ascrinvacumab	TRLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	161
Tesidolumab	TKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV-	161
Carotuximab	TKLELK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	159
ANX-007	TKLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Adalimumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Infliximab	TNLEVK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Golimumab	TKVDIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	164
Elezanumab	TKVTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV-	162
NI-301	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	159
PRX-004	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Pamrevlumab	TKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV-	161
Satralizumab	TKVEIE-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Sarilumab	TKLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Inebilizumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	164
Etrolizumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Romosozumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Lanadelumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	159
Siltuximab	TKLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	159
Clazakizumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	164
Sirukumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	159
Olokizumab	TKLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Gerilizumab	TKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV-	163
Tocilizumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Lecanemab	TKLEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	165
Ravulizumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Benralizumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Reslizumab	TKVEVK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Tralokinumab	TKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV-	161
Nemolizumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	159
Omalizumab	TKVEIK-RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	164
Tezepelumab	TKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV-	161
	*.: :	

		N	
Solanezumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		219
GSK933776	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		219
AL-001	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
ABBV-8E12	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		218
UCB-0107	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		219
NI-105	ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS--TVEKTVAPTCS-		213
VX15/2503	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		210
Prasinezumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		220
NI-202	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		220
MEDI-1341	ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS--TVEKTVAPTECS		221
NI-204.10D12	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		213
NI-204.12G7	ETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS--TVEKTVAPTECS		213
Eptinezuman	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		219
Fremanezumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Galcanezumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Sevacizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		219
LKA-651.NVS2	ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS--TVEKTVAPTECS		213
LKA-651.NVS3	ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS--TVEKTVAPTECS		213
Ascrinvacumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		215
Tesidolumab	ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS--TVEKTVAPTECS		214
Carotuximab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		213
ANX-007	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Adalimumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Infliximab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Golimumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		218
Elezanumab	ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS--TVEKTVAPTECS		215
NI-301	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		213
PRX-004	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		219
Pamrevlumab	ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS--TVEKTVAPTECS		214
Satralizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Sarilumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Inebilizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		218
Etrolizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Romosozumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Lanadelumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		213
Siltuximab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		213
Clazakizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		218
Sirukumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		213
Olokizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Gerilizumab	ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS--TVEKTVAPTECS		216
Tocilizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Lecanemab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		219
Ravulizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Benralizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Reslizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		214
Tralokinumab	ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS—TVEKTVAPTECS		214
Nemolizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC-		213
Omalizumab	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR----		215
Tezepelumab	ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS--		214

FIG. 21

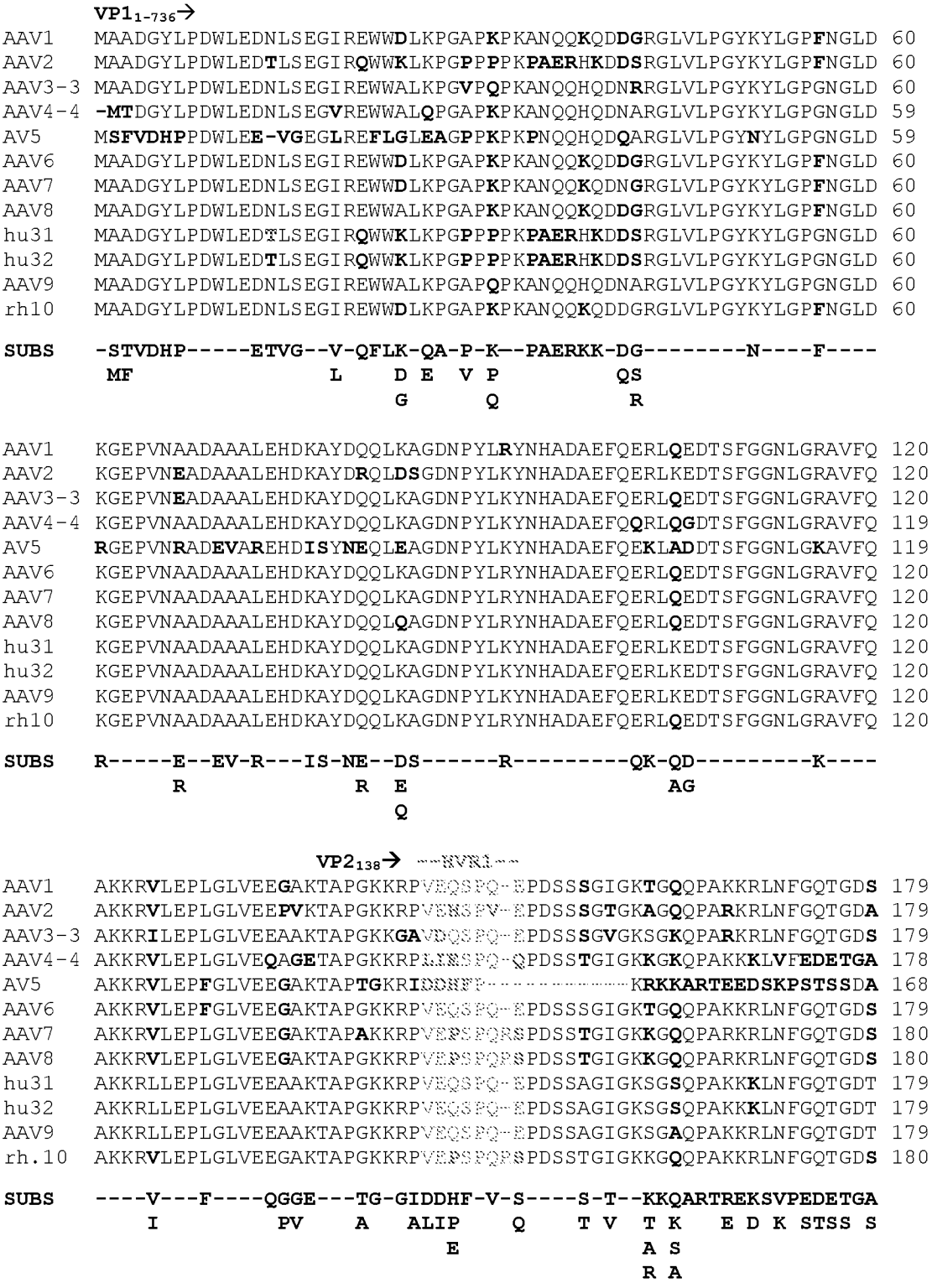

VP1 1-736→
AAV1 MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
AAV2 MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLD 60
AAV3-3 MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKYLGPGNGLD 60
AAV4-4 -MTDGYLPDWLEDNLSEGVREWWALQPGAPKPKANQQHQDNARGLVLPGYKYLGPGNGLD 59
AV5 MSFVDHPPDWLEE-VGEGLREFLGLEAGPPKPKPNQQHQDQARGLVLPGYNYLGPGNGLD 59
AAV6 MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
AAV7 MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDNGRGLVLPGYKYLGPFNGLD 60
AAV8 MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
hu31 MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPGNGLD 60
hu32 MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPGNGLD 60
AAV9 MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGLD 60
rh10 MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
SUBS -STVDHP-----ETVG--V-QFLK-QA-P-K--PAERKK-DG--------N----F----
MF L D E V P QS
G Q R
AAV1 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV2 KGEPVNEADAAALEHDKAYDRQLDSGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
AAV3-3 KGEPVNEADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV4-4 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQQRLQGDTSFGGNLGRAVFQ 119
AV5 RGEPVNRADEVAREHDISYNEQLEAGDNPYLKYNHADAEFQEKLADDTSFGGNLGKAVFQ 119
AAV6 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV7 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV8 KGEPVNAADAAALEHDKAYDQQLQAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
hu31 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
hu32 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
AAV9 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
rh10 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
SUBS R-----E--EV-R---IS-NE--DS------R---------QK-QD---------K----
R R E AG
Q
VP2 138→
AAV1 AKKRVLEPLGLVEEGAKTAPGKKRPVEQSPQEPDSSSGIGKTGQQPAKKRLNFGQTGDS 179
AAV2 AKKRVLEPLGLVEEPVKTAPGKKRPVENSPVEPDSSSGTGKAGQQPARKRLNFGQTGDA 179
AAV3-3 AKKRILEPLGLVEEAAKTAPGKKGAVDQSPQEPDSSSGVGKSGKQPARKRLNFGQTGDS 179
AAV4-4 AKKRVLEPLGLVEQAGETAPGKKRPLIESPQQPDSSTGIGKKGKQPAKKKLVFEDETGA 178
AV5 AKKRVLEPFGLVEEGAKTAPTGKRIDDNFP----------KRKKARTEEDSKPSTSSDA 168
AAV6 AKKRVLEPFGLVEEGAKTAPGKKRPVEQSPQEPDSSSGIGKTGQQPAKKRLNFGQTGDS 179
AAV7 AKKRVLEPLGLVEEGAKTAPAKKRPVEPSPQRSPDSSTGIGKKGQQPARKRLNFGQTGDS 180
AAV8 AKKRVLEPLGLVEEGAKTAPGKKRPVEPSPQPSPDSSTGIGKKGQQPARKRLNFGQTGDS 180
hu31 AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGSQPAKKKLNFGQTGDT 179
hu32 AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGSQPAKKKLNFGQTGDT 179
AAV9 AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDT 179
rh.10 AKKRVLEPLGLVEEGAKTAPGKKRPVEPSPQPSPDSSTGIGKKGQQPAKKRLNFGQTGDS 180
SUBS ----V---F----QGGE---TG-GIDDHF-V-S----S-T--KKQARTREKSVPEDETGA
I PV A ALIP Q T V T K E D K STSS S
E A S
R A

FIG. 21 (CON'T)

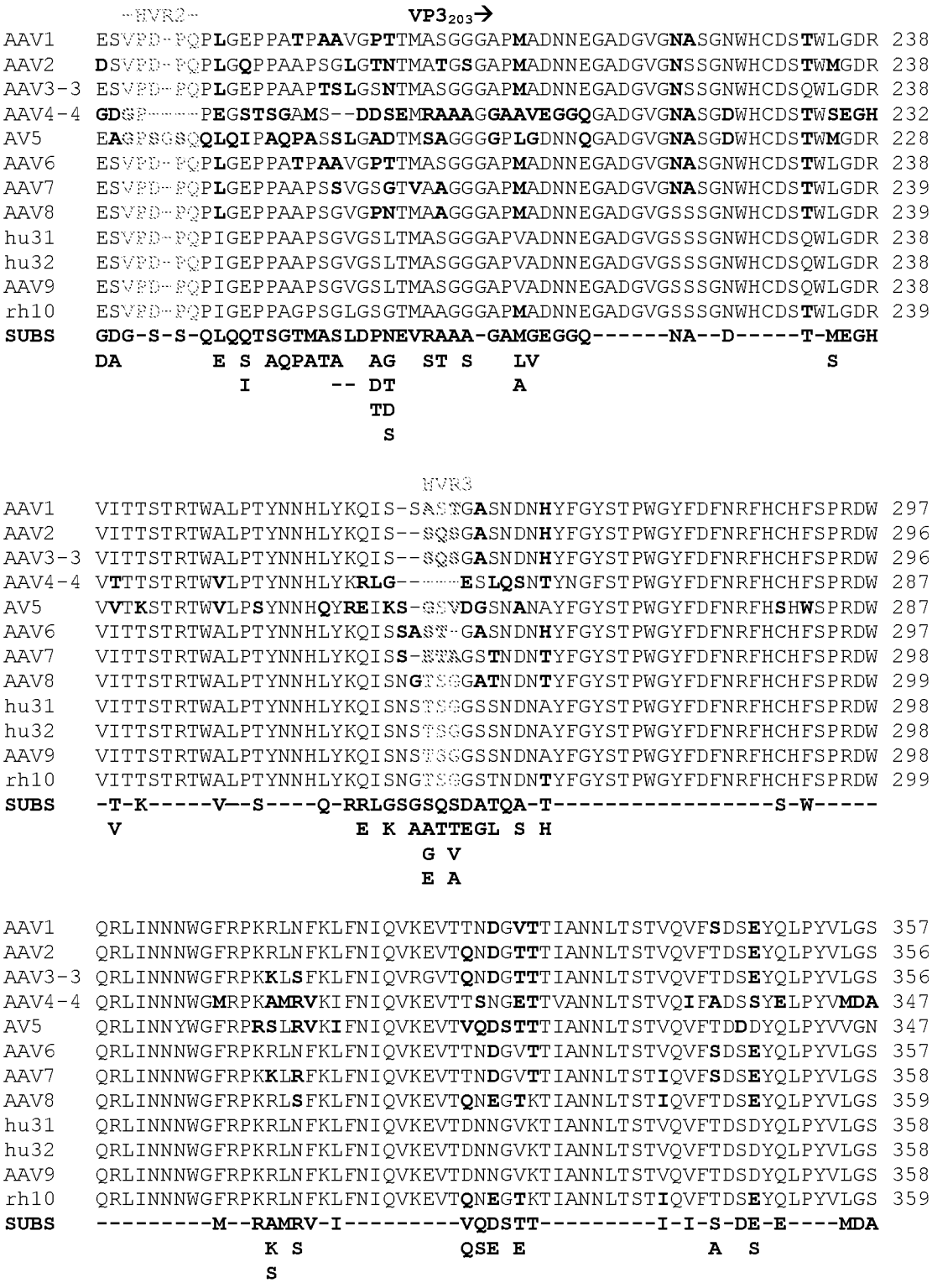

~HVR2~
VP3203→
AAV1 ESVPD~PQPLGEPPATPAAVGPTTMASGGGAPMADNNEGADGVGNASGNWHCDSTWLGDR 238
AAV2 DSVPD~PQPLGQPPAAPSGLGTNTMATGSGAPMADNNEGADGVGNSSGNWHCDSTWMGDR 238
AAV3-3 ESVPD~PQPLGEPPAAPTSLGSNTMASGGGAPMADNNEGADGVGNSSGNWHCDSQWLGDR 238
AAV4-4 GDGP~~~~~PEGSTSGAMS--DDSEMRAAAGGAAVEGGQGADGVGNASGDWHCDSTWSEGH 232
AV5 EAGPSGSQQLQIPAQPASSLGADTMSAGGGGPLGDNNQGADGVGNASGDWHCDSTWMGDR 228
AAV6 ESVPD~PQPLGEPPATPAAVGPTTMASGGGAPMADNNEGADGVGNASGNWHCDSTWLGDR 238
AAV7 ESVPD~PQPLGEPPAAPSSVGSGTVAAGGGAPMADNNEGADGVGNASGNWHCDSTWLGDR 239
AAV8 ESVPD~PQPLGEPPAAPSGVGPNTMAAGGGAPMADNNEGADGVGSSSGNWHCDSTWLGDR 239
hu31 ESVPD~PQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDR 238
hu32 ESVPD~PQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDR 238
AAV9 ESVPD~PQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDR 238
rh10 ESVPD~PQPIGEPPAGPSGLGSGTMAAGGGAPMADNNEGADGVGSSSGNWHCDSTWLGDR 239
SUBS GDG-S-S-QLQQTSGTMASLDPNEVRAAA-GAMGEGGQ------NA--D-----T-MEGH
DA E S AQPATA AG ST S LV S
I -- DT A
TD
S
HVR3
AAV1 VITTSTRTWALPTYNNHLYKQIS-SASTGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 297
AAV2 VITTSTRTWALPTYNNHLYKQIS--SQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 296
AAV3-3 VITTSTRTWALPTYNNHLYKQIS--SQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 296
AAV4-4 VTTTSTRTWVLPTYNNHLYKRLG-~~~~ESLQSNTYNGFSTPWGYFDFNRFHCHFSPRDW 287
AV5 VVTKSTRTWVLPSYNNHQYREIKS-GSVDGSNANAYFGYSTPWGYFDFNRFHSHWSPRDW 287
AAV6 VITTSTRTWALPTYNNHLYKQISSASS-GASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 297
AAV7 VITTSTRTWALPTYNNHLYKQISS-SNAGSTNDNTYFGYSTPWGYFDFNRFHCHFSPRDW 298
AAV8 VITTSTRTWALPTYNNHLYKQISNGTSGGATNDNTYFGYSTPWGYFDFNRFHCHFSPRDW 299
hu31 VITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDW 298
hu32 VITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDW 298
AAV9 VITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDW 298
rh10 VITTSTRTWALPTYNNHLYKQISNGTSGGSTNDNTYFGYSTPWGYFDFNRFHCHFSPRDW 299
SUBS -T-K-----V--S----Q-RRLGSGSQSDATQA-T----------S-W-----
V E K AATTEGL S H
G V
E A
AAV1 QRLINNNWGFRPKRLNFKLFNIQVKEVTTNDGVTTIANNLTSTVQVFSDSEYQLPYVLGS 357
AAV2 QRLINNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
AAV3-3 QRLINNNWGFRPKKLSFKLFNIQVRGVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
AAV4-4 QRLINNNWGMRPKAMRVKIFNIQVKEVTTSNGETTVANNLTSTVQIFADSSYELPYVMDA 347
AV5 QRLINNYWGFRPRSLRVKIFNIQVKEVTVQDSTTTIANNLTSTVQVFTDDDYQLPYVVGN 347
AAV6 QRLINNNWGFRPKRLNFKLFNIQVKEVTTNDGVTTIANNLTSTVQVFSDSEYQLPYVLGS 357
AAV7 QRLINNNWGFRPKKLRFKLFNIQVKEVTTNDGVTTIANNLTSTIQVFSDSEYQLPYVLGS 358
AAV8 QRLINNNWGFRPKRLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
hu31 QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
hu32 QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
AAV9 QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
rh10 QRLINNNWGFRPKRLNFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
SUBS ---------M--RAMRV-I---------VQDSTT---------I-I-S-DE-E----MDA
K S QSE E A S
S

FIG. 21 (CON'T)

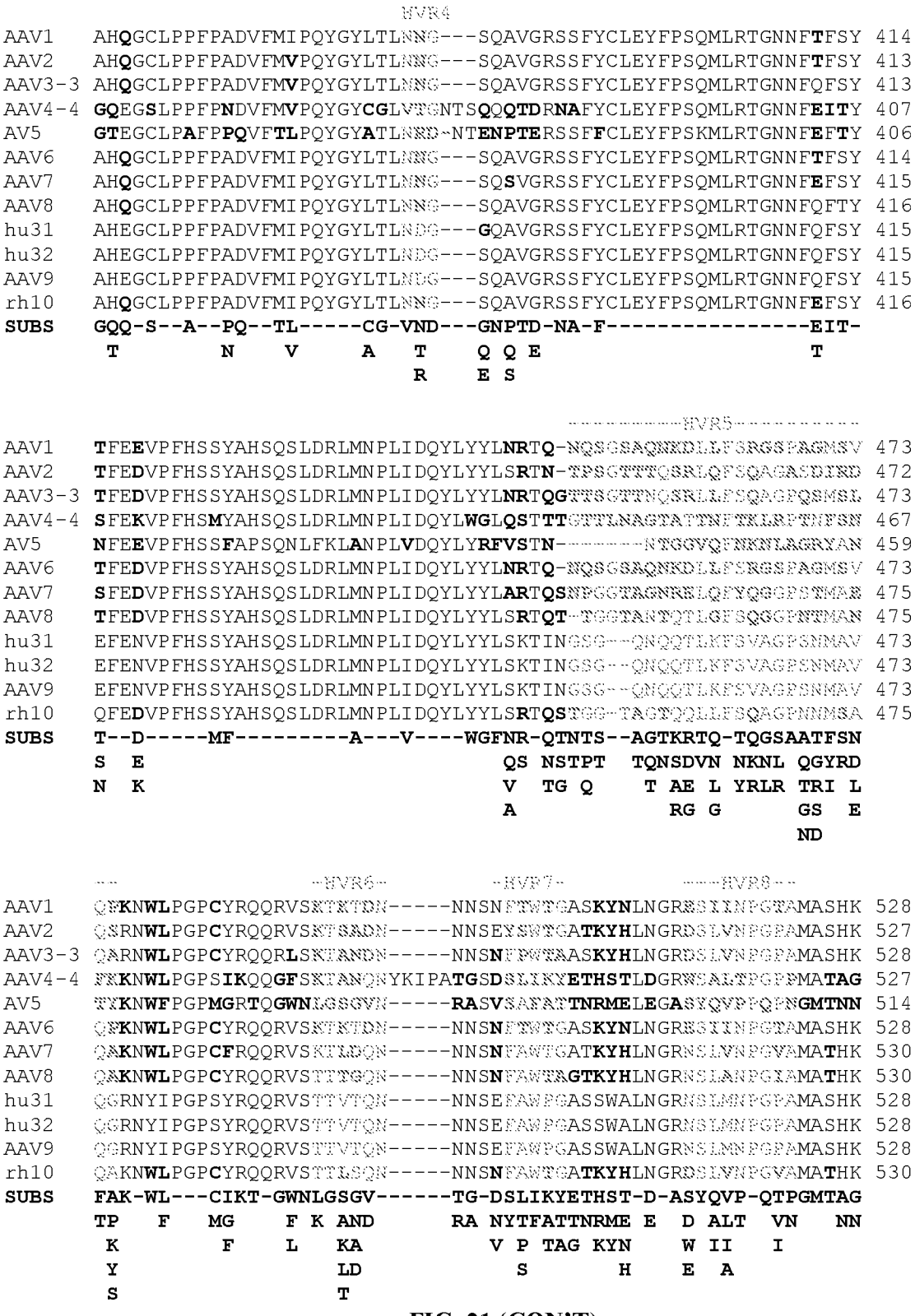


FIG. 21 (CON'T)

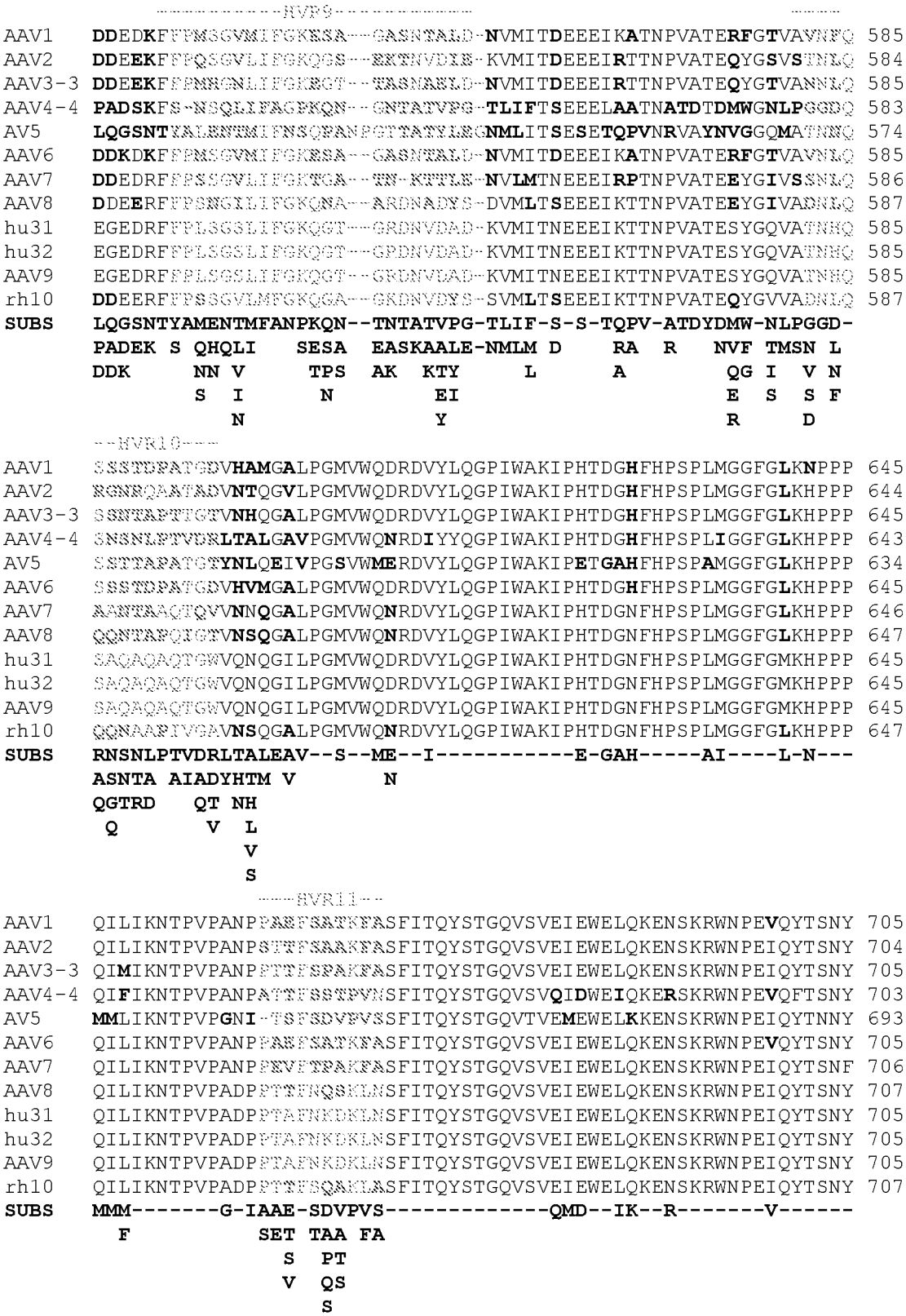


FIG. 21 (CON'T)

```
        --------HVR12-------
AAV1    AKSANVDFTVDNNGLYTEPRPIGTRYLTRPL 736 (SEQ ID NO: 274)
AAV2    NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 735 (SEQ ID NO: 275)
AAV3-3  NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 736 (SEQ ID NO: 276)
AAV4-4  GQQNSLLNAPDAAGKYTEPRAIGTRYLTHHL 734 (SEQ ID NO: 277)
AV5     NDPQFVDFAPDSTGEYRTTRPIGTRYLTRPL 724 (SEQ ID NO: 278)
AAV6    AKSANVDFTVDNNGLYTEPRPIGTRYLTRPL 736 (SEQ ID NO: 279)
AAV7    EKQTGVDFAVDSQGVYSEPRPIGTRYLTRNL 737 (SEQ ID NO: 280)
AAV8    YKSTSVDFAVNTEGVYSEPRPIGTRYLTRNL 738 (SEQ ID NO: 143)
hu31    YKSNNVEFAVSTEGVYSEPRPIGTRYLTRNL 736 (SEQ ID NO: 281)
hu32    YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL 736 (SEQ ID NO: 282)
AAV9    YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL 736 (SEQ ID NO: 144)
rh10    YKSTNVDFAVNTDGTYSEPRPIGTRYLTRNL 738 (SEQ ID NO: 145)
SUBS    GQQVSLLWTPDAA-K-RTT-A-------HP-
        NDPQF D   SSN E T            H
        A  TG      NQ L
        E  A        T
```

FIG. 22

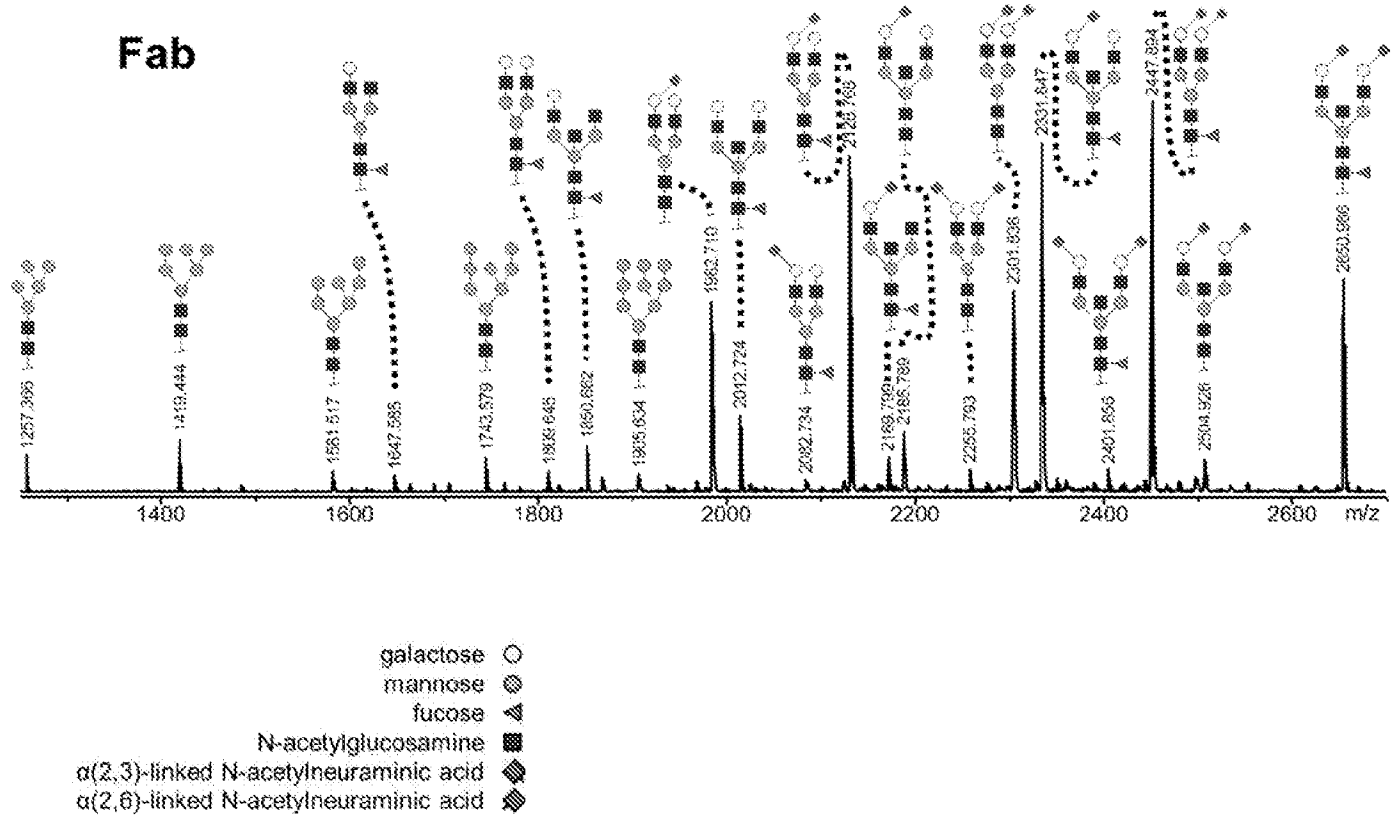

Fab
1257.395
1419.444
1581.517
1647.595
1743.579
1838.646
1850.682
1965.634
1982.710
2012.724
2082.734
2169.799
2185.789
2255.793
2301.838
2401.855
2447.894
2504.926
2650.986
1400
1600
1800
2000
2200
2400
2600
m/z
galactose
mannose
fucose
N-acetylglucosamine
α(2,3)-linked N-acetylneuraminic acid
α(2,6)-linked N-acetylneuraminic acid

