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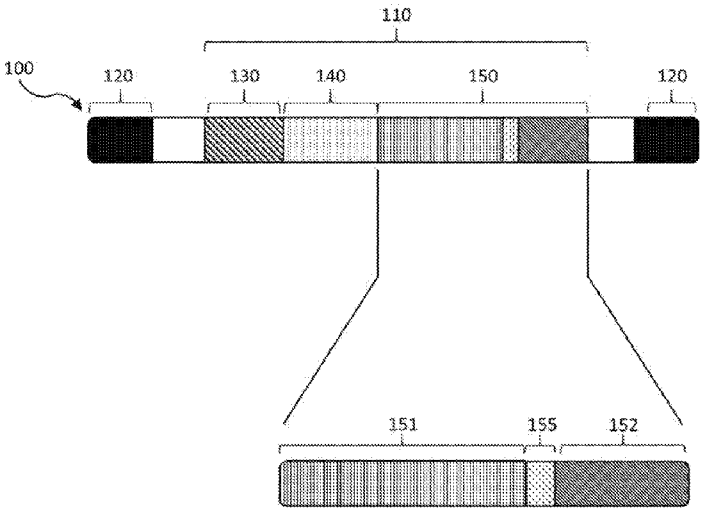
FIG. 2



(57) Abstract: The invention provides compositions and methods for the preparation, manufacture and therapeutic use of viral vectors, such as adeno-associated virus (AAV) particles having viral genomes encoding one or more antibodies or antibody fragments or antibody-like polypeptides, for the prevention and/or treatment of diseases and/or disorders.

[Continued on next page]

WO 2017/189963 A1

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COMPOSITIONS FOR THE TREATMENT OF DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to US Provisional Patent Application No. 62/329,457, filed on April 29, 2016, entitled Compositions for the Treatment of Disease, US Provisional Patent Application No. 62/367,351, filed on July 27, 2016, entitled Compositions for the Treatment of Disease, and US Provisional Patent Application No. 62/433,973, filed on December 14, 2016, entitled Compositions for the Treatment of Disease, the contents of each of which are herein incorporated by reference in their entireties.

REFERENCE TO THE SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing file, entitled 20571301PCTSL.txt, was created on April 27, 2017, and is 7,120,305 bytes in size. The information in electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] The invention relates to compositions and methods for vectored antibody delivery (VAD).

BACKGROUND OF THE INVENTION

[0004] Antibody-based therapies have been developed for a wide variety of diseases, disorders and conditions, including infectious and non-infectious diseases. The U.S. Food and Drug Administration (FDA) has approved antibodies for treatment of cancers, autoimmune and immune system disorders, ocular diseases, nervous system diseases, inflammations, and infections, amongst many others. Naturally, antibodies are components of the adaptive immune response and they function by recognizing specific foreign antigens and stimulating humoral immunity responses. As a consequence, antibodies may be applied to the treatment, prevention, management, diagnosis and research of diseases, disorders, and/or conditions.

[0005] Antibodies have relatively short half-lives and this presents an ongoing and long-felt challenge for antibody-based therapies. In order to achieve a sufficiently high concentration of an antibody for long lasting therapeutic effects, antibody therapies are traditionally delivered by repeated administration, e.g. by multiple injections. This dosing regimen results in an inconsistent level of antibody throughout the treatment period, limited efficiency per administration, high cost of administration and consumption of the antibody. Hence, there remains a need in the art for delivery of antibodies and antibody-based therapeutics through alternative routes or modalities of administration.

[0006] One such alternative route of administration is by expression vectors (e.g. plasmid or viral vector), including but not limited to, adeno-associated viral vectors (AAVs). Adeno-associated viral vectors are widely used in gene therapy approaches due to a number of advantageous features. As dependoparvoviruses, AAV are non-replicating in infected cells and therefore not associated with any known disease. Further, AAVs may be introduced to a wide variety of host cells, do not integrate into the genome of the host cell, and are capable of infecting both quiescent and dividing cells. AAVs transduce non-replicating and long-lived cells *in vivo*, resulting in long term expression of the protein of interest. Further, AAVs can be manipulated with cellular and molecular biology techniques to produce non-toxic particles carrying a payload encoded in the AAV viral genome that can be delivered to a target tissue or set of cells with limited or no side-effects. Given the foregoing, the use of AAVs for vectored antibody delivery (VAD) would allow for longer lasting efficacy, fewer dose treatments, and more consistent levels of the antibody throughout the treatment period.

[0007] In vectored antibody delivery (VAD), an AAV is used as the delivery modality for a nucleic acid sequence encoding the antibody, which results in *in vivo* expression of the encoded payload, e.g., functional antibody.

[0008] The mechanism underlying VAD is thought to proceed through the following steps. First, the AAV vector enters the cell via endocytosis, then escapes from the endosomal compartment and is transported to the nucleus wherein the viral genome is released and converted into a double-stranded episomal molecule of DNA by the host. The transcriptionally active episome results in the expression of encoded antibodies that may then be secreted from the cell into the circulation. VAD may therefore enable continuous, sustained and long-term delivery of antibodies administered by a single injection of an AAV particle.