FIG. 23

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

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

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

IgG1    PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK  447 (SEQ ID NO: 283)
IgG2    PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK  447 (SEQ ID NO: 284)
IgG4    PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK  447 (SEQ ID NO: 285)
        **:***********:*********:************************:**
```

FIGS. 24A-D

FIG. 24A

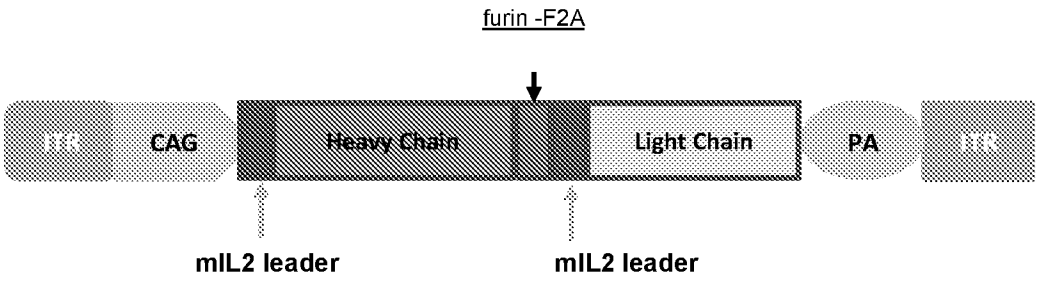


FIG. 24B

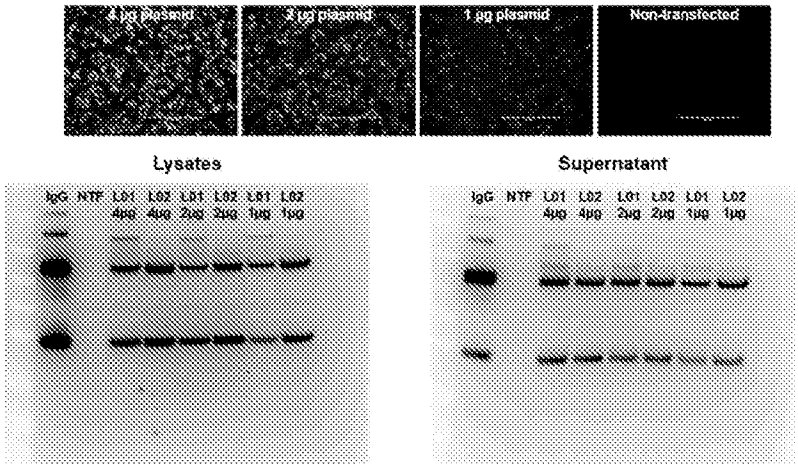


FIG. 24C

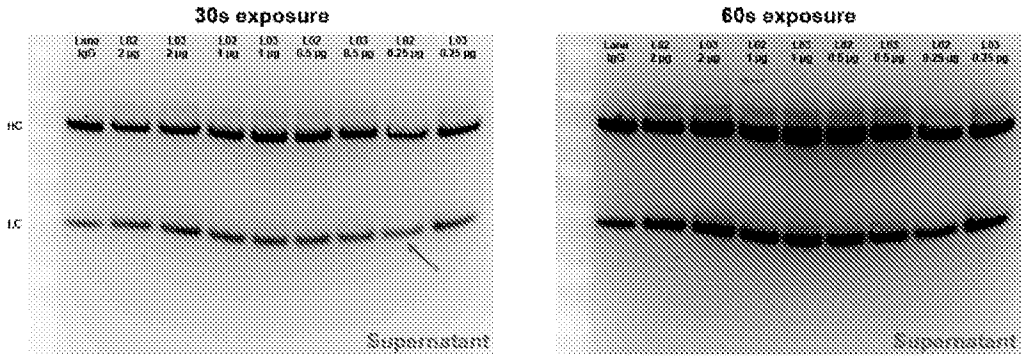


FIG. 24D

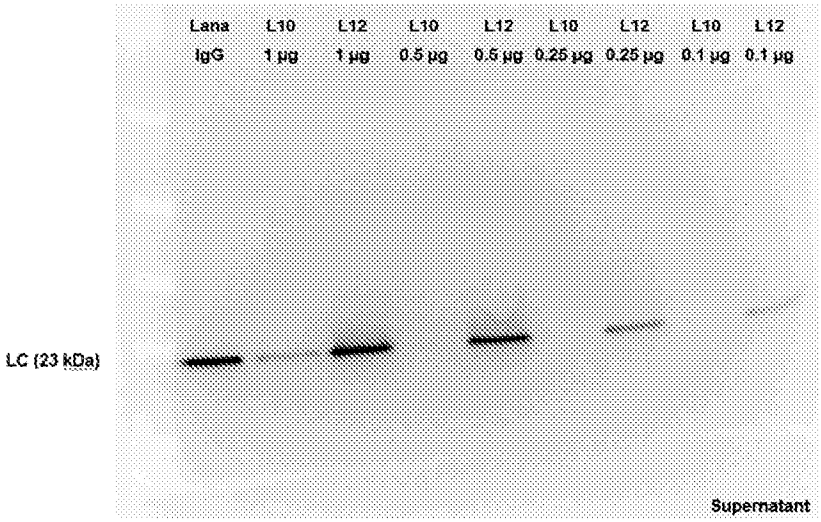

Lane
IgG
L10
1 µg
L12
1 µg
L10
0.5 µg
L12
0.5 µg
L10
0.25 µg
L12
0.25 µg
L10
0.1 µg
L12
0.1 µg
LC (23 kDa)
Supernatant

FIG. 25

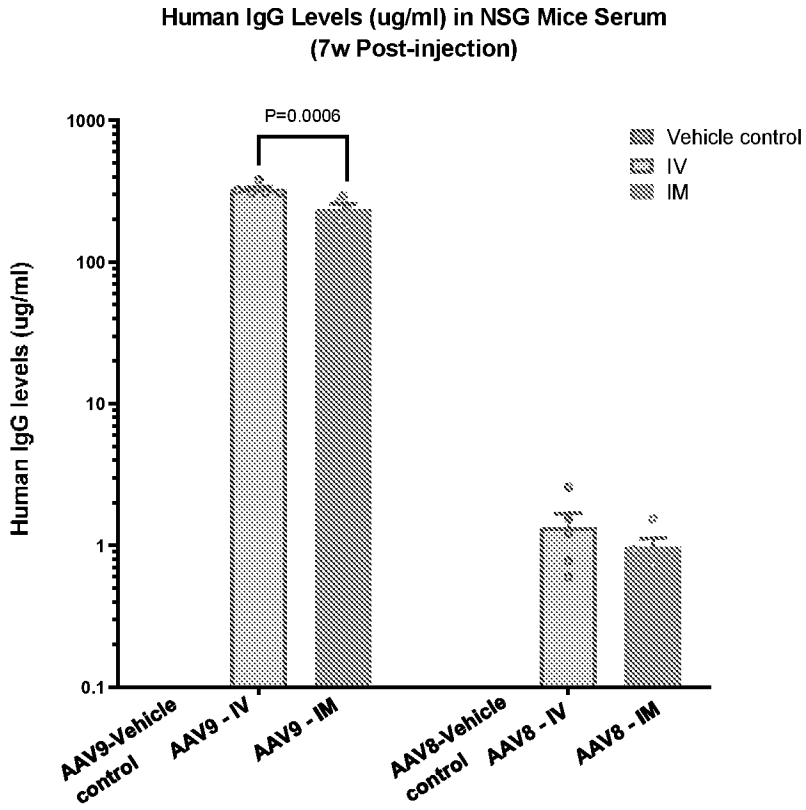

Human IgG Levels (ug/ml) in NSG Mice Serum
(7w Post-injection)
P=0.0006
Vehicle control
IV
IM
Human IgG levels (ug/ml)
1000
100
10
1
0.1
AAV9-Vehicle control
AAV9 - IV
AAV9 - IM
AAV8-Vehicle control
AAV8 - IV
AAV8 - IM

FIG. 26

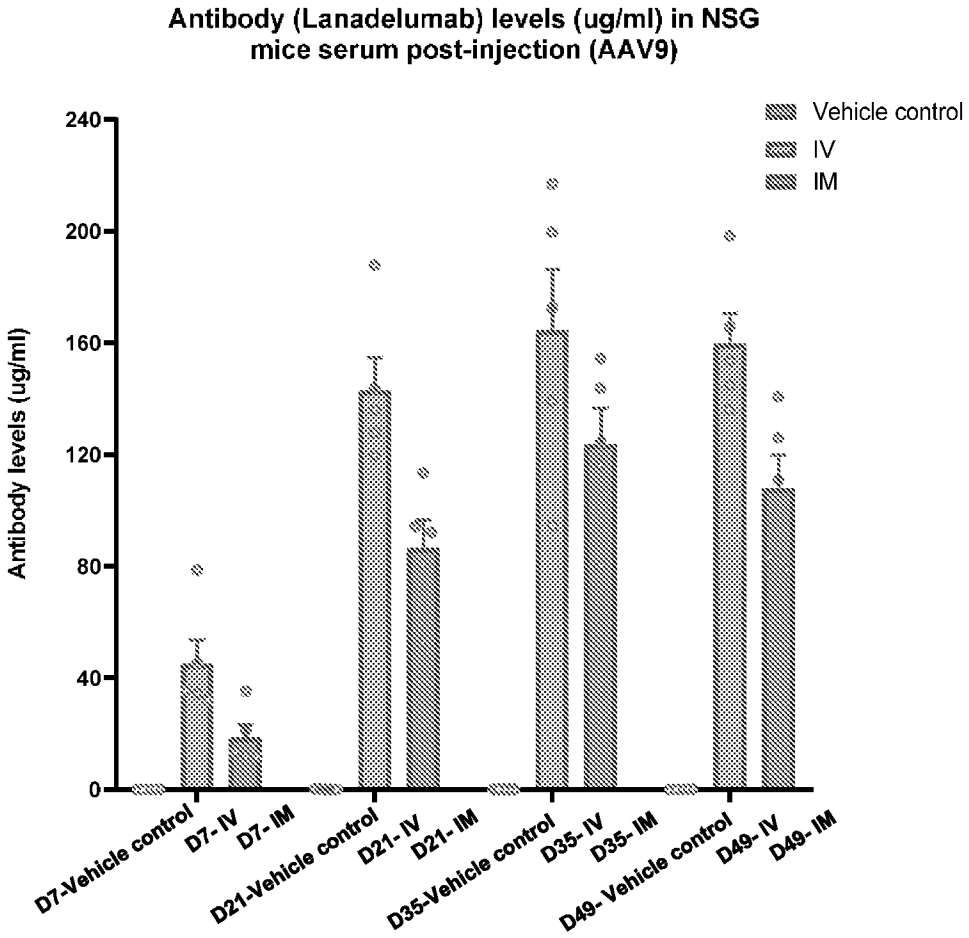

Antibody (Lanadelumab) levels (ug/ml) in NSG mice serum post-injection (AAV9)
Vehicle control
IV
IM
Antibody levels (ug/ml)
240
200
160
120
80
40
0
D7-Vehicle control
D7- IV
D7- IM
D21-Vehicle control
D21- IV
D21- IM
D35-Vehicle control
D35- IV
D35- IM
D49- Vehicle control
D49- IV
D49- IM

FIG. 27

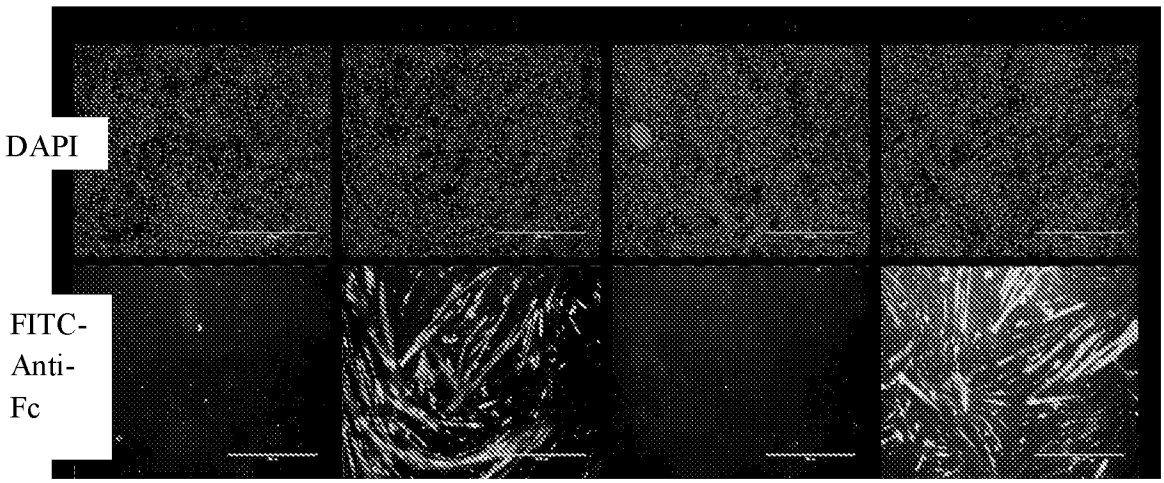


FIG. 28A

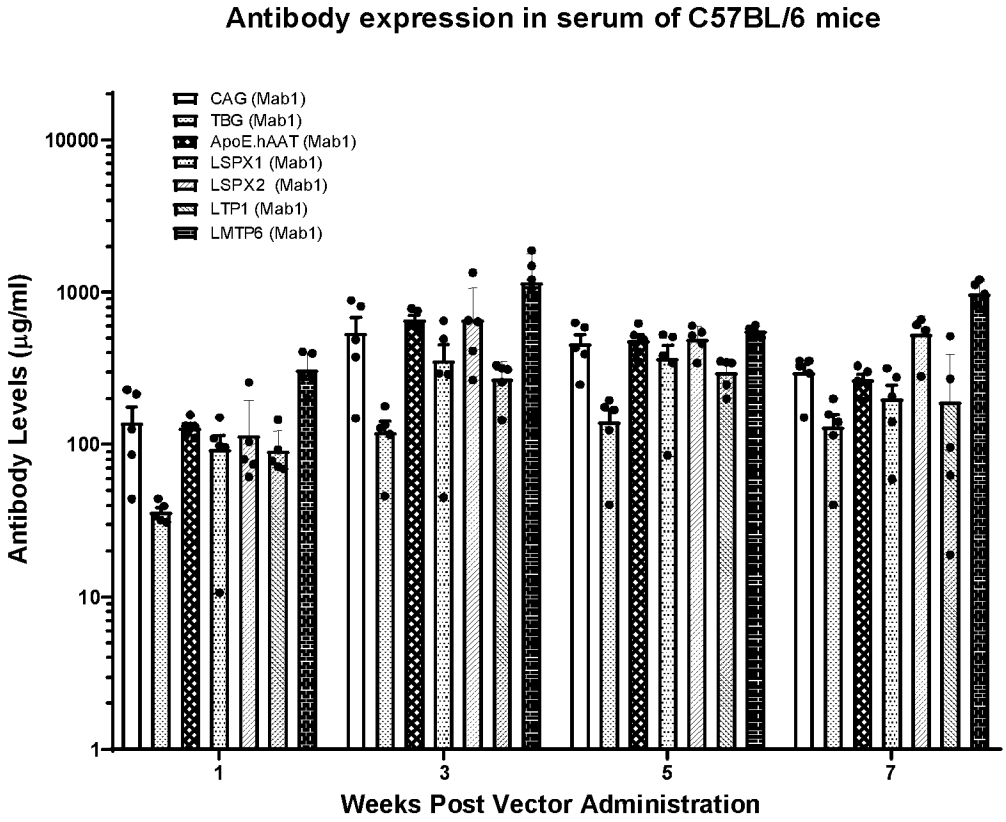

Antibody expression in serum of C57BL/6 mice
CAG (Mab1)
TBG (Mab1)
ApoE.hAAT (Mab1)
LSPX1 (Mab1)
LSPX2 (Mab1)
LTP1 (Mab1)
LMTP6 (Mab1)
Antibody Levels (µg/ml)
10000
1000
100
10
1
1
3
5
7
Weeks Post Vector Administration

FIG. 28B

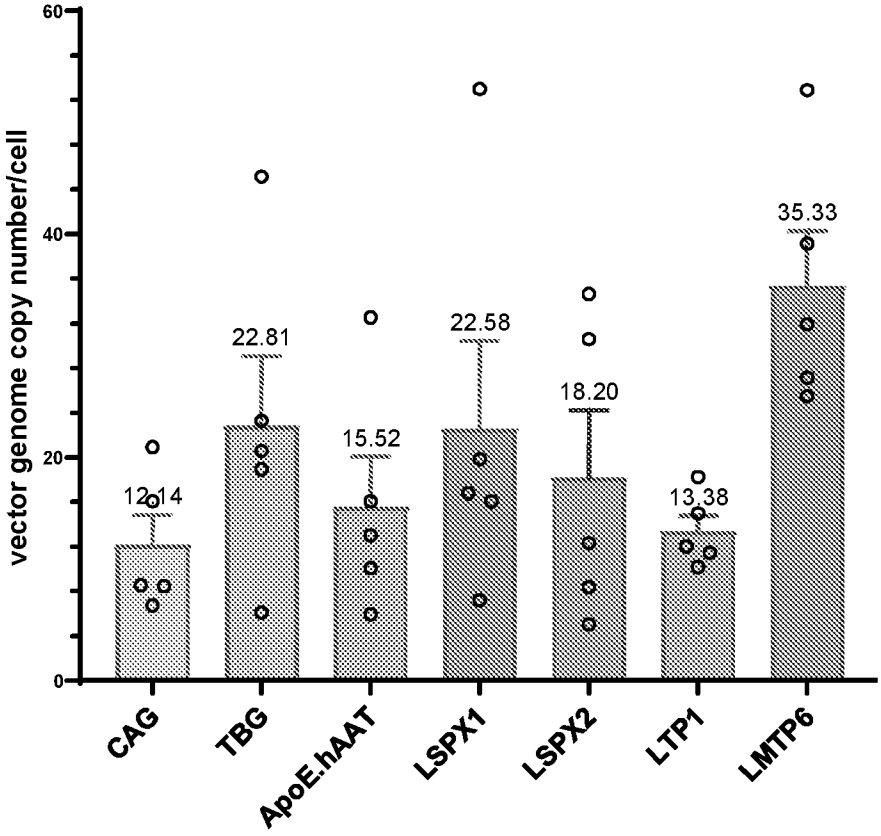

vector genome copy number/cell
60
40
20
0
12.14
22.81
15.52
22.58
18.20
13.38
35.33
CAG
TBG
ApoE.hAAT
LSPX1
LSPX2
LTP1
LMTP6

FIG. 29A BENRALIZUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Benralizumab Heavy Chain (SEQ ID NO: 364):
EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVIHWVRQRPGQGLAWMGYINPYNDGTKY
NERFKGKVTITSDRSTSTVYMELSSLRS*EDTAVY*LCGREGIRYYGLLGDYWG**QGT**LVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV*EPKSCD +/- KTHT (or*
*KTHL) +/- CPPCPA +/- PELLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Benralizumab Light Chain (SEQ ID NO: 365):
DIQMTQSPSSLSASVGDRVTITCGTSEDIINYLNWYQQKPGKAPKLLIYHTSRLQSGVPS
RFSGSGSGTDFTLTISSLQP*EDFATYY*CQQGYTLPYTFG**QGT**KVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored.
EDTAVY = Y-sulfation site (SEQ ID NO: 250).
QGT= Glutamine (Q) glycosylation site.
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored.
EDFATYY = Y-sulfation site (SEQ ID NO: 242)
QGT = Glutamine (Q) glycosylation site.
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site.

FIG. 29B RESLIZUMAB IgG4 FAB CONSTRUCT:

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Reslizumab Heavy Chain (SEQ ID NO: 366):
EVQLVESGGGLVQPGGSLRLSCAVSGLSLTSN**SVN**WIRQAPGKGLEWVGLIWSNGDTDYN
SAIKSRFTISRDTSKSTVYLQMNSLRA*EDTAVYY*CAREYYGYFDYWG**QGT**LVTVSSASTK
GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTKTY**TCN**VDHKPSNTKVDKRV*ESKY+/- GPPCPPCPA (or GPPCP*
*SCPA) +/- PEFLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Reslizumab Light Chain (SEQ ID NO: 367):
DIQMTQSPSSLSASVGDRVTITCLASEGISSYLAWYQQKPGKAPKLLIYGANSLQTGVPS
RFSGSGSATDYTLTISSLQP*EDFATYY*CQQSYKFPNTFG**QGT**KVEVKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC
Heavy Chain Legend:
CDRs are underscored.
EDTAVYY = Y-sulfation site (SEQ ID NO: 236).
QGT= Glutamine (Q) glycosylation site.
(S/T)*X*N = Nonconsensus Asparaginal (N) glycosylation site
ESKYGPPCPPCPAPEFLGG = Hinge region (SEQ ID NO: 214)
Or
ESKYGPPCPSCPAPEFLGG = Hinge region (SEQ ID NO: 215)

Light Chain Legend:
CDRs are underscored.
EDFATYY = Y-sulfation site (SEQ ID NO: 242)
QGT = Glutamine (Q) glycosylation site.
(S/T)*X*N = Nonconsensus Asparaginal (N) glycosylation site.

FIG. 29C TRALOKINUMAB IgG4 FAB CONSTRUCT:

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Tralokinumab Heavy Chain (SEQ ID NO: 368):
QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGLSWVRQAPGQGLEWMGWI**SAN**NGDTN
YGQEFQGRVTMTTDTSTSTAYMELRSLRS*DDTAVYY*CARDSSSSWARWFFDLWGRGTLV
TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTY**TCN**VDHKPSNTKVDKRV*ESKY+/- GPPCPPCP*
*A (or GPPCPSCPA) +/- PEFLGG*PSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Tralokinumab Light Chain (SEQ ID NO: 369):
SYVLTQPPSVSVAPGKTARITCGGNIIGSKLVHWYQQKPGQAPVLVIYDDGDRPSGIPER
FSGSN**SGN**TATLTISRVEAG*DEADYY*CQVWDTGSDPVVFGGGTKLTVLGQPKAAPSVTLF
PPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ**SNN**KYAASSYL
SLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
Heavy Chain Legend:
CDRs are underscored.
DDTAVYY = Y-sulfation site (SEQ ID NO: 273).
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site
ESKYGPPCPPCPAPEFLGG = Hinge region (SEQ ID NO: 214)
Or
ESKYGPPCPSCPAPEFLGG = Hinge region (SEQ ID NO: 215)

Light Chain Legend:
CDRs are underscored.
DEADYY = Y-sulfation site (SEQ ID NO: 255)
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site.

FIG. 29D NEMOLIZUMAB IgG2 FAB CONSTRUCT:

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Nemolizumab Heavy Chain (SEQ ID NO: 370):
QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYIMNWVRQAPGQGLEWMGLINPYNGGTDY
NPQFQDRVTITADKSTSTAYMELSSLRS*EDTAVYY*CARDGYDDGPYTLETWGQGTLVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQS
SGLYSLSSVVTVP**SSN**FGTQTY**TCN**VDHKPSNTKVDKTV*ERKSCVE +/- CPPCPA +/-P*
PVAG
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Nemolizumab Light Chain (SEQ ID NO: 371):
DIQMTQSPSSLSASVGDRVTITCQASEDIYSFVAWYQQKPGKAPKLLIYNAQTEAQGVPS
RFSGSGSGTDFTLTISSLQP*EDFATYY*CQHHYDSPLTFGGGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC

Heavy Chain Legend:
CDRs are underscored.
EDTAVYY = Y-sulfation site (SEQ ID NO: 236).
QGT= Glutamine (Q) glycosylation site.
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site
ERKSCVECPPCPAPPVAG = Hinge region (SEQ ID NO: 433)

Light Chain Legend:
CDRs are underscored.
EDFATYY = Y-sulfation site (SEQ ID NO: 242)
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site.

FIG. 29E OMALIZUMAB IgG1 FAB CONSTRUCT:

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Omalizumab Heavy Chain (SEQ ID NO: 372):
EVQLVESGGGLVQPGGSLRLSCAVSGYSITSGY**SWN**WIRQAPGKGLEWVASITYDG**STN**Y
ADSVKGRFTISRDD**SKN**TFYLQMNSLRA*EDTAVYY*CARGSHYFGHWHFAVWG**QGT**LVTVS
SGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKA*EPKSCD +/- KTHT (or*
KTHL) +/- CPPCPA +/- PELLGGPSVFL
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Omalizumab Light Chain (SEQ ID NO: 373):
DIQLTQSPSSLSASVGDRVTITCRASQSVDYDGDSYMNWYQQKPGKAPKLLIYAASYLES
GVPSRFSGSGSGTDFTLTISSLQP*EDFATYY*CQQSHEDPYTFG**QGT**KVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ**SGN**SQESVTEQDSKDSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTK**SFN**RGEC
Heavy Chain Legend:
CDRs are underscored.
EDTAVYY = Y-sulfation site (SEQ ID NO: 236).
QGT= Glutamine (Q) glycosylation site.
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site
EPKSCDKTHTCPPCPAPELLGG = Hinge Region (SEQ ID NO: 194)
Or
EPKSCDKTHLCPPCPAPELLGG = Hinge Region (SEQ ID NO: 195)

Light Chain Legend:
CDRs are underscored.
EDFATYY = Y-sulfation site (SEQ ID NO: 242)
QGT= Glutamine (Q) glycosylation site.
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site.

FIG. 29F TEZEPELUMAB IgG2 FAB CONSTRUCT:

Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Tezepelumab Heavy Chain (SEQ ID NO: 374):
QMQLVESGGGVVQPGRSLRLSCAASGFTFRTYGMHWVRQAPGKGLEWVAVIWYDGSNKHY
ADSVKGRFTITRDN**SKNTLN**LQMNSLRA*EDTAVYY*CARAPQWELVHEAFDIWG**QGT**MVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV**SWN**SGALTSGVHTFPAVLQ
SSGLYSLSSVVTVP**SSN**FGTQTY**TCN**VDHKPSNTKVDKTV*ERKCCVE +/- CPPCPA +/- P*
PVAG
Linker: RKRR +/- GSG + (EGRGSLLTCGDVEENPGP or APVKQTLNFDLLKLAGDVESNPGP)
(SEQ ID NOs: 222, 227, 230; full-length sequences disclosed as SEQ ID NOS 231 and 429, respectively)
Leader (SEQ ID NO: 146):
MYRMQLLLLIALSLALVTNS
Tezepelumab Light Chain (SEQ ID NO: 375):
SYVLTQPPSVSVAPGQTARITCGGNNLGSKSVHWYQQKPGQAPVLVVYDDSDRPSWIPER
FSGSN**SGN**TATLTISRGEAG*DEADYY*CQVWDSSSDHVVFGGGTKLTVLGQPKAAPSVTLF
PPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ**SNN**KYAASSYL
SLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Heavy Chain Legend:
CDRs are underscored.
EDTAVYY = Y-sulfation site (SEQ ID NO: 236).
QGT= Glutamine (Q) glycosylation site.
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site
ERKCCVECPPCPAPPVAG = Hinge region (SEQ ID NO: 220)

Light Chain Legend:
CDRs are underscored.
DEADYY = Y-sulfation site (SEQ ID NO: 255)
(S/T)XN = Nonconsensus Asparaginal (N) glycosylation site.

FIG. 30A

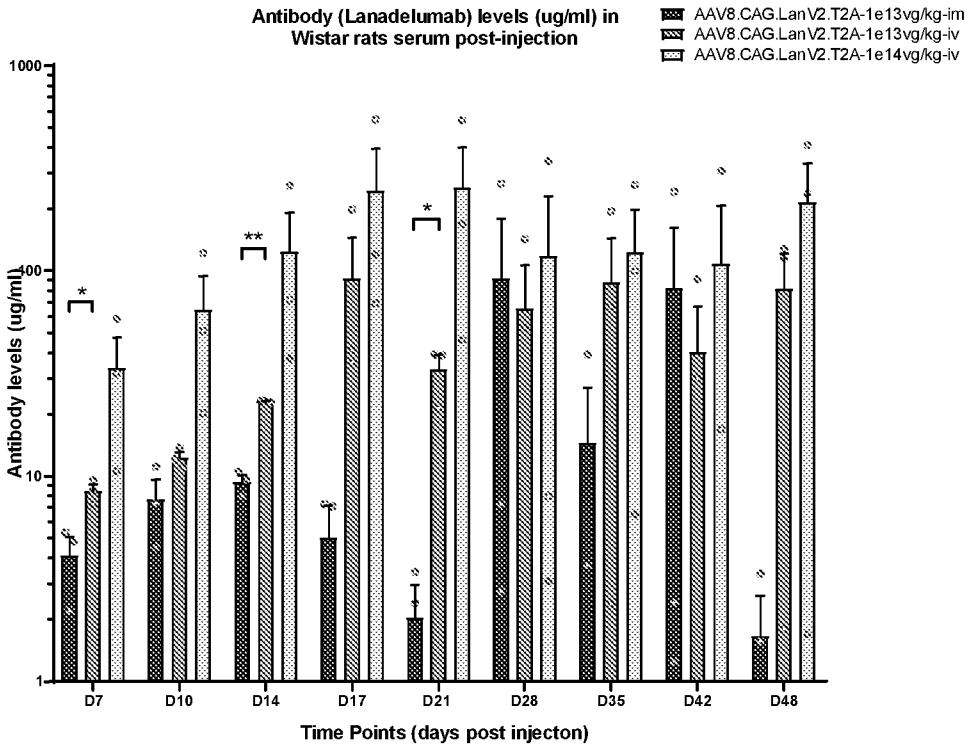

Antibody (Lanadelumab) levels (ug/ml) in Wistar rats serum post-injection
AAV8.CAG.LanV2.T2A-1e13vg/kg-im
AAV8.CAG.LanV2.T2A-1e13vg/kg-iv
AAV8.CAG.LanV2.T2A-1e14vg/kg-iv
Antibody levels (ug/ml)
1000
100
10
1
*
**
*
D7
D10
D14
D17
D21
D28
D35
D42
D48
Time Points (days post injecton)

FIG. 30B

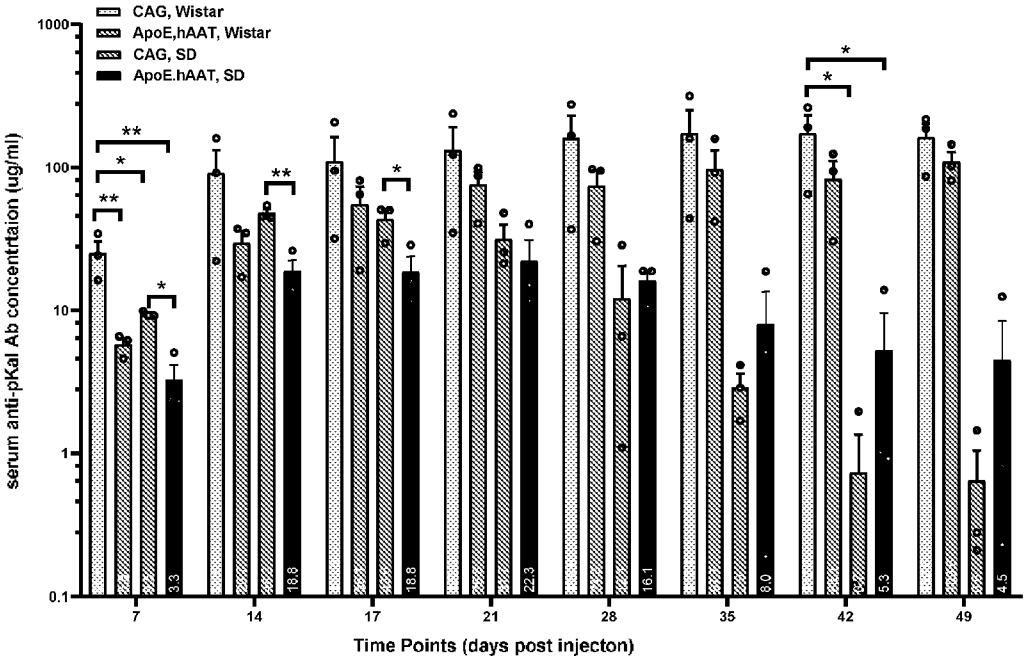

CAG, Wistar
ApoE,hAAT, Wistar
CAG, SD
ApoE.hAAT, SD
serum anti-pKal Ab concentrtaion (ug/ml)
1000
100
10
1
0.1
7
14
17
21
28
35
42
49
Time Points (days post injecton)
3.3
18.8
18.8
22.3
16.1
8.0
5.3
4.5

FIG. 31A

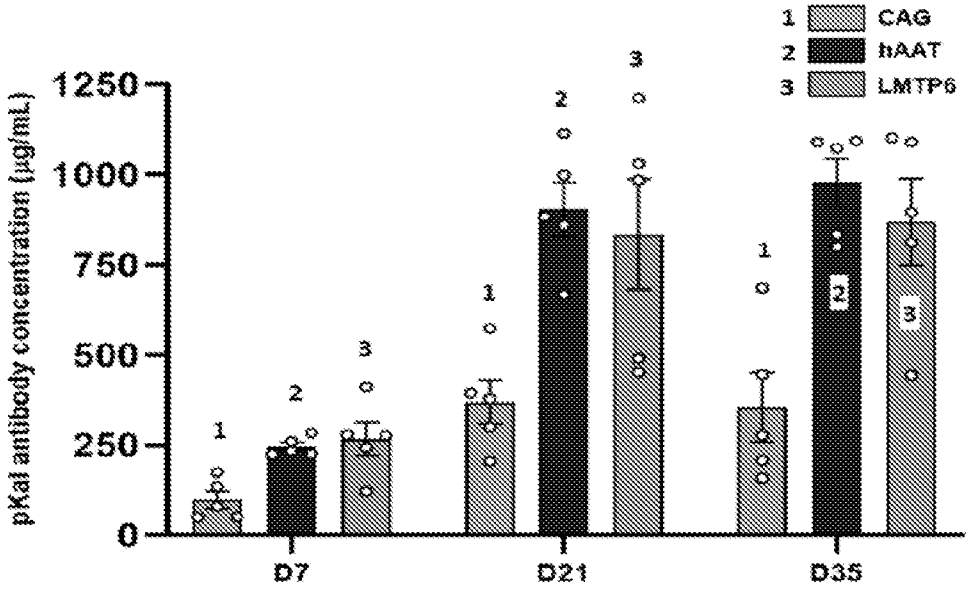

1 CAG
2 hAAT
3 LMTP6
pKal antibody concentration (µg/mL)
1250
1000
750
500
250
0
D7
D21
D35

FIG. 31B

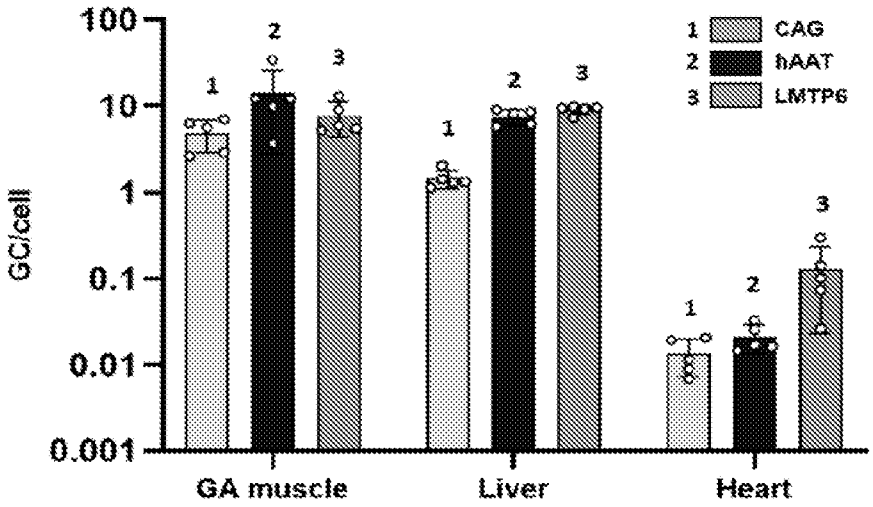

100
10
1
0.1
0.01
0.001
GC/cell
1
2
3
GA muscle
Liver
Heart
CAG
hAAT
LMTP6

FIG. 31C

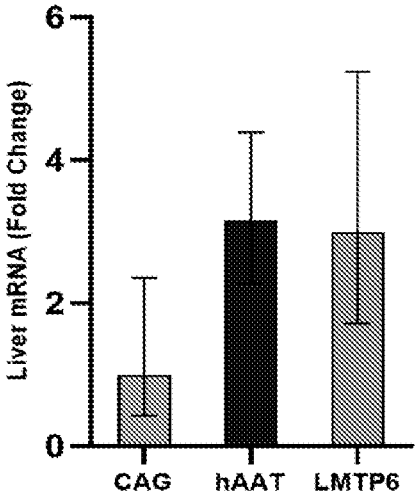


FIG. 31D

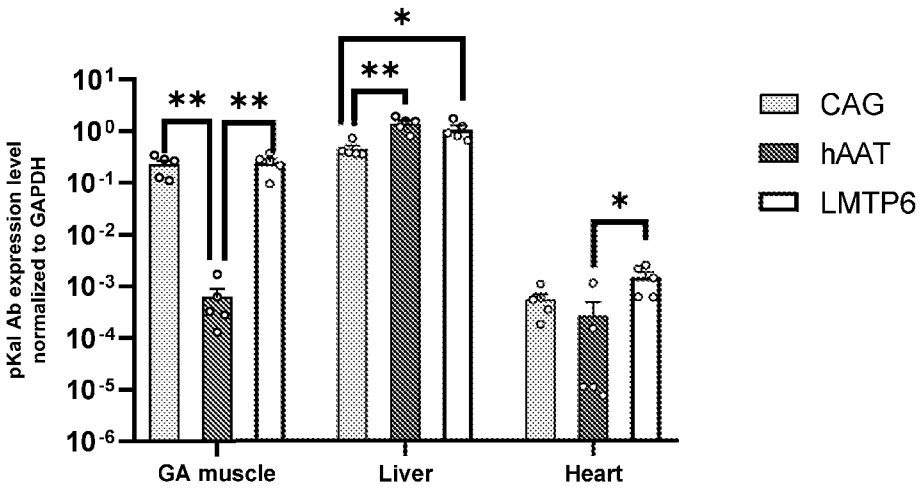
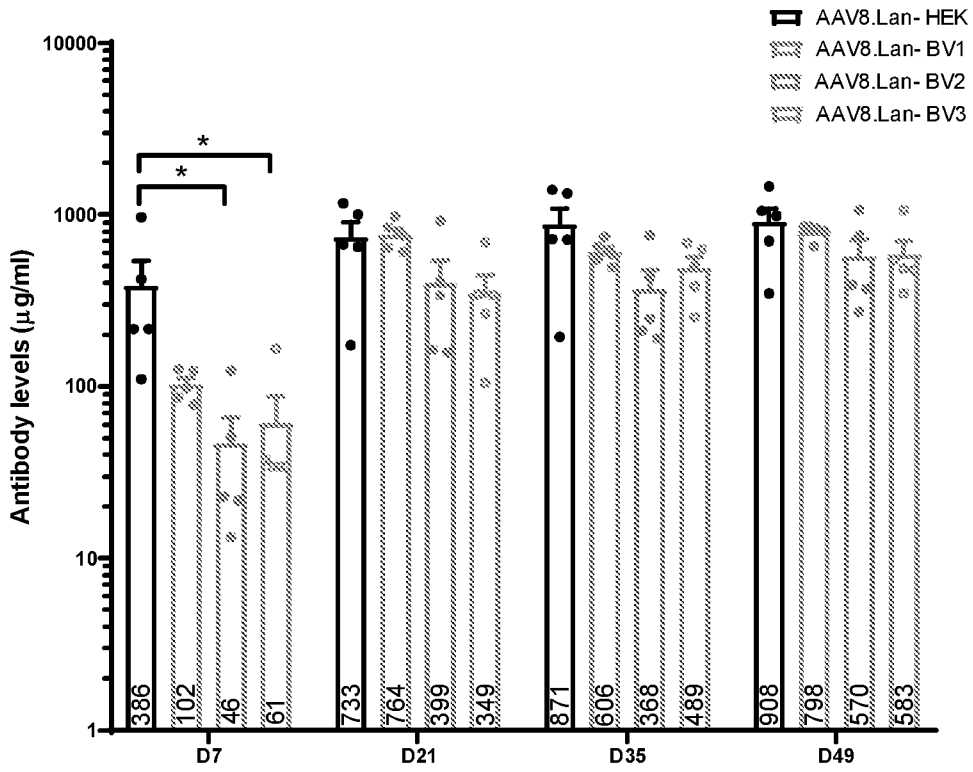

pKal Ab expression level normalized to GAPDH
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
**
**
*
**
*
GA muscle
Liver
Heart
CAG
hAAT
LMTP6

FIG. 32


AAV8.Lan- HEK
AAV8.Lan- BV1
AAV8.Lan- BV2
AAV8.Lan- BV3
Antibody levels (µg/ml)
10000
1000
100
10
1
*
*
386
102
46
61
733
764
399
349
871
606
368
489
908
798
570
583
D7
D21
D35
D49

FIGS. 33A/B

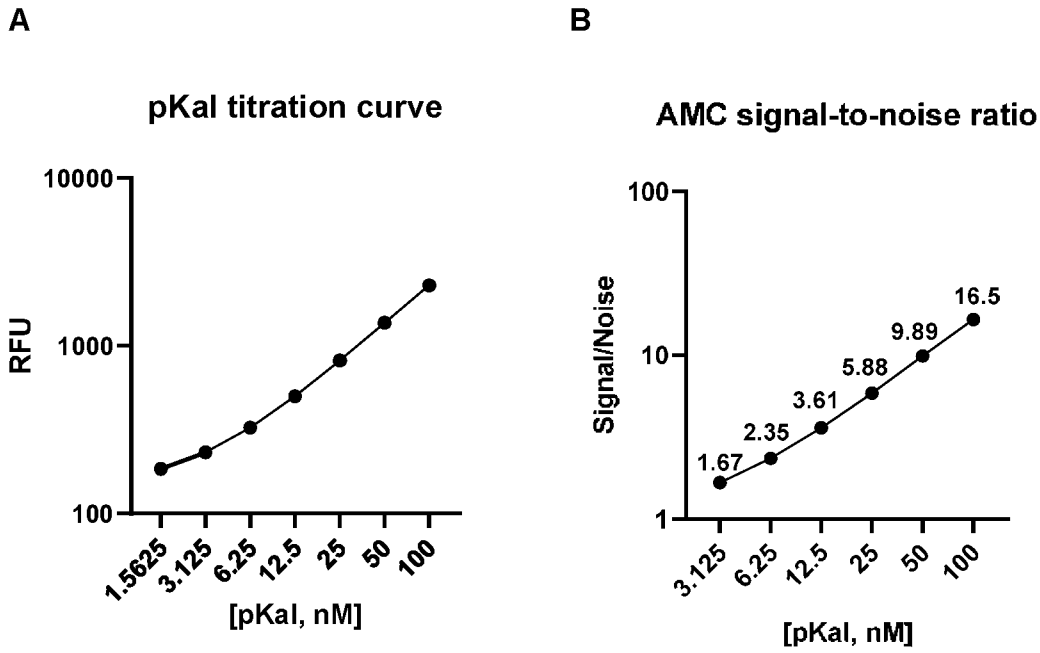
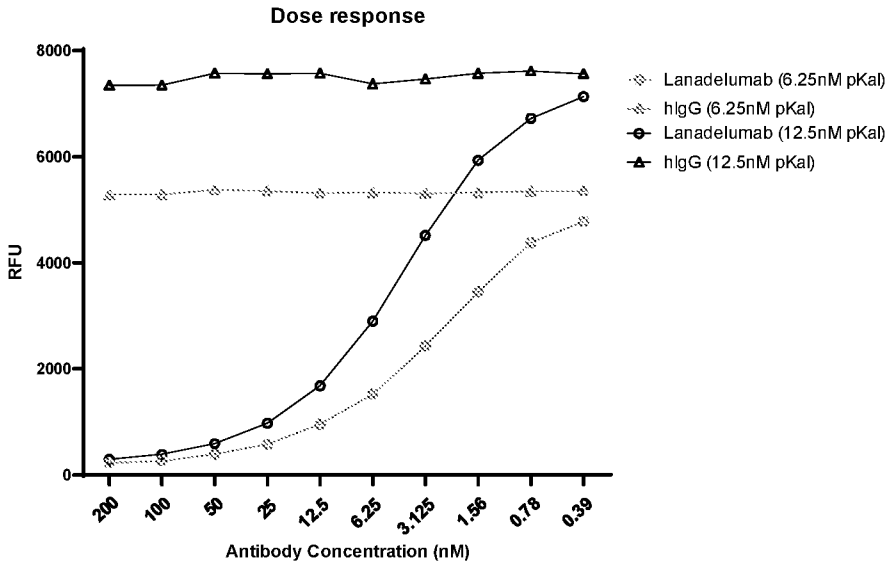

A
pKal titration curve
RFU
10000
1000
100
1.5625
3.125
6.25
12.5
25
50
100
[pKal, nM]
B
AMC signal-to-noise ratio
Signal/Noise
100
10
1
1.67
2.35
3.61
5.88
9.89
16.5
3.125
6.25
12.5
25
50
100
[pKal, nM]

FIG. 33C


Dose response
8000
6000
4000
2000
0
RFU
200
100
50
25
12.5
6.25
3.125
1.56
0.78
0.39
Antibody Concentration (nM)
Lanadelumab (6.25nM pKal)
hIgG (6.25nM pKal)
Lanadelumab (12.5nM pKal)
hIgG (12.5nM pKal)

FIGS. 33D/E

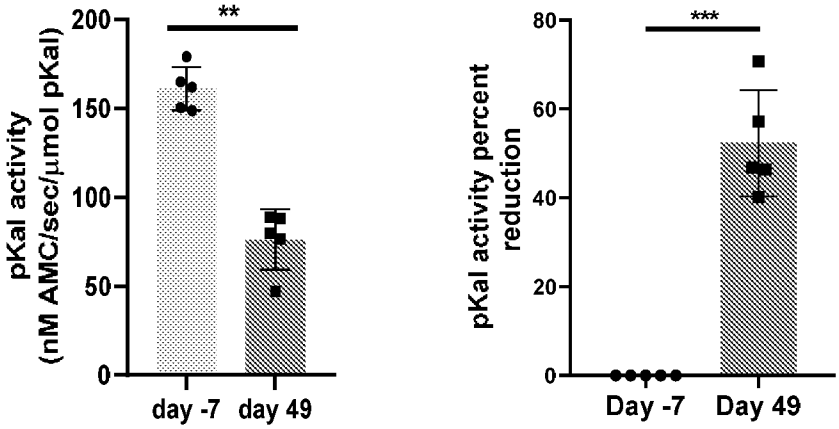
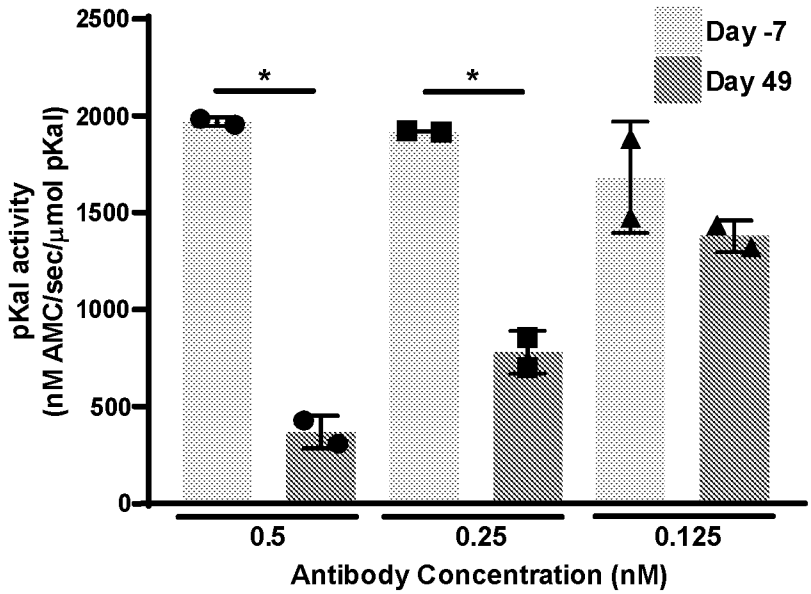
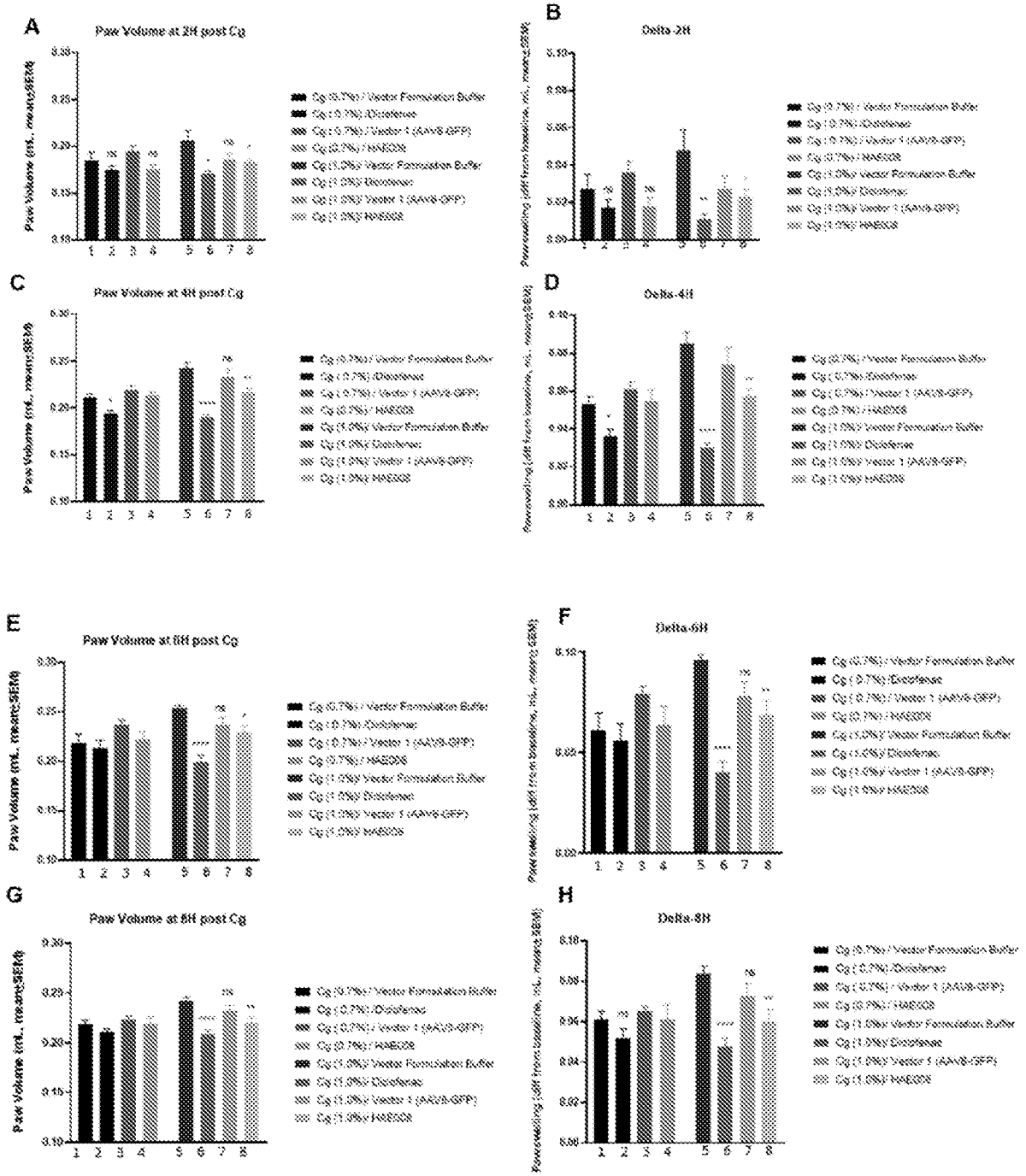
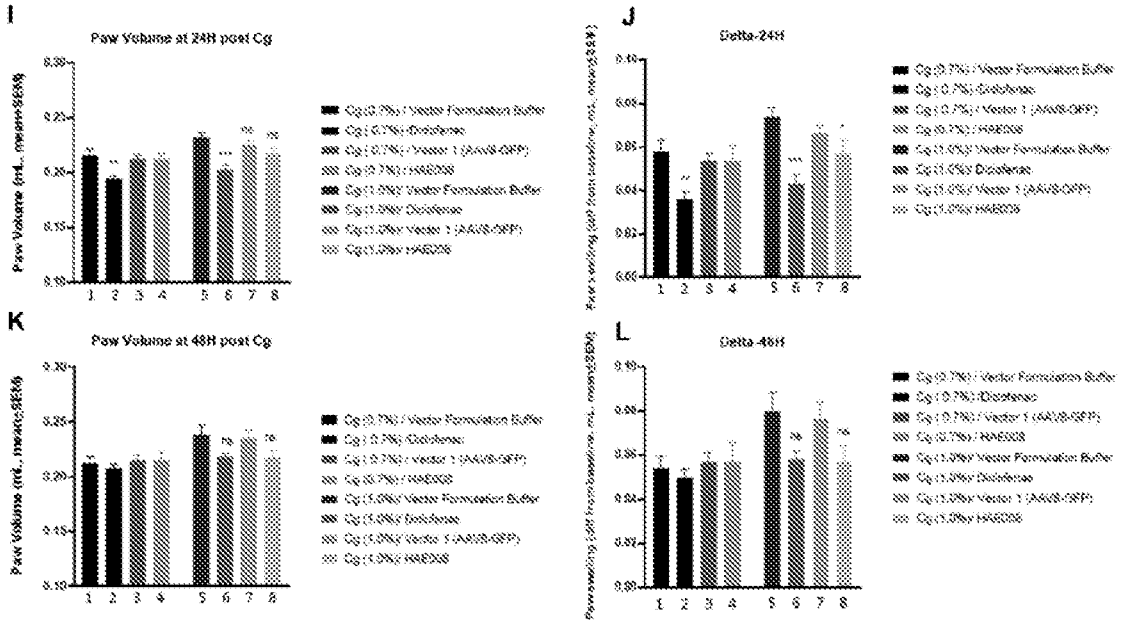

pKal activity
(nM AMC/sec/μmol pKal)
200
150
100
50
0
**
day -7
day 49
pKal activity percent
reduction
80
60
40
20
0
***
Day -7
Day 49

FIG. 33F

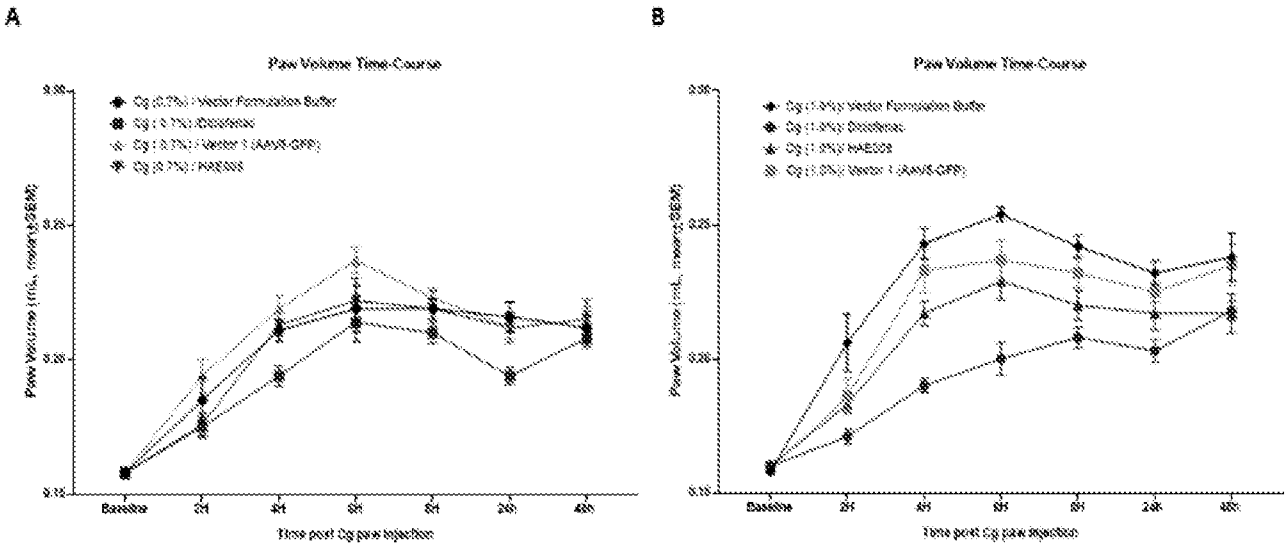

2500
2000
1500
1000
500
0
pKal activity
(nM AMC/sec/µmol pKal)
*
*
Day -7
Day 49
0.5
0.25
0.125
Antibody Concentration (nM)

FIGS. 34A-L

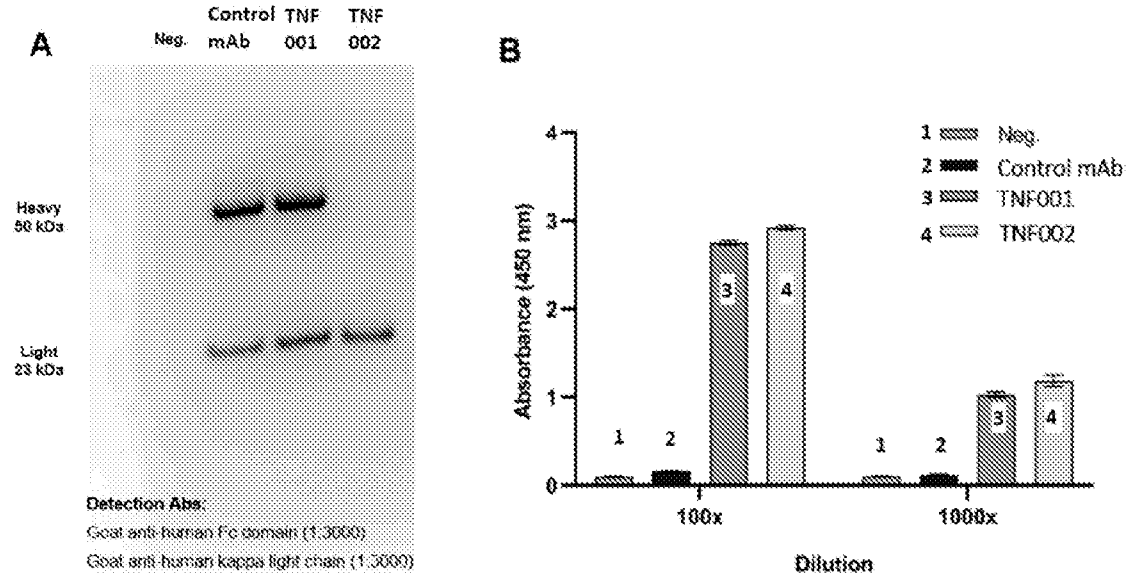

A
Paw Volume at 2H post Cg
B
Delta-2H
C
Paw Volume at 4H post Cg
D
Delta-4H
E
Paw Volume at 6H post Cg
F
Delta-6H
G
Paw Volume at 8H post Cg
H
Delta-8H


I
Paw Volume at 24H post Cg
J
Delta-24H
K
Paw Volume at 48H post Cg
L
Delta-48H

FIGS. 35A/B



FIGS. 36 A/B


A
Neg.
Control mAb
TNF 001
TNF 002
Heavy 50 kDa
Light 23 kDa
Detection Abs:
Goat anti-human Fc domain (1:3000)
Goat anti-human kappa light chain (1:3000)
B
Absorbance (450 nm)
0
1
2
3
4
1 Neg.
2 Control mAb
3 TNF001
4 TNF002
100x
1000x
Dilution

FIGS. 37A-C

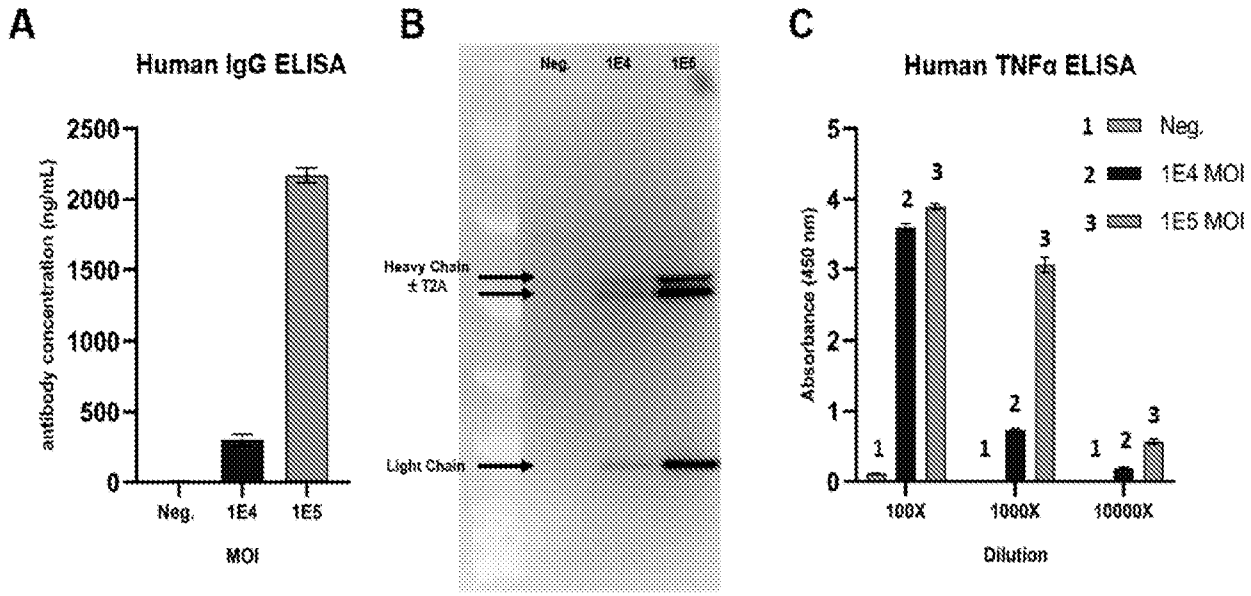

A
Human IgG ELISA
antibody concentration (ng/mL)
2500
2000
1500
1000
500
0
Neg.
1E4
1E5
MOI
B
Neg.
1E4
1E5
Heavy Chain
± T2A
Light Chain
C
Human TNFα ELISA
Absorbance (450 nm)
5
4
3
2
1
0
1 Neg.
2 1E4 MOI
3 1E5 MOI
100X
1000X
10000X
Dilution

FIG. 38

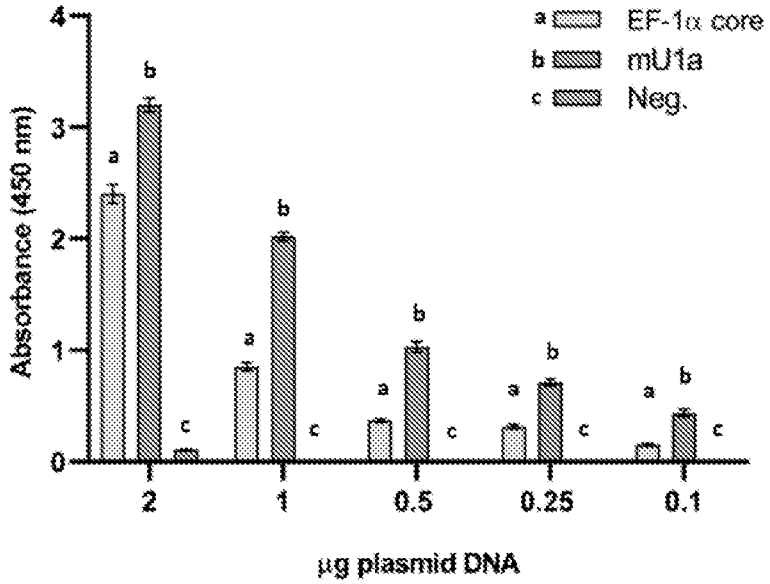
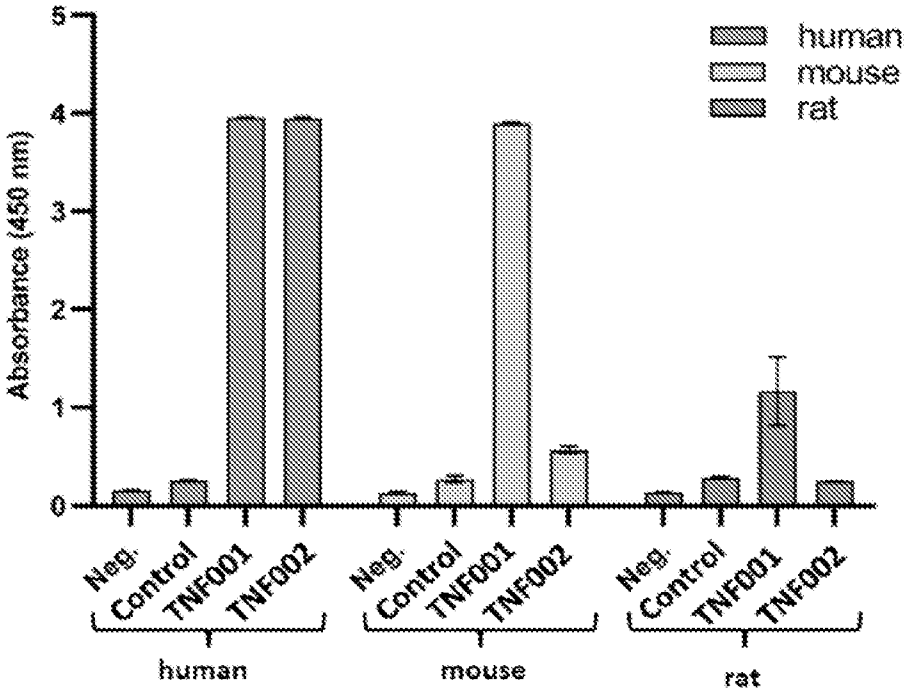

a EF-1α core
b mU1a
c Neg.
Absorbance (450 nm)
0
1
2
3
4
2
1
0.5
0.25
0.1
µg plasmid DNA

FIG. 39


human
mouse
rat
Absorbance (450 nm)
0
1
2
3
4
5
Neg. Control
TNF001
TNF002
human
mouse
rat

SEQUENCE LISTING

<110> REGENXBIO INC.

<120> FULLY-HUMAN POST-TRANSLATIONALLY MODIFIED ANTIBODY THERAPEUTICS

<130> 38013.0001P1

<140>
<141>

<150> 62/967,472
<151> 2020-01-29

<150> 62/838,165
<151> 2019-04-24

<160> 454

<170> PatentIn version 3.5

<210> 1
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (217)..(237)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (220)..(220)
<223> /replace="Leu"

<220>
<221> SITE
<222> (221)..(237)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (227)..(237)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE

<222> (1)..(237)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 1

```
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 Arg Tyr
            20                  25                  30


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala 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 Ser Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110


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


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


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175
```

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


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


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


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


<210> 2
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 2
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1               5                   10                  15


Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Ile Tyr Ser
            20                  25                  30


Asp Gly Asn Ala Tyr Leu His Trp Phe Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60


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


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Ser
                85                  90                  95


Thr His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

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


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


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


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


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


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


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> 3
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> VARIANT
<222> (24)..(24)
<223> /replace="Val"

<220>
<221> SITE
<222> (220)..(240)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (223)..(223)
```

<223> /replace="Leu"

<220>
<221> SITE
<222> (224)..(240)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (230)..(240)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(240)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 3
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 Asp Asn
20 25 30

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

Ser Phe Ile Ser Asn Leu Ala Tyr Ser Ile Asp Tyr Ala 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

Val Ser Gly Thr Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro

```
        115                 120                 125

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

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

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

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

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

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

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


<210> 4
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 4
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Val Ser Gln Ser Leu Leu His Ser
            20                  25                  30

Asn Gly Tyr Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45
```

```
Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

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

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Thr
                85                  90                  95

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

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

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

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

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

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

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

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

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

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (234)..(254)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (237)..(237)
<223> /replace="Leu"

<220>
<221> SITE
<222> (238)..(254)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (244)..(254)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(254)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 5
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Lys Tyr
20 25 30

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

Gly Ile Ile Asn Pro Ile Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

Ala Arg Asp Pro Ser Gly Ile Ala Leu Ala Gly Pro Ala Ser Arg Gly
            100                 105                 110

Tyr Gln 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 Arg 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
```

<210> 6
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 6
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1   5   10   15

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

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

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ala Arg Leu Gly Pro Trp
                85   90   95

Thr Phe Gly Gly 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> 7
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (218)..(237)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (223)..(223)
<223> /replace="Ser"

<220>
<221> SITE
<222> (227)..(237)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(237)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 7
Glu Val Lys Val Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Met Lys Leu Ser Cys Val Val Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

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

```
Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Glu Glu
    50                  55                  60

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

Val Tyr Leu Gln Met Asn Asn Leu Arg Ala Glu Asp Ser Gly Ile Tyr
                85                  90                  95

Tyr Cys Thr Asn Trp Glu Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110

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

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
    130                 135                 140

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

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

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

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

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

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
225                 230                 235
```

<210> 8
<211> 218
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 8
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

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

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

Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ser
50 55 60

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

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

Glu Ile Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu 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

<210> 9
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> VARIANT
<222> (61)..(61)
<223> /replace="Thr"

<220>
<221> SITE
<222> (221)..(240)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (226)..(226)
<223> /replace="Ser"

<220>
<221> SITE
<222> (230)..(240)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(240)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 9
Glu 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 Thr Val Ser Gly Phe Ser Leu Thr Ser Asn
            20                  25                  30

Asp Ile Ala Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

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

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg His Arg Leu Tyr Tyr Gly Ala Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

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

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

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

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

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

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

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

Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
```

225 230 235 240

<210> 10
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 10
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Glu Tyr Ser
20 25 30

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

Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

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

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Ala
85 90 95

Thr His Asn Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

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

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

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

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


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


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


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> 11
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (229)..(249)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (232)..(232)
<223> /replace="Leu"

<220>
<221> SITE
<222> (233)..(249)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (239)..(249)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(249)
<223> /note="Variant residues given in the sequence have no
      preference with respect to those in the annotations
      for variant positions"
```

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 11
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

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

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

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

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

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

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

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

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

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

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

Leu Ala Gly Ala Pro Ser Val Phe Leu
245

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

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 12
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys Arg Tyr Val
20 25 30

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

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

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ser Asn Gly His His
85 90 95

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

```
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125


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


Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160


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


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


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


Ala Pro Thr Cys Ser
    210


<210> 13
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (226)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (231)..(231)
<223> /replace="Ser"

<220>
<221> SITE
<222> (235)..(245)
<223> /note="This region may be absent in its entirety"
```

<220>
<221> SITE
<222> (1)..(245)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 13
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Ser Asp Tyr
20 25 30

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

Gly Gln Ile Asn Pro Thr Thr Gly Gly Ala Ser Tyr Asn Gln Lys Phe
50 55 60

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

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

Ala Arg Tyr Tyr Tyr Gly Arg His Phe Asp Val Trp Gly Gln Gly Thr
100 105 110

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

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

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

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

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

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

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

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu
245

<210> 14
<211> 210
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 14
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

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

Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Val Pro Asp
50 55 60

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

```
Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Ser Asn
                85                  90                  95


Glu Asp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Phe
            100                 105                 110


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


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


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


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


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


Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
        195                 200                 205


Glu Cys
    210
```

<210> 15
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (221)..(241)
<223> /note="This region may be absent in its entirety"

<220>

<221> VARIANT
<222> (224)..(224)
<223> /replace="Leu"

<220>
<221> SITE
<222> (225)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (231)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(241)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<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 Asn Tyr
20 25 30

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp 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 Gly Gly Ala Gly Ile Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg 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
```

<210> 16
<211> 220
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 16

```
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 Lys Ser Ile Gln Thr Leu Leu Tyr Ser
            20                  25                  30
```

```
Ser Asn Gln Lys Asn Tyr Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys
        35                  40                  45

Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ile Arg Lys Ser Gly Val
    50                  55                  60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Pro Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln
                85                  90                  95

Tyr Tyr Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
            100                 105                 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
        115                 120                 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
    130                 135                 140

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

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

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

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

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215                 220
```

<210> 17
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (229)..(249)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (232)..(232)
<223> /replace="Leu"

<220>
<221> SITE
<222> (233)..(249)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (239)..(249)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(249)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 17
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

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

Gly Trp Ile Asn Ala Gly Asn Gly Lys Arg Lys Tyr Ser Gln Lys Phe
50 55 60

```
Gln Asp Arg Val Thr Ile Asn Arg Asp Thr Ser Ala Ser Thr Ile Tyr
65                  70                  75                  80

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

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

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

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

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

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

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

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

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

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

Leu Leu Gly Gly Pro Ser Val Phe Leu
                245
```

<210> 18
<211> 220
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<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 Lys Ser Ile Gln Thr Leu Leu Tyr Ser
20 25 30

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

Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ile Arg Lys Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Pro Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
115 120 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140

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

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

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

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

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

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

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> SITE
<222> (227)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (230)..(230)
<223> /replace="Leu"

<220>
<221> SITE
<222> (231)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (237)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(247)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 19
Glu Val Gln Leu Leu 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 Ser Tyr
            20                  25                  30

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

Ser Ser Ile Ser His Leu Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe 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 Gly Gly Ala Asn His Gly Lys Tyr Tyr Tyr Gly Met Asp Lys Trp
            100                 105                 110

Gly Gln Gly Thr Thr 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 Arg Val Glu Pro Lys Ser
    210                 215                 220
```

```
Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu
225                 230                 235                 240


Gly Gly Pro Ser Val Phe Leu
                245


<210> 20
<211> 221
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 20
Gln Ala Val Leu Thr Gln Pro Ala Ser Leu Ser Ala Ser Pro Gly Ala
1               5                   10                  15


Ser Ala Ser Leu Thr Cys Thr Leu Arg Ser Gly Ala Pro Leu Pro Lys
            20                  25                  30


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


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


Pro Ser Arg Phe Ser Gly Ser Lys Asp Ala Ser Ala Asn Ala Gly Ile
65                  70                  75                  80


Leu Leu Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys
                85                  90                  95


Met Val Trp Asp His Gly Val Trp Tyr Phe Gly Gly Gly Thr Lys Leu
            100                 105                 110


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


Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
    130                 135                 140
```

```
Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
145                 150                 155                 160


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


Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
            180                 185                 190


Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
        195                 200                 205


Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215                 220


<210> 21
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (231)..(251)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (234)..(234)
<223> /replace="Leu"

<220>
<221> SITE
<222> (235)..(251)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (241)..(251)
<223> /note="This region may be absent in its entirety"

<220>
```

<221> SITE
<222> (1)..(251)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 21
Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Arg Pro Gly Gly
1 5 10 15

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

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

Ser Arg Thr Asn Thr Asp Gly Arg Asn Thr Ala Tyr Ala Asp Tyr Ala
50 55 60

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

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

Ala Arg Leu Arg Arg Asn Val Ala Asp Gln Ile Thr His Asn Tyr Tyr
100 105 110

Met Asp Val Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

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

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

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

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


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


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


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


Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
                245                 250


<210> 22
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<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 Ala Cys Arg Ala Ser Gln Ser Val Gly Thr Tyr Leu
            20                  25                  30


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


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


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


Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ser Pro Pro Thr
```

```
               85                  90                  95

Phe Gly Gln 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> 23
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (228)..(248)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (231)..(231)
```

<223> /replace="Leu"

<220>
<221> SITE
<222> (232)..(248)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (238)..(248)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(248)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 23
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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

Tyr Ile His Trp Val Arg Gln Ala Arg Glu Gln Gly Leu Glu Trp Met
35 40 45

Gly Val Ile Asn Pro Ser Thr Gly Thr Thr Phe Tyr Ala Gln Asn Phe
50 55 60

Pro Asp Arg Val Ser Val Thr Arg Asp Thr Ser Thr Ser Thr Val Phe
65 70 75 80

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

Ala Arg Ala Ile Ser Glu His Gly Ser Gly Ser Tyr Ser Pro Tyr Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly

```
        115                 120                 125

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

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

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

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

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

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

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

Ala Gly Gly Pro Ser Val Phe Leu
                245


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

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 24
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Leu Gly Gln
1               5                   10                  15

Met Ala Ala Ile Thr Cys Ser Gly Glu Ala Leu Pro Lys Lys Tyr Gly
            20                  25                  30
```

```
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Val Pro Val Leu Leu Ile Tyr
        35                  40                  45

Arg Asp Val Glu Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60

Ser Ser Gly Thr Met Val Thr Leu Thr Ile Ser Gly Val Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Leu Ser Ala Asp Ser Ser Gly Thr Trp
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
            100                 105                 110

Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
        115                 120                 125

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

Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys Ala Gly Val
145                 150                 155                 160

Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
                165                 170                 175

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
            180                 185                 190

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

Pro Thr Glu Cys Ser
    210
```

<210> 25
<211> 236
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (216)..(236)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (219)..(219)
<223> /replace="Leu"

<220>
<221> SITE
<222> (220)..(236)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (226)..(236)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(236)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 25
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 Val Ser Gly Ile Asp Leu Ser Gly Tyr
20 25 30

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

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

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


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


Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
            100                 105                 110


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


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


Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145                 150                 155                 160


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


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


Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Ala Arg
        195                 200                 205


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


Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Thr Leu
225                 230                 235


<210> 26
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"
```

<400> 26
Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1   5   10   15

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

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

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

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

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Thr
                85   90   95

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

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

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

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

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

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

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

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

210 215

<210> 27
<211> 238
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> SITE
<222> (228)..(238)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (234)..(238)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 27
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 Asn Tyr
20 25 30

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

Ala Glu Ile Arg Ser Glu Ser Asp Ala Ser Ala Thr His Tyr Ala Glu
50 55 60

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

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

```
Tyr Cys Leu Ala Tyr Phe Asp Tyr Gly Leu Ala Ile Gln Asn Tyr Trp
            100                 105                 110


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


Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser 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 Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205


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


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


<210> 28
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 28
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 Lys Ala Ser Lys Arg Val Thr Thr Tyr
            20                  25                  30
```

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Ser Tyr Asn Tyr 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> 29
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (222)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (227)..(227)
<223> /replace="Ser"

<220>
<221> SITE
<222> (231)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(241)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 29
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Gly Asn Tyr
20 25 30

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

Gly Ala Ile Tyr Glu Gly Thr Gly Lys Thr Val Tyr Ile Gln Lys Phe
50 55 60

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

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

Ala Arg Leu Ser Asp Tyr Val Ser Gly Phe Gly Tyr 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
        195                 200                 205

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

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

Leu
```

<210> 30
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 30
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 Lys Asp Ile Ser Lys 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 Gly Tyr His 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 Thr Tyr Tyr Cys Gln Gln Gly Asp Ala Leu Pro Pro
85 90 95

Thr Phe Gly Gly 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> 31
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (227)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (230)..(230)
<223> /replace="Leu"

<220>
<221> SITE
<222> (231)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (237)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(247)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 31
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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

```
Asp Val Met Cys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Ile Gly Cys Ile Met Thr Thr Asp Val Val Thr Glu Tyr Ala Asn Trp
    50                  55                  60

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

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

Cys Ala Arg Asp Ser Val Gly Ser Pro Leu Met Ser Phe Asp Leu Trp
            100                 105                 110

Gly Pro Gly Thr Leu 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> 32
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 32
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 Asn Cys Gln Ala Ser Gln Ser Ile Tyr Asn Asn
20 25 30

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

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

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

Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gly Gly Tyr Lys Ser Tyr
85 90 95

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

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

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

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

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


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


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


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> 33
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (222)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (225)..(225)
<223> /replace="Leu"

<220>
<221> SITE
<222> (232)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(242)
<223> /note="Variant residues given in the sequence have no
      preference with respect to those in the annotations
      for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
      substitutions and preferred embodiments"
```

<400> 33
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1   5   10   15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20   25   30

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

Gly Trp Ile Asp Pro Tyr Arg Ser Glu Ile Arg Tyr Ser Pro Ser Phe
    50   55   60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Arg Val Ser Ser Glu Pro Phe Asp Ser Trp Gly Gln Gly Thr Leu
            100   105   110

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

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

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

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

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

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

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His

210 215 220

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

Phe Leu

<210> 34
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 34
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp His Tyr Ala
20 25 30

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

Asp Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Thr Phe Glu Gly Asp Tyr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

```
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
    130                 135                 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145                 150                 155                 160

Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
                165                 170                 175

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
            180                 185                 190

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

Pro Thr Glu Cys Ser
    210
```

<210> 35
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (232)..(252)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (235)..(235)
<223> /replace="Leu"

<220>
<221> SITE
<222> (236)..(252)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (242)..(252)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(252)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 35
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

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

Thr Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

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

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

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

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

Ala Phe Ala Tyr Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala
115 120 125

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

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

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


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


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


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


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


Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
                245                 250


<210> 36
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 36
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1               5                   10                  15


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


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


Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60


Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65                  70                  75                  80
```

```
Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Phe Ala Ser Trp Ser Asp Ser
                85                  90                  95


Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
            100                 105                 110


Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
        115                 120                 125


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


Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145                 150                 155                 160


Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
                165                 170                 175


Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
            180                 185                 190


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


Pro Thr Glu Cys Ser
    210


<210> 37
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (224)..(234)
<223> /note="This region may be absent in its entirety"

<220>
```

<221> SITE
<222> (230)..(234)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 37
Gln 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 Ser Ser Gly
20 25 30

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

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

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

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

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

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

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

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

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

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

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

<210> 38
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 38
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

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

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


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


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


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


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


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


Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> 39
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (221)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (224)..(224)
<223> /replace="Leu"

<220>
<221> SITE
<222> (225)..(241)
<223> /note="This region may be absent in its entirety"
```

<220>
<221> SITE
<222> (231)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(241)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 39
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20   25   30

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

Gly Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65   70   75   80

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

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


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


Leu
```

<210> 40
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 40

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


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


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


Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60
```

```
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65                  70                  75                  80


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


Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110


Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125


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


Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160


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


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


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


Ala Pro Thr Glu Cys Ser
    210


<210> 41
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
```

<221> SITE
<222> (223)..(243)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (226)..(226)
<223> /replace="Leu"

<220>
<221> SITE
<222> (227)..(243)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (233)..(243)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(243)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 41
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 Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala
20 25 30

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

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

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

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

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

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

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

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

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

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

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

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

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

Val Phe Leu
```

<210> 42
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 42

```
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
```

```
1               5                   10                  15

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

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45

Ala 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 Val Glu Ala Glu
65                  70                  75                  80

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

Phe Gly Ala Gly Thr Lys Leu Glu Leu 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> 43
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (226)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (229)..(229)
<223> /replace="Leu"

<220>
<221> SITE
<222> (230)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (236)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(246)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 43
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ser Ser Gly Tyr His Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

```
        35                  40                  45

Gly Val Ile His Pro Asn Ser Gly Ser Ile Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Glu Ser Arg Val Thr Ile Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

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

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

Gln Gly Thr Thr 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 Arg 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> 44
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 44
Asp Val Gln Ile Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Asn Lys Tyr
20 25 30

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

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

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

Glu Asp Phe Ala Met Tyr Tyr Cys Gln Gln His Asn Glu Tyr Pro Leu
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> 45
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (226)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (229)..(229)
<223> /replace="Leu"

<220>
<221> SITE
<222> (230)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (236)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(246)
<223> /note="Variant residues given in the sequence have no
      preference with respect to those in the annotations
      for variant positions"

<220>
<221> source
```

<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 45

```
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
245

<210> 46
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 46
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 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

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> 47
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (225)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (228)..(228)
<223> /replace="Leu"

<220>
<221> SITE
<222> (229)..(245)
<223> /note="This region may be absent in its entirety"

<220>
```

<221> SITE
<222> (235)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(245)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 47
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

<210> 48
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 48
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
    210


<210> 49
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (234)..(254)
```

<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (237)..(237)
<223> /replace="Leu"

<220>
<221> SITE
<222> (238)..(254)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (244)..(254)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(254)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 49
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
```

<210> 50
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 50

```
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
```

<210> 51

<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (225)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (228)..(228)
<223> /replace="Leu"

<220>
<221> SITE
<222> (229)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (235)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(245)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 51
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Asp Trp Met
35 40 45

```
Gly Trp Ile Ser Pro Tyr Ser Gly Asn Thr Asn Tyr Ala Gln Lys Leu
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Val Gly Ser Gly Pro Tyr Tyr Tyr Met Asp Val 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 Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

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

Pro Ser Val Phe Leu
                245
```

<210> 52

<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 52
Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Ser Val Gly Asp Ser
20 25 30

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

Met Leu Tyr Asp Val Thr Lys Arg Pro Ser Gly Val 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 Tyr Ser Tyr Ala Gly Thr
85 90 95

Asp Thr Leu Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Gln Pro
100 105 110

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

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160

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

```
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190


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


Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> 53
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (225)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (228)..(228)
<223> /replace="Leu"

<220>
<221> SITE
<222> (229)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (235)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(245)
<223> /note="Variant residues given in the sequence have no
      preference with respect to those in the annotations
      for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
      substitutions and preferred embodiments"
```

<400> 53
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 Ser Val Ser Gly Gly Ser Ile Ile Ser Arg
            20   25   30

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

Trp Ile Gly Gly Ile Tyr His Ser Gly Asn Thr Tyr Asp Asn Pro Ser
    50   55   60

Leu Lys Ser Arg Leu Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe
65   70   75   80

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

Cys Ala Arg Ile Val Pro Gly Gly Asp Ala Phe Asp Ile Trp Gly Gln
            100   105   110

Gly Thr Met 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
    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> 54
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 54

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

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

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

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

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

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ser Pro Pro Thr
                85                  90                  95

Phe Gly Gln 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> 55
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (222)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (225)..(225)
<223> /replace="Leu"

<220>
<221> SITE
<222> (226)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (232)..(242)
```

<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(242)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 55
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15

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

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

Ser Ser Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Lys
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 Tyr Tyr Tyr Gly Gln Tyr Phe Asp Phe Trp Gly Gln Gly Thr Leu
100 105 110

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

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

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

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


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


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


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


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


Phe Leu
```

<210> 56
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 56

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


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


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


Tyr Ser Ala Ser Tyr Arg Ser Thr 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 Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Leu
                85                  90                  95

Thr Phe Gly Gly 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> 57
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (221)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (224)..(224)
<223> /replace="Leu"

<220>
<221> SITE
<222> (225)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (231)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(241)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 57
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20   25   30

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

Gly Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65   70   75   80

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

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


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


Leu
```

<210> 58
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 58

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


Thr Ala Arg Ile Thr Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
```

```
            20                  25                  30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65                  70                  75                  80

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

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

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

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

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

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190

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

Ala Pro Thr Glu Cys Ser
    210


<210> 59
<211> 235
<212> PRT
```

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (225)..(235)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (231)..(235)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 59
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> 60
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 60
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> 61
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"
```

<220>
<221> SITE
<222> (221)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (224)..(224)
<223> /replace="Leu"

<220>
<221> SITE
<222> (225)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (231)..(241)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(241)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 61
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

<210> 62
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 62

```
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
    210
```

<210> 63
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (226)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (229)..(229)
<223> /replace="Leu"

<220>
<221> SITE
<222> (230)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (236)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(246)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 63
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 Ser Ser
20 25 30

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

Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Asn Val Lys Phe
    50                  55                  60

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

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

Ala Arg Ser Gly Phe Ile Thr Thr Val Arg Asp Phe 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 Arg 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> 64
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 64
Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Thr Phe
20 25 30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Asp Gln Ser Pro
35 40 45

Lys Leu Leu Ile His Glu Ala Ser Asn Gln Gly Ser Gly Val Pro Ser
50 55 60

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

Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Phe Thr Phe Gly Gly Gly Thr Lys Val Glu 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


<210> 65
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (222)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (225)..(225)
<223> /replace="Leu"

<220>
<221> SITE
<222> (226)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (232)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(242)
<223> /note="Variant residues given in the sequence have no
      preference with respect to those in the annotations
      for variant positions"

<220>
```

<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 65
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 Phe Ile Thr Asn Asn
20 25 30

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

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

Ser Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr Phe 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 Thr Gly Ser Ser Gly Tyr Phe Asp Phe Trp Gly Gln Gly Thr Leu
100 105 110

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

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

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

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

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

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

195 200 205

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

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

Phe Leu

<210> 66
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 66
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 Glu Ser Val Asp Asp Leu
20 25 30

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

Lys Tyr Ala Ser Gln Ser Ile 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 Thr Tyr Tyr Cys Gln Gln Gly Asn Ser Leu Pro Asn
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> 67
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (229)..(239)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (235)..(239)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
      substitutions and preferred embodiments"
```

<400> 67
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30

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

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

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65   70   75   80

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

Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr Phe Asp Val
            100   105   110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115   120   125

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

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

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

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

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

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys

210 215 220

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

<210> 68
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 68
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 Asn 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 Leu 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 Thr Tyr Tyr Cys Gln Gln Gly Asp Thr Leu Pro Tyr
85 90 95

Thr Phe Gly Gly 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> 69
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (227)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (230)..(230)
<223> /replace="Leu"

<220>
<221> SITE
<222> (231)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (237)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(247)
```

<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 69
Glu Val Gln Leu Leu 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 His Tyr
20 25 30

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

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

Lys Gly Arg Phe 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 Tyr Arg Arg Ile Gly Val Pro Arg Arg Asp Glu Phe Asp Ile 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 Arg 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> 70
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 70

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


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


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


Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Thr Tyr Trp Thr
                85                  90                  95
```

```
Phe Gly Gln 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> 71
<211> 711
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"


<220>
<221> misc_feature
<222> (649)..(711)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (658)..(660)
<223> /replace="ctg"
```

<220>
<221> misc_feature
<222> (661)..(711)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (679)..(711)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(711)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 71
gaggtgcagc tggtggagag cggcggcggc ctggtgcagc ccggcggcag cctgaggctg 60

agctgcgccg ccagcggctt caccttcagc aggtacagca tgagctgggt gaggcaggcc 120

cccggcaagg gcctggagct ggtggcccag atcaacagcg tgggcaacag cacctactac 180

cccgacaccg tgaagggcag gttcaccatc agcagggaca acgccaagaa caccctgtac 240

ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcgc cagcggcgac 300

tactggggcc agggcaccct ggtgaccgtg agcagcgcca gcaccaaggg ccccagcgtg 360

ttccccctgg cccccagcag caagagcacc agcggcggca ccgccgccct gggctgcctg 420

gtgaaggact acttccccga gcccgtgacc gtgagctgga acagcggcgc cctgaccagc 480

ggcgtgcaca ccttccccgc cgtgctgcag agcagcggcc tgtacagcct gagcagcgtg 540

gtgaccgtgc ccagcagcag cctgggcacc cagacctaca tctgcaacgt gaaccacaag 600

cccagcaaca ccaaggtgga caagaaggtg gagcccaaga gctgcgacaa gacccacacc 660

tgcccccccct gccccgcccc cgagctgctg ggcggcccca gcgtgttcct g 711

<210> 72
<211> 657
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 72
gacgtggtga tgacccagag ccccctgagc ctgcccgtga ccctgggcca gcccgccagc 60

atcagctgca ggagcagcca gagcctgatc tacagcgacg gcaacgccta cctgcactgg 120

ttcctgcaga agcccggcca gagccccagg ctgctgatct acaaggtgag caacaggttc 180

agcggcgtgc ccgacaggtt cagcggcagc ggcagcggca ccgacttcac cctgaagatc 240

agcagggtgg aggccgagga cgtgggcgtg tactactgca gccagagcac ccacgtgccc 300

tggaccttcg gccagggcac caaggtggag atcaagagga ccgtggccgc ccccagcgtg 360

ttcatcttcc cccccagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgcctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtgaccgag caggacagca aggacagcac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgcgag 600

gtgacccacc agggcctgag cagccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 73
<211> 720
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> variation
<222> (70)..(72)
<223> /replace="gtg"

<220>
<221> misc_feature
<222> (658)..(720)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (667)..(669)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (670)..(720)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (688)..(720)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(720)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 73
gaggtgcagc tggtggagag cggcggcggc ctggtgcagc ccggcggcag cctgaggctg 60

agctgcgccg ccagcggctt caccttcagc gacaacggca tggcctgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtgagcttc atcagcaacc tggcctacag catcgactac 180

gccgacaccg tgaccggcag gttcaccatc agcagggaca acgccaagaa cagcctgtac 240

ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcgt gagcggcacc 300

tggttcgcct actggggcca gggcaccctg gtgaccgtga gcagcgccag caccaagggc 360

cccagcgtgt tcccccctggc ccccagcagc aagagcacca gcggcggcac cgccgccctg 420

ggctgcctgg tgaaggacta cttccccgag cccgtgaccg tgagctggaa cagcggcgcc 480

ctgaccagcg gcgtgcacac cttccccgcc gtgctgcaga gcagcggcct gtacagcctg 540

agcagcgtgg tgaccgtgcc cagcagcagc ctgggcaccc agacctacat ctgcaacgtg 600

aaccacaagc ccagcaacac caaggtggac aagaaggtgg agcccaagag ctgcgacaag 660

acccacacct gccccccctg ccccgccccc gagctggccg gcgcccccag cgtgttcctg 720

<210> 74
<211> 657
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 74
gacatcgtga tgacccagag ccccctgagc ctgcccgtga cccccggcga gcccgccagc 60

atcagctgca gggtgagcca gagcctgctg cacagcaacg gctacaccta cctgcactgg 120

tacctgcaga agcccggcca gagcccccag ctgctgatct acaaggtgag caacaggttc 180

agcggcgtgc ccgacaggtt cagcggcagc ggcagcggca ccgacttcac cctgaagatc 240

agcagggtgg aggccgagga cgtgggcgtg tactactgca gccagaccag gcacgtgccc 300

tacaccttcg gcggcggcac caaggtggag atcaagagga ccgtggccgc ccccagcgtg 360

ttcatcttcc cccccagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgcctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtgaccgag caggacagca aggacagcac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgcgag 600

gtgacccacc agggcctgag cagccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 75
<211> 762
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (700)..(762)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (709)..(711)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (712)..(762)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (730)..(762)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(762)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 75
caggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcgccag cgtgaaggtg 60

agctgcaagg ccagcggcta caccttcacc aagtactaca tgagctgggt gaggcaggcc 120

cccggccagg gcctggagtg gatgggcatc atcaacccca tcggcggcag caccagctac 180

gcccagaagt tccagggcag ggtgaccatg accagggaca ccagcaccag caccgtgtac 240

atggagctga gcagcctgag gagcgaggac accgccgtgt actactgcgc cagggacccc 300

agcggcatcg ccctggccgg ccccgccagc aggggctacc agggcatgga 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 gcccagcaac 660

accaaggtgg acaagagggt ggagcccaag agctgcgaca agacccacac ctgccccccc 720

tgccccgccc ccgagctgct gggcggcccc agcgtgttcc tg 762

<210> 76
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 76
gagatcgtga tgacccagag ccccgccacc ctgagcgtga gccccggcga gagggccacc 60

ctgagctgca gggccagcca gagcgtgagc agcaacctgg cctggtacca gcagaagccc 120

ggccaggccc ccaggctgct gatctacggc gccagcacca gggccaccgg catccccgcc 180

aggttcagcg gcagcggcag cggcaccgag ttcaccctga ccatcagcag cctgcagagc 240

gaggacttcg ccgtgtacta ctgccagcag gccaggctgg gcccctggac cttcggcggc 300

ggcaccaagg tggagatcaa 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> 77
<211> 711
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (652)..(711)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (667)..(668)
<223> /replace="ag"

<220>
<221> misc_feature
<222> (679)..(711)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(711)

<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 77
gaggtgaagg tggtggagag cggcggcggc ctggtgcagc ccggcggcag catgaagctg 60

agctgcgtgg tgagcggctt caccttcagc aactactggg tgaactgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtggcccag atcaggctga agagcgacaa ctacgccacc 180

cactacgagg agagcgtgaa gggcaggttc accatcagca gggacgacag caagagcagc 240

gtgtacctgc agatgaacaa cctgagggcc gaggacagcg gcatctacta ctgcaccaac 300

tgggaggact actggggcca gggcaccacc gtgaccgtga gcagcgccag caccaagggc 360

cccagcgtgt tccccctggc cccctgcagc aggagcacca gcgagagcac cgccgccctg 420

ggctgcctgg tgaaggacta cttccccgag cccgtgaccg tgagctggaa cagcggcgcc 480

ctgaccagcg gcgtgcacac cttccccgcc gtgctgcaga gcagcggcct gtacagcctg 540

agcagcgtgg tgaccgtgcc cagcagcagc ctgggcacca agacctacac ctgcaacgtg 600

gaccacaagc ccagcaacac caaggtggac aagagggtgg agagcaagta cggccccccc 660

tgcccccccct gccccgcccc cgagttcctg ggcggcccca gcgtgttcct g 711

<210> 78
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 78
gacatcgtgc tgacccagag ccccgacagc ctggccgtga gcctgggcga gagggccacc 60

atcagctgca gggccagcca gagcgtgagc accagcaggt acagctacat ccactggtac 120

cagcagaagc ccggccagtt ccccaagctg ctgatcaagt acgccagcaa cctggagagc 180

ggcgtgccca gcaggttcag cggcagcggc agcggcaccg acttcaccct gaacatccac 240

```
cccctggagc ccgaggactt cgccacctac tactgccacc acagctggga gatccccctg      300

accttcggcc agggcaccaa gctggagatc 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> 79
<211> 720
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> variation
<222> (181)..(183)
<223> /replace="acc"

<220>
<221> misc_feature
<222> (661)..(720)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (676)..(677)
<223> /replace="ag"

<220>
<221> misc_feature
<222> (688)..(720)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(720)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>

<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 79
gaggtgcagc tgcaggagag cggccccggc ctggtgaagc ccagcgagac cctgagcctg 60

acctgcaccg tgagcggctt cagcctgacc agcaacgaca tcgcctggat caggcagccc 120

cccggcaagg gcctggagtg gatgggcacc atctggaccg acggcagcac caactacaac 180

gccgccgtgc agagcagggt gaccatcagc gtggacacca gcaagaacca gttcagcctg 240

aagctgagca gcgtgaccgc cgccgacacc gccgtgtact actgcgccag gcacaggctg 300

tactacggcg ccttcgacta ctggggccag ggcaccatgg tgaccgtgag cagcgccagc 360

accaagggcc ccagcgtgtt ccccctggcc ccctgcagca ggagcaccag cgagagcacc 420

gccgccctgg gctgcctggt gaaggactac ttccccgagc ccgtgaccgt gagctggaac 480

agcggcgccc tgaccagcgg cgtgcacacc ttccccgccg tgctgcagag cagcggcctg 540

tacagcctga gcagcgtggt gaccgtgccc agcagcagcc tgggcaccaa gacctacacc 600

tgcaacgtgg accacaagcc cagcaacacc aaggtggaca agagggtgga gagcaagtac 660

ggcccccccct gccccccctg ccccgccccc gagttcctgg gcggccccag cgtgttcctg 720

<210> 80
<211> 657
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 80
gacatcgtga tgacccagac ccccctgagc ctgagcgtga cccccggcca gcccgccagc 60

atcagctgca ggagcagcca gagcctggag tacagcgacg gctacaccta cctggagtgg 120

tacctgcaga agcccggcca gagcccccag ctgctgatct acgaggtgag caacaggttc 180

agcggcgtgc ccgacaggtt cagcggcagc ggcagcggca ccgacttcac cctgaagatc 240

agcagggtgg aggccgagga cgtgggcgtg tactactgct tccaggccac ccacaacccc 300

tacaccttcg gccagggcac caagctggag atcaagagga ccgtggccgc ccccagcgtg 360

ttcatcttcc cccccagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgcctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtgaccgag caggacagca aggacagcac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgcgag 600

gtgacccacc agggcctgag cagccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 81
<211> 747
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (685)..(747)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (694)..(696)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (697)..(747)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (715)..(747)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(747)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 81

caggtgcagc tggtggagag cggcggcggc gtggtgcagc ccggcaggag cctgagggtg 60

agctgcgccg ccagcggctt caccttcagc agctacgaca tgcactgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtggccgtg atctggttcg acggcagcaa cgagttctac 180

gccgacagcg tgaagggcag gttcaccatc agcagggaca acagcaagaa caccctgttc 240

cagatgaaca gcctgagggc cgaggacacc gccgtgtact actgcgccag ggacctgggc 300

gccagcgtga ccaccagcaa cgccgagaac ttccaccact ggggccaggg caccctggtg 360

accgtgagca gcgccagcac caagggcccc agcgtgttcc ccctggcccc cagcagcaag 420

agcaccagcg gcggcaccgc cgccctgggc tgcctggtga aggactactt ccccgagccc 480

gtgaccgtga gctggaacag cggcgccctg accagcggcg tgcacacctt ccccgccgtg 540

ctgcagagca gcggcctgta cagcctgagc agcgtggtga ccgtgcccag cagcagcctg 600

ggcacccaga cctacatctg caacgtgaac cacaagccca gcaacaccaa ggtggacaag 660

aaggtggagc ccaagagctg cgacaagacc cacacctgcc ccccctgccc cgcccccgag 720

ctggccggcg cccccagcgt gttcctg 747

<210> 82
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 82
agctacgagc tgacccagcc ccccagcgtg agcgtgagcc ccggccagac cgccaggatc 60

acctgcagcg gcgacgccct gcccaagagg tacgtgtact ggtaccagca gaagagcggc 120

caggcccccg tgctggtgat ctacgaggac agcaagaggc ccagcggcat ccccgagacc 180

ttcagcggca gcagcagcgg caccatggcc accctgacca tcagcggcgc ccaggtggag 240

gacgaggccg actactactg ctacagcacc gacagcaacg gccaccactg ggtgttcggc 300

ggcggcacca agctgaccgt gctgggccag cccaaggccg cccccagcgt gaccctgttc 360

cccccagca gcgaggagct gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctaccccg gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacca ccacccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac aggagctaca gctgccaggt gacccacgag 600

ggcagcaccg tggagaagac cgtggccccc acctgcagc 639

<210> 83
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (676)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (691)..(692)
<223> /replace="ag"

<220>
<221> misc_feature
<222> (703)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(735)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 83
caggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcagcag cgtgaaggtg 60

agctgcaagg ccagcggcta cagcttcagc gactactaca tgcactgggt gaggcaggcc 120

cccggccagg gcctggagtg gatgggccag atcaacccca ccaccggcgg cgccagctac 180

aaccagaagt tcaagggcaa ggccaccatc accgtggaca agagcaccag caccgcctac 240

atggagctga gcagcctgag gagcgaggac accgccgtgt actactgcgc caggtactac 300

tacggcaggc acttcgacgt gtggggccag ggcaccaccg tgaccgtgag cagcgccagc 360

accaagggcc ccagcgtgtt ccccctggcc ccctgcagca ggagcaccag cgagagcacc 420

gccgccctgg gctgcctggt gaaggactac ttccccgagc ccgtgaccgt gagctggaac 480

agcggcgccc tgaccagcgg cgtgcacacc ttccccgccg tgaccgtgag cagcgtgctg 540

cagagcagcg gcctgtacag cctgagcagc gtggtgaccg tgcccagcag cagcctgggc 600

accaagacct acacctgcaa cgtggaccac aagcccagca acaccaaggt ggacaagagg 660

gtggagagca agtacggccc cccctgcccc ccctgccccg cccccgagtt cctgggcggc 720

cccagcgtgt tcctg 735

<210> 84
<211> 630
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 84
gacatcgtga tgacccagag ccccgacagc ctggccgtga gcctgggcga gagggccacc 60

atcaactgca aggccagcca gagcgtggac tacgacggcg acagctacat gaactggtac 120

cagcagaagc ccggccagcc ccccaagctg ctgatctacg ccgccagcaa cctggagagc 180

ggcgtgcccg acaggttcag cggcagcggc agcggcaccg acttcaccct gaccatcagc 240

agcctgcagg ccgaggacgt ggccgtgtac tactgccagc agagcaacga ggacccctac 300

accttcggcc agggcaccaa gctggagatc aagttcatct tcccccccag cgacgagcag 360

ctgaagagcg gcaccgccag cgtggtgtgc ctgctgaaca acttctaccc cagggaggcc 420

aaggtgcagt ggaaggtgga caacgccctg cagagcggca acagccagga gagcgtgacc 480

gagcaggaca gcaaggacag cacctacagc ctgagcagca ccctgaccct gagcaaggcc 540

gactacgaga agcacaaggt gtacgcctgc gaggtgaccc accagggcct gagcagcccc 600

gtgaccaaga gcttcaacag gggcgagtgc 630

<210> 85

<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (661)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (670)..(672)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (673)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (691)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(723)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 85
gaggtgcagc tggtggagag cggcggcggc ctggtgcagc ccggcggcag cctgaggctg 60

agctgcgccg ccagcggctt caccttcagc aactacggca tgagctgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtggccagc atcagcagcg gcggcggcag cacctactac 180

cccgacaacg tgaagggcag gttcaccatc agcagggacg acgccaagaa cagcctgtac 240

ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcgc caggggcggc 300

gccggcatcg actactgggg ccagggcacc ctggtgaccg tgagcagcgc cagcaccaag 360

ggccccagcg tgttcccct 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 gacaagaggg tggagcccaa gagctgcgac 660

aagacccaca cctgcccccc ctgccccgcc cccgagctgc tgggcggccc cagcgtgttc 720

ctg 723

<210> 86
<211> 660
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 86
gacatccaga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagggtgacc 60

atcacctgca agagcatcca gaccctgctg tacagcagca accagaagaa ctacctggcc 120

tggttccagc agaagcccgg caaggccccc aagctgctga tctactgggc cagcatcagg 180

aagagcggcg tgcccagcag gttcagcggc agcggcagcg gcaccgactt caccctgacc 240

atcagcagcc tgcagcccga ggacctggcc acctactact gccagcagta ctacagctac 300

cccctgacct tcggcggcgg caccaagctg gagatcaaga ggaccgtggc cgcccccagc 360

gtgttcatct tcccccccag cgacgagcag ctgaagagcg gcaccgccag cgtggtgtgc 420

ctgctgaaca acttctaccc cagggaggcc aaggtgcagt ggaaggtgga caacgccctg 480

cagagcggca acagccagga gagcgtgacc gagcaggaca gcaaggacag cacctacagc 540

ctgagcagca ccctgaccct gagcaaggcc gactacgaga agcacaaggt gtacgcctgc 600

gaggtgaccc accagggcct gagcagcccc gtgaccaaga gcttcaacag gggcgagtgc 660

<210> 87
<211> 747
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (685)..(747)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (694)..(696)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (697)..(747)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (715)..(747)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(747)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 87
gaggtgcagc tggtggagag cggcgccgag gtgaagaagc ccggcgccag cgtgaaggtg 60

agctgcaagg ccagcggcta caccttcacc aactacgcca tgcactgggt gaggcaggcc 120

cccggccaga ggctggagtg gatgggctgg atcaacgccg gcaacggcaa gaggaagtac 180

agccagaagt tccaggacag ggtgaccatc aacagggaca ccagcgccag caccatctac 240

atggagctga gcagcctggg cagcgaggac accgccgtgt actactgcgc cagggaggag 300

gaccacgccg gcagcggcag ctacctgagc atggacgtgt ggggccaggg caccctggtg 360

accgtgagca gcgccagcac caagggcccc agcgtgttcc ccctggcccc cagcagcaag 420

agcaccagcg gcggcaccgc cgccctgggc tgcctggtga aggactactt ccccgagccc 480

gtgaccgtga gctggaacag cggcgccctg accagcggcg tgcacacctt ccccgccgtg 540

ctgcagagca gcggcctgta cagcctgagc agcgtggtga ccgtgcccag cagcagcctg 600

ggcacccaga cctacatctg caacgtgaac cacaagccca gcaacaccaa ggtggacaag 660

agggtggagc ccaagagctg cgacaagacc cacacctgcc ccccctgccc cgcccccgag 720

ctgctgggcg gccccagcgt gttcctg 747

<210> 88
<211> 660
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 88
gacatccaga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagggtgacc 60

atcacctgca agagcatcca gaccctgctg tacagcagca accagaagaa ctacctggcc 120

tggttccagc agaagcccgg caaggccccc aagctgctga tctactgggc cagcatcagg 180

aagagcggcg tgcccagcag gttcagcggc agcggcagcg gcaccgactt caccctgacc 240

atcagcagcc tgcagcccga ggacctggcc acctactact gccagcagta ctacagctac 300

cccctgacct tcggcggcgg caccaagctg gagatcaaga ggaccgtggc cgccccagc 360

gtgttcatct tcccccccag cgacgagcag ctgaagagcg gcaccgccag cgtggtgtgc 420

ctgctgaaca acttctaccc cagggaggcc aaggtgcagt ggaaggtgga caacgccctg 480

cagagcggca acagccagga gagcgtgacc gagcaggaca gcaaggacag cacctacagc 540

ctgagcagca ccctgaccct gagcaaggcc gactacgaga agcacaaggt gtacgcctgc 600

gaggtgaccc accagggcct gagcagcccc gtgaccaaga gcttcaacag gggcgagtgc 660

<210> 89
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (679)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (688)..(690)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (691)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (709)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(741)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 89
gaggtgcagc tgctggagag cggcggcggc ctggtgcagc ccggcggcag cctgaggctg 60

agctgcgccg ccagcggctt caccttcagc agctacgcca tgagctgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtgagcagc atcagccacc tgggcggcag cacctactac 180

gccgacagcg tgaagggcag gttcaccatc agcagggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcgc cggcggcgcc 300

aaccacggca agtactacta cggcatggac aagtggggcc agggcaccac cgtgaccgtg 360

agcagcgcca gcaccaaggg ccccagcgtg ttccccctgg cccccagcag caagagcacc 420

agcggcggca ccgccgccct gggctgcctg gtgaaggact acttccccga gcccgtgacc 480

gtgagctgga acagcggcgc cctgaccagc ggcgtgcaca ccttccccgc cgtgctgcag 540

agcagcggcc tgtacagcct gagcagcgtg gtgaccgtgc ccagcagcag cctgggcacc 600

cagacctaca tctgcaacgt gaaccacaag cccagcaaca ccaaggtgga caagagggtg 660

gagcccaaga gctgcgacaa gacccacacc tgccccccct gccccgcccc cgagttcgag 720

ggcggcccca gcgtgttcct g 741

<210> 90
<211> 663
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 90
caggccgtgc tgacccagcc cgccagcctg agcgccagcc ccggcgccag cgccagcctg 60

acctgcaccc tgaggagcgg cgcccccctg cccaagtaca ggatctactg gtaccagcag 120

aagcccggca gccccccccа gtacctgctg aggtacaaga gcgacgccga caagcaccag 180

ggcagcggcg tgcccagcag gttcagcggc agcaaggacg ccagcgccaa cgccggcatc 240

ctgctgatca gcggcctgca gagcgaggac gaggccgact actactgcat ggtgtgggac 300

cacggcgtgt ggtacttcgg cggcggcacc aagctgaccg tgctgggcca gcccaaggcc 360

gcccccagcg tgaccctgtt ccccccccagc agcgaggagc tgcaggccaa caaggccacc 420

ctggtgtgcc tgatcagcga cttctacccc ggcgccgtga ccgtggcctg gaaggccgac 480

agcagccccg tgaaggccgg cgtggagacc accaccccca gcaagcagag caacaacaag 540

tacgccgcca gcagctacct gagcctgacc cccgagcagt ggaagagcca caggagctac 600

agctgccagg tgacccacga gggcagcacc gtggagaaga ccgtggcccc caccgagtgc 660

agc 663

<210> 91
<211> 753
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<220>
<221> misc_feature
<222> (691)..(753)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (700)..(702)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (703)..(753)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (721)..(753)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(753)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 91
gaggtgcagc tggtggagag cggcggcgac ctggtgaggc ccggcggcag cctgaggctg 60

agctgcgtgg ccagcggctt caccttcagc aactactgga tgcactgggt gaggcaggcc 120

cccggccaga ggcccgtgtg ggtgagcagg accaacaccg acggcaggaa caccgcctac 180

gccgactacg ccaagggcag gttcaccatc agcagggaca acgccaagag caccctgtac 240

ctgcagctga acagcctgag ggccgaggac accgccgtgt acttctgcgc caggctgagg 300

aggaacgtgg ccgaccagat cacccacaac tactacatgg acgtgtgggg caagggcacc 360

ctggtgaccg tgagcagcgc cagcaccaag ggccccagcg tgttcccccc ggcccccagc 420

agcaagagca ccagcggcgg caccgccgcc ctgggctgcc tggtgaagga ctacttcccc 480

gagcccgtga ccgtgagctg gaacagcggc gccctgacca gcggcgtgca caccttcccc 540

gccgtgctgc agagcagcgg cctgtacagc ctgagcagcg tggtgaccgt gcccagcagc 600

agcctgggca cccagaccta catctgcaac gtgaaccaca agcccagcaa caccaaggtg 660

gacaagaagg tggagcccaa gagctgcgac aagacccaca cctgcccccc ctgccccgcc 720

cccgaggccg ccggcggccc cagcgtgttc ctg 753

<210> 92
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 92
gacatccaga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagggtgacc 60

gcctgcaggg ccagccagag cgtgggcacc tacctgaact ggtaccagca gaagaggggc 120

aaggccccca agctgctgat cttcgccgcc agcagcctgc agagcggcgt gcccagcagg 180

ttcagcggca gcggcagcgg caccgacttc accctgacca tcagcagcct gcagcccgag 240

gacttcgcca cctactactg ccagcagagc tacagcagcc cccccacctt cggccagggc 300

accaaggtgg agatcaagag gaccgtggcc gcccccagcg tgttcatctt cccccccagc 360

gacgagcagc tgaagagcgg caccgccagc gtggtgtgcc tgctgaacaa cttctacccc 420

agggaggcca aggtgcagtg gaaggtggac aacgccctgc agagcggcaa cagccaggag 480

agcgtgaccg agcaggacag caaggacagc acctacagcc tgagcagcac cctgaccctg 540

agcaaggccg actacgagaa gcacaaggtg tacgcctgcg aggtgaccca ccagggcctg 600

agcagccccg tgaccaagag cttcaacagg ggcgagtgc 639

<210> 93
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (682)..(744)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (691)..(693)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (694)..(744)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (712)..(744)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(744)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 93
caggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcgccag cgtgaccctg 60

agctgcaagg ccagcggcta caccttcacc gcctactaca tccactgggt gaggcaggcc 120

agggagcagg gcctggagtg gatgggcgtg atcaacccca gcaccggcac caccttctac 180

gcccagaact tccccgacag ggtgagcgtg accagggaca ccagcaccag caccgtgttc 240

atggagctgc acaacctgaa gagcgaggac accgccgtgt actactgcgc cagggccatc 300

agcgagcacg gcagcggcag ctacagcccc tactactggg gccagggcac cctggtgacc 360

gtgagcagcg ccagcaccaa gggccccagc gtgttccccc tggccccag cagcaagagc 420

accagcggcg gcaccgccgc cctgggctgc ctggtgaagg actacttccc cgagcccgtg 480

accgtgagct ggaacagcgg cgccctgacc agcggcgtgc acaccttccc cgccgtgctg 540

cagagcagcg gcctgtacag cctgagcagc gtggtgaccg tgcccagcag cagcctgggc 600

acccagacct acatctgcaa cgtgaaccac aagcccagca acaccaaggt ggacaagaag 660

gtggagccca agagctgcga caagacccac acctgccccc cctgccccgc ccccgaggcc 720

gccggcggcc ccagcgtgtt cctg 744

<210> 94
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 94
agctacgagc tgacccagcc ccccagcgtg agcgtgagcc tgggccagat ggccgccatc 60

acctgcagcg gcgaggccct gcccaagaag tacggctact ggtaccagca gaagcccggc 120

caggtgcccg tgctgctgat ctacagggac gtggagaggc ccagcggcgt gcccgacagg 180

ttcagcggca gcagcagcgg caccatggtg accctgacca tcagcggcgt gcaggccgag 240

gacgaggccg actactactg cctgagcgcc gacagcagcg gcacctgggt gttcggcggc 300

ggcaccaagc tgaccgtgct g 321

<210> 95
<211> 708
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (646)..(708)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (655)..(657)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (658)..(708)

<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (676)..(708)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(708)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 95
gaggtgcagc tggtggagag cggcggcggc ctggtgcagc ccggcggcag cctgaggctg 60

agctgcgccg tgagcggcat cgacctgagc ggctactaca tgaactgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtgggcgtg atcggcatca acggcgccac ctactacgcc 180

agctgggcca agggcaggtt caccatcagc agggacaaca gcaagaccac cgtgtacctg 240

cagatgaaca gcctgagggc cgaggacacc gccgtgtact tctgcgccag gggcgacatc 300

tggggccagg gcaccctggt gaccgtgagc agcgccagca ccaagggccc cagcgtgttc 360

cccctggccc ccagcagcaa gagcaccagc ggcggcaccg ccgccctggg ctgcctggtg 420

aaggactact tccccgagcc cgtgaccgtg agctggaaca gcggcgccct gaccagcggc 480

gtgcacacct tccccgccgt gctgcagagc agcggcctgt acagcctgag cagcgtggtg 540

accgtgccca gcagcagcct gggcacccag acctacatct gcaacgtgaa ccacaagccc 600

agcaacacca aggtggacgc cagggtggag cccaagagct gcgacaagac ccacacctgc 660

ccccccctgcc ccgcccccga gctgctgggc ggccccagcg tgaccctg 708

<210> 96
<211> 657
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 96
caggtgctga cccagagccc cagcagcctg agcgccagcg tgggcgacag ggtgaccatc 60

aactgccagg ccagccagag cgtgtaccac aacacctacc tggcctggta ccagcagaag 120

cccggcaagg tgcccaagca gctgatctac gacgccagca ccctggccag cggcgtgccc 180

agcaggttca gcggcagcgg cagcggcacc gacttcaccc tgaccatcag cagcctgcag 240

cccgaggacg tggccaccta ctactgcctg ggcagctacg actgcaccaa cggcgactgc 300

ttcgtgttcg gcggcggcac caaggtggag atcaagagga ccgtggccgc ccccagcgtg 360

ttcatcttcc cccccagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgcctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtgaccgag caggacagca aggacagcac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgcgag 600

gtgacccacc agggcctgag cagccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 97
<211> 714
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (682)..(714)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (700)..(714)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 97
gaggtgcagc tggtggagag cggcggcggc ctggtgcagc ccggcggcag cctgaggctg 60

agctgcgccg ccagcggctt caccttcagc aactactgga tcagctgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtggccgag atcaggagcg agagcgacgc cagcgccacc 180

cactacgccg aggccgtgaa gggcaggttc accatcagca gggacaacgc caagaacagc 240

ctgtacctgc agatgaacag cctgagggcc gaggacaccg ccgtgtacta ctgcctggcc 300

tacttcgact acggcctggc catccagaac tactggggcc agggcaccct ggtgaccgtg 360

agcagcgcca gcaccaaggg ccccagcgtg ttccccctgg cccctgcag caggagcacc 420

agcgagagca ccgccgccct gggctgcctg gtgaaggact acttccccga gcccgtgacc 480

gtgagctgga acagcggcgc cctgaccagc ggcgtgcaca ccttccccgc cgtgctgcag 540

agcagcggcc tgtacagcct gagcagcgtg gtgaccgtgc ccagcagcaa cttcggcacc 600

cagacctaca cctgcaacgt ggaccacaag cccagcaaca ccaaggtgga caagaccgtg 660

gagaggaagt gctgcgtgga gtgccccccc tgccccgccc cccccgtggc cggc 714

<210> 98
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 98
gagatcgtgc tgacccagag ccccgccacc ctgagcctga gccccggcga gagggccacc 60

ctgagctgca aggccagcaa gagggtgacc acctacgtga gctggtacca gcagaagccc 120

ggccaggccc ccaggctgct gatctacggc gccagcaaca ggtacctggg catccccgcc 180

aggttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctggagccc 240

gaggacttcg ccgtgtacta ctgcagccag agctacaact acccctacac cttcggccag 300

ggcaccaagc tggagatcaa 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> 99
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (664)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (679)..(680)
<223> /replace="ag"

<220>
<221> misc_feature
<222> (691)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(723)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 99
caggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcagcag cgtgaaggtg 60

agctgcaagg ccagcggcta caccttcggc aactactgga tgcagtgggt gaggcaggcc 120

cccggccagg gcctggagtg gatgggcgcc atctacgagg gcaccggcaa gaccgtgtac 180

atccagaagt tcgccgacag ggtgaccatc accgccgaca agagcaccag caccgcctac 240

atggagctga gcagcctgag gagcgaggac accgccgtgt actactgcgc caggctgagc 300

gactacgtga gcggcttcgg ctactggggc cagggcacca ccgtgaccgt gagcagcgcc 360

agcaccaagg gccccagcgt gttccccctg gccccctgca gcaggagcac cagcgagagc 420

accgccgccc tgggctgcct ggtgaaggac tacttccccg agcccgtgac cgtgagctgg 480

aacagcggcg ccctgaccag cggcgtgcac accttccccg ccgtgctgca gagcagcggc 540

ctgtacagcc tgagcagcgt ggtgaccgtg cccagcagca gcctgggcac caagacctac 600

acctgcaacg tggaccacaa gcccagcaac accaaggtgg acaagagggt ggagagcaag 660

tacggccccc cctgcccccc ctgccccgcc cccgaggccg ccggcggccc agcgtgttc 720

ctg 723

<210> 100
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 100
gacatccaga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagggtgacc 60

atcacctgca gggccagcaa ggacatcagc aagtacctga actggtacca gcagaagccc 120

ggcaaggccc ccaagctgct gatctactac accagcggct accacagcgg cgtgcccagc 180

aggttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagccc 240

gaggacttcg ccacctacta ctgccagcag ggcgacgccc tgccccccac cttcggcggc 300

ggcaccaagg tggagatcaa 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> 101
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (679)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (688)..(690)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (691)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (709)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(741)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 101
gaggtgcagc tggtggagag cggcggcggc ctggtgaagc ccggcggcag cctgaggctg 60

agctgcgccg ccagcggctt cagcttcagc aacaacgacg tgatgtgctg ggtgaggcag 120

gcccccggca agggcctgga gtggatcggc tgcatcatga ccaccgacgt ggtgaccgag 180

tacgccaact gggccaagag caggttcacc gtgagcaggg acagcgccaa gaacagcgtg 240

tacctgcaga tgaacagcct gagggccgag gacaccgccg tgtacttctg cgccagggac 300

agcgtgggca gccccctgat gagcttcgac ctgtggggcc ccggcaccct ggtgaccgtg 360

agcagcgcca gcaccaaggg ccccagcgtg ttccccctgg cccccagcag caagagcacc 420

agcggcggca ccgccgccct gggctgcctg gtgaaggact acttccccga gcccgtgacc 480

gtgagctgga acagcggcgc cctgaccagc ggcgtgcaca ccttccccgc cgtgctgcag 540

agcagcggcc tgtacagcct gagcagcgtg gtgaccgtgc ccagcagcag cctgggcacc 600

cagacctaca tctgcaacgt gaaccacaag cccagcaaca ccaaggtgga caagaaggtg 660

gagcccaaga gctgcgacaa gacccacacc tgccccccct gccccgcccc cgagctgctg 720

ggcggcccca gcgtgttcct g 741

<210> 102
<211> 657
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 102
gacatccaga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagggtgacc 60

atcaactgcc aggccagcca gagcatctac aacaacaacg agctgagctg gtaccagcag 120

aagcccggca agcccccaa gctgctgatc tacagggcca gcaccctggc cagcggcgtg 180

cccagcaggt tcagcggcag cggcagcggc accgacttca ccctgaccat cagcagcctg 240

cagcccgagg acgtggccac ctactactgc ggcggctaca agagctacag caacgacggc 300

aacggcttcg gcggcggcac caaggtggag atcaagagga ccgtggccgc ccccagcgtg 360

ttcatcttcc cccccagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgcctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtgaccgag caggacagca aggacagcac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgcgag 600

gtgacccacc agggcctgag cagccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 103
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<220>
<221> misc_feature
<222> (664)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (673)..(675)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (676)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (694)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(726)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 103
gaggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcgagag cctgaagatc 60

agctgcaagg gcagcggcta cagcttcacc agctactgga tcggctgggt gaggcagatg 120

cccggcaagg gcctggagtg gatgggctgg atcgaccct acaggagcga gatcaggtac 180

agccccagct tccagggcca ggtgaccatc agcgccgaca agagcatcag caccgcctac 240

ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc cagggtgagc 300

agcgagccct tcgacagctg gggccagggc accctggtga ccgtgagcag cgccagcacc 360

aagggcccca gcgtgttccc cctggccccc agcagcaaga gcaccagcgg cggcaccgcc 420

gccctgggct gcctggtgaa ggactacttc cccgagcccg tgaccgtgag ctggaacagc 480

ggcgccctga ccagcggcgt gcacaccttc cccgccgtgc tgcagagcag cggcctgtac 540

agcctgagca gcgtggtgac cgtgcccagc agcagcctgg gcacccagac ctacatctgc 600

aacgtgaacc acaagcccag caacaccaag gtggacaaga gggtggagcc caagagctgc 660

gacaagaccc acacctgccc cccctgcccc gcccccgagc tgctgggcgg ccccagcgtg 720

ttcctg 726

<210> 104
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 104
agctacgtgc tgacccagcc ccccagcgtg agcgtggccc ccggcaagac cgccaggatc 60

acctgcagcg gcgacaagct gggcgaccac tacgcctact ggtaccagca gaagcccggc 120

caggcccccg tgctggtgat ctacgacgac agcaagaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacca tcagcagggt ggaggccggc 240

gacgaggccg actactactg cgccacctgg accttcgagg gcgactacgt gttcggcggc 300

ggcaccaagc tgaccgtgct gggccagccc aaggccgccc ccagcgtgac cctgttcccc 360

cccagcagcg aggagctgca ggccaacaag gccaccctgg tgtgcctgat cagcgacttc 420

taccccggcg ccgtgaccgt ggcctggaag gccgacagca gccccgtgaa ggccggcgtg 480

gagaccacca cccccagcaa gcagagcaac aacaagtacg ccgccagcag ctacctgagc 540

ctgacccccg agcagtggaa gagccacagg agctacagct gccaggtgac ccacgagggc 600

agcaccgtgg agaagaccgt ggcccccacc gagtgcagc 639

<210> 105
<211> 756
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (694)..(756)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (703)..(705)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (706)..(756)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (724)..(756)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(756)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 105
caggtgcagc tgcagcagag cggccccggc ctggtgaagc ccagccagac cctgagcctg 60

acctgcgcca tcagcggcga cagcgtgagc agcaacaccg ccgcctggaa ctggatcagg 120

cagagcccca gcaggggcct ggagtggctg ggcgtgatct actacaggag caagtggtac 180

aacgactacg ccgtgagcgt gaagagcagg atcaccatca accccgacac cagcaagaac 240

cagttcagcc tgcagctgaa cagcgtgacc cccgaggaca ccgccgtgta ctactgcgcc 300

aggagcgtgc ccggcggcga ccccggcctg gagcacgcct tcgcctactg gggcaggggc 360

accctggtga ccgtgagcag cgccagcacc aagggcccca gcgtgttccc cctggccccc 420

agcagcaaga gcaccagcgg cggcaccgcc gccctgggct gcctggtgaa ggactacttc 480

cccgagcccg tgaccgtgag ctggaacagc ggcgccctga ccagcggcgt gcacaccttc 540

cccgccgtgc tgcagagcag cggcctgtac agcctgagca gcgtggtgac cgtgcccagc 600

agcagcctgg gcacccagac ctacatctgc aacgtgaacc acaagcccag caacaccaag 660

gtggacaaga gggtggagcc caagagctgc gacaagaccc acacctgccc cccctgcccc 720

gcccccgagc tgctgggcgg ccccagcgtg ttcctg 756

<210> 106
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 106
agctacgtgc tgacccagcc ccccagcgtg agcgtggccc ccggcaagac cgccaggatc 60

acctgcagcg gcgacaacct gggcacctac tacgtggagt ggtaccagca gaagcccggc 120

caggcccccg tgctggtgat ctacgacgac agcgacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacca tcagcagggt ggaggccggc 240

gacgaggccg actactactg cgccagcttc gccagctgga gcgacagcgt gttcggcggc 300

ggcaccaagc tgaccgtgct gggccagccc aaggccgccc ccagcgtgac cctgttcccc 360

cccagcagcg aggagctgca ggccaacaag gccaccctgg tgtgcctgat cagcgacttc 420

taccccggcg ccgtgaccgt ggcctggaag gccgacagca gccccgtgaa ggccggcgtg 480

gagaccacca cccccagcaa gcagagcaac aacaagtacg ccgccagcag ctacctgagc 540

ctgacccccg agcagtggaa gagccacagg agctacagct gccaggtgac ccacgagggc 600

agcaccgtgg agaagaccgt ggcccccacc gagtgcagc 639

<210> 107
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (610)..(642)

<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (628)..(642)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 107
acctgcaccg tgagcggcgg cagcatcagc agcggcgagt actactggaa ctggatcagg 60

cagcaccccg gcaagggcct ggagtggatc ggctacatct actacagcgg cagcacctac 120

tacaacccca gcctgaagag cagggtgacc atcagcgtgg acaccagcaa gaaccagttc 180

agcctgaagc tgagcagcgt gaccgccgcc gacaccgccg tgtactactg cgccagggag 240

agcgtggccg gcttcgacta ctggggccag ggcaccctgg tgaccgtgag cagcgccagc 300

accaagggcc ccagcgtgtt ccccctggcc ccctgcagca ggagcaccag cgagagcacc 360

gccgccctgg gctgcctggt gaaggactac ttccccgagc ccgtgaccgt gagctggaac 420

agcggcgccc tgaccagcgg cgtgcacacc ttccccgccg tgctgcagag cagcggcctg 480

tacagcctga gcagcgtggt gaccgtgccc agcagcaact tcggcaccca gacctacacc 540

tgcaacgtgg accacaagcc cagcaacacc aaggtggaca agaccgtgga gaggaagtgc 600

tgcgtggagt gccccccctg ccccgccccc cccgtggccg gc 642

<210> 108
<211> 645
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 108
gagatcgtgc tgacccagag ccccggcacc ctgagcctga gccccggcga gagggccacc 60

ctgagctgca gggccagcca gagcgtgagc agcagctacc tggcctggta ccagcagaag 120

cccggccagg cccccaggct gctgatctac ggcaccagca gcagggccac cggcatcccc 180

gacaggttca gcggcagcgg cagcggcacc gacttcaccc tgaccatcag caggctggag 240

cccgaggact tcgccgtgta ctactgccag cagtacggca gcagccccat caccttcggc 300

cagggcacca ggctggagat caagaggacc gtggccgccc ccagcgtgtt catcttcccc 360

cccagcgacg agcagctgaa gagcggcacc gccagcgtgg tgtgcctgct gaacaacttc 420

taccccaggg aggccaaggt gcagtggaag gtggacaacg ccctgcagag cggcaacagc 480

caggagagcg tgaccgagca ggacagcaag gacagcacct acagcctgag cagcaccctg 540

accctgagca aggccgacta cgagaagcac aaggtgtacg cctgcgaggt gacccaccag 600

ggcctgagca gccccgtgac caagagcttc aacaggggcg agtgc 645

<210> 109
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (661)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (670)..(672)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (673)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (691)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(723)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 109
gaggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcagcag cgtgaaggtg 60

agctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gaggcaggcc 120

cccggccagg gcctggagtg gatgggcggc atcggccctt tcttcggcac cgccaactac 180

gcccagaagt tccagggcag ggtgaccatc accgccgacg agagcaccag caccgcctac 240

atggagctga gcagcctgag gagcgaggac accgccgtgt actactgcgc cagggacacc 300

ccctacttcg actactgggg ccagggcacc ctggtgaccg tgagcagcgc cagcaccaag 360

ggccccagcg tgttcccctt ggccccagc 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 gacaagaggg tggagcccaa gagctgcgac 660

aagacccaca cctgcccccc ctgccccgcc cccgaggccg ccggcggccc cagcgtgttc 720

ctg 723

<210> 110
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 110
agctacgagc tgacccagcc cctgagcgtg agcgtggccc tgggccagac cgccaggatc 60

acctgcagcg gcgacagcat ccccaactac tacgtgtact ggtaccagca gaagcccggc 120

caggcccccg tgctggtgat ctacgacgac agcaacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacca tcagcagggc ccaggccggc 240

gacgaggccg actactactg ccagagcttc gacagcagcc tgaacgccga ggtgttcggc 300

ggcggcacca agctgaccgt gctgggccag cccaaggccg cccccagcgt gaccctgttc 360

ccccccagca gcgaggagct gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctaccccg gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacca ccacccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac aggagctaca gctgccaggt gacccacgag 600

ggcagcaccg tggagaagac cgtggccccc accgagtgca gc 642

<210> 111
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (667)..(729)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (676)..(678)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (679)..(729)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (697)..(729)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(729)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of

substitutions and preferred embodiments"

<400> 111
gaggtgaagc tggaggagag cggcggcggc ctggtgcagc ccggcggcag catgaagctg 60

agctgcgccg ccagcggctt caccttcagc gacgcctgga tggactgggt gaggcagagc 120

cccgagaagg gcctggagtg ggtggccgag atcaggagca aggccagcaa ccacgccacc 180

tactacgccg agagcgtgaa gggcaggttc accatcagca gggacgacag caagagcagc 240

gtgtacctgc agatgaacag cctgagggcc gaggacaccg gcatctacta ctgcaccagg 300

tggaggaggt tcttcgacag ctggggccag ggcaccaccc tgaccgtgag cagcgccagc 360

accaagggcc ccagcgtgtt ccccctggcc cccagcagca agagcaccag cggcggcacc 420

gccgccctgg gctgcctggt gaaggactac ttccccgagc ccgtgaccgt gagctggaac 480

agcggcgccc tgaccagcgg cgtgcacacc ttccccgccg tgctgcagag cagcggcctg 540

tacagcctga gcagcgtggt gaccgtgccc agcagcagcc tgggcaccca gacctacatc 600

tgcaacgtga accacaagcc cagcaacacc aaggtggaca agaaggtgga gcccaagagc 660

tgcgacaaga cccacacctg ccccccctgc cccgcccccg agctgctggg cggccccagc 720

gtgttcctg 729

<210> 112
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 112
cagatcgtgc tgagccagag ccccgccatc ctgagcgcca gccccggcga gaaggtgacc 60

atgacctgca gggccagcag cagcgtgagc tacatgcact ggtaccagca gaagcccggc 120

agcagcccca agccctggat ctacgccacc agcaacctgg ccagcggcgt gcccgtgagg 180

ttcagcggca gcggcagcgg caccagctac agcctgacca tcagcagggt ggaggccgag 240

gacgccgcca cctactactg ccagcagtgg agcagcaacc ccctgacctt cggcgccggc 300

accaagctgg agctgaagag gaccgtggcc gcccccagcg tgttcatctt cccccccagc 360

gacgagcagc tgaagagcgg caccgccagc gtggtgtgcc tgctgaacaa cttctacccc 420

agggaggcca aggtgcagtg gaaggtggac aacgccctgc agagcggcaa cagccaggag 480

agcgtgaccg agcaggacag caaggacagc acctacagcc tgagcagcac cctgaccctg 540

agcaaggccg actacgagaa gcacaaggtg tacgcctgcg aggtgaccca ccagggcctg 600

agcagccccg tgaccaagag cttcaacagg ggcgagtgc 639

<210> 113
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (676)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (685)..(687)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (688)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (706)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(738)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 113

caggtgcagc tggtgcagag cggcgccgag ctgaagaagc ccggcgccag cgtgaaggtg 60

agctgcaaga gcagcggcta ccacttcacc agctactgga tgcactgggt gaagcaggcc 120

cccggccagg gcctggagtg gatcggcgtg atccacccca acagcggcag catcaactac 180

aacgagaagt tcgagagcag ggtgaccatc accgtggaca agagcaccag caccgcctac 240

atggagctga gcagcctgag gagcgaggac accgccgtgt actactgcgc cggcgagagg 300

gacagcaccg aggtgctgcc catggactac tggggccagg gcaccaccgt gaccgtgagc 360

agcgccagca ccaagggccc cagcgtgttc cccctggccc ccagcagcaa gagcaccagc 420

ggcggcaccg ccgccctggg ctgcctggtg aaggactact tccccgagcc cgtgaccgtg 480

agctggaaca gcggcgccct gaccagcggc gtgcacacct tccccgccgt gctgcagagc 540

agcggcctgt acagcctgag cagcgtggtg accgtgccca gcagcagcct gggcacccag 600

acctacatct gcaacgtgaa ccacaagccc agcaacacca aggtggacaa gagggtggag 660

cccaagagct gcgacaagac ccacacctgc ccccccctgcc ccgcccccga gctgctgggc 720

ggccccagcg tgttcctg 738

<210> 114
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 114
gacgtgcaga tcacccagag ccccagcagc ctgagcgcca gcctgggcga gagggccacc 60

atcaactgca gggccagcaa gagcatcaac aagtacctgg cctggtacca gcagaagccc 120

ggcaaggccc ccaagctgct gatctacagc ggcagcaccc tgcagagcgg catccccgcc 180

aggttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctggagccc 240

gaggacttcg ccatgtacta ctgccagcag cacaacgagt acccccctgac cttcggccag 300

ggcaccaagc 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

<210> 115
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (676)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (685)..(687)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (688)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (706)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(738)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 115
gaggtgcagc tggtggagag cggcggcggc ctggtgcagc ccggcaggag cctgaggctg 60

agctgcgccg ccagcggctt caccttcgac gactacgcca tgcactgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtgagcgcc atcacctgga acagcggcca catcgactac 180

gccgacagcg tggagggcag gttcaccatc agcagggaca acgccaagaa cagcctgtac 240

ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcgc caaggtgagc 300

tacctgagca ccgccagcag cctggactac tggggccagg gcaccctggt gaccgtgagc 360

agcgccagca ccaagggccc cagcgtgttc cccctggccc ccagcagcaa gagcaccagc 420

ggcggcaccg ccgccctggg ctgcctggtg aaggactact tccccgagcc cgtgaccgtg 480

agctggaaca gcggcgccct gaccagcggc gtgcacacct tccccgccgt gctgcagagc 540

agcggcctgt acagcctgag cagcgtggtg accgtgccca gcagcagcct gggcacccag 600

acctacatct gcaacgtgaa ccacaagccc agcaacacca aggtggacaa gaaggtggag 660

cccaagagct gcgacaagac ccacacctgc cccccctgcc ccgccccga gctgctgggc 720

ggccccagcg tgttcctg 738

<210> 116
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 116
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 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> 117
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (673)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (682)..(684)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (685)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (703)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(735)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 117
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

cccagcgtgt tcctg 735

<210> 118
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 118
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> 119
<211> 720
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (658)..(720)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (667)..(669)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (670)..(720)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (688)..(720)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(720)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 119
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 gccccccctg ccccgccccc gagctgctgg gcggccccag cgtgttcctg 720

<210> 120
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 120
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> 121
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (673)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (682)..(684)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (685)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (703)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(735)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 121
gaggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcgccag cgtgaaggtg 60

agctgcaagg ccagcggcta caccttcacc agccacggca tcagctgggt gaggcaggcc 120

cccggccagg gcctggactg gatgggctgg atcagccccct acagcggcaa caccaactac 180

gcccagaagc tgcagggcag ggtgaccatg accaccgaca ccagcaccag caccgcctac 240

atggagctga gcagcctgag gagcgaggac accgccgtgt actactgcgc cagggtgggc 300

agcggccccct actactacat ggacgtgtgg ggccagggca ccctggtgac 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 cccccgaggc cgccggcggc 720

cccagcgtgt tcctg 735

<210> 122
<211> 645
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 122
cagagcgccc tgacccagcc caggagcgtg agcggcagcc ccggccagag cgtgaccatc 60

agctgcaccg gcaccagcag cagcgtgggc gacagcatct acgtgagctg gtaccagcag 120

caccccggca aggcccccaa gctgatgctg tacgacgtga ccaagaggcc cagcggcgtg 180

cccgacaggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctg 240

caggccgagg acgaggccga ctactactgc tacagctacg ccggcaccga caccctgttc 300

ggcggcggca ccaaggtgac cgtgctgggc cagcccaagg ccgccccag cgtgaccctg 360

ttcccccca gcagcgagga gctgcaggcc aacaaggcca ccctggtgtg cctgatcagc 420

gacttctacc ccggcgccgt gaccgtggcc tggaaggccg acagcagccc cgtgaaggcc 480

ggcgtggaga ccaccacccc cagcaagcag agcaacaaca agtacgccgc cagcagctac 540

ctgagcctga cccccgagca gtggaagagc cacaggagct acagctgcca ggtgacccac 600

gagggcagca ccgtggagaa gaccgtggcc cccaccgagt gcagc 645

<210> 123
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (673)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (682)..(684)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (685)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (703)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(735)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 123
caggtgcagc tgcaggagag cggccccggc ctggtgaagc ccagcgagac cctgagcctg 60

acctgcagcg tgagcggcgg cagcatcatc agcaggagca gctactgggg ctggatcagg 120

cagccccccg gcaagggcct ggagtggatc ggcggcatct accacagcgg caacacctac 180

gacaacccca gcctgaagag caggctgacc atgagcgtgg acaccagcaa gaaccagttc 240

agcctgaacc tgaggagcgt gaccgccgcc gacaccgccg tgtactactg cgccaggatc 300

gtgcccggcg gcgacgcctt cgacatctgg ggccagggca ccatggtgac 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 tggacaagag ggtggagccc 660

aagagctgcg acaagaccca cacctgcccc ccctgccccg cccccgagct gctgggcggc 720

cccagcgtgt tcctg 735

<210> 124
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 124
gacatccaga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagggtgacc 60

gcctgcaggg ccagccagag cgtgggcacc tacctgaact ggtaccagca gaagaggggc 120

aaggccccca agctgctgat cttcgccgcc agcagcctgc agagcggcgt gcccagcagg 180

ttcagcggca gcggcagcgg caccgacttc accctgacca tcagcagcct gcagcccgag 240

gacttcgcca cctactactg ccagcagagc tacagcagcc cccccacctt cggccagggc 300

accaaggtgg agatcaagag gaccgtggcc gcccccagcg tgttcatctt cccccccagc 360

gacgagcagc tgaagagcgg caccgccagc gtggtgtgcc tgctgaacaa cttctacccc 420

agggaggcca aggtgcagtg gaaggtggac aacgccctgc agagcggcaa cagccaggag 480

agcgtgaccg agcaggacag caaggacagc acctacagcc tgagcagcac cctgaccctg 540

agcaaggccg actacgagaa gcacaaggtg tacgcctgcg aggtgaccca ccagggcctg 600

agcagccccg tgaccaagag cttcaacagg ggcgagtgc 639

<210> 125
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (664)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (673)..(675)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (676)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (694)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(726)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 125
gaggtgcagc tggtggagag cggcggcggc ctgatccagc ccggcggcag cctgaggctg 60

agctgcgccg ccagcggctt caccttcagc aactacgcca tgagctgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtgagcagc atcagcagcg gcggcagcac ctactacccc 180

gacagcgtga agggcaggtt caccatcagc agggacaaca gcaagaacac cctgtacctg 240

cagatgaaca gcctgagggc cgaggacacc gccgtgtact actgcgccag gtactactac 300

ggccagtact tcgacttctg gggccagggc accctggtga ccgtgagcag cgccagcacc 360

aagggcccca gcgtgttccc cctggccccc agcagcaaga gcaccagcgg cggcaccgcc 420

gccctgggct gcctggtgaa ggactacttc cccgagcccg tgaccgtgag ctggaacagc 480

ggcgccctga ccagcggcgt gcacaccttc cccgccgtgc tgcagagcag cggcctgtac 540

agcctgagca gcgtggtgac cgtgcccagc agcagcctgg gcacccagac ctacatctgc 600

aacgtgaacc acaagcccag caacaccaag gtggacaaga gggtggagcc caagagctgc 660

gacaagaccc acacctgccc cccctgcccc gcccccgagc tgctgggcgg ccccagcgtg 720

ttcctg 726

<210> 126
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 126
gacatcgtga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagggtgacc 60

atcacctgca aggccagcca ggacgtgagc accaccgtgg cctggtacca gcagaagccc 120

ggcaaggccc ccaagctgct gatctacagc gccagctaca ggagcaccgg cgtgcccagc 180

aggttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagccc 240

gaggacttcg ccgtgtacta ctgccagcag cactacagca ccccccctgac cttcggcggc 300

ggcaccaagg tggagatcaa 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> 127
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature

<222> (661)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (669)..(672)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (673)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (691)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(723)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 127
gaggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcagcag cgtgaaggtg 60

agctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gaggcaggcc 120

cccggccagg gcctggagtg gatgggcggc atcggccccc tcttcggcac cgccaactac 180

gcccagaagt tccagggcag ggtgaccatc accgccgacg agagcaccag caccgcctac 240

atggagctga gcagcctgag gagcgaggac accgccgtgt actactgcgc cagggacacc 300

ccctacttcg actactgggg ccagggcacc ctggtgaccg 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 gacaagaggg tggagcccaa gagctgcgac 660

aagacccaca cctgcccccc ctgccccgcc cccgaggccg ccggcggccc cagcgtgttc 720

ctg 723

<210> 128
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 128
agctacgagc tgacccagcc cctgagcgtg agcgtggccc tgggccagac cgccaggatc 60

acctgcagcg gcgacagcat ccccaactac tacgtgtact ggtaccagca gaagcccggc 120

caggcccccg tgctggtgat ctacgacgac agcaacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacca tcagcagggc ccaggccggc 240

gacgaggccg actactactg ccagagcttc gacagcagcc tgaacgccga ggtgttcggc 300

ggcggcacca agctgaccgt gctgggccag cccaaggccg cccccagcgt gaccctgttc 360

ccccccagca gcgaggagct gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctaccccg gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacca ccaccccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac aggagctaca gctgccaggt gacccacgag 600

ggcagcaccg tggagaagac cgtggccccc accgagtgca gc 642

<210> 129
<211> 705
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (673)..(705)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (691)..(705)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 129
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> 130
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 130
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 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> 131
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (661)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (670)..(672)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (673)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (691)..(723)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(723)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 131
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> 132
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 132
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> 133
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (676)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (685)..(687)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (688)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (706)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(738)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of

substitutions and preferred embodiments"

<400> 133
gaggtgcagc tggtggagag cggcggcggc ctggtgcagc ccggcggcag cctgaggctg 60

agctgcgccg ccagcggctt caccttcagc agcagctgga tgaactgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtgggcagg atctaccccg gcgacggcga caccaactac 180

aacgtgaagt tcaagggcag gttcaccatc agcagggacg acagcaagaa cagcctgtac 240

ctgcagatga acagcctgaa gaccgaggac accgccgtgt actactgcgc caggagcggc 300

ttcatcacca ccgtgaggga cttcgactac tggggccagg gcaccctggt gaccgtgagc 360

agcgccagca ccaagggccc cagcgtgttc cccctggccc ccagcagcaa gagcaccagc 420

ggcggcaccg ccgccctggg ctgcctggtg aaggactact tccccgagcc cgtgaccgtg 480

agctggaaca gcggcgccct gaccagcggc gtgcacacct tccccgccgt gctgcagagc 540

agcggcctgt acagcctgag cagcgtggtg accgtgccca gcagcagcct gggcacccag 600

acctacatct gcaacgtgaa ccacaagccc agcaacacca aggtggacaa gagggtggag 660

cccaagagct gcgacaagac ccacacctgc ccccccctgcc ccgccccga gctgctgggc 720

ggccccagcg tgttcctg 738

<210> 134
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 134
gagatcgtgc tgacccagag ccccgacttc cagagcgtga cccccaagga gaaggtgacc 60

atcacctgca gggccagcga gagcgtggac accttcggca tcagcttcat gaactggttc 120

cagcagaagc ccgaccagag ccccaagctg ctgatccacg aggccagcaa ccagggcagc 180

ggcgtgccca gcaggttcag cggcagcggc agcggcaccg acttcaccct gaccatcaac 240

agcctggagg ccgaggacgc cgccacctac tactgccagc agagcaagga ggtgcccttc 300

accttcggcg gcggcaccaa ggtggagatc 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> 135
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (664)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (673)..(675)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (676)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (694)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(726)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 135

gaggtgcagc tggtggagag cggcggcggc ctggtgcagc ccggcggcag cctgaggctg 60

agctgcgccg ccagcggctt cttcatcacc aacaactact ggggctgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtgggctac atcagctaca gcggcagcac cagctacaac 180

cccagcctga agagcaggtt caccatcagc agggacacca gcaagaacac cttctacctg 240

cagatgaaca gcctgagggc cgaggacacc gccgtgtact actgcgccag gaccggcagc 300

agcggctact tcgacttctg gggccagggc accctggtga ccgtgagcag cgccagcacc 360

aagggcccca gcgtgttccc cctggccccc agcagcaaga gcaccagcgg cggcaccgcc 420

gccctgggct gcctggtgaa ggactacttc cccgagcccg tgaccgtgag ctggaacagc 480

ggcgccctga ccagcggcgt gcacaccttc cccgccgtgc tgcagagcag cggcctgtac 540

agcctgagca gcgtggtgac cgtgcccagc agcagcctgg gcacccagac ctacatctgc 600

aacgtgaacc acaagcccag caacaccaag gtggacaaga aggtggagcc caagagctgc 660

gacaagaccc acacctgccc cccctgcccc gcccccgagc tgctgggcgg ccccagcgtg 720

ttcctg 726

<210> 136
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 136
gacatccaga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagggtgacc 60

atcacctgca gggccagcga gagcgtggac gacctgctgc actggtacca gcagaagccc 120

ggcaaggccc ccaagctgct gatcaagtac gccagccaga gcatcagcgg cgtgcccagc 180

aggttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagccc 240

gaggacttcg ccacctacta ctgccagcag ggcaacagcc tgcccaacac 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

<210> 137
<211> 717
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (685)..(717)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (703)..(717)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 137
gaggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcgccag cgtgaaggtg 60

agctgcaagg ccagcggcta caccttcacc gactacaaca tgcactgggt gaggcaggcc 120

cccggccagg gcctggagtg gatgggcgag atcaacccca acagcggcgg cgccggctac 180

aaccagaagt tcaagggcag ggtgaccatg accaccgaca ccagcaccag caccgcctac 240

atggagctga ggagcctgag gagcgacgac accgccgtgt actactgcgc caggctgggc 300

tacgacgaca tctacgacga ctggtacttc gacgtgtggg gccagggcac caccgtgacc 360

gtgagcagcg ccagcaccaa gggccccagc gtgttccccc tggcccccctg cagcaggagc 420

accagcgaga gcaccgccgc cctgggctgc ctggtgaagg actacttccc cgagcccgtg 480

accgtgagct ggaacagcgg cgccctgacc agcggcgtgc acaccttccc cgccgtgctg 540

cagagcagcg gcctgtacag cctgagcagc gtggtgaccg tgcccagcag caacttcggc 600

acccagacct acacctgcaa cgtggaccac aagcccagca acaccaaggt ggacaagacc 660

gtggagagga agtgctgcgt ggagtgcccc ccctgccccg ccccccccgt ggccggc 717

<210> 138
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 138
gacatccaga tgacccagag ccccagcagc ctgagcgcca gcgtgggcga cagggtgacc 60

atcacctgca gggccagcca ggacatcagc aactacctga actggtacca gcagaagccc 120

ggcaaggccc ccaagctgct gatctactac accagcaggc tgctgagcgg cgtgcccagc 180

aggttcagcg gcagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagccc 240

gaggacttcg ccacctacta ctgccagcag ggcgacaccc tgccctacac cttcggcggc 300

ggcaccaagg tggagatcaa 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> 139
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (679)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (688)..(690)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (691)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (709)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(741)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 139
gaggtgcagc tgctggagag cggcggcggc ctggtgcagc ccggcggcag cctgaggctg 60

agctgcgccg ccagcggctt caccttcagc cactacatca tgatgtgggt gaggcaggcc 120

cccggcaagg gcctggagtg ggtgagcggc atctacagca gcggcggcat caccgtgtac 180

gccgacagcg tgaagggcag gttcaccatc agcagggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcgc ctacaggagg 300

atcggcgtgc ccaggaggga cgagttcgac atctggggcc agggcaccat ggtgaccgtg 360

agcagcgcca gcaccaaggg ccccagcgtg ttccccctgg cccccagcag caagagcacc 420

agcggcggca ccgccgccct gggctgcctg gtgaaggact acttccccga gcccgtgacc 480

gtgagctgga acagcggcgc cctgaccagc ggcgtgcaca ccttccccgc cgtgctgcag 540

agcagcggcc tgtacagcct gagcagcgtg gtgaccgtgc ccagcagcag cctgggcacc 600

cagacctaca tctgcaacgt gaaccacaag cccagcaaca ccaaggtgga caagagggtg 660

gagcccaaga gctgcgacaa gacccacacc tgccccccct gccccgcccc cgagctgctg 720

ggcggcccca gcgtgttcct g 741

<210> 140
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 140
gacatccaga tgacccagag ccccagcacc ctgagcgcca gcgtgggcga cagggtgacc 60

atcacctgca gggccagcca gagcatcagc agctggctgg cctggtacca gcagaagccc 120

ggcaaggccc ccaagctgct gatctacaag gccagcaccc tggagagcgg cgtgcccagc 180

aggttcagcg gcagcggcag cggcaccgag ttcaccctga ccatcagcag cctgcagccc 240

gacgacttcg ccacctacta ctgccagcag tacaacacct actggacctt cggccagggc 300

accaaggtgg agatcaagag gaccgtggcc gcccccagcg tgttcatctt cccccccagc 360

gacgagcagc tgaagagcgg caccgccagc gtggtgtgcc tgctgaacaa cttctacccc 420

agggaggcca aggtgcagtg gaaggtggac aacgccctgc agagcggcaa cagccaggag 480

agcgtgaccg agcaggacag caaggacagc acctacagcc tgagcagcac cctgaccctg 540

agcaaggccg actacgagaa gcacaaggtg tacgcctgcg aggtgaccca ccagggcctg 600

agcagccccg tgaccaagag cttcaacagg ggcgagtgc 639

<210> 141
<211> 2205
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 141
atgtaccgga tgcagctgct gctgctcatt gccctgtctc tggccctggt caccaatagc 60

gaagtccagc tgctggaatc tggcggcgga cttgttcaac ctggcggctc tctgagactg 120

agctgtgccg cttccggctt caccttcagc cactatatca tgatgtgggt ccgacaggcc 180

cctggcaaag gccttgaatg ggtgtccggc atctatagca gcggcggcat cacagtgtac 240

gccgactctg tgaagggcag attcaccatc agccgggaca acagcaagaa caccctgtac 300

ctgcagatga acagcctgag agccgaggac accgccgtgt actactgcgc ctatagaaga 360

atcggcgtgc ccagacggga cgagttcgat atttggggcc agggcaccat ggtcaccgtg 420

tctagcgcct ctacaaaggg ccctagcgtg ttccctctgg ctcctagcag caagagcaca 480

agcggaggaa cagccgctct gggctgtctg gtcaaggact actttcccga gcctgtgacc 540

gtgtcctgga atagcggagc actgacaagc ggcgtgcaca cctttccagc tgtgctgcaa 600

agcagcggcc tgtactctct gagcagcgtg gtcacagtgc caagctctag cctgggcacc 660

cagacctaca tctgcaatgt gaaccacaag cctagcaaca ccaaggtgga caagagagtg 720

gaacccaaga gctgcgacaa gacccacacc tgtcctccat gtcctgctcc agaactgctc 780

ggcggacctt ccgtgttcct gtttcctcca aagcctaagg acaccctgat gatcagcaga 840

acccctgaag tgacctgcgt ggtggtggat gtgtcccacg aggatcccga agtgaagttc 900

aattggtacg tggacggcgt ggaagtgcac aacgccaaga ccaagcctag agaggaacag 960

tacaacagca cctacagagt ggtgtccgtg ctgaccgtgc tgcaccagga ttggctgaac 1020

ggcaaagagt acaagtgcaa ggtgtccaac aaggccctgc ctgctcctat cgagaaaacc 1080

atcagcaagg ccaagggcca gcctagggaa ccccaggttt acacactgcc tccaagccgg 1140

gaagagatga ccaagaacca ggtgtccctg acctgcctcg tgaagggctt ctacccttcc 1200

gatatcgccg tggaatggga gagcaatggc cagccagaga acaactacaa gacaacccct 1260

cctgtgctgg acagcgacgg ctcattcttc ctgtacagca agctgacagt ggacaagtcc 1320

agatggcagc agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac 1380

tacacccaga agagtctgag cctgtctcca ggcctgcgga agagaagggc tcctgtgaag 1440

cagaccctga acttcgacct gctgaaactg gccggcgacg tggaaagcaa ccccggacct 1500

atgtatagaa tgcagctcct cctgctgatc gcactgagcc tggctctcgt gaccaacagc 1560

gacatccaga tgacacagag ccccagcaca ctgtctgcca gcgtgggaga cagagtgacc 1620

atcacctgta gagccagcca gtccatctcc tcttggctgg cctggtatca gcaaaagcct 1680

ggcaaggccc ctaagctgct gatctacaag gcctccacac tggaaagcgg ggtgccctcc 1740

agattttctg gcagcggatc tggcaccgag ttcaccctga ccatcagtag cctgcagcct 1800

gacgacttcg ccacctacta ctgccagcag tacaatacct actggacctt cggccaggga 1860

acaaaggtgg aaatcaagcg gactgtggcc gctccaagcg tgttcatctt tccacctagc 1920

gacgagcagc tgaagtccgg cacagcctct gttgtgtgcc tgctgaacaa cttctacccc 1980

agagaagcca aggtgcagtg gaaagtggac aatgccctgc agagcggcaa ctcccaagag 2040

agcgtgacag agcaggactc caaggattcc acctacagcc tgtctagcac cctgacactg 2100

agcaaggccg actacgagaa gcacaaagtg tatgcctgcg aagtgaccca ccagggcctt 2160

agctctccag tgaccaagag cttcaaccgg ggcgagtgtt gataa 2205

<210> 142

<400> 142
000

<210> 143
<211> 738
<212> PRT
<213> Adeno-associated virus 8

<400> 143
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> 144
<211> 736

<212> PRT
<213> Adeno-associated virus 9

<400> 144
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> 145
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 145
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> 146
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 146
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> 147
<211> 26
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown: VEGF-A signal peptide"

<400> 147
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> 148
<211> 29
<212> PRT
<213> Unknown

<220>
<221> source

<223> /note="Description of Unknown:
Fibulin-1 signal peptide"

<400> 148
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> 149
<211> 19
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Vitronectin signal peptide"

<400> 149
Met Ala Pro Leu Arg Pro Leu Leu Ile Leu Ala Leu Leu Ala Trp Val
1 5 10 15

Ala Leu Ala

<210> 150
<211> 18
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Complement Factor H signal peptide"

<400> 150
Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1 5 10 15

Val Ala

<210> 151
<211> 19
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Opticin signal peptide"

<400> 151
Met Arg Leu Leu Ala Phe Leu Ser Leu Leu Ala Leu Val Leu Gln Glu
1 5 10 15

Thr Gly Thr

<210> 152
<211> 18
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Albumin signal peptide"

<400> 152
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser

<210> 153
<211> 18
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Chymotrypsinogen signal peptide"

<400> 153
Met Ala Phe Leu Trp Leu Leu Ser Cys Trp Ala Leu Leu Gly Thr Thr
1 5 10 15

Phe Gly

<210> 154

<211> 20
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Interleukin-2 signal peptide"

<400> 154
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> 155
<211> 15
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Trypsinogen-2 signal peptide"

<400> 155
Met Asn Leu Leu Leu Ile Leu Thr Phe Val Ala Ala Ala Val Ala
1 5 10 15

<210> 156
<211> 17
<212> PRT
<213> Homo sapiens

<400> 156
Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu
1 5 10 15

Ala

<210> 157
<211> 22
<212> PRT
<213> Homo sapiens

<400> 157
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> 158
<211> 19
<212> PRT
<213> Homo sapiens

<400> 158
Met Lys Leu Val Phe Leu Val Leu Leu Phe Leu Gly Ala Leu Gly Leu
1 5 10 15

Cys Leu Ala

<210> 159
<211> 22
<212> PRT
<213> Homo sapiens

<400> 159
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> 160
<211> 18
<212> PRT
<213> Homo sapiens

<400> 160
Met Ser Leu Ser Ala Phe Thr Leu Phe Leu Ala Leu Ile Gly Gly Thr
1 5 10 15

Ser Gly

<210> 161
<211> 27
<212> PRT
<213> Homo sapiens

<400> 161
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> 162
<211> 22
<212> PRT
<213> Homo sapiens

<400> 162
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> 163
<211> 19
<212> PRT
<213> Homo sapiens

<400> 163
Met Gln Ala Leu Val Leu Leu Leu Cys Ile Gly Ala Leu Leu Gly His
1   5   10   15

Ser Ser Cys

<210> 164
<211> 23
<212> PRT
<213> Homo sapiens

<400> 164
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> 165
<211> 20
<212> PRT

<213> Homo sapiens

<400> 165
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> 166
<211> 23
<212> PRT
<213> Homo sapiens

<400> 166
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> 167
<211> 31
<212> PRT
<213> Homo sapiens

<400> 167
Met Leu Arg Gly Pro Gly Pro Gly Leu Leu Leu Leu Ala Val Gln Cys
1   5   10   15

Leu Gly Thr Ala Val Pro Ser Thr Gly Ala Ser Lys Ser Lys Arg
            20   25   30

<210> 168
<211> 15
<212> PRT
<213> Homo sapiens

<400> 168
Met Trp Cys Ile Val Leu Phe Ser Leu Leu Ala Trp Val Tyr Ala
1   5   10   15

<210> 169
<211> 17
<212> PRT
<213> Homo sapiens

<400> 169
Met Asn Pro Thr Leu Ile Leu Ala Ala Phe Cys Leu Gly Ile Ala Ser
1   5   10   15

Ala

<210> 170
<211> 17
<212> PRT
<213> Homo sapiens

<400> 170
Met Trp Gln Leu Trp Ala Ser Leu Cys Cys Leu Leu Val Leu Ala Asn
1   5   10   15

Ala

<210> 171
<211> 16
<212> PRT
<213> Homo sapiens

<400> 171
Met Leu Leu Ile Leu Leu Ser Val Ala Leu Leu Ala Phe Ser Ser Ala
1   5   10   15

<210> 172
<211> 20
<212> PRT
<213> Homo sapiens

<400> 172
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> 173
<211> 18
<212> PRT
<213> Homo sapiens

<400> 173
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala

1 5 10 15

Tyr Ser

<210> 174
<211> 24
<212> PRT
<213> Homo sapiens

<400> 174
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> 175
<211> 18
<212> PRT
<213> Homo sapiens

<400> 175
Met Lys Ala Ala Val Leu Thr Leu Ala Val Leu Phe Leu Thr Gly Ser
1 5 10 15

Gln Ala

<210> 176
<211> 18
<212> PRT
<213> Homo sapiens

<400> 176
Met Lys Leu Leu Ala Ala Thr Val Leu Leu Leu Thr Ile Cys Ser Leu
1 5 10 15

Glu Gly

<210> 177
<211> 27
<212> PRT
<213> Homo sapiens

<400> 177
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> 178
<211> 28
<212> PRT
<213> Homo sapiens

<400> 178
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> 179
<211> 20
<212> PRT
<213> Homo sapiens

<400> 179
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> 180
<211> 18
<212> PRT
<213> Homo sapiens

<400> 180
Met Trp Leu Leu Val Ser Val Ile Leu Ile Ser Arg Ile Ser Ser Val
1   5   10   15

Gly Gly

<210> 181
<211> 18
<212> PRT

<213> Homo sapiens

<400> 181
Met Leu Leu Leu Phe Ser Val Ile Leu Ile Ser Trp Val Ser Thr Val
1   5   10   15

Gly Gly

<210> 182
<211> 19
<212> PRT
<213> Homo sapiens

<400> 182
Met Phe Ser Met Arg Ile Val Cys Leu Val Leu Ser Val Val Gly Thr
1   5   10   15

Ala Trp Thr

<210> 183
<211> 30
<212> PRT
<213> Homo sapiens

<400> 183
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> 184
<211> 26
<212> PRT
<213> Homo sapiens

<400> 184
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> 185

<211> 18
<212> PRT
<213> Homo sapiens

<400> 185
Met Lys Ser Leu Val Leu Leu Leu Cys Leu Ala Gln Leu Trp Gly Cys
1   5   10   15

His Ser

<210> 186
<211> 23
<212> PRT
<213> Homo sapiens

<400> 186
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> 187
<211> 18
<212> PRT
<213> Homo sapiens

<400> 187
Met Lys Leu Ile Thr Ile Leu Phe Leu Cys Ser Arg Leu Leu Leu Ser
1   5   10   15

Leu Thr

<210> 188
<211> 20
<212> PRT
<213> Homo sapiens

<400> 188
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> 189
<211> 19
<212> PRT
<213> Homo sapiens

<400> 189
Met Glu His Lys Glu Val Val Leu Leu Leu Leu Leu Phe Leu Lys Ser
1   5   10   15

Gly Gln Gly

<210> 190
<211> 24
<212> PRT
<213> Homo sapiens

<400> 190
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> 191
<211> 29
<212> PRT
<213> Homo sapiens

<400> 191
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> 192
<211> 32
<212> PRT
<213> Homo sapiens

<400> 192
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> 193
<211> 19
<212> PRT
<213> Homo sapiens

<400> 193
Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu
1 5 10 15

Cys Leu Ala

<210> 194
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 194
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> 195
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 195
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> 196
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 196
Glu Pro Lys Ser Cys Asp Lys Thr His Leu
1 5 10

<210> 197
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 197
Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10

<210> 198
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 198
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

<210> 199
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 199
Glu Pro Lys Ser Cys Asp Lys Thr His Leu Cys Pro Pro Cys Pro Ala
1 5 10 15

<210> 200
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 200
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> 201
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 201
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> 202
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 202
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> 203
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 203
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
            20

<210> 204
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 204
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> 205
<211> 27
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 205
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> 206
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 206
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> 207
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 207
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
20

<210> 208
<211> 27
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 208
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> 209
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 209
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> 210
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 210
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> 211
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 211
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
20

<210> 212
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 212
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 Pro Ser Val Phe Leu
20 25

<210> 213
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 213
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> 214
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 214
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly

<210> 215
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 215
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly

<210> 216
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 216
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10

<210> 217
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 217
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala
1 5 10

<210> 218
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 218
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> 219
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 219
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> 220
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 220
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
1 5 10 15

Ala Gly

<210> 221
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 221
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
1 5 10

<210> 222
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 222
Arg Lys Arg Arg
1

<210> 223
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 223
Arg Arg Arg Arg
1

<210> 224
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 224
Arg Arg Lys Arg
1

<210> 225
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 225
Arg Lys Lys Arg
1

<210> 226

<400> 226
000

<210> 227
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> SITE
<222> (1)..(3)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 227
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> 228
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> SITE
<222> (1)..(3)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 228
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> 229

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

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> SITE
<222> (1)..(3)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 229
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> 230
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> SITE
<222> (1)..(3)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 230
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> 231
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 231
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> 232
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 232
Cys Pro Pro Cys Pro Ala
1   5

<210> 233
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 233
Cys Pro Pro Cys Pro
1   5

<210> 234

<400> 234
000

<210> 235

<400> 235
000

<210> 236
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 236
Glu Asp Thr Ala Val Tyr Tyr
1   5

<210> 237
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 237
Tyr Cys Ala Ser Gly Asp Tyr Trp
1   5

<210> 238
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 238
Glu Asp Val Gly Val Tyr Tyr

1 5

<210> 239
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 239
Glu Asp Phe Ala Val Tyr Tyr
1 5

<210> 240
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 240
Glu Asp Ser Gly Ile Tyr Tyr
1 5

<210> 241
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 241
Asn Trp Glu Asp Tyr Trp
1 5

<210> 242
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 242
Glu Asp Phe Ala Thr Tyr Tyr
1 5

<210> 243
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 243
Asp Thr Ala Val Tyr Tyr
1 5

<210> 244
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 244
Tyr Tyr Gly Ala Phe Asp
1 5

<210> 245
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 245
Glu Asp Glu Ala Asp Tyr Tyr
1 5

<210> 246
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 246
Tyr Tyr Tyr Gly Arg His Phe Asp
1 5

<210> 247
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 247
Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr
1 5 10

<210> 248
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 248
Glu Asp Val Ala Val Tyr Tyr
1 5

<210> 249
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 249
Glu Asp Leu Ala Thr Tyr Tyr
1   5

<210> 250
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 250
Glu Asp Thr Ala Val Tyr
1   5

<210> 251
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 251
Asp Asp Phe Ala Thr Tyr Tyr
1   5

<210> 252
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 252
Asp Leu Ser Gly Tyr Tyr
1   5

<210> 253
<211> 7
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 253
Glu Asp Val Ala Thr Tyr Tyr
1 5

<210> 254
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 254
Asp Thr Ala Met Tyr Tyr
1 5

<210> 255
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 255
Asp Glu Ala Asp Tyr Tyr
1 5

<210> 256
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 256
Thr Phe Glu Gly Asp Tyr Val Phe

1 5

<210> 257
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 257
Asp Asn Leu Gly Thr Tyr Tyr Val Glu
1 5

<210> 258

<400> 258
000

<210> 259
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 259
Asp Ser Ile Pro Asn Tyr
1 5

<210> 260
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 260
Tyr Cys Gln Ser Phe Asp
1 5

<210> 261
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 261
Glu Asp Thr Gly Ile Tyr Tyr
1 5

<210> 262
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 262
Glu Asp Ala Ala Thr Tyr Tyr
1 5

<210> 263
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 263
Tyr Asn Glu Lys Phe Glu
1 5

<210> 264
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 264
Glu Asp Phe Ala Met Tyr Tyr
1   5

<210> 265
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 265
Phe Thr Phe Asp Asp Tyr Ala
1   5

<210> 266
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 266
Glu Asp Thr Gly Val Tyr Tyr
1   5

<210> 267
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      peptide"

<400> 267
Glu Asp Ile Ala Asp Tyr Tyr
1   5

<210> 268
<211> 6
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 268
Tyr Tyr Tyr Gly Met Asp
1 5

<210> 269
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 269
Glu Leu Leu Ile Tyr Tyr
1 5

<210> 270
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 270
Glu Asp Thr Ala Leu Tyr Tyr
1 5

<210> 271
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 271
Glu Asp Phe Ala Ser Tyr Tyr

1 5

<210> 272
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 272
Asp Leu Leu His Trp Tyr
1 5

<210> 273
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 273
Asp Asp Thr Ala Val Tyr Tyr
1 5

<210> 274
<211> 736
<212> PRT
<213> Adeno-associated virus 1

<400> 274
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> 275
<211> 735
<212> PRT
<213> Adeno-associated virus 2

<400> 275
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> 276
<211> 736
<212> PRT
<213> Adeno-associated virus 3

<400> 276
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> 277
<211> 734
<212> PRT
<213> Adeno-associated virus 4

<400> 277
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> 278
<211> 724
<212> PRT
<213> Adeno-associated virus 5

<400> 278
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> 279
<211> 736
<212> PRT
<213> Adeno-associated virus 6

<400> 279
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> 280
<211> 737
<212> PRT
<213> Adeno-associated virus 7

<400> 280
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> 281
<211> 736
<212> PRT
<213> Adeno-associated virus

<400> 281
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 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 Ser Gln Pro Ala Lys Lys Lys 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 Gly 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 Ser 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> 282
<211> 736
<212> PRT
<213> Adeno-associated virus

<400> 282
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 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 Ser Gln Pro Ala Lys Lys Lys 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> 283
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 283
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

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

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

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

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

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

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


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


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


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


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


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


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


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


Ser Leu Ser Leu Ser Pro Gly Lys
225                 230


<210> 284
<211> 228
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 284
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
1               5                   10                  15


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

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

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
    50                  55                  60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
65                  70                  75                  80

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

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

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

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

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

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

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

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

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

Ser Pro Gly Lys
225
```

<210> 285

<211> 229
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 285
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1 5 10 15

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

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

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

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

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

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

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

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
180 185 190

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

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

Leu Ser Leu Gly Lys
225

<210> 286
<211> 2193
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 286
atgtacagaa tgcagctgct gctgctcatt gccctgtctc tggccctggt caccaattct 60

gaggtccagc tgcttgagag tggtggtgga ctggttcagc ctggtggcag cctgagactg 120

tcttgtgctg cctctggctt caccttcagc cactatatca tgatgtgggt cagacaggcc 180

cctggcaaag gcctggaatg ggtgtcaggc atctacagca gtggtggcat cacagtgtat 240

gctgactctg tgaagggcag attcaccatc agcagagaca acagcaagaa caccctgtac 300

ctgcagatga actccctgag agctgaggac acagcagtgt actactgtgc ctatagaaga 360

attggggtgc ccagaaggga tgagtttgac atctggggcc agggcaccat ggttacagtg 420

tcctctgcca gcacaaaggg cccctctgtt tttccactgg ctcccagcag caagagcacc 480

agtggtggaa cagctgccct gggctgtctg gtcaaggatt acttccctga gcctgtgact 540

gtgtcctgga actctggggc tctgacttct ggggtgcaca cctttccagc tgtgctgcag 600

tcctctggcc tgtactctct gtcctctgtg gtcacagtgc ctagctctag cctgggcaca 660

cagacctaca tctgcaatgt gaaccacaag cctagcaaca ccaaggtgga caagagagtg 720

gaacccaaga gctgtgacaa gacccacacc tgtcctccat gtcctgctcc agaactgctt 780

ggaggccctt ctgtgttcct gtttcctcca aagcctaagg acaccctgat gatcagcaga 840

acccctgaag tgacctgtgt ggtggttgat gtgtcccatg aggacccaga agtgaagttc 900

aattggtatg tggatggggt tgaagtgcac aatgccaaga ccaagcctag agaggaacag 960

tacaacagca cctacagagt ggtttctgtg ctgacagtgc tgcaccagga ctggctgaat 1020

ggcaaagagt acaagtgcaa ggtgtccaac aaggccctgc ctgctcctat tgagaaaacc 1080

atctccaagg ccaagggcca gccaagagaa ccccaggttt acaccctgcc acctagcaga 1140

gaagagatga ccaagaacca ggtgtccctg acctgcctgg ttaagggctt ctacccctct 1200

gacattgctg tggaatggga gagcaatggc cagcctgaaa acaactacaa gacaacccct 1260

cctgtgctgg actctgatgg ctcattcttc ctgtacagca agctgactgt ggacaagtcc 1320

agatggcagc agggaaatgt gttcagctgc tctgtgatgc atgaggccct gcacaaccac 1380

tacacccaga aaagtctgtc tctgtcccct ggcagaaaga gaagaggctc tggagaaggc 1440

agaggctccc tgctgacatg tggggatgtt gaagagaatc ctgggcctat gtataggatg 1500

caactgctcc tcctgattgc tctgagcctg gctcttgtga ccaactctga catccagatg 1560

acacagagcc cctccacact gtctgcatct gtgggagaca gagtgaccat cacctgtaga 1620

gccagccagt ctatctctag ctggctggcc tggtatcagc aaaagcctgg caaggcccct 1680

aagctgctga tctacaaggc cagcacactt gagtcagggg tgccctccag attttctggc 1740

tctggatctg gcacagagtt caccctgacc atcagctccc tgcagccaga tgactttgcc 1800

acctactact gccagcagta caatacctac tggacctttg gccagggaac aaaggtggaa 1860

atcaagagaa cagtggctgc cccatctgtg ttcatcttcc caccatctga tgaacagctg 1920

aagtctggca ctgcctctgt tgtgtgcctg ctgaacaact tttaccccag agaagccaag 1980

gtgcagtgga aagtggataa tgccctgcag tctggcaata gccaagaatc tgtgacagag 2040

caggactcca aggattccac ctacagcctg agcagcaccc tgacactgag caaggctgac 2100

tatgagaagc acaaagtgta tgcctgtgaa gtgacacacc agggactgag cagcccagtg 2160

accaagagct tcaacagggg agagtgctga taa 2193

<210> 287
<211> 2211
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 287
atgtacagaa tgcagctgct gctgctcatt gccctgtctc tggccctggt caccaattct 60

gaggtccagc tgcttgagag tggtggtgga ctggttcagc ctggtggcag cctgagactg 120

tcttgtgctg cctctggctt caccttcagc cactatatca tgatgtgggt cagacaggcc 180

cctggcaaag gcctggaatg ggtgtcaggc atctacagca gtggtggcat cacagtgtat 240

gctgactctg tgaagggcag attcaccatc agcagagaca acagcaagaa caccctgtac 300

ctgcagatga actccctgag agctgaggac acagcagtgt actactgtgc ctatagaaga 360

attggggtgc ccagaaggga tgagtttgac atctggggcc agggcaccat ggttacagtg 420

tcctctgcca gcacaaaggg cccctctgtt tttccactgg ctcccagcag caagagcacc 480

agtggtggaa cagctgccct gggctgtctg gtcaaggatt acttccctga gcctgtgact 540

gtgtcctgga actctggggc tctgacctct ggggtgcaca cctttccagc tgtgctgcag 600

tcctctggcc tgtactctct gtcctctgtg gtcacagtgc ctagctctag cctgggcaca 660

cagacctaca tctgcaatgt gaaccacaag cctagcaaca ccaaggtgga caagagagtg 720

gaacccaaga gctgtgacaa gacccacacc tgtcctccat gtcctgctcc agaactgctt 780

ggaggccctt ctgtgttcct gtttcctcca aagcctaagg acaccctgat gatcagcaga 840

acccctgaag tgacctgtgt ggtggttgat gtgtcccatg aggacccaga agtgaagttc 900

aattggtatg tggatggggt tgaagtgcac aatgccaaga ccaagcctag agaggaacag 960

tacaacagca cctacagagt ggtttctgtg ctgacagtgc tgcaccagga ctggctgaat 1020

ggcaaagagt acaagtgcaa ggtgtccaac aaggccctgc ctgctcctat tgagaaaacc 1080

atctccaagg ccaagggcca gccaagagaa ccccaggttt acaccctgcc acctagcaga 1140

gaagagatga ccaagaacca ggtgtccctg acctgcctgg ttaagggctt ctacccctct 1200

gacattgctg tggaatggga gagcaatggc cagcctgaaa acaactacaa gacaacccct 1260

cctgtgctgg actctgatgg ctcattcttc ctgtacagca agctgactgt ggacaagtcc 1320

agatggcagc agggaaatgt gttcagctgc tctgtgatgc atgaggccct gcacaaccac 1380

tacacccaga aaagtctgtc tctgtcccct ggcagaaaga gaagaggatc aggggcccca 1440

gtgaagcaga ccctgaactt tgatctgctg aagctggctg gggatgttga gagcaaccct 1500

ggacctatgt ataggatgca actgctcctc ctgattgctc tgagcctggc tcttgtgacc 1560

aactctgaca tccagatgac acagagcccc tccacactgt ctgcatctgt gggagacaga 1620

gtgaccatca cctgtagagc cagccagtct atctcttcct ggctggcctg gtatcagcaa 1680

aagcctggca aggcccctaa gctgctgatc tacaaggcca gcacacttga gtcaggggtg 1740

ccctccagat tttctggctc tggatctggc acagagttca ccctgaccat cagctccctg 1800

cagccagatg actttgccac ctactactgc cagcagtaca atacctactg gacctttggc 1860

cagggaacaa aggtggaaat caagagaaca gtggctgccc catctgtgtt catcttccca 1920

ccatctgatg aacagctgaa gtctggcact gcctctgttg tgtgcctgct gaacaacttt 1980

taccctagag aagccaaggt gcagtggaaa gtggataatg ccctgcagtc tggcaatagc 2040

caagaatctg tgacagagca ggactccaag gattccacct acagcctgag cagcaccctg 2100

acactgagca aggctgacta tgagaagcac aaagtgtatg cctgtgaagt gacacaccag 2160

ggactgagca gcccagtgac caagagcttc aacaggggag agtgctgata a 2211

<210> 288
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 288
Leu Gly Glu Thr Thr Arg Pro
1 5

<210> 289
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 289
Leu Ala Leu Gly Glu Thr Thr Arg Pro
1 5

<210> 290
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 290
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> 291
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 291
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> 292
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 292

```
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> 293
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 293
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 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> 294
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 294
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 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

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> 295
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
```

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 295

```
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 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> 296
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 296
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> 297
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 297
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 Ser Ser 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 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

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> 298
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 298

```
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> 299
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 299
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> 300
<211> 210
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 300
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                   10                  15


Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
```

```
            20                  25                  30

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
    50                  55                  60

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

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

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Lys
    210


<210> 301
<211> 205
<212> PRT
```

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 301
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 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> 302
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 302
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> 303
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 303
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> 304
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 304
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> 305
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 305
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> 306
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 306

```
Phe Pro Pro Lys Pro Lys Asp Gln 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 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 Leu 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> 307
<211> 205
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 307
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 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> 308
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 308
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 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> 309
<211> 208
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 309
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1 5 10 15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
20 25 30

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
35 40 45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
50 55 60

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

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

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

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


Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140


Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
145                 150                 155                 160


Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                165                 170                 175


Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190


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


<210> 310
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 310
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> 311
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 311
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 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> 312
<211> 204
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 312
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 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
        195                 200
```

<210> 313
<211> 210
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 313
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1 5 10 15

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

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
35 40 45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
50 55 60

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

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

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
130 135 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
145 150 155 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
165 170 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
180 185 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
195 200 205

Gly Lys
210

<210> 314
<211> 204
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 314
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 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
        195                 200
```

<210> 315
<211> 969
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 315
aggttaattt ttaaaaagca gtcaaaagtc caagtggccc ttggcagcat ttactctctc 60

tgtttgctct ggttaataat ctcaggagca caaacattcc agatccaggt taatttttaa 120

aaagcagtca aaagtccaag tggcccttgg cagcatttac tctctctgtt tgctctggtt 180

aataatctca ggagcacaaa cattccagat ccggcgcgcc agggctggaa gctacctttg 240

tctagaaggc tcagaggcac acaggagttt ctgggctcac cctgccccct tccaacccct 300

cagttcccat cctccagcag ctgtttgtgt gctgcctctg aagtccacac tgaacaaact 360

tcagcctact catgtcccta aaatgggcaa acattgcaag cagcaaacag caaacacaca 420

gccctccctg cctgctgacc ttggagctgg ggcagaggtc agagacctct ctgggcccat 480

gccacctcca acatccactc gacccccttgg aatttcggtg gagaggagca gaggttgtcc 540

tggcgtggtt taggtagtgt gagaggggta cccggggatc ttgctaccag tggaacagcc 600

actaaggatt ctgcagtgag agcagagggc cagctaagtg gtactctccc agagactgtc 660

tgactcacgc caccccctcc accttggaca caggacgctg tggtttctga gccaggtaca 720

atgactcctt tcggtaagtg cagtggaagc tgtacactgc ccaggcaaag cgtccgggca 780

gcgtaggcgg gcgactcaga tcccagccag tggacttagc ccctgtttgc tcctccgata 840

actggggtga ccttggttaa tattcaccag cagcctcccc cgttgcccct ctggatccac 900

tgcttaaata cggacgagga cagggccctg tctcctcagc ttcaggcacc accactgacc 960

tgggacagt 969

<210> 316
<211> 1050
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 316
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gtctagaagg ctcagaggca cacaggagtt tctgggctca 360

ccctgccccc ttccaacccc tcagttccca tcctccagca gctgtttgtg tgctgcctct 420

gaagtccaca ctgaacaaac ttcagcctac tcatgtccct aaaatgggca aacattgcaa 480

gcagcaaaca gcaaacacac agccctccct gcctgctgac cttggagctg gggcagaggt 540

cagagacctc tctgggccca tgccacctcc aacatccact cgacccctg gaatttcggt 600

ggagaggagc agaggttgtc ctggcgtggt ttaggtagtg tgagaggggt acccggggat 660

cttgctacca gtggaacagc cactaaggat tctgcagtga gagcagaggg ccagctaagt 720

ggtactctcc cagagactgt ctgactcacg ccacccccctc caccttggac acaggacgct 780

gtggtttctg agccaggtac aatgactcct ttcggtaagt gcagtggaag ctgtacactg 840

cccaggcaaa gcgtccgggc agcgtaggcg ggcgactcag atcccagcca gtggacttag 900

cccctgtttg ctcctccgat aactggggtg accttggtta atattcacca gcagcctccc 960

ccgttgcccc tctggatcca ctgcttaaat acggacgagg acagggccct gtctcctcag 1020

cttcaggcac caccactgac ctgggacagt 1050

<210> 317
<211> 1089
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 317
aggttaattt ttaaaaagca gtcaaaagtc caagtggccc ttggcagcat ttactctctc 60

tgtttgctct ggttaataat ctcaggagca caaacattcc agatccaggt taatttttaa 120

aaagcagtca aaagtccaag tggcccttgg cagcatttac tctctctgtt tgctctggtt 180

aataatctca ggagcacaaa cattccagat ccggcgcgcc agggctggaa gctacctttg 240

acatcatttc ctctgcgaat gcatgtataa tttctacaga acctattaga aaggatcacc 300

cagcctctgc ttttgtacaa ctttccctta aaaaactgcc aattccactg ctgtttggcc 360

caatagtgag aacttttcc tgctgcctct tggtgctttt gcctatggcc cctattctgc 420

ctgctgaaga cactcttgcc agcatggact taaacccctc cagctctgac aatcctcttt 480

ctcttttgtt ttacatgaag ggtctggcag ccaaagcaat cactcaaagt tcaaacctta 540

tcatttttg ctttgttcct cttggccttg gttttgtaca tcagctttga aaataccatc 600

ccagggttaa tgctggggtt aatttataac taagagtgct ctagttttgc aatacaggac 660

atgctataaa aatggaaaga tgttgctttc tgagaggatc ttgctaccag tggaacagcc 720

actaaggatt ctgcagtgag agcagagggc cagctaagtg gtactctccc agagactgtc 780

tgactcacgc caccccctcc accttggaca caggacgctg tggtttctga gccaggtaca 840

gtgactcctt tcggtaagtg cagtggaagc tgtacactgc ccaggcaaag cgtccgggca 900

gcgtaggcgg gcgactcaga tcccagccag tggacttagc ccctgtttgc tcctccgata 960

actggggtga ccttggttaa tattcaccag cagcctcccc cgttgcccct ctggatccac 1020

tgcttaaata cggacgagga cagggccctg tctcctcagc ttcaggcacc accactgacc 1080

tgggacagt 1089

<210> 318
<211> 1430
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 318
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gtctagagcc cttaagctag caggttaatt tttaaaaagc 360

agtcaaaagt ccaagtggcc cttggcagca tttactctct ctgtttgctc tggttaataa 420

tctcaggagc acaaacattc cagatccagg ttaattttta aaaagcagtc aaaagtccaa 480

gtggcccttg gcagcattta ctctctctgt ttgctctggt taataatctc aggagcacaa 540

acattccaga tccggcgcgc cagggctgga agctaccttt gacatcattt cctctgcgaa 600

tgcatgtata atttctacag aacctattag aaaggatcac ccagcctctg cttttgtaca 660

actttccctt aaaaaactgc caattccact gctgtttggc ccaatagtga gaacttttc 720

ctgctgcctc ttggtgcttt tgcctatggc ccctattctg cctgctgaag acactcttgc 780

cagcatggac ttaaacccct ccagctctga caatcctctt tctcttttgt tttacatgaa 840

gggtctggca gccaaagcaa tcactcaaag ttcaaacctt atcatttttt gctttgttcc 900

tcttggcctt ggttttgtac atcagctttg aaaataccat cccagggtta atgctggggt 960

taatttataa ctaagagtgc tctagttttg caatacagga catgctataa aaatggaaag 1020

atgttgcttt ctgagaggat cttgctacca gtggaacagc cactaaggat tctgcagtga 1080

gagcagaggg ccagctaagt ggtactctcc cagagactgt ctgactcacg ccacccctc 1140

caccttggac acaggacgct gtggtttctg agccaggtac agtgactcct ttcggtaagt 1200

gcagtggaag ctgtacactg cccaggcaaa gcgtccgggc agcgtaggcg ggcgactcag 1260

atcccagcca gtggacttag cccctgtttg ctcctccgat aactggggtg accttggtta 1320

atattcacca gcagcctccc ccgttgcccc tctggatcca ctgcttaaat acggacgagg 1380

acagggccct gtctcctcag cttcaggcac caccactgac ctgggacagt 1430

<210> 319
<211> 1318
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 319
aggttaattt ttaaaaagca gtcaaaagtc caagtggccc ttggcagcat ttactctctc 60

tgtttgctct ggttaataat ctcaggagca caaacattcc agatccaggt taatttttaa 120

aaagcagtca aaagtccaag tggcccttgg cagcatttac tctctctgtt tgctctggtt 180

aataatctca ggagcacaaa cattccagat ccggcgcgcc agggctggaa gctacctttg 240

acatcatttc ctctgcgaat gcatgtataa tttctacaga acctattaga aaggatcacc 300

cagcctctgc ttttgtacaa ctttccctta aaaaactgcc aattccactg ctgtttggcc 360

caatagtgag aacttttcc tgctgcctct tggtgctttt gcctatggcc cctattctgc 420

ctgctgaaga cactcttgcc agcatggact taaacccctc cagctctgac aatcctcttt 480

ctcttttgtt ttacatgaag ggtctggcag ccaaagcaat cactcaaagt tcaaacctta 540

tcatttttg ctttgttcct cttggccttg gttttgtaca tcagctttga aaataccatc 600

ccagggttaa tgctggggtt aatttataac taagagtgct ctagttttgc aatacaggac 660

atgctataaa aatggaaaga tgttgctttc tgagaggatc ttgctaccag tggaacagcc 720

actaaggatt ctgcagtgag agcagagggc cagctaagtg gtactctccc agagactgtc 780

tgactcacgc cacccctcc accttggaca caggacgctg tggtttctga gccaggtaca 840

gtgactcctt tcggtaagtg cagtggaagc tgtacactgc ccaggcaaag cgtccgggca 900

gcgtaggcgg gcgactcaga tcccagccag tggacttagc ccctgtttgc tcctccgata 960

actggggtga ccttggttaa tattcaccag cagcctcccc cgttgcccct ctggatccac 1020

tgcttaaata cggacgagga cagggccctg tctcctcagc ttcaggcacc accactgacc 1080

tgggacagta aaacaggtaa gtccgctgtt tgtgtgctgc ctctgaagtc cacactgaac 1140

aaacttcagc ctactcatgt ccctaaaatg ggcaaacatt gcaagcagca aacagcaaac 1200

acacagccct ccctgcctgc tgaccttgga gctggggcag aggtcagaga cctctctggc 1260

ctctactaac catgttcatg ttttcttttt ttttctacag gtcctgggtg acgaacag 1318

<210> 320
<211> 1579
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 320
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gccactacgg gtttaggctg cccatgtaag gaggcaaggc 360

ctggggacac ccgagatgcc tggttataat taacccagac atgtggctgc ccccccccc 420

cccaacacct gctgcctcta aaaataaccc tgtccctggt ggatcccact acgggtttag 480

gctgcccatg taaggaggca aggcctgggg acacccgaga tgcctggtta taattaaccc 540

agacatgtgg ctgccccccc ccccccaac acctgctgcc tctaaaaata accctgtccc 600

tggtggatcc cactacgggt ttaggctgcc catgtaagga ggcaaggcct ggggacaccc 660

gagatgcctg gttataatta acccagacat gtggctgccc ccccccccc caacacctgc 720

tgcctctaaa aataaccctg tccctggtgg atcccctgca tgcgaagatc ttcgaacaag 780

gctgtggggg actgagggca ggctgtaaca ggcttggggg ccagggctta tacgtgcctg 840

ggactcccaa agtattactg ttccatgttc ccggcgaagg gccagctgtc ccccgccagc 900

tagactcagc acttagttta ggaaccagtg agcaagtcag cccttggggc agcccataca 960

aggccatggg gctgggcaag ctgcacgcct gggtccgggg tgggcacggt gcccgggcaa 1020

cgagctgaaa gctcatctgc tctcaggggc ccctccctgg ggacagcccc tcctggctag 1080

tcacaccctg taggctcctc tatataaccc aggggcacag gggctgccct cattctacca 1140

ccacctccac agcacagaca gacactcagg agccagccag cgtcgagatc ttgctaccag 1200

tggaacagcc actaaggatt ctgcagtgag agcagagggc cagctaagtg gtactctccc 1260

agagactgtc tgactcacgc caccccctcc accttggaca caggacgctg tggtttctga 1320

gccaggtaca gtgactcctt tcggtaagtg cagtggaagc tgtacactgc ccaggcaaag 1380

cgtccgggca gcgtaggcgg gcgactcaga tcccagccag tggacttagc ccctgtttgc 1440

tcctccgata actggggtga ccttggttaa tattcaccag cagcctcccc cgttgcccct 1500

ctggatccac tgcttaaata cggacgagga cagggccctg tctcctcagc ttcaggcacc 1560

accactgacc tgggacagt 1579

<210> 321
<211> 1080
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 321
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg ggtacccggg gatcttgcta ccagtctaga ggccgtccgc 360

cctcggcacc atcctcacga cacccaaata tggcgacggg tgaggaatgg tggggagtta 420

tttttagagc ggtgaggaag gtgggcaggc agcaggtgtt ggcgctctaa aaataactcc 480

cgggagttat ttttagagcg gaggaatggt ggacacccaa atatggcgac ggttcctcac 540

ccgtcgccat atttgggtgt ccgccctcgg ccggggccgc attcctgggg gccgggcggt 600

gctcccgccc gcctcgataa aaggctccgg ggccggcggc ggcccacgag ctacccggag 660

gagcgggagg cgccaagcgt gagtatcgat cttgctacca gtggaacagc cactaaggat 720

tctgcagtga gagcagaggg ccagctaagt ggtactctcc cagagactgt ctgactcacg 780

ccacccccctc caccttggac acaggacgct gtggtttctg agccaggtac agtgactcct 840

ttcggtaagt gcagtggaag ctgtacactg cccaggcaaa gcgtccgggc agcgtaggcg 900

ggcgactcag atcccagcca gtggacttag cccctgtttg ctcctccgat aactggggtg 960

accttggtta atattcacca gcagcctccc ccgttgcccc tctggatcca ctgcttaaat 1020

acggacgagg acagggccct gtctcctcag cttcaggcac caccactgac ctgggacagt 1080

<210> 322
<211> 568
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 322
gaatggtgga cacccaaata tggcgacggt tcctcacccg tcgccatatt tgggtgtccg 60

ccctcggccg gggccgcatt cctgggggcc gggcggtgct cccgcccgcc tcgataaaag 120

gctccggggc cggcggcggc ccacgagcta cccggaggag cgggaggcgc caagcgatct 180

tgctaccagt ggaacagcca ctaaggattc tgcagtgaga gcagagggcc agctaagtgg 240

tactctccca gagactgtct gactcacgcc acccccctcca ccttggacac aggacgctgt 300

ggtttctgag ccaggtacag tgactccttt cggtaagtgc agtggaagct gtacactgcc 360

caggcaaagc gtccgggcag cgtaggcggg cgactcagat cccagccagt ggacttagcc 420

cctgtttgct cctccgataa ctggggtgac cttggttaat attcaccagc agcctccccc 480

gttgcccctc tggatccact gcttaaatac ggacgaggac agggccctgt ctcctcagct 540

tcaggcacca ccactgacct gggacagt 568

<210> 323
<211> 895
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 323
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gtctagagaa tggtggacac ccaaatatgg cgacggttcc 360

tcacccgtcg ccatatttgg gtgtccgccc tcggccgggg ccgcattcct gggggccggg 420

cggtgctccc gcccgcctcg ataaaaggct ccggggccgg cggcggccca cgagctaccc 480

ggaggagcgg gaggcgccaa gcgatcttgc taccagtgga acagccacta aggattctgc 540

agtgagagca gagggccagc taagtggtac tctcccagag actgtctgac tcacgccacc 600

ccctccacct tggacacagg acgctgtggt ttctgagcca ggtacagtga ctcctttcgg 660

taagtgcagt ggaagctgta cactgcccag gcaaagcgtc cgggcagcgt aggcgggcga 720

ctcagatccc agccagtgga cttagcccct gtttgctcct ccgataactg gggtgacctt 780

ggttaatatt caccagcagc ctcccccgtt gcccctctgg atccactgct taaatacgga 840

cgaggacagg gccctgtctc ctcagcttca ggcaccacca ctgacctggg acagt 895

<210> 324
<211> 1291
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 324
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gccactacgg gtttaggctg cccatgtaag gaggcaaggc 360

ctggggacac ccgagatgcc tggttataat taacccagac atgtggctgc ccccccccc 420

cccaacacct gctgcctcta aaaataaccc tgtccctggt ggatcccctg catgcgaaga 480

tcttcgaaca aggctgtggg ggactgaggg caggctgtaa caggcttggg ggccagggct 540

tatacgtgcc tgggactccc aaagtattac tgttccatgt tcccggcgaa gggccagctg 600

tcccccgcca gctagactca gcacttagtt taggaaccag tgagcaagtc agcccttggg 660

gcagcccata caaggccatg gggctgggca agctgcacgc ctgggtccgg ggtgggcacg 720

gtgcccgggc aacgagctga aagctcatct gctctcaggg gcccctccct ggggacagcc 780

cctcctggct agtcacaccc tgtaggctcc tctatataac ccaggggcac aggggctgcc 840

ctcattctac caccacctcc acagcacaga cagacactca ggagccagcc agcgtcgaga 900

tcttgctacc agtggaacag ccactaagga ttctgcagtg agagcagagg gccagctaag 960

tggtactctc ccagagactg tctgactcac gccacccccc ccaccttgga cacaggacgc 1020

tgtggtttct gagccaggta cagtgactcc tttcggtaag tgcagtggaa gctgtacact 1080

gcccaggcaa agcgtccggg cagcgtaggc gggcgactca gatcccagcc agtggactta 1140

gcccctgttt gctcctccga taactggggt gaccttggtt aatattcacc agcagcctcc 1200

cccgttgccc ctctggatcc actgcttaaa tacggacgag gacagggccc tgtctcctca 1260

gcttcaggca ccaccactga cctgggacag t 1291

<210> 325
<211> 1147
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 325
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gccctgcatg cgaagatctt cgaacaaggc tgtgggggac 360

tgagggcagg ctgtaacagg cttgggggcc agggcttata cgtgcctggg actcccaaag 420

tattactgtt ccatgttccc ggcgaagggc cagctgtccc ccgccagcta gactcagcac 480

ttagtttagg aaccagtgag caagtcagcc cttggggcag cccatacaag gccatggggc 540

tgggcaagct gcacgcctgg gtccggggtg ggcacggtgc ccgggcaacg agctgaaagc 600

tcatctgctc tcaggggccc ctccctgggg acagcccctc ctggctagtc acaccctgta 660

ggctcctcta tataacccag gggcacaggg gctgccctca ttctaccacc acctccacag 720

cacagacaga cactcaggag ccagccagcg tcgagatctt gctaccagtg gaacagccac 780

taaggattct gcagtgagag cagagggcca gctaagtggt actctcccag agactgtctg 840

actcacgcca ccccctccac cttggacaca ggacgctgtg gtttctgagc caggtacagt 900

gactcctttc ggtaagtgca gtggaagctg tacactgccc aggcaaagcg tccgggcagc 960

gtaggcgggc gactcagatc ccagccagtg gacttagccc ctgtttgctc ctccgataac 1020

tggggtgacc ttggttaata ttcaccagca gcctcccccg ttgcccctct ggatccactg 1080

cttaaatacg gacgaggaca gggccctgtc tcctcagctt caggcaccac cactgacctg 1140

ggacagt 1147

<210> 326
<211> 1490
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 326
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gcccttcaga ttaaaaataa ctgaggtaag ggcctgggta 360

ggggaggtgg tgtgagacgc tcctgtctct cctctatctg cccatcggcc ctttggggag 420

gaggaatgtg cccaaggact aaaaaaaggc catggagcca gaggggcgag ggcaacagac 480

ctttcatggg caaaccttgg ggccctgctg aagctttggc ccactacggg tttaggctgc 540

ccatgtaagg aggcaaggcc tggggacacc cgagatgcct ggttataatt aacccagaca 600

tgtggctgcc ccccccccca ccaacacctg ctgcctctaa aaataaccct gtccctggtg 660

gatcccctgc atgcgaagat cttcgaacaa ggctgtgggg gactgagggc aggctgtaac 720

aggcttgggg gccagggctt atacgtgcct gggactccca aagtattact gttccatgtt 780

cccggcgaag ggccagctgt cccccgccag ctagactcag cacttagttt aggaaccagt 840

gagcaagtca gcccttgggg cagcccatac aaggccatgg ggctgggcaa gctgcacgcc 900

tgggtccggg gtgggcacgg tgcccgggca acgagctgaa agctcatctg ctctcagggg 960

cccctccctg gggacagccc ctcctggcta gtcacaccct gtaggctcct ctatataacc 1020

caggggcaca ggggctgccc tcattctacc accacctcca cagcacagac agacactcag 1080

gagccagcca gcgtcgagat cttgctacca gtggaacagc cactaaggat tctgcagtga 1140

gagcagaggg ccagctaagt ggtactctcc cagagactgt ctgactcacg ccacccccctc 1200

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> 327
<211> 969
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 327

aggttaattt ttaaaaagca gtcaaaagtc caagtggccc ttggcagcat ttactctctc 60

tgtttgctct ggttaataat ctcaggagca caaacattcc agatccaggt taatttttaa 120

aaagcagtca aaagtccaag tggcccttgg cagcatttac tctctctgtt tgctctggtt 180

aataatctca ggagcacaaa cattccagat ccggcgcgcc agggctggaa gctacctttg 240

tctagaaggc tcagaggcac acaggagttt ctgggctcac cctgccccct tccaacccct 300

cagttcccat cctccagcag ctgtttgtgt gctgcctctg aagtccacac tgaacaaact 360

tcagcctact catgtcccta aaatgggcaa acattgcaag cagcaaacag caaacacaca 420

gccctccctg cctgctgacc ttggagctgg ggcagaggtc agagacctct ctgggcccat 480

gccacctcca acatccactc gacccttgg aatttcggtg gagaggagca gaggttgtcc 540

tggcgtggtt taggtagtgt gagaggggta cccggggatc ttgctaccag tggaacagcc 600

actaaggatt ctgcagtgag agcagagggc cagctaagtg gtactctccc agagactgtc 660

tgactcacgc caccccctcc accttggaca caggacgctg tggtttctga gccaggtaca 720

atgactcctt tcggtaagtg cagtggaagc tgtacactgc ccaggcaaag cgtccgggca 780

gcgtaggcgg gcgactcaga tcccagccag tggacttagc ccctgtttgc tcctccgata 840

actggggtga ccttggttaa tattcaccag cagcctcccc cgttgcccct ctggatccac 900

tgcttaaata cggacgagga cagggccctg tctcctcagc ttcaggcacc accactgacc 960

tgggacagt 969

<210> 328
<211> 2074
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 328
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gcacacatac acgaacacac atacatatac atacattcac 360

atatatgcac acacatacac atatacacgc atacacgtac acacaaatgc acactcacac 420

atgcacacac atacataata tacacactct cacacatgca catacacaca tacatacaca 480

tacatgtgca tgcacacaca caaatacaca tgcatacatc cacattcaca cagatgcaga 540

cacaaatgca cacacacaca cacacacaca cacacacaca cacacacaca cgcacactgc 600

caccctgaac tagtggtggc taaatgaaca ataagtctcc atcaccagct tgggggggagg 660

taggtggtag tgtaggtgcc cccattgtgt gatcatgttc attgtatgag tttgtctgtg 720

ttcattcatc atagtgacag tccccatgtg ggtagcagag agtacgtgtg catgcatcat 780

ctccgtgttt gctcatgagt gtgtatgtca gtgtgttcca gtctttctgt gtgagtgtcg 840

tccccaatcc cccatccccc cccccagatc tctaattagt ggtttggggt ttgttccttt 900

tccctcctgt tcctttcctc agcagcgcgg cagcagcggc ggcagcctcg gtggtagcag 960

cagcagcagc agcagcagca gcagcagcag cagcagcagc agcaacagaa gctgccgcgc 1020

cgctgagtag cagcaaggac tccgagtcaa gagtaggatt gtaggattgg atctgagtgg 1080

gaacaagagt gagctggcct gagagaggag cagatgcctc ccagcgccct caggccaccc 1140

attgccagta atcttcaagc cagacctctt gagaggagac gggacagcca accctagcct 1200

acccaggtac agacactggg cagttctggg ggactgccca cagatgccta ttggattcct 1260

ggggtatgta ggactcccgg gtctaccagc ccttttcacc tttccccata gcacccccaa 1320

ggaagctctg acaacttgcc catattcctg tttcccaccc gtcccctggg cacccccttt 1380

tcttctctcc ctcccagatc ccttctttgg ggagctcagc aaatggagca ggaaatttgg 1440

accctctgcc tccctctctc gccttcctca ttggatccgg agtcttctcc gctgggaaag 1500

ctgtaattag agggtggatc cctacagaca gagagcagcc cccccacccc caccccccag 1560

tcccttctaa ctttagatct cttctctccc attctcccat tctccctccc tctcccttct 1620

ccctctccca ctggctcctc ggttctctcc atctgcctga ctccttggga cccggtcccc 1680

agatcttgct accagtggaa cagccactaa ggattctgca gtgagagcag agggccagct 1740

aagtggtact ctcccagaga ctgtctgact cacgccaccc cctccacctt ggacacagga 1800

cgctgtggtt tctgagccag gtacagtgac tcctttcggt aagtgcagtg gaagctgtac 1860

actgcccagg caaagcgtcc gggcagcgta ggcgggcgac tcagatccca gccagtggac 1920

ttagcccctg tttgctcctc cgataactgg ggtgaccttg gttaatattc accagcagcc 1980

tcccccgttg cccctctgga tccactgctt aaatacggac gaggacaggg ccctgtctcc 2040

tcagcttcag gcaccaccac tgacctggga cagt 2074

<210> 329
<211> 1360
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 329
cacacataca cgaacacaca tacatataca tacattcaca tatatgcaca cacatacaca 60

tatacacgca tacacgtaca cacaaatgca cactcacaca tgcacacaca tacataatat 120

acacactctc acacatgcac atacacacat acatacacat acatgtgcat gcacacacac 180

aaatacacat gcatacatcc acattcacac agatgcagac acaaatgcac acacacacac 240

acacacacac acacacacac acacacacac gcacactgcc accctgaact agtggtggct 300

aaatgaacaa taagtctcca tcaccagctt ggggggaggt aggtggtagt gtaggtgccc 360

ccattgtgtg atcatgttca ttgtatgagt ttgtctgtgt tcattcatca tagtgacagt 420

ccccatgtgg gtagcagaga gtacgtgtgc atgcatcatc tccgtgtttg ctcatgagtg 480

tgtatgtcag tgtgttccag tctttctgtg tgagtgtcgt ccccaatccc ccatcccccc 540

ccccagatct ctaattagtg gtttggggtt tgttcctttt ccctcctgtt cctttcctca 600

gcagcgcggc agcagcggcg gcagcctcgg tggtagcagc agcagcagca gcagcagcag 660

cagcagcagc agcagcagca gcaacagaag ctgccgcgcc gctgagtagc agcaaggact 720

ccgagtcaag agtaggattg taggattgga tctgagtggg aacaagagtg agctggcctg 780

agagaggagc agatgcctcc cagcgccctc aggccaccca ttgccagtaa tcttcaagcc 840

agacctcttg agaggagacg ggacagccaa ccctagccta cccaggtaca gacactgggc 900

agttctgggg gactgcccac agatgcctat tggattcctg gggtatgtag gactcccggg 960

tctaccagcc cttttcacct ttccccatag cacccccaag gaagctctga caacttgccc 1020

atattcctgt ttcccacccg tcccctgggc acccccttt cttctctccc tcccagatcc 1080

cttctttggg gagctcagca aatggagcag gaaatttgga ccctctgcct ccctctctcg 1140

ccttcctcat tggatccgga gtcttctccg ctgggaaagc tgtaattaga gggtggatcc 1200

ctacagacag agagcagccc ccccaccccc acccccagt cccttctaac tttagatctc 1260

ttctctccca ttctcccatt ctccctccct ctcccttctc cctctcccac tggctcctcg 1320

gttctctcca tctgcctgac tccttgggac ccggtcccca 1360

<210> 330
<211> 756
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 330
cgcggcagca gcggcggcag cctcggtggt agcagcagca gcagcagcag cagcagcagc 60

agcagcagca gcagcagcaa cagaagctgc cgcgccgctg agtagcagca aggactccga 120

gtcaagagta ggattgtagg attggatctg agtgggaaca agagtgagct ggcctgagag 180

aggagcagat gcctcccagc gccctcaggc cacccattgc cagtaatctt caagccagac 240

ctcttgagag gagacgggac agccaaccct agcctaccca ggtacagaca ctgggcagtt 300

ctgggggact gcccacagat gcctattgga ttcctggggt atgtaggact cccgggtcta 360

ccagcccttt tcacctttcc ccatagcacc cccaaggaag ctctgacaac ttgcccatat 420

tcctgtttcc cacccgtccc ctgggcaccc ccttttcttc tctccctccc agatcccttc 480

tttggggagc tcagcaaatg gagcaggaaa tttggaccct ctgcctccct ctctcgcctt 540

cctcattgga tccggagtct tctccgctgg gaaagctgta attagagggt ggatccctac 600

agacagagag cagccccccc acccccaccc cccagtccct tctaacttta gatctcttct 660

ctcccattct cccattctcc ctccctctcc cttctccctc tcccactggc tcctcggttc 720

tctccatctg cctgactcct tgggacccgg tcccca 756

<210> 331
<211> 244
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (224)..(244)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (227)..(227)
<223> /replace="Leu"

<220>
<221> SITE
<222> (228)..(244)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (234)..(244)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(244)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 331
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> 332
<211> 213
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 332
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> 333
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> SITE
<222> (225)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (228)..(228)
<223> /replace="Leu"

<220>
<221> SITE
<222> (229)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (235)..(245)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(245)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 333

```
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 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
    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> 334
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 334
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> 335
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (224)..(244)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (227)..(227)
<223> /replace="Leu"

<220>
<221> SITE
<222> (228)..(244)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (234)..(244)
<223> /note="This region may be absent in its entirety"
```

<220>
<221> SITE
<222> (1)..(244)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 335
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> 336
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 336

```
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> 337
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (223)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT

<222> (228)..(228)
<223> /replace="Ser"

<220>
<221> SITE
<222> (232)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(242)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 337
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> 338
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 338

```
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> 339
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (227)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (230)..(230)
<223> /replace="Leu"

<220>
<221> SITE
<222> (231)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (237)..(247)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(247)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 339
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> 340
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 340
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> 341
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (224)..(244)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (227)..(227)
<223> /replace="Leu"

<220>
<221> SITE
<222> (228)..(244)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (234)..(244)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(244)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 341
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> 342
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 342
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> 343
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (670)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (679)..(681)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (682)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (700)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(732)
<223> /note="Variant nucleotides given in the sequence have no preference with respect to those in the annotations for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 343
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> 344
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 344
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> 345
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (673)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (682)..(684)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (685)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (703)..(735)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(735)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of

substitutions and preferred embodiments"

<400> 345
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> 346
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (670)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (679)..(681)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (682)..(732)

<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (700)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(732)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 346
gcgattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgcc aggcgagcca gagcattaac aacgaactga gctggtatca gcagaaaccg 120

ggcaaagcgc cgaaactgct gatttatcgc gcgagcaccc tggcgagcgg cgtgccgagc 180

cgctttagcg gcagcggcag cggcaccgat ttttaccctga 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> 347
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (670)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (679)..(681)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (682)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (700)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(732)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 347
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> 348
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 348
gaaattgtgc tgacccagag cccggcgacc ctgagcctga gcccgggcga acgcgcgacc 60

ctgagctgca gcgcgagcat tagcgtgagc tatatgtatt ggtatcagca gaaaccgggc 120

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> 349
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (667)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (682)..(683)
<223> /replace="ag"

<220>
<221> misc_feature
<222> (694)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(726)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 349
gaagtgcagc tggtggaaag cggcggcggc ctggtgcagc cgggcggcag cctgcgcctg 60

agctgcgcgg cgagcggctt taactttaac gattatttta tgaactgggt gcgccaggcg 120

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> 350
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 350
gatattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgcc aggcgagcca ggatattggc attagcctga gctggtatca gcagaaaccg 120

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> 351
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (679)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation

<222> (688)..(690)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (691)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (709)..(741)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(741)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 351
gaagtgcagc tgcaggaaag cggcccgggc ctggtgaaac cgagccagac cctgagcctg 60

acctgcaccg tgagcggcgg cagcattacc agccgctatt atgcgtggag ctggattcgc 120

cagccgccgg gcaaaggcct ggaatggatt ggcgtgattg attatgatgg cgatacctat 180

tatagcccga gcctgaaaag ccgcgtgagc attagctggg ataccagcaa aaaccagttt 240

agcctgaaac tgagcagcgt gaccccggcg gataccgcgg tgtattattg cgcgcgcgat 300

ccggatgtgg tgaccggctt tcattatgat tattggggcc agggcaccat ggtgaccgtg 360

agcagcgcga gcaccaaagg cccgagcgtg tttccgctgg cgccgagcag caaaagcacc 420

agcggcggca ccgcggcgct gggctgcctg gtgaaagatt attttccgga accggtgacc 480

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> 352

<211> 648
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 352
cagagcgcgc tgacccagcc gccgagcgtg agcggcaccc cgggccagag cgtgaccatt 60

agctgcgcgg gcgcgaacaa cgatattggc acctatgcgt atgtgagctg gtatcagcag 120

ctgccgggca ccgcgccgaa actgatgatt tataaagtga ccacccgcgc gagcggcatt 180

ccggatcgct ttagcggcag caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caggcggaag atgaagcgga ttattattgc gcgagctatc gcaactttaa caacgcggtg 300

tttggcaccg gcaccaaact gaccgtgctg ggccagccga aagcggcgcc gagcgtgacc 360

ctgtttccgc cgagcagcga agaactgcag gcgaacaaag cgaccctggt gtgcctgatt 420

agcgattttt atccgggcgc ggtgaccgtg gcgtggaaag cggatagcag cccggtgaaa 480

gcgggcgtgg aaaccaccac cccgagcaaa cagagcaaca acaaatatgc ggcgagcagc 540

tatctgagcc tgaccccgga acagtggaaa agccatcgca gctatagctg ccaggtgacc 600

catgaaggca gcaccgtgga aaaaaccgtg gcgccgaccg aatgcagc 648

<210> 353
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (670)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (679)..(681)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (682)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (700)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(732)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 353
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> 354
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 354
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> 355
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 355
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> 356
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 356
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> 357
<211> 205
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 357
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> 358
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 358
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> 359
<211> 204
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 359
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> 360
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<220>
<221> SITE
<222> (229)..(249)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (233)..(249)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (239)..(249)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
      substitutions and preferred embodiments"

<400> 360
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 Ser Ala Ser Gly Phe Thr Phe Ser Ser Phe
            20                  25                  30

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

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

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

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

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

Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
        115                 120                 125

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

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

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

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

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

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

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

Leu Leu Gly Gly Pro Ser Val Phe Leu
245

<210> 361
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 361
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Ala Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

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

Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Pro Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys
100 105 110

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

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

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

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

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

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

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 362
<211> 238
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (228)..(238)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (234)..(238)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 362
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly His Ile Phe Ser Asn Tyr

```
            20                  25                  30

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

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

Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

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

Ala Arg Tyr Phe Phe Gly Ser Ser Pro Asn Trp Tyr Phe Asp Val Trp
            100                 105                 110

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

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser 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 Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

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

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

<210> 363
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 363
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 Gly Ala Ser Glu Asn Ile Tyr Gly Ala
20 25 30

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

Tyr Gly Ala Thr 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 Gln Asn Val Leu Asn Thr Pro Leu
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> 364
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (226)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (229)..(229)
<223> /replace="Leu"

<220>
<221> SITE
<222> (230)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (236)..(246)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(246)
<223> /note="Variant residues given in the sequence have no
      preference with respect to those in the annotations
      for variant positions"

<220>
<221> source
```

<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 364

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


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


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


Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Arg Phe
    50                  55                  60


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


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


Gly Arg Glu Gly Ile Arg Tyr Tyr Gly Leu Leu Gly 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> 365
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 365
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 Gly Thr Ser Glu Asp Ile Ile Asn Tyr
20 25 30

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

Tyr His Thr Ser Arg 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 Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr 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> 366
<211> 238
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (219)..(238)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (224)..(224)
<223> /replace="Ser"

<220>
<221> SITE
<222> (228)..(238)
<223> /note="This region may be absent in its entirety"

<220>
```

<221> SITE
<222> (1)..(238)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 366

```
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 Val Ser Gly Leu Ser Leu Thr Ser Asn
            20                  25                  30


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


Gly Leu Ile Trp Ser Asn Gly Asp Thr Asp Tyr Asn Ser Ala Ile Lys
    50                  55                  60


Ser Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Ser Thr Val 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 Glu Tyr Tyr Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110


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


Pro Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
        195                 200                 205


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


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


<210> 367
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 367
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 Leu Ala Ser Glu Gly Ile Ser Ser Tyr
            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 Asn Ser Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


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


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


Thr Phe Gly Gln Gly Thr Lys Val 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
    210


<210> 368
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (225)..(244)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (230)..(230)
<223> /replace="Ser"

<220>
<221> SITE
```

<222> (234)..(244)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(244)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 368
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

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

Gly Trp Ile Ser Ala Asn Asn Gly Asp Thr Asn Tyr Gly Gln Glu Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Ser Ser Ser Ser Trp Ala Arg Trp Phe Phe Asp Leu Trp
100 105 110

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

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

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

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

Ser Val Phe Leu
```

<210> 369
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 369

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

Thr Ala Arg Ile Thr Cys Gly Gly Asn Ile Ile Gly Ser Lys Leu Val
            20                  25                  30

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

Asp Asp Gly Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
```

65 70 75 80

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

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

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

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

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

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

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

Ala Pro Thr Glu Cys Ser
210

<210> 370
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (227)..(237)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (233)..(237)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 370
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

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

Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Asp Tyr Asn Pro Gln Phe
50 55 60

Gln Asp Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gly Tyr Asp Asp Gly Pro Tyr Thr Leu Glu Thr 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 Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
        195                 200                 205


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


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


<210> 371
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 371
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 Glu Asp Ile Tyr Ser Phe
            20                  25                  30


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


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


Thr Phe Gly Gly 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> 372
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"


<220>
<221> SITE
<222> (222)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> VARIANT
<222> (225)..(225)
<223> /replace="Leu"

<220>
<221> SITE
```

<222> (226)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (232)..(242)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (1)..(242)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 372
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 Val Ser Gly Tyr Ser Ile Thr Ser Gly
20 25 30

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

Val Ala Ser Ile Thr Tyr Asp Gly Ser Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Phe 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 Gly Ser His Tyr Phe Gly His Trp His Phe Ala Val Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys

```
    130                 135                 140

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

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

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

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

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

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

Phe Leu
```

<210> 373
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 373

```
Asp Ile Gln Leu 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 Ser Val Asp Tyr Asp
            20                  25                  30

Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
        35                  40                  45
```

```
Lys Leu Leu Ile Tyr Ala Ala Ser Tyr Leu Glu Ser Gly Val Pro Ser
    50                  55                  60

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

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

Glu Asp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu 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
    210                 215
```

<210> 374
<211> 238
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> SITE
<222> (228)..(238)
<223> /note="This region may be absent in its entirety"

<220>
<221> SITE
<222> (234)..(238)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 374
Gln Met Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

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

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

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

Lys Gly Arg Phe Thr Ile Thr Arg Asp Asn Ser Lys Asn Thr Leu Asn
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 Ala Pro Gln Trp Glu Leu Val His Glu Ala Phe Asp Ile 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
195 200 205

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

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

<210> 375
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 375
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Leu Gly Ser Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Ser Trp Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

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

```
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
                85                  90                  95


Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110


Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125


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


Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160


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


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


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


Ala Pro Thr Glu Cys Ser
    210


<210> 376
<211> 747
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"


<220>
<221> misc_feature
<222> (685)..(747)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
```

<222> (694)..(696)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (697)..(747)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (715)..(747)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(747)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 376
gaagtgcagc tggtggaaag cggcggcggc ctggtgcagc cgggcggcag cctgcgcctg 60

agctgcagcg cgagcggctt tacctttagc agctttggca tgcattgggt gcgccaggcg 120

ccgggcaaag gcctggaatg ggtggcgtat attagcagcg gcagcagcac catttattat 180

ggcgataccg tgaaaggccg ctttaccatt agccgcgata acgcgaaaaa cagcctgttt 240

ctgcagatga gcagcctgcg cgcggaagat accgcggtgt attattgcgc gcgcgaaggc 300

ggctattatt atggccgcag ctattatacc atggattatt ggggccaggg caccaccgtg 360

accgtgagca gcgcgagcac caaaggcccg agcgtgtttc cgctggcgcc gagcagcaaa 420

agcaccagcg gcggcaccgc ggcgctgggc tgcctggtga aagattattt tccggaaccg 480

gtgaccgtga gctggaacag cggcgcgctg accagcggcg tgcatacctt tccggcggtg 540

ctgcagagca gcggcctgta tagcctgagc agcgtggtga ccgtgccgag cagcagcctg 600

ggcacccaga cctatatttg caacgtgaac cataaaccga gcaacaccaa agtggataaa 660

cgcgtggaac cgaaaagctg cgataagacc cacacctgcc ccccctgccc cgcccccgag 720

ctggccggcg cccccagcgt gttcctg 747

<210> 377

<211> 657
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 377
gatgtggtga tgacccagag cccgctgagc ctgccggtga ccccgggcgc gccggcgagc 60

attagctgcc gcagcagcca gagcattgtg catagcaacg gcaacaccta tctggaatgg 120

tatctgcaga aaccgggcca gagcccgaaa ctgctgattt ataaagtgag caaccgcttt 180

agcggcgtgc cggatcgctt tagcggcagc ggcagcggca ccgattttac cctgcgcatt 240

agccgcgtgg aagcggaaga tgtgggcatt tattattgct ttcagggcag ccatgtgccg 300

ccgacctttg gcccgggcac caaactggaa attaaacgca ccgtggcggc gccgagcgtg 360

tttatttttc cgccgagcga tgaacagctg aaaagcggca ccgcgagcgt ggtgtgcctg 420

ctgaacaact tttatccgcg cgaagcgaaa gtgcagtgga aagtggataa cgcgctgcag 480

agcggcaaca gccaggaaag cgtgaccgaa caggatagca aagatagcac ctatagcctg 540

agcagcaccc tgaccctgag caaagcggat tatgaaaaac ataaagtgta tgcgtgcgaa 600

gtgacccatc agggcctgag cagcccggtg accaaaagct ttaaccgcgg cgaatgc 657

<210> 378
<211> 714
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (682)..(714)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (700)..(714)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 378
caggtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg 60

agctgcaaag cgagcggcca tatttttagc aactattgga ttcagtgggt gcgccaggcg 120

ccgggccagg gcctggaatg gatgggcgaa attctgccgg gcagcggcca taccgaatat 180

accgaaaact ttaaagatcg cgtgaccatg acccgcgata ccagcaccag caccgtgtat 240

atggaactga gcagcctgcg cagcgaagat accgcggtgt attattgcgc gcgctatttt 300

tttggcagca gcccgaactg gtattttgat gtgtggggcc agggcaccct ggtgaccgtg 360

agcagcgcga gcaccaaagg cccgagcgtg tttccgctgg cgccgtgcag ccgcagcacc 420

agcgaaagca ccgcggcgct gggctgcctg gtgaaagatt attttccgga accggtgacc 480

gtgagctgga acagcggcgc gctgaccagc ggcgtgcata cctttccggc ggtgctgcag 540

agcagcggcc tgtatagcct gagcagcgtg gtgaccgtgc cgagcagcaa ctttggcacc 600

cagacctata cctgcaacgt ggatcataaa ccgagcaaca ccaaagtgga taaaaccgtg 660

gaacgcaaat gctgcgtgga atgccccccc tgccccgccc cccccgtggc cggc 714

<210> 379
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 379
gatattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgcg gcgcgagcga aaacatttat ggcgcgctga actggtatca gcagaaaccg 120

ggcaaagcgc cgaaactgct gatttatggc gcgaccaacc tggcggatgg cgtgccgagc 180

cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240

gaagattttg cgacctatta ttgccagaac gtgctgaaca ccccgctgac 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> 380
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (676)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (685)..(687)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (688)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (706)..(738)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(738)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 380
gaagtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg 60

agctgcaaag cgagcggcta tacctttacc agctatgtga ttcattgggt gcgccagcgc 120

ccgggccagg gcctggcgtg gatgggctat attaacccgt ataacgatgg caccaaatat 180

aacgaacgct ttaaaggcaa agtgaccatt accagcgatc gcagcaccag caccgtgtat 240

atggaactga gcagcctgcg cagcgaagat accgcggtgt atctgtgcgg ccgcgaaggc 300

attcgctatt atggcctgct gggcgattat tggggccagg gcaccctggt gaccgtgagc 360

agcgcgagca ccaaaggccc gagcgtgttt ccgctggcgc cgagcagcaa aagcaccagc 420

ggcggcaccg cggcgctggg ctgcctggtg aaagattatt ttccggaacc ggtgaccgtg 480

agctggaaca gcggcgcgct gaccagcggc gtgcatacct ttccggcggt gctgcagagc 540

agcggcctgt atagcctgag cagcgtggtg accgtgccga gcagcagcct gggcacccag 600

acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660

ccgaaaagct gcgataagac ccacacctgc ccccccctgcc ccgcccccga gctggccggc 720

gcccccagcg tgttcctg 738

<210> 381
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 381
gatattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgcg gcaccagcga agatattatt aactatctga actggtatca gcagaaaccg 120

ggcaaagcgc cgaaactgct gatttatcat accagccgcc tgcagagcgg cgtgccgagc 180

cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240

gaagattttg cgacctatta ttgccagcag ggctataccc 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> 382
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (667)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (682)..(683)
<223> /replace="ag"

<220>
<221> misc_feature
<222> (694)..(726)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(726)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 382
gaagtgcagc tggtggaaag cggcggcggc ctggtgcagc cgggcggcag cctgcgcctg 60

agctgcgcgg tgagcggcct gagcctgacc agcaacagcg tgaactggat tcgccaggcg 120

ccgggcaaag gcctggaatg ggtgggcctg atttggagca acggcgatac cgattataac 180

agcgcgatta aaagccgctt taccattagc cgcgatacca gcaaaagcac cgtgtatctg 240

cagatgaaca gcctgcgcgc ggaagatacc gcggtgtatt attgcgcgcg cgaatattat 300

ggctattttg attattgggg ccagggcacc ctggtgaccg tgagcagcgc gagcaccaaa 360

ggcccgagcg tgtttccgct ggcgccgtgc agccgcagca ccagcgaaag caccgcggcg 420

ctgggctgcc tggtgaaaga ttattttccg gaaccggtga ccgtgagctg gaacagcggc 480

gcgctgacca gcggcgtgca tacctttccg gcggtgctgc agagcagcgg cctgtatagc 540

ctgagcagcg tggtgaccgt gccgagcagc agcctgggca ccaaaaccta tacctgcaac 600

gtggatcata aaccgagcaa caccaaagtg gataaacgcg tggaaagcaa atatgagagc 660

aagtacggcc ccccctgccc cccctgcccc gcccccgagt tcctgggcgg ccccagcgtg 720

ttcctg 726

<210> 383
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 383
gatattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgcc tggcgagcga aggcattagc agctatctgg cgtggtatca gcagaaaccg 120

ggcaaagcgc cgaaactgct gatttatggc gcgaacagcc tgcagaccgg cgtgccgagc 180

cgctttagcg gcagcggcag cgcgaccgat tataccctga ccattagcag cctgcagccg 240

gaagattttg cgacctatta ttgccagcag agctataaat ttccgaacac ctttggccag 300

ggcaccaaag tggaagtgaa 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> 384
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (673)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (688)..(689)
<223> /replace="ag"

<220>
<221> misc_feature
<222> (700)..(732)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(732)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 384
caggtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg 60

agctgcaaag cgagcggcta tacctttacc aactatggcc tgagctgggt gcgccaggcg 120

ccgggccagg gcctggaatg gatgggctgg attagcgcga acaacggcga taccaactat 180

ggccaggaat ttcagggccg cgtgaccatg accaccgata ccagcaccag caccgcgtat 240

atggaactgc gcagcctgcg cagcgatgat accgcggtgt attattgcgc gcgcgatagc 300

agcagcagct gggcgcgctg gttttttgat ctgtggggcc gcggcaccct ggtgaccgtg 360

agcagcgcga gcaccaaagg cccgagcgtg tttccgctgg cgccgtgcag ccgcagcacc 420

agcgaaagca ccgcggcgct gggctgcctg gtgaaagatt attttccgga accggtgacc 480

gtgagctgga acagcggcgc gctgaccagc ggcgtgcata cctttccggc ggtgctgcag 540

agcagcggcc tgtatagcct gagcagcgtg gtgaccgtgc cgagcagcag cctgggcacc 600

aaaacctata cctgcaacgt ggatcataaa ccgagcaaca ccaaagtgga taaacgcgtg 660

gagagcaagt acggcccccc ctgcccccc tgccccgccc ccgagttcct gggcggcccc 720

agcgtgttcc tg 732

<210> 385
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 385
agctatgtgc tgacccagcc gccgagcgtg agcgtggcgc cgggcaaaac cgcgcgcatt 60

acctgcggcg gcaacattat tggcagcaaa ctggtgcatt ggtatcagca gaaaccgggc 120

caggcgccgg tgctggtgat ttatgatgat ggcgatcgcc cgagcggcat tccggaacgc 180

tttagcggca gcaacagcgg caacaccgcg accctgacca ttagccgcgt ggaagcgggc 240

gatgaagcgg attattattg ccaggtgtgg gataccggca gcgatccggt ggtgtttggc 300

ggcggcacca aactgaccgt gctgggccag ccgaaagcgg cgccgagcgt gaccctgttt 360

ccgccgagca gcgaagaact gcaggcgaac aaagcgaccc tggtgtgcct gattagcgat 420

ttttatccgg gcgcggtgac cgtggcgtgg aaagcggata gcagcccggt gaaagcgggc 480

gtggaaacca ccaccccgag caaacagagc aacaacaaat atgcggcgag cagctatctg 540

agcctgaccc cggaacagtg gaaaagccat cgcagctata gctgccaggt gacccatgaa 600

ggcagcaccg tggaaaaaac cgtggcgccg accgaatgca gc 642

<210> 386
<211> 711
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<220>
<221> misc_feature
<222> (679)..(711)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (697)..(711)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 386
caggtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg 60

agctgcaaag cgagcggcta tacctttacc ggctatatta tgaactgggt gcgccaggcg 120

ccgggccagg gcctggaatg gatgggcctg attaacccgt ataacggcgg caccgattat 180

aacccgcagt ttcaggatcg cgtgaccatt accgcggata aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg cagcgaagat accgcggtgt attattgcgc gcgcgatggc 300

tatgatgatg gcccgtatac cctggaaacc tggggccagg gcaccctggt gaccgtgagc 360

agcgcgagca ccaaaggccc gagcgtgttt ccgctggcgc cgagcagcaa aagcaccagc 420

ggcggcaccg cggcgctggg ctgcctggtg aaagattatt ttccggaacc ggtgaccgtg 480

agctggaaca gcggcgcgct gaccagcggc gtgcatacct ttccggcggt gctgcagagc 540

agcggcctgt atagcctgag cagcgtggtg accgtgccga gcagcaactt tggcacccag 600

acctatacct gcaacgtgga tcataaaccg agcaacacca aagtggataa aaccgtggaa 660

cgcaaaagct gcgtggaatg ccccccctgc cccgcccccc ccgtggccgg c 711

<210> 387
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 387
gatattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgcc aggcgagcga agatatttat agctttgtgg cgtggtatca gcagaaaccg 120

ggcaaagcgc cgaaactgct gatttataac gcgcagaccg aagcgcaggg cgtgccgagc 180

cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240

gaagattttg cgacctatta ttgccagcat cattatgata gcccgctgac ctttggcggc 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> 388
<211> 708
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (646)..(708)
<223> /note="This region may be absent in its entirety"

<220>
<221> variation
<222> (655)..(657)
<223> /replace="ctg"

<220>
<221> misc_feature
<222> (658)..(708)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (676)..(708)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (1)..(708)
<223> /note="Variant nucleotides given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 388
gaagtgcagc tggtggaaag cggcggcggc ctggtgcagc cgggcggcag cctgcgcctg 60

agctgcgcgg tgagcggcta tagcattacc agcggctata gctggaactg gattcgccag 120

gcgccgggca aaggcctgga atgggtggcg agcattacct atgatggcag caccaactat 180

gcggatagcg tgaaaggccg ctttaccatt agccgcgatg atagcaaaaa caccttttat 240

ctgcagatga acagcctgcg cgcggaagat accgcggtgt attattgcgc gcgcggcagc 300

cattattttg gccattggca ttttgcggtg tggggccagg gcaccctggt gaccgtgagc 360

agcggcccga gcgtgtttcc gctggcgccg agcagcaaaa gcaccagcgg cggcaccgcg 420

gcgctgggct gcctggtgaa agattatttt ccggaaccgg tgaccgtgag ctggaacagc 480

ggcgcgctga ccagcggcgt gcataccttt ccggcggtgc tgcagagcag cggcctgtat 540

agcctgagca gcgtggtgac cgtgccgagc agcagcctgg gcacccagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagcgaagac ccacacctgc 660

ccccctgcc ccgcccccga gctggccggc gcccccagcg tgttcctg 708

<210> 389
<211> 645
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 389
gatattcagc tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgcc gcgcgagcca gagcgtggat tatgatggcg atagctatat gaactggtat 120

cagcagaaac cgggcaaagc gccgaaactg ctgatttatg cggcgagcta tctggaaagc 180

ggcgtgccga gccgctttag cggcagcggc agcggcaccg attttaccct gaccattagc 240

agcctgcagc cggaagattt tgcgacctat tattgccagc agagccatga agatccgtat 300

acctttggcc agggcaccaa agtggaaatt aaacgcaccg tggcggcgcc gagcgtgttt 360

atttttccgc cgagcgatga acagctgaaa agcggcaccg cgagcgtggt gtgcctgctg 420

aacaactttt atccgcgcga agcgaaagtg cagtggaaag tggataacgc gctgcagagc 480

ggcaacagcc aggaaagcgt gaccgaacag gatagcaaag atagcaccta tagcctgagc 540

agcaccctga ccctgagcaa agcggattat gaaaaacata aagtgtatgc gtgcgaagtg 600

acccatcagg gcctgagcag cccggtgacc aaaagcttta accgc 645

<210> 390
<211> 693
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (661)..(693)
<223> /note="This region may be absent in its entirety"

<220>
<221> misc_feature
<222> (679)..(693)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 390
cagatgcagc tggtggaaag cggcggcggc gtggtgcagc cgggccgcag cctgcgcctg 60

agctgcgcgg cgagcggctt tacctttcgc acctatggca tgcattgggt gcgccaggcg 120

ccgggcaaag gcctggaatg ggtggcggtg atttggtatg atggcagcaa caaacattat 180

gcggatagcg tgaaaggccg ctttaccatt acccgcgata acagcaaaaa caccctgaac 240

ctgcagatga acagcctgcg cgcggaagat accgcggtgt attattgcgc gcgcgcgccg 300

cagtgggaac tggtgcatga agcgtttgat atttggggcc agggcaccat ggtgaccgtg 360

agcagcgcga gcaccaaagg cccgagcgtg tttccgctgg cgccgtgcag ccgcagcacc 420

agcgaaagca ccgcggcgct gggctgcctg gtgaaagatt attttccgga accggtgacc 480

gtgagctgga acagcggcgc gctgaccagc ggcgtgcata cctttccggc ggtgctgcag 540

agcagcggcc tgtatagcct gagcagcgtg gtgaccgtgc cgagcagcaa ctttggcacc 600

cagacctata cctgcaacgt ggatcataaa ccgagcaaca ccaaagtgga taaaaccgtg 660

tgcccccccc gccccgcccc ccccgtggcc ggc 693

<210> 391
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 391
agctatgtgc tgacccagcc gccgagcgtg agcgtggcgc cgggccagac cgcgcgcatt 60

acctgcggcg gcaacaacct gggcagcaaa agcgtgcatt ggtatcagca gaaaccgggc 120

caggcgccgg tgctggtggt gtatgatgat agcgatcgcc cgagctggat tccggaacgc 180

tttagcggca gcaacagcgg caacaccgcg accctgacca ttagccgcgg cgaagcgggc 240

gatgaagcgg attattattg ccaggtgtgg gatagcagca gcgatcatgt ggtgtttggc 300

ggcggcacca aactgaccgt gctgggccag ccgaaagcgg cgccgagcgt gaccctgttt 360

ccgccgagca gcgaagaact gcaggcgaac aaagcgaccc tggtgtgcct gattagcgat 420

ttttatccgg gcgcggtgac cgtggcgtgg aaagcggata gcagcccggt gaaagcgggc 480

gtggaaacca ccaccccgag caaacagagc aacaacaaat atgcggcgag cagctatctg 540

agcctgaccc cggaacagtg gaaaagccat cgcagctata gctgccaggt gacccatgaa 600

ggcagcaccg tggaaaaaac cgtggcgccg accgaatgca gc 642

<210> 392
<211> 205
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 392
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 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> 393
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 393
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 Leu His Glu Ala Leu His Ser
180 185 190

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
195 200 205

<210> 394
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 394
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> 395
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 395
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> 396
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 396
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> 397
<211> 203
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 397
```
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 Asn
            180                 185                 190

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200
```

<210> 398
<211> 205
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 398
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> 399
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 399
Glu Lys His Lys Val Tyr
1 5

<210> 400
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 400
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala
1 5 10 15

Ala Gly Gly

<210> 401

<400> 401
000

Ala Gly Gly

<210> 402

<400> 402
000

<210> 403
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 403
Glu Asp Ile Ala Thr Tyr Tyr
1 5

<210> 404

<400> 404
000

<210> 405

<400> 405
000

<210> 406

<400> 406
000

<210> 407

<400> 407
000

<210> 408

<400> 408
000

<210> 409
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 409
Glu Asp Val Gly Ile Val Tyr Tyr
1 5

<210> 410

<400> 410
000

<210> 411
<211> 1725
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 411
gacattgatt attgactagt tattaatagt aatcaattac ggggtcatta gttcatagcc 60

catatatgga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 120

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaatagga 180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240

aagtgtatca tatgccaagt acgccccta ttgacgtcaa tgacggtaaa tggcccgcct 300

ggcattatgc ccagtacatg accttatggg actttcctac ttggcagtac atctacgtat 360

tagtcatcgc tattaccatg gtcgaggtga gccccacgtt ctgcttcact ctccccatct 420

ccccccccctc cccacccca attttgtatt tatttatttt ttaattattt tgtgcagcga 480

tgggggcggg gggggggggg gggcgcgcgc caggcggggc ggggcggggc gaggggcggg 540

gcggggcgag gcggagaggt gcggcggcag ccaatcagag cggcgcgctc cgaaagtttc 600

cttttatggc gaggcggcgg cggcggcggc cctataaaaa gcgaagcgcg cggcgggcgg 660

gagtcgctgc gcgctgcctt cgccccgtgc cccgctccgc cgccgcctcg cgccgcccgc 720

cccggctctg actgaccgcg ttactcccac aggtgagcgg gcgggacggc ccttctcctc 780

cgggctgtaa ttagcgcttg gtttaatgac ggcttgtttc ttttctgtgg ctgcgtgaaa 840

gccttgaggg gctccgggag ggccctttgt gcgggggggag cggctcgggg ggtgcgtgcg 900

tgtgtgtgtg cgtggggagc gccgcgtgcg gctccgcgct gcccggcggc tgtgagcgct 960

gcgggcgcgg cgcggggctt tgtgcgctcc gcagtgtgcg cgaggggagc gcggccgggg 1020

gcggtgcccc gcggtgcggg gggggctgcg aggggaacaa aggctgcgtg cggggtgtgt 1080

gcgtgggggg gtgagcaggg ggtgtgggcg cgtcggtcgg gctgcaaccc cccctgcacc 1140

cccctccccg agttgctgag cacggcccgg cttcgggtgc ggggctccgt acggggcgtg 1200

gcgcggggct cgccgtgccg ggcgggggggt ggcggcaggt gggggtgccg ggcggggcgg 1260

ggccgcctcg ggccggggag ggctcggggg aggggcgcgg cggcccccgg agcgccggcg 1320

gctgtcgagg cgcggcgagc cgcagccatt gccttttatg gtaatcgtgc gagagggcgc 1380

agggacttcc tttgtcccaa atctgtgcgg agccgaaatc tgggaggcgc cgccgcaccc 1440

cctctagcgg gcgcggggcg aagcggtgcg gcgccggcag gaaggaaatg ggcggggagg 1500

gccttcgtgc gtcgccgcgc cgccgtcccc ttctccctct ccagcctcgg ggctgtccgc 1560

ggggggacgg ctgccttcgg gggggacggg gcagggcggg gttcggcttc tggcgtgtga 1620

ccggcggctc tagagcctct gctaaccatg ttcatgcctt cttcttttttc ctacagctcc 1680

tgggcaacgt gctggttatt gtgctgtctc atcattttgg caaag 1725

<210> 412
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 412
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg 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> 413
<211> 865
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 413
ccactacggg tttaggctgc ccatgtaagg aggcaaggcc tggggacacc cgagatgcct 60

ggttataatt aacccagaca tgtggctgcc ccccccccccc ccaacacctg ctgcctctaa 120

aaataaccct gtccctggtg gatcccacta cgggtttagg ctgcccatgt aaggaggcaa 180

ggcctgggga cacccgagat gcctggttat aattaaccca gacatgtggc tgccccccccc 240

ccccccaaca cctgctgcct ctaaaaataa ccctgtccct ggtggatccc actacgggtt 300

taggctgccc atgtaaggag gcaaggcctg gggacacccg agatgcctgg ttataattaa 360

cccagacatg tggctgcccc ccccccccccc aacacctgct gcctctaaaa ataaccctgt 420

ccctggtgga tcccctgcat gcgaagatct tcgaacaagg ctgtgggggga ctgagggcag 480

gctgtaacag gcttgggggc cagggcttat acgtgcctgg gactcccaaa gtattactgt 540

tccatgttcc cggcgaaggg ccagctgtcc cccgccagct agactcagca cttagtttag 600

gaaccagtga gcaagtcagc ccttggggca gcccatacaa ggccatgggg ctgggcaagc 660

tgcacgcctg ggtccggggt gggcacggtg cccgggcaac gagctgaaag ctcatctgct 720

ctcaggggcc cctccctggg gacagcccct cctggctagt cacaccctgt aggctcctct 780

atataaccca ggggcacagg ggctgccctc attctaccac cacctccaca gcacagacag 840

acactcagga gccagccagc gtcga 865

<210> 414
<211> 251
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 414
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> 415
<211> 212
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 415
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> 416
<211> 133
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 416
gtaagtatca aggttacaag acaggtttaa ggagaccaat agaaactggg cttgtcgaga 60

cagagaagac tcttgcgttt ctgataggca cctattggtc ttactgacat ccactttgcc 120

tttctctcca cag 133

<210> 417
<211> 82
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 417
gtgagtatct cagggatcca gacatgggga tatgggaggt gcctctgatc ccagggctca 60

ctgtgggtct ctctgttcac ag 82

<210> 418
<211> 130
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 418
ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgaccttt 60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtggccaa ctccatcact 120

aggggttcct 130

<210> 419
<211> 106
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 419
ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgaccttt 60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtgg 106

<210> 420
<211> 143
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 420
gaacccctag tgatggagtt ggccactccc tctctgcgcg ctcgctcgct cactgaggcc 60

gcccgggcaa agcccgggcg tcgggcgacc tttggtcgcc cggcctcagt gagcgagcga 120

gcgcgcagag agggagtggc caa 143

<210> 421
<211> 110
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 421
ttggccactc cctctctgcg cgctcgctcg ctcactgagg ccgggcgacc aaaggtcgcc 60

cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc gagcgcgcag 110

<210> 422
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 422

atgtatagga tgcaactgct cctcctgatt gctctgagcc tggctcttgt gaccaactct 60

<210> 423
<211> 460
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 423
gggctggaag ctacctttga catcatttcc tctgcgaatg catgtataat ttctacagaa 60

cctattagaa aggatcaccc agcctctgct tttgtacaac tttcccttaa aaaactgcca 120

attccactgc tgtttggccc aatagtgaga acttttcct gctgcctctt ggtgcttttg 180

cctatggccc ctattctgcc tgctgaagac actcttgcca gcatggactt aaaccctcc 240

agctctgaca atcctctttc tcttttgttt tacatgaagg gtctggcagc caaagcaatc 300

actcaaagtt caaaccttat catttttgc tttgttcctc ttggccttgg ttttgtacat 360

cagctttgaa aataccatcc cagggttaat gctggggtta atttataact aagagtgctc 420

tagttttgca atacaggaca tgctataaaa atggaaagat 460

<210> 424
<211> 75
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 424
agaaagagaa gaggctctgg agaaggcaga ggctccctgc tgacatgtgg ggatgttgaa 60

gagaatcctg ggcct 75

<210> 425
<211> 12
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 425
agaaagagaa ga 12

<210> 426
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 426
agaaagagaa gaggctctgg a 21

<210> 427
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 427
ggctctgga 9

<210> 428
<211> 54
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 428
gaaggcagag gctccctgct gacatgtggg gatgttgaag agaatcctgg gcct 54

<210> 429
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> SITE
<222> (5)..(7)
<223> /note="This region may be absent in its entirety"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 429
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> 430
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 430
Cys Pro Pro Cys Ala
1 5

<210> 431
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 431
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala
1 5 10 15

Ala Gly Gly

<210> 432
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 432
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Ala
1 5 10 15

Ala Gly Gly

<210> 433
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 433
Glu Arg Lys Ser Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
1 5 10 15

Ala Gly

<210> 434
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 434

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

<210> 435
<211> 4196
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 435
ctagtcgaca ttgattattg actagttatt aatagtaatc aattacgggg tcattagttc 60

atagcccata tatggagttc cgcgttacat aacttacggt aaatggcccg cctggctgac 120

cgcccaacga cccccgccca ttgacgtcaa taatgacgta tgttcccata gtaacgccaa 180

tagggacttt ccattgacgt caatgggtgg agtatttacg gtaaactgcc cacttggcag 240

tacatcaagt gtatcatatg ccaagtacgc cccctattga cgtcaatgac ggtaaatggc 300

ccgcctggca ttatgcccag tacatgacct tatgggactt tcctacttgg cagtacatct 360

acgtattagt catcgctatt accatggtcg aggtgagccc cacgttctgc ttcactctcc 420

ccatctcccc cccctcccca cccccaattt tgtatttatt tatttttaa ttattttgtg 480

cagcgatggg ggcgggggg ggggggggc gcgcgccagg cggggcgggg cggggcgagg 540

ggcggggcgg ggcgaggcgg agaggtgcgg cggcagccaa tcagagcggc gcgctccgaa 600

agtttccttt tatggcgagg cggcggcggc ggcggcccta taaaaagcga agcgcgcggc 660

gggcgggagt cgctgcgcgc tgccttcgcc ccgtgccccg ctccgccgcc gcctcgcgcc 720

gcccgccccg gctctgactg accgcgttac tcccacaggt gagcgggcgg gacggccctt 780

ctcctccggg ctgtaattag cgcttggttt aatgacggct tgtttctttt ctgtggctgc 840

gtgaaagcct tgaggggctc cgggagggcc ctttgtgcgg ggggagcggc tcgggggtg 900

cgtgcgtgtg tgtgtgcgtg gggagcgccg cgtgcggctc cgcgctgccc ggcggctgtg 960

agcgctgcgg gcgcggcgcg gggctttgtg cgctccgcag tgtgcgcgag gggagcgcgg 1020

ccgggggcgg tgccccgcgg tgcgggggg gctgcgaggg gaacaaaggc tgcgtgcggg 1080

gtgtgtgcgt gggggggtga gcaggggtg tgggcgcgtc ggtcgggctg caacccccc 1140

tgcacccccc tccccgagtt gctgagcacg gcccggcttc gggtgcgggg ctccgtacgg 1200

ggcgtggcgc ggggctcgcc gtgccgggcg gggggtggcg gcaggtgggg gtgccgggcg 1260

gggcggggcc gcctcgggcc ggggagggct cgggggaggg gcgcggcggc ccccggagcg 1320

ccggcggctg tcgaggcgcg gcgagccgca gccattgcct tttatggtaa tcgtgcgaga 1380

gggcgcaggg acttcctttg tcccaaatct gtgcggagcc gaaatctggg aggcgccgcc 1440

gcacccccctc tagcgggcgc ggggcgaagc ggtgcggcgc cggcaggaag gaaatgggcg 1500

gggagggcct tcgtgcgtcg ccgcgccgcc gtccccttct ccctctccag cctcggggct 1560

gtccgcgggg ggacggctgc cttcgggggg gacggggcag ggcggggttc ggcttctggc 1620

gtgtgaccgg cggctctaga gcctctgcta accatgttca tgccttcttc tttttcctac 1680

agctcctggg caacgtgctg gttattgtgc tgtctcatca ttttggcaaa gaattcgcta 1740

gcgggcactt tgcactggaa cttacaacac ccgagcaagg acgcgactct ccaccatgta 1800

ccggatgcag ctgctgctgc tcattgccct gtctctggcc ctggtcacca atagcgaagt 1860

ccagctgctg gaatctggcg gcggacttgt tcaacctggc ggctctctga gactgagctg 1920

tgccgcttcc ggcttcacct tcagccacta tatcatgatg tgggtccgac aggcccctgg 1980

caaaggcctt gaatgggtgt ccggcatcta tagcagcggc ggcatcacag tgtacgccga 2040

ctctgtgaag ggcagattca ccatcagccg ggacaacagc aagaacaccc tgtacctgca 2100

gatgaacagc ctgagagccg aggacaccgc cgtgtactac tgcgcctata gaagaatcgg 2160

cgtgcccaga cgggacgagt tcgatatttg gggccagggc accatggtca ccgtgtctag 2220

cgcctctaca aagggcccta gcgtgttccc tctggctcct agcagcaaga gcacaagcgg 2280

aggaacagcc gctctgggct gtctggtcaa ggactacttt cccgagcctg tgaccgtgtc 2340

ctggaatagc ggagcactga caagcggcgt gcacaccttt ccagctgtgc tgcaaagcag 2400

cggcctgtac tctctgagca gcgtggtcac agtgccaagc tctagcctgg gcacccagac 2460

ctacatctgc aatgtgaacc acaagcctag caacaccaag gtggacaaga gagtggaacc 2520

caagagctgc gacaagaccc acacctgtcc tccatgtcct gctccagaac tgctcggcgg 2580

accttccgtg ttcctgtttc ctccaaagcc taaggacacc ctgatgatca gcagaacccc 2640

tgaagtgacc tgcgtggtgg tggatgtgtc ccacgaggat cccgaagtga agttcaattg 2700

gtacgtggac ggcgtggaag tgcacaacgc caagaccaag cctagagagg aacagtacaa 2760

cagcacctac agagtggtgt ccgtgctgac cgtgctgcac caggattggc tgaacggcaa 2820

agagtacaag tgcaaggtgt ccaacaaggc cctgcctgct cctatcgaga aaaccatcag 2880

caaggccaag ggccagccta gggaacccca ggtttacaca ctgcctccaa gccgggaaga 2940

gatgaccaag aaccaggtgt ccctgacctg cctcgtgaag ggcttctacc cttccgatat 3000

cgccgtggaa tgggagagca atggccagcc agagaacaac tacaagacaa cccctcctgt 3060

gctggacagc gacggctcat tcttcctgta cagcaagctg acagtggaca agtccagatg 3120

gcagcagggc aacgtgttca gctgcagcgt gatgcacgag gccctgcaca accactacac 3180

ccagaagagt ctgagcctgt ctccaggcct gcggaagaga agggctcctg tgaagcagac 3240

cctgaacttc gacctgctga aactggccgg cgacgtggaa agcaaccccg gacctatgta 3300

tagaatgcag ctcctcctgc tgatcgcact gagcctggct ctcgtgacca acagcgacat 3360

ccagatgaca cagagcccca gcacactgtc tgccagcgtg ggagacagag tgaccatcac 3420

ctgtagagcc agccagtcca tctcctcttg gctggcctgg tatcagcaaa agcctggcaa 3480

ggcccctaag ctgctgatct acaaggcctc cacactggaa agcggggtgc cctccagatt 3540

ttctggcagc ggatctggca ccgagttcac cctgaccatc agtagcctgc agcctgacga 3600

cttcgccacc tactactgcc agcagtacaa tacctactgg accttcggcc agggaacaaa 3660

ggtggaaatc aagcggactg tggccgctcc aagcgtgttc atctttccac ctagcgacga 3720

gcagctgaag tccggcacag cctctgttgt gtgcctgctg aacaacttct accccagaga 3780

agccaaggtg cagtggaaag tggacaatgc cctgcagagc ggcaactccc aagagagcgt 3840

gacagagcag gactccaagg attccaccta cagcctgtct agcaccctga cactgagcaa 3900

ggccgactac gagaagcaca aagtgtatgc ctgcgaagtg acccaccagg gccttagctc 3960

tccagtgacc aagagcttca accggggcga gtgttgataa agcggccgcg gtacctctag 4020

agtcgacccg ggcggcctcg aggacggggt gaactacgcc tgaggatccg atctttttcc 4080

ctctgccaaa aattatgggg acatcatgaa gccccttgag catctgactt ctggctaata 4140

aaggaaattt attttcattg caatagtgtg ttggaatttt ttgtgtctct cactcg 4196

<210> 436
<211> 4106
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 436
gacattgatt attgactagt tattaatagt aatcaattac ggggtcatta gttcatagcc 60

catatatgga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 120

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaatagggа 180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240

aagtgtatca tatgccaagt acgccccctа ttgacgtcaa tgacggtaaa tggcccgcct 300

ggcattatgc ccagtacatg accttatggg actttcctac ttggcagtac atctacgtat 360

tagtcatcgc tattaccatg gtcgaggtga gccccacgtt ctgcttcact ctccccatct 420

ccccccccтc cccaccccca attttgtatt tatttatttt ttaattattt tgtgcagcga 480

tgggggcggg gggggggggg gggcgcgcgc caggcggggc ggggcggggc gaggggcggg 540

gcggggcgag gcggagaggt gcggcggcag ccaatcagag cggcgcgctc cgaaagtttc 600

cttttatggc gaggcggcgg cggcggcggc cctataaaaa gcgaagcgcg cggcgggcgg 660

gagtcgctgc gcgctgcctt cgccccgtgc cccgctccgc cgccgcctcg cgccgcccgc 720

cccggctctg actgaccgcg ttactcccac aggtgagcgg gcgggacggc ccttctcctc 780

cgggctgtaa ttagcgcttg gtttaatgac ggcttgtttc ttttctgtgg ctgcgtgaaa 840

gccttgaggg gctccgggag ggccctttgt gcgggggggag cggctcgggg ggtgcgtgcg 900

tgtgtgtgtg cgtggggagc gccgcgtgcg gctccgcgct gcccggcggc tgtgagcgct 960

gcgggcgcgg cgcggggctt tgtgcgctcc gcagtgtgcg cgaggggagc gcggccgggg 1020

gcggtgcccc gcggtgcggg gggggctgcg aggggaacaa aggctgcgtg cggggtgtgt 1080

gcgtgggggg gtgagcaggg ggtgtgggcg cgtcggtcgg gctgcaaccc cccctgcacc 1140

cccctccccg agttgctgag cacggcccgg cttcgggtgc ggggctccgt acggggcgtg 1200

gcgcggggct cgccgtgccg ggcgggggggt ggcggcaggt gggggtgccg ggcggggcgg 1260

ggccgcctcg ggccggggag ggctcggggg aggggcgcgg cggcccccgg agcgccggcg 1320

gctgtcgagg cgcggcgagc cgcagccatt gccttttatg gtaatcgtgc gagagggcgc 1380

agggacttcc tttgtcccaa atctgtgcgg agccgaaatc tgggaggcgc cgccgcaccc 1440

cctctagcgg gcgcggggcg aagcggtgcg gcgccggcag gaaggaaatg ggcggggagg 1500

gccttcgtgc gtcgccgcgc cgccgtcccc ttctccctct ccagcctcgg ggctgtccgc 1560

gggggggacgg ctgccttcgg gggggacggg gcagggcggg gttcggcttc tggcgtgtga 1620

ccggcggctc tagagcctct gctaaccatg ttcatgcctt cttctttttc ctacagctcc 1680

tgggcaacgt gctggttatt gtgctgtctc atcattttgg caaagaattc gccgccacca 1740

tgtacagaat gcagctgctg ctgctcattg ccctgtctct ggccctggtc accaattctg 1800

aggtccagct gcttgagagt ggtggtggac tggttcagcc tggtggcagc ctgagactgt 1860

cttgtgctgc ctctggcttc accttcagcc actatatcat gatgtgggtc agacaggccc 1920

ctggcaaagg cctggaatgg gtgtcaggca tctacagcag tggtggcatc acagtgtatg 1980

ctgactctgt gaagggcaga ttcaccatca gcagagacaa cagcaagaac accctgtacc 2040

tgcagatgaa ctccctgaga gctgaggaca cagcagtgta ctactgtgcc tatagaagaa 2100

ttggggtgcc cagaagggat gagtttgaca tctggggcca gggcaccatg gttacagtgt 2160

cctctgccag cacaaagggc ccctctgttt ttccactggc tcccagcagc aagagcacca 2220

gtggtggaac agctgccctg ggctgtctgg tcaaggatta cttccctgag cctgtgactg 2280

tgtcctggaa ctctggggct ctgacctctg gggtgcacac ctttccagct gtgctgcagt 2340

cctctggcct gtactctctg tcctctgtgg tcacagtgcc tagctctagc ctgggcacac 2400

agacctacat ctgcaatgtg aaccacaagc ctagcaacac caaggtggac aagagagtgg 2460

aacccaagag ctgtgacaag acccacacct gtcctccatg tcctgctcca gaactgcttg 2520

gaggcccttc tgtgttcctg tttcctccaa agcctaagga caccctgatg atcagcagaa 2580

cccctgaagt gacctgtgtg gtggttgatg tgtcccatga ggacccagaa gtgaagttca 2640

attggtatgt ggatggggtt gaagtgcaca atgccaagac caagcctaga gaggaacagt 2700

acaacagcac ctacagagtg gtttctgtgc tgacagtgct gcaccaggac tggctgaatg 2760

gcaaagagta caagtgcaag gtgtccaaca aggccctgcc tgctcctatt gagaaaacca 2820

tctccaaggc caagggccag ccaagagaac cccaggttta caccctgcca cctagcagag 2880

aagagatgac caagaaccag gtgtccctga cctgcctggt taagggcttc tacccctctg 2940

acattgctgt ggaatgggag agcaatggcc agcctgaaaa caactacaag acaacccctc 3000

ctgtgctgga ctctgatggc tcattcttcc tgtacagcaa gctgactgtg gacaagtcca 3060

gatggcagca gggaaatgtg ttcagctgct ctgtgatgca tgaggccctg cacaaccact 3120

acacccagaa aagtctgtct ctgtcccctg gcagaaagag aagaggatca ggggccccag 3180

tgaagcagac cctgaacttt gatctgctga agctggctgg ggatgttgag agcaaccctg 3240

gacctatgta taggatgcaa ctgctcctcc tgattgctct gagcctggct cttgtgacca 3300

actctgacat ccagatgaca cagagcccct ccacactgtc tgcatctgtg ggagacagag 3360

tgaccatcac ctgtagagcc agccagtcta tctcttcctg gctggcctgg tatcagcaaa 3420

agcctggcaa ggcccctaag ctgctgatct acaaggccag cacacttgag tcaggggtgc 3480

cctccagatt ttctggctct ggatctggca cagagttcac cctgaccatc agctccctgc 3540

agccagatga ctttgccacc tactactgcc agcagtacaa tacctactgg acctttggcc 3600

agggaacaaa ggtggaaatc aagagaacag tggctgcccc atctgtgttc atcttcccac 3660

catctgatga acagctgaag tctggcactg cctctgttgt gtgcctgctg aacaactttt 3720

accctagaga agccaaggtg cagtggaaag tggataatgc cctgcagtct ggcaatagcc 3780

aagaatctgt gacagagcag gactccaagg attccaccta cagcctgagc agcaccctga 3840

cactgagcaa ggctgactat gagaagcaca aagtgtatgc ctgtgaagtg acacaccagg 3900

gactgagcag cccagtgacc aagagcttca acaggggaga gtgctgataa ctcgaggacg 3960

gggtgaacta cgcctgagga tccgatcttt ttccctctgc caaaaattat ggggacatca 4020

tgaagcccct tgagcatctg acttctggct aataaaggaa atttattttc attgcaatag 4080

tgtgttggaa ttttttgtgt ctctca 4106

<210> 437
<211> 4092
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 437
gacattgatt attgactagt tattaatagt aatcaattac ggggtcatta gttcatagcc 60

catatatgga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 120

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaatagggа 180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240

aagtgtatca tatgccaagt acgccccta ttgacgtcaa tgacggtaaa tggcccgcct 300

ggcattatgc ccagtacatg accttatggg actttcctac ttggcagtac atctacgtat 360

tagtcatcgc tattaccatg gtcgaggtga gccccacgtt ctgcttcact ctccccatct 420

ccccccccctc cccaccccca attttgtatt tatttatttt ttaattattt tgtgcagcga 480

tgggggcggg gggggggggg gggcgcgcgc caggcggggc ggggcggggc gaggggcggg 540

gcggggcgag gcggagaggt gcggcggcag ccaatcagag cggcgcgctc cgaaagtttc 600

cttttatggc gaggcggcgg cggcggcggc cctataaaaa gcgaagcgcg cggcgggcgg 660

gagtcgctgc gcgctgcctt cgccccgtgc cccgctccgc cgccgcctcg cgccgcccgc 720

cccggctctg actgaccgcg ttactcccac aggtgagcgg gcgggacggc ccttctcctc 780

cgggctgtaa ttagcgcttg gtttaatgac ggcttgtttc ttttctgtgg ctgcgtgaaa 840

gccttgaggg gctccgggag ggccctttgt gcgggggggag cggctcgggg ggtgcgtgcg 900

tgtgtgtgtg cgtggggagc gccgcgtgcg gctccgcgct gcccggcggc tgtgagcgct 960

gcgggcgcgg cgcggggctt tgtgcgctcc gcagtgtgcg cgaggggagc gcggccgggg 1020

gcggtgcccc gcggtgcggg gggggctgcg aggggaacaa aggctgcgtg cggggtgtgt 1080

gcgtgggggg gtgagcaggg ggtgtgggcg cgtcggtcgg gctgcaaccc cccctgcacc 1140

cccctccccg agttgctgag cacggcccgg cttcgggtgc ggggctccgt acggggcgtg 1200

gcgcggggct cgccgtgccg ggcgggggggt ggcggcaggt gggggtgccg ggcggggcgg 1260

ggccgcctcg ggccggggag ggctcggggg aggggcgcgg cggcccccgg agcgccggcg 1320

gctgtcgagg cgcggcgagc cgcagccatt gccttttatg gtaatcgtgc gagagggcgc 1380

agggacttcc tttgtcccaa atctgtgcgg agccgaaatc tgggaggcgc cgccgcaccc 1440

cctctagcgg gcgcggggcg aagcggtgcg gcgccggcag gaaggaaatg ggcggggagg 1500

gccttcgtgc gtcgccgcgc cgccgtcccc ttctccctct ccagcctcgg ggctgtccgc 1560

ggggggacgg ctgccttcgg gggggacggg gcagggcggg gttcggcttc tggcgtgtga 1620

ccggcggctc tagagcctct gctaaccatg ttcatgcctt cttctttttc ctacagctcc 1680

tgggcaacgt gctggttatt gtgctgtctc atcattttgg caaagaattc gccgccacca 1740

tgtacagaat gcagctgctg ctgctcattg ccctgtctct ggccctggtc accaattctg 1800

aggtccagct gcttgagagt ggtggtggac tggttcagcc tggtggcagc ctgagactgt 1860

cttgtgctgc ctctggcttc accttcagcc actatatcat gatgtgggtc agacaggccc 1920

ctggcaaagg cctggaatgg gtgtcaggca tctacagcag tggtggcatc acagtgtatg 1980

ctgactctgt gaagggcaga ttcaccatca gcagagacaa cagcaagaac accctgtacc 2040

tgcagatgaa ctccctgaga gctgaggaca cagcagtgta ctactgtgcc tatagaagaa 2100

ttggggtgcc cagaagggat gagtttgaca tctggggcca gggcaccatg gttacagtgt 2160

cctctgccag cacaaagggc ccctctgttt ttccactggc tcccagcagc aagagcacca 2220

gtggtggaac agctgccctg ggctgtctgg tcaaggatta cttccctgag cctgtgactg 2280

tgtcctggaa ctctggggct ctgacttctg gggtgcacac ctttccagct gtgctgcagt 2340

cctctggcct gtactctctg tcctctgtgg tcacagtgcc tagctctagc ctgggcacac 2400

agacctacat ctgcaatgtg aaccacaagc ctagcaacac caaggtggac aagagagtgg 2460

aacccaagag ctgtgacaag acccacacct gtcctccatg tcctgctcca gaactgcttg 2520

gaggcccttc tgtgttcctg tttcctccaa agcctaagga caccctgatg atcagcagaa 2580

cccctgaagt gacctgtgtg gtggttgatg tgtcccatga ggacccagaa gtgaagttca 2640

attggtatgt ggatggggtt gaagtgcaca atgccaagac caagcctaga gaggaacagt 2700

acaacagcac ctacagagtg gtttctgtgc tgacagtgct gcaccaggac tggctgaatg 2760

gcaaagagta caagtgcaag gtgtccaaca aggccctgcc tgctcctatt gagaaaacca 2820

tctccaaggc caagggccag ccaagagaac cccaggttta caccctgcca cctagcagag 2880

aagagatgac caagaaccag gtgtccctga cctgcctggt taagggcttc tacccctctg 2940

acattgctgt ggaatgggag agcaatggcc agcctgaaaa caactacaag acaacccctc 3000

ctgtgctgga ctctgatggc tcattcttcc tgtacagcaa gctgactgtg gacaagtcca 3060

gatggcagca gggaaatgtg ttcagctgct ctgtgatgca tgaggccctg cacaaccact 3120

acacccagaa aagtctgtct ctgtcccctg gcagaaagag aagaggctct ggagaaggca 3180

gaggctccct gctgacatgt ggggatgttg aagagaatcc tgggcctatg tataggatgc 3240

aactgctcct cctgattgct ctgagcctgg ctcttgtgac caactctgac atccagatga 3300

cacagagccc ctccacactg tctgcatctg tgggagacag agtgaccatc acctgtagag 3360

ccagccagtc tatctctagc tggctggcct ggtatcagca aaagcctggc aaggccccta 3420

agctgctgat ctacaaggcc agcacacttg agtcaggggt gccctccaga ttttctggct 3480

ctggatctgg cacagagttc accctgacca tcagctccct gcagccagat gactttgcca 3540

cctactactg ccagcagtac aatacctact ggacctttgg ccagggaaca aaggtggaaa 3600

tcaagagaac agtggctgcc ccatctgtgt tcatcttccc accatctgat gaacagctga 3660

agtctggcac tgcctctgtt gtgtgcctgc tgaacaactt ttaccccaga gaagccaagg 3720

tgcagtggaa agtggataat gccctgcagt ctggcaatag ccaagaatct gtgacagagc 3780

aggactccaa ggattccacc tacagcctga gcagcaccct gacactgagc aaggctgact 3840

atgagaagca caaagtgtat gcctgtgaag tgacacacca gggactgagc agcccagtga 3900

ccaagagctt caacagggga gagtgctgat aactcgagga cggggtgaac tacgcctgag 3960

gatccgatct ttttccctct gccaaaaatt atggggacat catgaagccc cttgagcatc 4020

tgacttctgg ctaataaagg aaatttattt tcattgcaat agtgtgttgg aatttttgt 4080

gtctctcact cg 4092

<210> 438
<211> 3397
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 438
aggttaattt ttaaaaagca gtcaaaagtc caagtggccc ttggcagcat ttactctctc 60

tgtttgctct ggttaataat ctcaggagca caaacattcc agatccaggt taatttttaa 120

aaagcagtca aaagtccaag tggcccttgg cagcatttac tctctctgtt tgctctggtt 180

aataatctca ggagcacaaa cattccagat ccggcgcgcc agggctggaa gctacctttg 240

acatcatttc ctctgcgaat gcatgtataa tttctacaga acctattaga aaggatcacc 300

cagcctctgc ttttgtacaa ctttccctta aaaaactgcc aattccactg ctgtttggcc 360

caatagtgag aacttttcc tgctgcctct tggtgctttt gcctatggcc cctattctgc 420

ctgctgaaga cactcttgcc agcatggact taaacccctc cagctctgac aatcctcttt 480

ctcttttgtt ttacatgaag ggtctggcag ccaaagcaat cactcaaagt tcaaacctta 540

tcatttttg ctttgttcct cttggccttg gttttgtaca tcagctttga aaataccatc 600

ccagggttaa tgctggggtt aatttataac taagagtgct ctagttttgc aatacaggac 660

atgctataaa aatggaaaga tgttgctttc tgagagacag ctttattgcg gtagtttatc 720

acagttaaat tgctaacgca gtcagtgctt ctgacacaac agtctcgaac ttaagctgca 780

gaagttggtc gtgaggcact gggcaggtaa gtatcaaggt tacaagacag gtttaaggag 840

accaatagaa actgggcttg tcgagacaga gaagactctt gcgtttctga taggcaccta 900

ttggtcttac tgacatccac tttgcctttc tctccacagg tgtccactcc cagttcaatt 960

acagctctta aggctagagt acttaatacg actcactata ggctagcctc gagaattcac 1020

gcgtgccgcc accatgtaca gaatgcagct gctgctgctc attgccctgt ctctggccct 1080

ggtcaccaat tctgaggtcc agctgcttga gagtggtggt ggactggttc agcctggtgg 1140

cagcctgaga ctgtcttgtg ctgcctctgg cttcaccttc agccactata tcatgatgtg 1200

ggtcagacag gcccctggca aaggcctgga atgggtgtca ggcatctaca gcagtggtgg 1260

catcacagtg tatgctgact ctgtgaaggg cagattcacc atcagcagag acaacagcaa 1320

gaacaccctg tacctgcaga tgaactccct gagagctgag gacacagcag tgtactactg 1380

tgcctataga agaattgggg tgcccagaag ggatgagttt gacatctggg gccagggcac 1440

catggttaca gtgtcctctg ccagcacaaa gggcccctct gtttttccac tggctcccag 1500

cagcaagagc accagtggtg gaacagctgc cctgggctgt ctggtcaagg attacttccc 1560

tgagcctgtg actgtgtcct ggaactctgg ggctctgact tctggggtgc acacctttcc 1620

agctgtgctg cagtcctctg gcctgtactc tctgtcctct gtggtcacag tgcctagctc 1680

tagcctgggc acacagacct acatctgcaa tgtgaaccac aagcctagca acaccaaggt 1740

ggacaagaga gtggaaccca agagctgtga caagacccac acctgtcctc catgtcctgc 1800

tccagaactg cttggaggcc cttctgtgtt cctgtttcct ccaaagccta aggacaccct 1860

gatgatcagc agaacccctg aagtgacctg tgtggtggtt gatgtgtccc atgaggaccc 1920

agaagtgaag ttcaattggt atgtggatgg ggttgaagtg cacaatgcca agaccaagcc 1980

tagagaggaa cagtacaaca gcacctacag agtggtttct gtgctgacag tgctgcacca 2040

ggactggctg aatggcaaag agtacaagtg caaggtgtcc aacaaggccc tgcctgctcc 2100

tattgagaaa accatctcca aggccaaggg ccagccaaga gaaccccagg tttacaccct 2160

gccacctagc agagaagaga tgaccaagaa ccaggtgtcc ctgacctgcc tggttaaggg 2220

cttctacccc tctgacattg ctgtggaatg ggagagcaat ggccagcctg aaaacaacta 2280

caagacaacc cctcctgtgc tggactctga tggctcattc ttcctgtaca gcaagctgac 2340

tgtggacaag tccagatggc agcagggaaa tgtgttcagc tgctctgtga tgcatgaggc 2400

cctgcacaac cactacaccc agaaaagtct gtctctgtcc cctggcagaa agagaagagg 2460

ctctggagaa ggcagaggct ccctgctgac atgtggggat gttgaagaga atcctgggcc 2520

tatgtatagg atgcaactgc tcctcctgat tgctctgagc ctggctcttg tgaccaactc 2580

tgacatccag atgacacaga gcccctccac actgtctgca tctgtgggag acagagtgac 2640

catcacctgt agagccagcc agtctatctc tagctggctg gcctggtatc agcaaaagcc 2700

tggcaaggcc cctaagctgc tgatctacaa ggccagcaca cttgagtcag gggtgccctc 2760

cagattttct ggctctggat ctggcacaga gttcaccctg accatcagct ccctgcagcc 2820

agatgacttt gccacctact actgccagca gtacaatacc tactggacct ttggccaggg 2880

aacaaaggtg gaaatcaaga gaacagtggc tgccccatct gtgttcatct tcccaccatc 2940

tgatgaacag ctgaagtctg gcactgcctc tgttgtgtgc ctgctgaaca acttttaccc 3000

cagagaagcc aaggtgcagt ggaaagtgga taatgccctg cagtctggca atagccaaga 3060

atctgtgaca gagcaggact ccaaggattc cacctacagc ctgagcagca ccctgacact 3120

gagcaaggct gactatgaga agcacaaagt gtatgcctgt gaagtgacac accagggact 3180

gagcagccca gtgaccaaga gcttcaacag gggagagtgc tgataagtcg acccgggcgg 3240

cctcgaggac ggggtgaact acgcctgagg atccgatctt tttccctctg ccaaaaatta 3300

tggggacatc atgaagcccc ttgagcatct gacttctggc taataaagga aatttatttt 3360

cattgcaata gtgtgttgga atttttttgtg tctctca 3397

<210> 439
<211> 3227
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 439
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg 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

agtcaggtaa gtatcaaggt tacaagacag gtttaaggag accaatagaa actgggcttg 780

tcgagacaga gaagactctt gcgtttctga taggcaccta ttggtcttac tgacatccac 840

tttgcctttc tctccacagg ttcgaattcg ccgccaccat gtacagaatg cagctgctgc 900

tgctcattgc cctgtctctg gccctggtca ccaattctga ggtccagctg cttgagagtg 960

gtggtggact ggttcagcct ggtggcagcc tgagactgtc ttgtgctgcc tctggcttca 1020

ccttcagcca ctatatcatg atgtgggtca gacaggcccc tggcaaaggc ctggaatggg 1080

tgtcaggcat ctacagcagt ggtggcatca cagtgtatgc tgactctgtg aagggcagat 1140

tcaccatcag cagagacaac agcaagaaca ccctgtacct gcagatgaac tccctgagag 1200

ctgaggacac agcagtgtac tactgtgcct atagaagaat tggggtgccc agaagggatg 1260

agtttgacat ctggggccag ggcaccatgg ttacagtgtc ctctgccagc acaaagggcc 1320

cctctgtttt tccactggct cccagcagca agagcaccag tggtggaaca gctgccctgg 1380

gctgtctggt caaggattac ttccctgagc ctgtgactgt gtcctggaac tctggggctc 1440

tgacttctgg ggtgcacacc tttccagctg tgctgcagtc ctctggcctg tactctctgt 1500

cctctgtggt cacagtgcct agctctagcc tgggcacaca gacctacatc tgcaatgtga 1560

accacaagcc tagcaacacc aaggtggaca agagagtgga acccaagagc tgtgacaaga 1620

cccacacctg tcctccatgt cctgctccag aactgcttgg aggcccttct gtgttcctgt 1680

ttcctccaaa gcctaaggac accctgatga tcagcagaac ccctgaagtg acctgtgtgg 1740

tggttgatgt gtcccatgag gacccagaag tgaagttcaa ttggtatgtg gatggggttg 1800

aagtgcacaa tgccaagacc aagcctagag aggaacagta caacagcacc tacagagtgg 1860

tttctgtgct gacagtgctg caccaggact ggctgaatgg caaagagtac aagtgcaagg 1920

tgtccaacaa ggccctgcct gctcctattg agaaaaccat ctccaaggcc aagggccagc 1980

caagagaacc ccaggtttac accctgccac ctagcagaga agagatgacc aagaaccagg 2040

tgtccctgac ctgcctggtt aagggcttct acccctctga cattgctgtg gaatgggaga 2100

gcaatggcca gcctgaaaac aactacaaga caacccctcc tgtgctggac tctgatggct 2160

cattcttcct gtacagcaag ctgactgtgg acaagtccag atggcagcag ggaaatgtgt 2220

tcagctgctc tgtgatgcat gaggccctgc acaaccacta cacccagaaa agtctgtctc 2280

tgtcccctgg cagaaagaga agaggctctg gagaaggcag aggctccctg ctgacatgtg 2340

gggatgttga agagaatcct gggcctatgt ataggatgca actgctcctc ctgattgctc 2400

tgagcctggc tcttgtgacc aactctgaca tccagatgac acagagcccc tccacactgt 2460

ctgcatctgt gggagacaga gtgaccatca cctgtagagc cagccagtct atctctagct 2520

ggctggcctg gtatcagcaa aagcctggca aggcccctaa gctgctgatc tacaaggcca 2580

gcacacttga gtcaggggtg ccctccagat tttctggctc tggatctggc acagagttca 2640

ccctgaccat cagctccctg cagccagatg actttgccac ctactactgc cagcagtaca 2700

atacctactg gacctttggc cagggaacaa aggtggaaat caagagaaca gtggctgccc 2760

catctgtgtt catcttccca ccatctgatg aacagctgaa gtctggcact gcctctgttg 2820

tgtgcctgct gaacaacttt taccccagag aagccaaggt gcagtggaaa gtggataatg 2880

ccctgcagtc tggcaatagc caagaatctg tgacagagca ggactccaag gattccacct 2940

acagcctgag cagcaccctg acactgagca aggctgacta tgagaagcac aaagtgtatg 3000

cctgtgaagt gacacaccag ggactgagca gcccagtgac caagagcttc aacaggggag 3060

agtgctgata actcgaggac ggggtgaact acgcctgagg atccgatctt tttccctctg 3120

ccaaaaatta tggggacatc atgaagcccc ttgagcatct gacttctggc taataaagga 3180

aatttatttt cattgcaata gtgtgttgga atttttttgtg tctctca 3227

<210> 440
<211> 3472
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 440
aggttaattt ttaaaaagca gtcaaaagtc caagtggccc ttggcagcat ttactctctc 60

tgtttgctct ggttaataat ctcaggagca caaacattcc agatccaggt taatttttaa 120

aaagcagtca aaagtccaag tggcccttgg cagcatttac tctctctgtt tgctctggtt 180

aataatctca ggagcacaaa cattccagat ccggcgcgcc agggctggaa gctacctttg 240

tctagaaggc tcagaggcac acaggagttt ctgggctcac cctgccccct tccaacccct 300

cagttcccat cctccagcag ctgtttgtgt gctgcctctg aagtccacac tgaacaaact 360

tcagcctact catgtcccta aaatgggcaa acattgcaag cagcaaacag caaacacaca 420

gccctccctg cctgctgacc ttggagctgg ggcagaggtc agagacctct ctgggcccat 480

gccacctcca acatccactc gacccttgg aatttcggtg gagaggagca gaggttgtcc 540

tggcgtggtt taggtagtgt gagaggggta cccggggatc ttgctaccag tggaacagcc 600

actaaggatt ctgcagtgag agcagagggc cagctaagtg gtactctccc agagactgtc 660

tgactcacgc caccccctcc accttggaca caggacgctg tggtttctga gccaggtaca 720

atgactcctt tcggtaagtg cagtggaagc tgtacactgc ccaggcaaag cgtccgggca 780

gcgtaggcgg gcgactcaga tcccagccag tggacttagc ccctgtttgc tcctccgata 840

actggggtga ccttggttaa tattcaccag cagcctcccc cgttgccccct ctggatccac 900

tgcttaaata cggacgagga cagggccctg tctcctcagc ttcaggcacc accactgacc 960

tgggacagtc aggtaagtat caaggttaca agacaggttt aaggagacca atagaaactg 1020

ggcttgtcga gacagagaag actcttgcgt ttctgatagg cacctattgg tcttactgac 1080

atccactttg cctttctctc cacaggttga attcgccgcc accatgtaca gaatgcagct 1140

gctgctgctc attgccctgt ctctggccct ggtcaccaat tctgaggtcc agctgcttga 1200

gagtggtggt ggactggttc agcctggtgg cagcctgaga ctgtcttgtg ctgcctctgg 1260

cttcaccttc agccactata tcatgatgtg ggtcagacag gcccctggca aaggcctgga 1320

atgggtgtca ggcatctaca gcagtggtgg catcacagtg tatgctgact ctgtgaaggg 1380

cagattcacc atcagcagag acaacagcaa gaacaccctg tacctgcaga tgaactccct 1440

gagagctgag gacacagcag tgtactactg tgcctataga agaattgggg tgcccagaag 1500

ggatgagttt gacatctggg gccagggcac catggttaca gtgtcctctg ccagcacaaa 1560

gggcccctct gtttttccac tggctcccag cagcaagagc accagtggtg gaacagctgc 1620

cctgggctgt ctggtcaagg attacttccc tgagcctgtg actgtgtcct ggaactctgg 1680

ggctctgact tctggggtgc acacctttcc agctgtgctg cagtcctctg gcctgtactc 1740

tctgtcctct gtggtcacag tgcctagctc tagcctgggc acacagacct acatctgcaa 1800

tgtgaaccac aagcctagca acaccaaggt ggacaagaga gtggaaccca agagctgtga 1860

caagacccac acctgtcctc catgtcctgc tccagaactg cttggaggcc cttctgtgtt 1920

cctgtttcct ccaaagccta aggacaccct gatgatcagc agaacccctg aagtgacctg 1980

tgtggtggtt gatgtgtccc atgaggaccc agaagtgaag ttcaattggt atgtggatgg 2040

ggttgaagtg cacaatgcca agaccaagcc tagagaggaa cagtacaaca gcacctacag 2100

agtggtttct gtgctgacag tgctgcacca ggactggctg aatggcaaag agtacaagtg 2160

caaggtgtcc aacaaggccc tgcctgctcc tattgagaaa accatctcca aggccaaggg 2220

ccagccaaga gaaccccagg tttacaccct gccacctagc agagaagaga tgaccaagaa 2280

ccaggtgtcc ctgacctgcc tggttaaggg cttctacccc tctgacattg ctgtggaatg 2340

ggagagcaat ggccagcctg aaaacaacta caagacaacc cctcctgtgc tggactctga 2400

tggctcattc ttcctgtaca gcaagctgac tgtggacaag tccagatggc agcagggaaa 2460

tgtgttcagc tgctctgtga tgcatgaggc cctgcacaac cactacaccc agaaaagtct 2520

gtctctgtcc cctggcagaa agagaagagg ctctggagaa ggcagaggct ccctgctgac 2580

atgtggggat gttgaagaga atcctgggcc tatgtatagg atgcaactgc tcctcctgat 2640

tgctctgagc ctggctcttg tgaccaactc tgacatccag atgacacaga gcccctccac 2700

actgtctgca tctgtgggag acagagtgac catcacctgt agagccagcc agtctatctc 2760

tagctggctg gcctggtatc agcaaaagcc tggcaaggcc cctaagctgc tgatctacaa 2820

ggccagcaca cttgagtcag gggtgccctc cagattttct ggctctggat ctggcacaga 2880

gttcaccctg accatcagct ccctgcagcc agatgacttt gccacctact actgccagca 2940

gtacaatacc tactggacct ttggccaggg aacaaaggtg gaaatcaaga gaacagtggc 3000

tgccccatct gtgttcatct tcccaccatc tgatgaacag ctgaagtctg gcactgcctc 3060

tgttgtgtgc ctgctgaaca acttttaccc cagagaagcc aaggtgcagt ggaaagtgga 3120

taatgccctg cagtctggca atagccaaga atctgtgaca gagcaggact ccaaggattc 3180

cacctacagc ctgagcagca ccctgacact gagcaaggct gactatgaga agcacaaagt 3240

gtatgcctgt gaagtgacac accagggact gagcagccca gtgaccaaga gcttcaacag 3300

gggagagtgc tgataactcg aggacggggt gaactacgcc tgaggatccg atcttttcc 3360

ctctgccaaa aattatgggg acatcatgaa gccccttgag catctgactt ctggctaata 3420

aaggaaattt attttcattg caatagtgtg ttggaatttt ttgtgtctct ca 3472

<210> 441
<211> 3553
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 441
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gtctagaagg ctcagaggca cacaggagtt tctgggctca 360

ccctgccccc ttccaacccc tcagttccca tcctccagca gctgtttgtg tgctgcctct 420

gaagtccaca ctgaacaaac ttcagcctac tcatgtccct aaaatgggca aacattgcaa 480

gcagcaaaca gcaaacacac agccctccct gcctgctgac cttggagctg gggcagaggt 540

cagagacctc tctgggccca tgccacctcc aacatccact cgacccccttg gaatttcggt 600

ggagaggagc agaggttgtc ctggcgtggt ttaggtagtg tgagaggggt acccggggat 660

cttgctacca gtggaacagc cactaaggat tctgcagtga gagcagaggg ccagctaagt 720

ggtactctcc cagagactgt ctgactcacg ccacccccctc caccttggac acaggacgct 780

gtggtttctg agccaggtac aatgactcct ttcggtaagt gcagtggaag ctgtacactg 840

cccaggcaaa gcgtccgggc agcgtaggcg ggcgactcag atcccagcca gtggacttag 900

cccctgtttg ctcctccgat aactggggtg accttggtta atattcacca gcagcctccc 960

ccgttgcccc tctggatcca ctgcttaaat acggacgagg acagggccct gtctcctcag 1020

cttcaggcac caccactgac ctgggacagt caggtaagta tcaaggttac aagacaggtt 1080

taaggagacc aatagaaact gggcttgtcg agacagagaa gactcttgcg tttctgatag 1140

gcacctattg gtcttactga catccacttt gcctttctct ccacaggttg aattcgccgc 1200

caccatgtac agaatgcagc tgctgctgct cattgccctg tctctggccc tggtcaccaa 1260

ttctgaggtc cagctgcttg agagtggtgg tggactggtt cagcctggtg gcagcctgag 1320

actgtcttgt gctgcctctg gcttcacctt cagccactat atcatgatgt gggtcagaca 1380

ggcccctggc aaaggcctgg aatgggtgtc aggcatctac agcagtggtg gcatcacagt 1440

gtatgctgac tctgtgaagg gcagattcac catcagcaga gacaacagca agaacaccct 1500

gtacctgcag atgaactccc tgagagctga ggacacagca gtgtactact gtgcctatag 1560

aagaattggg gtgcccagaa gggatgagtt tgacatctgg ggccagggca ccatggttac 1620

agtgtcctct gccagcacaa agggcccctc tgtttttcca ctggctccca gcagcaagag 1680

caccagtggt ggaacagctg ccctgggctg tctggtcaag gattacttcc ctgagcctgt 1740

gactgtgtcc tggaactctg gggctctgac ttctggggtg cacacctttc cagctgtgct 1800

gcagtcctct ggcctgtact ctctgtcctc tgtggtcaca gtgcctagct ctagcctggg 1860

cacacagacc tacatctgca atgtgaacca caagcctagc aacaccaagg tggacaagag 1920

agtggaaccc aagagctgtg acaagaccca cacctgtcct ccatgtcctg ctccagaact 1980

gcttggaggc ccttctgtgt tcctgtttcc tccaaagcct aaggacaccc tgatgatcag 2040

cagaacccct gaagtgacct gtgtggtggt tgatgtgtcc catgaggacc cagaagtgaa 2100

gttcaattgg tatgtggatg gggttgaagt gcacaatgcc aagaccaagc ctagagagga 2160

acagtacaac agcacctaca gagtggtttc tgtgctgaca gtgctgcacc aggactggct 2220

gaatggcaaa gagtacaagt gcaaggtgtc caacaaggcc ctgcctgctc ctattgagaa 2280

aaccatctcc aaggccaagg gccagccaag agaaccccag gtttacaccc tgccacctag 2340

cagagaagag atgaccaaga accaggtgtc cctgacctgc ctggttaagg gcttctaccc 2400

ctctgacatt gctgtggaat gggagagcaa tggccagcct gaaaacaact acaagacaac 2460

ccctcctgtg ctggactctg atggctcatt cttcctgtac agcaagctga ctgtggacaa 2520

gtccagatgg cagcagggaa atgtgttcag ctgctctgtg atgcatgagg ccctgcacaa 2580

ccactacacc cagaaaagtc tgtctctgtc ccctggcaga aagagaagag gctctggaga 2640

aggcagaggc tccctgctga catgtgggga tgttgaagag aatcctgggc ctatgtatag 2700

gatgcaactg ctcctcctga ttgctctgag cctggctctt gtgaccaact ctgacatcca 2760

gatgacacag agcccctcca cactgtctgc atctgtggga gacagagtga ccatcacctg 2820

tagagccagc cagtctatct ctagctggct ggcctggtat cagcaaaagc ctggcaaggc 2880

ccctaagctg ctgatctaca aggccagcac acttgagtca ggggtgccct ccagattttc 2940

tggctctgga tctggcacag agttcaccct gaccatcagc tccctgcagc cagatgactt 3000

tgccacctac tactgccagc agtacaatac ctactggacc tttggccagg gaacaaaggt 3060

ggaaatcaag agaacagtgg ctgccccatc tgtgttcatc ttcccaccat ctgatgaaca 3120

gctgaagtct ggcactgcct ctgttgtgtg cctgctgaac aacttttacc ccagagaagc 3180

caaggtgcag tggaaagtgg ataatgccct gcagtctggc aatagccaag aatctgtgac 3240

agagcaggac tccaaggatt ccacctacag cctgagcagc accctgacac tgagcaaggc 3300

tgactatgag aagcacaaag tgtatgcctg tgaagtgaca caccagggac tgagcagccc 3360

agtgaccaag agcttcaaca ggggagagtg ctgataactc gaggacgggg tgaactacgc 3420

ctgaggatcc gatcttttc cctctgccaa aaattatggg gacatcatga agccccttga 3480

gcatctgact tctggctaat aaaggaaatt tattttcatt gcaatagtgt gttggaattt 3540

tttgtgtctc tca 3553

<210> 442
<211> 3592
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 442
aggttaattt ttaaaaagca gtcaaaagtc caagtggccc ttggcagcat ttactctctc 60

tgtttgctct ggttaataat ctcaggagca caaacattcc agatccaggt taatttttaa 120

aaagcagtca aaagtccaag tggcccttgg cagcatttac tctctctgtt tgctctggtt 180

aataatctca ggagcacaaa cattccagat ccggcgcgcc agggctggaa gctacctttg 240

acatcatttc ctctgcgaat gcatgtataa tttctacaga acctattaga aaggatcacc 300

cagcctctgc ttttgtacaa ctttccctta aaaaactgcc aattccactg ctgtttggcc 360

caatagtgag aacttttcc tgctgcctct tggtgctttt gcctatggcc cctattctgc 420

ctgctgaaga cactcttgcc agcatggact taaacccctc cagctctgac aatcctcttt 480

ctcttttgtt ttacatgaag ggtctggcag ccaaagcaat cactcaaagt tcaaacctta 540

tcatttttg ctttgttcct cttggccttg gttttgtaca tcagctttga aaataccatc 600

ccagggttaa tgctggggtt aatttataac taagagtgct ctagttttgc aatacaggac 660

atgctataaa aatggaaaga tgttgctttc tgagaggatc ttgctaccag tggaacagcc 720

actaaggatt ctgcagtgag agcagagggc cagctaagtg gtactctccc agagactgtc 780

tgactcacgc caccccctcc accttggaca caggacgctg tggtttctga gccaggtaca 840

gtgactcctt tcggtaagtg cagtggaagc tgtacactgc ccaggcaaag cgtccgggca 900

gcgtaggcgg gcgactcaga tcccagccag tggacttagc ccctgtttgc tcctccgata 960

actggggtga ccttggttaa tattcaccag cagcctcccc cgttgcccct ctggatccac 1020

tgcttaaata cggacgagga cagggccctg tctcctcagc ttcaggcacc accactgacc 1080

tgggacagtc aggtaagtat caaggttaca agacaggttt aaggagacca atagaaactg 1140

ggcttgtcga gacagagaag actcttgcgt ttctgatagg cacctattgg tcttactgac 1200

atccactttg cctttctctc cacaggttga attcgccgcc accatgtaca gaatgcagct 1260

gctgctgctc attgccctgt ctctggccct ggtcaccaat tctgaggtcc agctgcttga 1320

gagtggtggt ggactggttc agcctggtgg cagcctgaga ctgtcttgtg ctgcctctgg 1380

cttcaccttc agccactata tcatgatgtg ggtcagacag gcccctggca aaggcctgga 1440

atgggtgtca ggcatctaca gcagtggtgg catcacagtg tatgctgact ctgtgaaggg 1500

cagattcacc atcagcagag acaacagcaa gaacaccctg tacctgcaga tgaactccct 1560

gagagctgag gacacagcag tgtactactg tgcctataga agaattgggg tgcccagaag 1620

ggatgagttt gacatctggg gccagggcac catggttaca gtgtcctctg ccagcacaaa 1680

gggcccctct gtttttccac tggctcccag cagcaagagc accagtggtg gaacagctgc 1740

cctgggctgt ctggtcaagg attacttccc tgagcctgtg actgtgtcct ggaactctgg 1800

ggctctgact tctggggtgc acacctttcc agctgtgctg cagtcctctg gcctgtactc 1860

tctgtcctct gtggtcacag tgcctagctc tagcctgggc acacagacct acatctgcaa 1920

tgtgaaccac aagcctagca acaccaaggt ggacaagaga gtggaaccca agagctgtga 1980

caagacccac acctgtcctc catgtcctgc tccagaactg cttggaggcc cttctgtgtt 2040

cctgtttcct ccaaagccta aggacaccct gatgatcagc agaacccctg aagtgacctg 2100

tgtggtggtt gatgtgtccc atgaggaccc agaagtgaag ttcaattggt atgtggatgg 2160

ggttgaagtg cacaatgcca agaccaagcc tagagaggaa cagtacaaca gcacctacag 2220

agtggtttct gtgctgacag tgctgcacca ggactggctg aatggcaaag agtacaagtg 2280

caaggtgtcc aacaaggccc tgcctgctcc tattgagaaa accatctcca aggccaaggg 2340

ccagccaaga gaaccccagg tttacaccct gccacctagc agagaagaga tgaccaagaa 2400

ccaggtgtcc ctgacctgcc tggttaaggg cttctacccc tctgacattg ctgtggaatg 2460

ggagagcaat ggccagcctg aaaacaacta caagacaacc cctcctgtgc tggactctga 2520

tggctcattc ttcctgtaca gcaagctgac tgtggacaag tccagatggc agcagggaaa 2580

tgtgttcagc tgctctgtga tgcatgaggc cctgcacaac cactacaccc agaaaagtct 2640

gtctctgtcc cctggcagaa agagaagagg ctctggagaa ggcagaggct ccctgctgac 2700

atgtggggat gttgaagaga atcctgggcc tatgtatagg atgcaactgc tcctcctgat 2760

tgctctgagc ctggctcttg tgaccaactc tgacatccag atgacacaga gcccctccac 2820

actgtctgca tctgtgggag acagagtgac catcacctgt agagccagcc agtctatctc 2880

tagctggctg gcctggtatc agcaaaagcc tggcaaggcc cctaagctgc tgatctacaa 2940

ggccagcaca cttgagtcag gggtgccctc cagattttct ggctctggat ctggcacaga 3000

gttcaccctg accatcagct ccctgcagcc agatgacttt gccacctact actgccagca 3060

gtacaatacc tactggacct ttggccaggg aacaaaggtg gaaatcaaga gaacagtggc 3120

tgccccatct gtgttcatct tcccaccatc tgatgaacag ctgaagtctg gcactgcctc 3180

tgttgtgtgc ctgctgaaca acttttaccc cagagaagcc aaggtgcagt ggaaagtgga 3240

taatgccctg cagtctggca atagccaaga atctgtgaca gagcaggact ccaaggattc 3300

cacctacagc ctgagcagca ccctgacact gagcaaggct gactatgaga agcacaaagt 3360

gtatgcctgt gaagtgacac accagggact gagcagccca gtgaccaaga gcttcaacag 3420

gggagagtgc tgataactcg aggacggggt gaactacgcc tgaggatccg atcttttcc 3480

ctctgccaaa aattatgggg acatcatgaa gccccttgag catctgactt ctggctaata 3540

aaggaaattt attttcattg caatagtgtg ttggaatttt ttgtgtctct ca 3592

<210> 443
<211> 4083
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 443
aggctcagag gcacacagga gtttctgggc tcaccctgcc cccttccaac ccctcagttc 60

ccatcctcca gcagctgttt gtgtgctgcc tctgaagtcc acactgaaca aacttcagcc 120

tactcatgtc cctaaaatgg gcaaacattg caagcagcaa acagcaaaca cacagccctc 180

cctgcctgct gaccttggag ctggggcaga ggtcagagac ctctctgggc ccatgccacc 240

tccaacatcc actcgacccc ttggaatttc ggtggagagg agcagaggtt gtcctggcgt 300

ggtttaggta gtgtgagagg gccactacgg gtttaggctg cccatgtaag gaggcaaggc 360

ctggggacac ccgagatgcc tggttataat taacccagac atgtggctgc ccccccccc 420

cccaacacct gctgcctcta aaaataaccc tgtccctggt ggatcccact acgggtttag 480

gctgcccatg taaggaggca aggcctgggg acacccgaga tgcctggtta taattaaccc 540

agacatgtgg ctgccccccc ccccccccaac acctgctgcc tctaaaaata accctgtccc 600

tggtggatcc cactacgggt ttaggctgcc catgtaagga ggcaaggcct ggggacaccc 660

gagatgcctg gttataatta acccagacat gtggctgccc ccccccccc caacacctgc 720

tgcctctaaa aataaccctg tccctggtgg atcccctgca tgcgaagatc ttcgaacaag 780

gctgtggggg actgagggca ggctgtaaca ggcttggggg ccagggctta tacgtgcctg 840

ggactcccaa agtattactg ttccatgttc ccggcgaagg gccagctgtc ccccgccagc 900

tagactcagc acttagttta ggaaccagtg agcaagtcag cccttggggc agcccataca 960

aggccatggg gctgggcaag ctgcacgcct gggtccgggg tgggcacggt gcccgggcaa 1020

cgagctgaaa gctcatctgc tctcaggggc ccctccctgg ggacagcccc tcctggctag 1080

tcacaccctg taggctcctc tatataaccc aggggcacag gggctgccct cattctacca 1140

ccacctccac agcacagaca gacactcagg agccagccag cgtcgagatc ttgctaccag 1200

tggaacagcc actaaggatt ctgcagtgag agcagagggc cagctaagtg gtactctccc 1260

agagactgtc tgactcacgc caccccctcc accttggaca caggacgctg tggtttctga 1320

gccaggtaca gtgactcctt tcggtaagtg cagtggaagc tgtacactgc ccaggcaaag 1380

cgtccgggca gcgtaggcgg gcgactcaga tcccagccag tggacttagc ccctgtttgc 1440

tcctccgata actggggtga ccttggttaa tattcaccag cagcctcccc cgttgcccct 1500

ctggatccac tgcttaaata cggacgagga cagggccctg tctcctcagc ttcaggcacc 1560

accactgacc tgggacagtc aggtaagtat caaggttaca agacaggttt aaggagacca 1620

atagaaactg ggcttgtcga gacagagaag actcttgcgt ttctgatagg cacctattgg 1680

tcttactgac atccactttg cctttctctc cacaggttcg aattcgccgc caccatgtac 1740

agaatgcagc tgctgctgct cattgccctg tctctggccc tggtcaccaa ttctgaggtc 1800

cagctgcttg agagtggtgg tggactggtt cagcctggtg gcagcctgag actgtcttgt 1860

gctgcctctg gcttcacctt cagccactat atcatgatgt gggtcagaca ggcccctggc 1920

aaaggcctgg aatgggtgtc aggcatctac agcagtggtg gcatcacagt gtatgctgac 1980

tctgtgaagg gcagattcac catcagcaga gacaacagca agaacaccct gtacctgcag 2040

atgaactccc tgagagctga ggacacagca gtgtactact gtgcctatag aagaattggg 2100

gtgcccagaa gggatgagtt tgacatctgg ggccagggca ccatggttac agtgtcctct 2160

gccagcacaa agggcccctc tgtttttcca ctggctccca gcagcaagag caccagtggt 2220

ggaacagctg ccctgggctg tctggtcaag gattacttcc ctgagcctgt gactgtgtcc 2280

tggaactctg gggctctgac ttctggggtg cacacctttc cagctgtgct gcagtcctct 2340

ggcctgtact ctctgtcctc tgtggtcaca gtgcctagct ctagcctggg cacacagacc 2400

tacatctgca atgtgaacca caagcctagc aacaccaagg tggacaagag agtggaaccc 2460

aagagctgtg acaagaccca cacctgtcct ccatgtcctg ctccagaact gcttggaggc 2520

ccttctgtgt tcctgtttcc tccaaagcct aaggacaccc tgatgatcag cagaacccct 2580

gaagtgacct gtgtggtggt tgatgtgtcc catgaggacc cagaagtgaa gttcaattgg 2640

tatgtggatg gggttgaagt gcacaatgcc aagaccaagc ctagagagga acagtacaac 2700

agcacctaca gagtggtttc tgtgctgaca gtgctgcacc aggactggct gaatggcaaa 2760

gagtacaagt gcaaggtgtc caacaaggcc ctgcctgctc ctattgagaa aaccatctcc 2820

aaggccaagg gccagccaag agaaccccag gtttacaccc tgccacctag cagagaagag 2880

atgaccaaga accaggtgtc cctgacctgc ctggttaagg gcttctaccc ctctgacatt 2940

gctgtggaat gggagagcaa tggccagcct gaaaacaact acaagacaac ccctcctgtg 3000

ctggactctg atggctcatt cttcctgtac agcaagctga ctgtggacaa gtccagatgg 3060

cagcagggaa atgtgttcag ctgctctgtg atgcatgagg ccctgcacaa ccactacacc 3120

cagaaaagtc tgtctctgtc ccctggcaga aagagaagag gctctggaga aggcagaggc 3180

tccctgctga catgtgggga tgttgaagag aatcctgggc ctatgtatag gatgcaactg 3240

ctcctcctga ttgctctgag cctggctctt gtgaccaact ctgacatcca gatgacacag 3300

agcccctcca cactgtctgc atctgtggga gacagagtga ccatcacctg tagagccagc 3360

cagtctatct ctagctggct ggcctggtat cagcaaaagc ctggcaaggc ccctaagctg 3420

ctgatctaca aggccagcac acttgagtca ggggtgccct ccagattttc tggctctgga 3480

tctggcacag agttcaccct gaccatcagc tccctgcagc cagatgactt tgccacctac 3540

tactgccagc agtacaatac ctactggacc tttggccagg gaacaaaggt ggaaatcaag 3600

agaacagtgg ctgccccatc tgtgttcatc ttcccaccat ctgatgaaca gctgaagtct 3660

ggcactgcct ctgttgtgtg cctgctgaac aacttttacc ccagagaagc caaggtgcag 3720

tggaaagtgg ataatgccct gcagtctggc aatagccaag aatctgtgac agagcaggac 3780

tccaaggatt ccacctacag cctgagcagc accctgacac tgagcaaggc tgactatgag 3840

aagcacaaag tgtatgcctg tgaagtgaca caccagggac tgagcagccc agtgaccaag 3900

agcttcaaca ggggagagtg ctgataactc gaggacgggg tgaactacgc ctgaggatcc 3960

gatctttttc cctctgccaa aaattatggg gacatcatga agccccttga gcatctgact 4020

tctggctaat aaaggaaatt tattttcatt gcaatagtgt gttggaattt tttgtgtctc 4080

tca 4083

<210> 444
<211> 1353
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 444
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> 445
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 445
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> 446
<211> 294
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 446
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> 447
<211> 651
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 447
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> 448
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 448
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 gagaacagtg gctgccccat ctgtgttcat cttcccacca 360

tctgatgaac agctgaagtc tggcactgcc tctgttgtgt gcctgctgaa caacttctac 420

cctagagaag ccaaggtgca gtggaaggtt gacaatgccc tgcagtctgg caatagccaa 480

gaatctgtga cagagcagga ctccaaggat tccacctaca gcctgagcag caccctgaca 540

ctgagcaagg ctgactatga gaagcacaaa gtgtatgcct gtgaagtgac acaccaggga 600

ctgagcagcc cagtgaccaa gagcttcaac aggggagagt gc 642

<210> 449
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 449
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> 450
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 450
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> 451
<211> 4092
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 451
gacattgatt attgactagt tattaatagt aatcaattac ggggtcatta gttcatagcc 60

catatatgga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 120

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaatagggа 180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240

aagtgtatca tatgccaagt acgcccccta ttgacgtcaa tgacggtaaa tggcccgcct 300

ggcattatgc ccagtacatg accttatggg actttcctac ttggcagtac atctacgtat 360

tagtcatcgc tattaccatg gtcgaggtga gccccacgtt ctgcttcact ctccccatct 420

ccccccccctc cccaccccca attttgtatt tatttatttt ttaattattt tgtgcagcga 480

tgggggcggg ggggggggggg 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 cttctttttc ctacagctcc 1680

tgggcaacgt gctggttatt gtgctgtctc atcattttgg caaagaattc gccaccatgt 1740

acagaatgca gctgctgctg ctcattgccc tgtctctggc cctggtcacc aattctgaag 1800

tgcagctggt ggaaagtggt ggtggactgg tgcagcctgg cagaagcctg agactgtctt 1860

gtgctgcctc tggcttcacc tttgatgact atgccatgca ctgggtcaga caggcccctg 1920

gcaaaggact ggaatgggtg tcagccatca cctggaactc tggccacatt gactatgctg 1980

actctgtgga aggcagattc accatcagca gagacaatgc caagaacagc ctgtacctgc 2040

agatgaactc cctgagagct gaggacacag cagtgtacta ctgtgccaag gtgtcctacc 2100

tgagcacagc cagcagcctg gattattggg gccagggcac actggttaca gtgtcctctg 2160

ccagcacaaa gggcccctct gtttttccac tggctcccag cagcaagagc accagtggtg 2220

gaacagctgc cctgggctgt ctggtcaagg attacttccc tgagcctgtg acagtgtctt 2280

ggaactcagg ggctctgacc tctggggtgc acacatttcc agctgtgctg cagtcctctg 2340

gcctgtactc tctgtcctct gtggtcacag tgcctagctc tagcctgggc acccagacct 2400

acatctgcaa tgtgaaccac aagcctagca acaccaaggt ggacaagaag gtggaaccca 2460

agagctgtga caagacccac acctgtcctc catgtcctgc tccagaactg cttggaggcc 2520

cttctgtgtt cctgtttcct ccaaagccta aggacaccct gatgatcagc agaacccctg 2580

aagtgacctg tgtggtggtt gatgtgtccc atgaggaccc agaagtgaag ttcaattggt 2640

atgtggatgg ggttgaagtg cacaatgcta agaccaagcc tagagaggaa cagtacaaca 2700

gcacctacag agtggtgtct gtgctgacag tgctgcatca ggactggctg aatggcaaag 2760

agtacaagtg caaagtgtcc aacaaggccc tgcctgctcc tattgagaaa accatctcca 2820

aggccaaggg ccagccaaga gaaccccagg tttacacact gccacctagc agagatgagc 2880

tgaccaagaa ccaggtgtcc ctgacctgcc tggttaaggg cttctacccc tctgacattg 2940

ctgtggaatg ggagagcaat ggccagcctg agaacaacta caagacaacc cctcctgtgc 3000

tggactctga tggctcattc ttcctgtaca gcaagctgac tgtggacaag tccagatggc 3060

agcaggggaa tgtgttcagc tgctctgtga tgcatgaggc cctgcacaac cactacaccc 3120

agaaaagtct gagtctgagc cctggcaaga gaaagagaag aggctctgga gaaggcagag 3180

gctccctgct gacatgtggg gatgttgaag agaatcctgg gcctatgtat aggatgcaac 3240

tgctcctcct gattgctctg agcctggctc ttgtgaccaa ctctgacatc cagatgacac 3300

agagccctag cagcctgtct gcttctgtgg gagacagagt gaccatcaca tgcagagcca 3360

gccagggaat cagaaactac ctggcctggt atcagcaaaa gcctggcaag gcccctaagc 3420

tgctgatcta tgcagccagc acactgcagt caggggtgcc aagcagattt tcaggctctg 3480

gctctggcac agacttcacc ctgaccattt ctagcctgca gcctgaggat gtggccacct 3540

actactgcca gagatacaac agagccccat acacctttgg acagggcaca aaggtggaaa 3600

tcaagagaac agtggctgcc ccatctgtgt tcatcttccc accatctgat gaacagctga 3660

agtctggcac tgcctctgtt gtgtgcctgc tgaacaactt ctaccctaga gaagccaagg 3720

tgcagtggaa ggttgacaat gccctgcagt ctggcaatag ccaagaatct gtgacagagc 3780

aggactccaa ggattccacc tacagcctga gcagcaccct gacactgagc aaggctgact 3840

atgagaagca caaagtgtat gcctgtgaag tgacacacca gggactgagc agcccagtga 3900

ccaagagctt caacagggga gagtgctgat aactcgagga cggggtgaac tacgcctgag 3960

gatccgatct ttttccctct gccaaaaatt atggggacat catgaagccc cttgagcatc 4020

tgacttctgg ctaataaagg aaatttattt tcattgcaat agtgtgttgg aatttttgt 4080

gtctctcact cg 4092

<210> 452
<211> 2193
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 452
atgtacagaa tgcagctgct gctgctcatt gccctgtctc tggccctggt caccaattct 60

gaagtgcagc tggtggaaag tggtggtgga ctggtgcagc ctggcagaag cctgagactg 120

tcttgtgctg cctctggctt cacctttgat gactatgcca tgcactgggt cagacaggcc 180

cctggcaaag gactggaatg ggtgtcagcc atcacctgga actctggcca cattgactat 240

gctgactctg tggaaggcag attcaccatc agcagagaca atgccaagaa cagcctgtac 300

ctgcagatga actccctgag agctgaggac acagcagtgt actactgtgc caaggtgtcc 360

tacctgagca cagccagcag cctggattat tggggccagg gcacactggt tacagtgtcc 420

tctgccagca caaagggccc ctctgttttt ccactggctc ccagcagcaa gagcaccagt 480

ggtggaacag ctgccctggg ctgtctggtc aaggattact tccctgagcc tgtgacagtg 540

tcttggaact caggggctct gacctctggg gtgcacacat ttccagctgt gctgcagtcc 600

tctggcctgt actctctgtc ctctgtggtc acagtgccta gctctagcct gggcacccag 660

acctacatct gcaatgtgaa ccacaagcct agcaacacca aggtggacaa gaaggtggaa 720

cccaagagct gtgacaagac ccacacctgt cctccatgtc ctgctccaga actgcttgga 780

ggcccttctg tgttcctgtt tcctccaaag cctaaggaca ccctgatgat cagcagaacc 840

cctgaagtga cctgtgtggt ggttgatgtg tcccatgagg acccagaagt gaagttcaat 900

tggtatgtgg atggggttga agtgcacaat gctaagacca agcctagaga ggaacagtac 960

aacagcacct acagagtggt gtctgtgctg acagtgctgc atcaggactg gctgaatggc 1020

aaagagtaca agtgcaaagt gtccaacaag gccctgcctg ctcctattga gaaaaccatc 1080

tccaaggcca agggccagcc aagagaaccc caggtttaca cactgccacc tagcagagat 1140

gagctgacca agaaccaggt gtccctgacc tgcctggtta agggcttcta cccctctgac 1200

attgctgtgg aatgggagag caatggccag cctgagaaca actacaagac aacccctcct 1260

gtgctggact ctgatggctc attcttcctg tacagcaagc tgactgtgga caagtccaga 1320

tggcagcagg ggaatgtgtt cagctgctct gtgatgcatg aggccctgca caaccactac 1380

acccagaaaa gtctgagtct gagccctggc aagagaaaga gaagaggctc tggagaaggc 1440

agaggctccc tgctgacatg tggggatgtt gaagagaatc ctgggcctat gtataggatg 1500

caactgctcc tcctgattgc tctgagcctg gctcttgtga ccaactctga catccagatg 1560

acacagagcc ctagcagcct gtctgcttct gtgggagaca gagtgaccat cacatgcaga 1620

gccagccagg gaatcagaaa ctacctggcc tggtatcagc aaaagcctgg caaggcccct 1680

aagctgctga tctatgcagc cagcacactg cagtcagggg tgccaagcag attttcaggc 1740

tctggctctg gcacagactt caccctgacc atttctagcc tgcagcctga ggatgtggcc 1800

acctactact gccagagata caacagagcc ccatacacct ttggacaggg cacaaaggtg 1860

gaaatcaaga gaacagtggc tgccccatct gtgttcatct tcccaccatc tgatgaacag 1920

ctgaagtctg gcactgcctc tgttgtgtgc ctgctgaaca acttctaccc tagagaagcc 1980

aaggtgcagt ggaaggttga caatgccctg cagtctggca atagccaaga atctgtgaca 2040

gagcaggact ccaaggattc cacctacagc ctgagcagca ccctgacact gagcaaggct 2100

gactatgaga agcacaaagt gtatgcctgt gaagtgacac accagggact gagcagccca 2160

gtgaccaaga gcttcaacag gggagagtgc tga 2193

<210> 453
<211> 3423
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 453
gacattgatt attgactagt tattaatagt aatcaattac ggggtcatta gttcatagcc 60

catatatgga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 120

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaatagggа 180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240

aagtgtatca tatgccaagt acgcccccta ttgacgtcaa tgacggtaaa tggcccgcct 300

ggcattatgc ccagtacatg accttatggg actttcctac ttggcagtac atctacgtat 360

tagtcatcgc tattaccatg gtcgaggtga gccccacgtt ctgcttcact ctccccatct 420

ccccccccctc cccaccccca attttgtatt tatttatttt ttaattattt tgtgcagcga 480

tgggggcggg gggggggggg gggcgcgcgc caggcggggc ggggcggggc gaggggcggg 540

gcggggcgag gcggagaggt gcggcggcag ccaatcagag cggcgcgctc cgaaagtttc 600

cttttatggc gaggcggcgg cggcggcggc cctataaaaa gcgaagcgcg cggcgggcgg 660

gagtcgctgc gcgctgcctt cgccccgtgc cccgctccgc cgccgcctcg cgccgcccgc 720

cccggctctg actgaccgcg ttactcccac aggtgagcgg gcgggacggc ccttctcctc 780

cgggctgtaa ttagcgcttg gtttaatgac ggcttgtttc ttttctgtgg ctgcgtgaaa 840

gccttgaggg gctccgggag ggccctttgt gcgggggggag cggctcgggg ggtgcgtgcg 900

tgtgtgtgtg cgtggggagc gccgcgtgcg gctccgcgct gcccggcggc tgtgagcgct 960

gcgggcgcgg cgcggggctt tgtgcgctcc gcagtgtgcg cgaggggagc gcggccgggg 1020

gcggtgcccc gcggtgcggg gggggctgcg aggggaacaa aggctgcgtg cggggtgtgt 1080

gcgtgggggg gtgagcaggg ggtgtgggcg cgtcggtcgg gctgcaaccc cccctgcacc 1140

cccctccccg agttgctgag cacggcccgg cttcgggtgc ggggctccgt acggggcgtg 1200

gcgcggggct cgccgtgccg ggcgggggggt ggcggcaggt gggggtgccg ggcggggcgg 1260

ggccgcctcg ggccggggag ggctcggggg aggggcgcgg cggcccccgg agcgccggcg 1320

gctgtcgagg cgcggcgagc cgcagccatt gccttttatg gtaatcgtgc gagagggcgc 1380

agggacttcc tttgtcccaa atctgtgcgg agccgaaatc tgggaggcgc cgccgcaccc 1440

cctctagcgg gcgcggggcg aagcggtgcg gcgccggcag gaaggaaatg ggcggggagg 1500

gccttcgtgc gtcgccgcgc cgccgtcccc ttctccctct ccagcctcgg ggctgtccgc 1560

ggggggacgg ctgccttcgg gggggacggg gcagggcggg gttcggcttc tggcgtgtga 1620

ccggcggctc tagagcctct gctaaccatg ttcatgcctt cttctttttc ctacagctcc 1680

tgggcaacgt gctggttatt gtgctgtctc atcattttgg caaagaattc gccaccatgt 1740

acagaatgca gctgctgctg ctcattgccc tgtctctggc cctggtcacc aattctgaag 1800

tgcagctggt ggaaagtggt ggtggactgg tgcagcctgg cagaagcctg agactgtctt 1860

gtgctgcctc tggcttcacc tttgatgact atgccatgca ctgggtcaga caggcccctg 1920

gcaaaggact ggaatgggtg tcagccatca cctggaactc tggccacatt gactatgctg 1980

actctgtgga aggcagattc accatcagca gagacaatgc caagaacagc ctgtacctgc 2040

agatgaactc cctgagagct gaggacacag cagtgtacta ctgtgccaag gtgtcctacc 2100

tgagcacagc cagcagcctg gattattggg gccagggcac actggttaca gtgtcctctg 2160

ccagcacaaa gggcccctct gtttttccac tggctcccag cagcaagagc accagtggtg 2220

gaacagctgc cctgggctgt ctggtcaagg attacttccc tgagcctgtg acagtgtctt 2280

ggaactcagg ggctctgacc tctggggtgc acacatttcc agctgtgctg cagtcctctg 2340

gcctgtactc tctgtcctct gtggtcacag tgcctagctc tagcctgggc acccagacct 2400

acatctgcaa tgtgaaccac aagcctagca acaccaaggt ggacaagaag gtggaaccca 2460

agagctgtga caagacccac agaaagagaa gaggctctgg agaaggcaga ggctccctgc 2520

tgacatgtgg ggatgttgaa gagaatcctg ggcctatgta taggatgcaa ctgctcctcc 2580

tgattgctct gagcctggct cttgtgacca actctgacat ccagatgaca cagagcccta 2640

gcagcctgtc tgcttctgtg ggagacagag tgaccatcac atgcagagcc agccagggca 2700

tcagaaacta cctggcctgg tatcagcaga agccaggcaa ggcccctaag ctgctgatct 2760

atgcagccag cacactgcag agtggggtgc caagcagatt ttcaggctct ggctctggca 2820

cagacttcac cctgaccatt tctagcctgc agcctgagga tgtggccacc tactactgcc 2880

agagatacaa cagagcccca tacacctttg gacagggcac aaaggtggaa atcaagagaa 2940

cagttgcagc accctcagtt ttcatcttcc ccccctcaga tgaacagctg aagtctggca 3000

ctgcctctgt tgtgtgcctg ctgaacaact tctaccccag agaagccaag gtgcagtgga 3060

aggttgacaa tgccctgcag tcaggcaaca gccaagaatc tgtgactgaa caggattcca 3120

aggatagcac ctacagcctg agcagcaccc tgacactgag caaggctgac tatgagaagc 3180

acaaagtgta tgcctgtgaa gtgacccacc agggactgag cagcccagtg accaagagct 3240

tcaacagggg agagtgctga taactcgagg acggggtgaa ctacgcctga ggatccgatc 3300

tttttccctc tgccaaaaat tatggggaca tcatgaagcc ccttgagcat ctgacttctg 3360

gctaataaag gaaatttatt ttcattgcaa tagtgtgttg gaatttttg tgtctctcac 3420

tcg 3423

<210> 454
<211> 1524
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 454
atgtacagaa tgcagctgct gctgctcatt gccctgtctc tggccctggt caccaattct 60

gaagtgcagc tggtggaaag tggtggtgga ctggtgcagc ctggcagaag cctgagactg 120

tcttgtgctg cctctggctt cacctttgat gactatgcca tgcactgggt cagacaggcc 180

cctggcaaag gactggaatg ggtgtcagcc atcacctgga actctggcca cattgactat 240

gctgactctg tggaaggcag attcaccatc agcagagaca atgccaagaa cagcctgtac 300

ctgcagatga actccctgag agctgaggac acagcagtgt actactgtgc caaggtgtcc 360

tacctgagca cagccagcag cctggattat tggggccagg gcacactggt tacagtgtcc 420

tctgccagca caaagggccc ctctgttttt ccactggctc ccagcagcaa gagcaccagt 480

ggtggaacag ctgccctggg ctgtctggtc aaggattact tccctgagcc tgtgacagtg 540

tcttggaact caggggctct gacctctggg gtgcacacat ttccagctgt gctgcagtcc 600

tctggcctgt actctctgtc ctctgtggtc acagtgccta gctctagcct gggcacccag 660

acctacatct gcaatgtgaa ccacaagcct agcaacacca aggtggacaa gaaggtggaa 720

cccaagagct gtgacaagac ccacagaaag agaagaggct ctggagaagg cagaggctcc 780

ctgctgacat gtggggatgt tgaagagaat cctgggccta tgtataggat gcaactgctc 840

ctcctgattg ctctgagcct ggctcttgtg accaactctg acatccagat gacacagagc 900

cctagcagcc tgtctgcttc tgtgggagac agagtgacca tcacatgcag agccagccag 960

ggcatcagaa actacctggc ctggtatcag cagaagccag gcaaggcccc taagctgctg 1020

atctatgcag ccagcacact gcagagtggg gtgccaagca gattttcagg ctctggctct 1080

ggcacagact tcaccctgac catttctagc ctgcagcctg aggatgtggc cacctactac 1140

tgccagagat acaacagagc cccatacacc tttggacagg gcacaaaggt ggaaatcaag 1200

agaacagttg cagcaccctc agttttcatc ttcccccccct cagatgaaca gctgaagtct 1260

ggcactgcct ctgttgtgtg cctgctgaac aacttctacc ccagagaagc caaggtgcag 1320

tggaaggttg acaatgccct gcagtcaggc aacagccaag aatctgtgac tgaacaggat 1380

tccaaggata gcacctacag cctgagcagc accctgacac tgagcaaggc tgactatgag 1440

aagcacaaag tgtatgcctg tgaagtgacc caccagggac tgagcagccc agtgaccaag 1500

agcttcaaca ggggagagtg ctga 1524