[0009] Previous studies of an AAV-mediated antibody technique known as vectored immunoprophylaxis (VIP) have focused on neutralization of human immunodeficiency virus (HIV) (see, e.g. Johnson et al., 2009, Nature Med., 15, 901 – 906, Saunders et al., 2015, J. Virol., 89(16), 8334-8345, Balasz et al., 2012, Nature 481, 81–84, the contents of which are incorporated herein by reference in their entirety). Balasz *et al.* reported a long-term, even lifelong, expression of monoclonal antibody at high concentration from a single intramuscular administration in mice that resulted in full protection against HIV infection. AAV-mediated VIP has also been demonstrated against influenza strains (see, e.g. Balasz, et al. Nat. Biotechnol., 2013, 31(7):647-52) and *Plasmodium Falciparum*, a sporozoite causing malaria infection (see, e.g. Deal at al., 2014, PNAS, 111 (34), 12528-12532), as well as cancer, RSV and drug addiction (see, e.g. review by Schnepp and Johnson, Microbiol. Spectrum 2(4), 2014). Though promising,

these studies emphasize efforts to merely prevent disease. There still remains a need for improved methods of prevention, and new antibody-mediated therapies for research, diagnosis, and treatment of disease.

[00010] The present invention addresses this need by providing novel AAV particles having viral genomes engineered to encode antibodies and antibody-based compositions and methods of using these constructs (e.g., VAD) for the treatment, prevention, diagnosis and research of diseases, disorders and/or conditions. The present invention further embraces optimized AAV particles for delivery of nucleic acids (e.g., viral genomes) encoding antibodies and antibody-based compositions to a subject in need thereof.

SUMMARY OF THE INVENTION

[0010] The invention provides AAV particles comprising a capsid and a viral genome, said viral genome comprising at least one inverted terminal repeat (ITR) region and a payload region, said payload region comprising a regulatory sequence operably linked to at least a first nucleic acid segment, said first nucleic acid segment encoding one or more polypeptides given in Table 3, variants and fragments thereof. The capsid of the AAV particle may be any of the serotypes described herein and/or described in Table 1.

[0011] In one aspect, the first nucleic acid segment may encode one or more polypeptides such as, but not limited to, an antibody heavy chain, an antibody light chain, a linker, and combinations thereof. The first nucleic acid segment may encode one or more polypeptides which is humanized. As a non-limiting example, the first nucleic acid segment encodes from 5' to 3', an antibody heavy chain, a linker, and an antibody light chain. As another non-limiting example, the first nucleic acid segment encodes from 5' to 3', an antibody light chain, a linker, and an antibody heavy chain. As yet another non-limiting example, the first nucleic acid segment encodes one or more antibody heavy chains. As yet another non-limiting example, the first nucleic acid segment encodes one or more antibody light chains.

[0012] In one aspect, the first nucleic acid segment encodes an antibody, having at least 95% identity to any of the sequences of Table 3 or Table 4.

[0013] In one aspect the regulatory sequence may comprise a promoter such as but not limited to, human elongation factor 1α-subunit (EF1α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β-actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC). Tissue-specific expression elements can be used to restrict expression to certain cell types such as, but not limited to, muscle specific promoters, B cell promoters, monocyte promoters, leukocyte promoters, macrophage promoters, pancreatic acinar cell promoters, endothelial cell promoters, lung tissue promoters, astrocyte promoters, or nervous

system promoters which can be used to restrict expression to neurons, astrocytes, or oligodendrocytes.

[0014] In one aspect, the linker in the viral genome is selected from one or more of the linkers given in Table 2.

[0015] In one aspect, the AAV particles described herein may comprise a viral genome which is single stranded.

[0016] In one aspect, the AAV particles described herein may comprise a viral genome which is self-complementary.

[0017] In one aspect, the AAV particles described herein may comprise a viral genome comprising at least one intron sequence.

[0018] In one aspect, the AAV particles described herein may comprise a viral genome comprising at least one stuffer sequence to adjust the length of the viral genome to increase efficacy and/or efficiency.

[0019] In one aspect, the AAV particles described herein may comprise at least one region which has been codon optimized. As a non-limiting example, the viral genome may be codon optimized. As another non-limiting example, the first nucleic acid segment is codon-optimized.

[0020] In one aspect, the AAV particles described herein may comprise a viral genome with 2 ITR regions. At least one of the ITR regions may be derived from the same or different parental serotype of the capsid. As a non-limiting example, at least one ITR region is derived from AAV2.

[0021] In one aspect, the AAV particles comprise a viral genome which comprises a second nucleic acid segment. The second nucleic acid segment may encode an aptamer, siRNA, saRNA, ribozyme, microRNA, mRNA or combination thereof.

[0022] In one aspect, the AAV particles comprise a viral genome which comprises a second nucleic acid segment encoding an siRNA designed to target the mRNA that encodes the target of the antibody encoded by the first nucleic acid segment.

[0023] In one aspect, the AAV particles comprise a viral genome which comprises a second nucleic acid segment encoding a microRNA, the microRNA is selected to target the mRNA that encodes the target of the antibody encoded by the first nucleic acid segment.

[0024] In one aspect, the AAV particles comprise a viral genome which comprises a second nucleic acid segment encoding an mRNA, the mRNA encodes one or more peptides inhibitors of the same target of the antibody encoded by the first nucleic acid segment.

[0025] In one aspect, the AAV particles comprise a viral genome which comprises a third nucleic acid segment. The third nucleic acid segment may encode a nuclear export signal, a

polynucleotide or polypeptide which acts as a regulator of expression of the viral genome in which it is encoded, a polynucleotide or polypeptide which acts as a regulator of expression of the payload region of the viral genome in which it is encoded, and/or a polynucleotide or polypeptide which acts as a regulator of expression of the first nucleic acid segment of the payload region of the viral genome in which it is encoded.

[0026] The invention provides AAV particles comprising a capsid and a viral genome, said viral genome comprising at least one inverted terminal repeat (ITR) region and a payload region comprising a regulatory sequence operably linked to at least a first nucleic acid segment, the first nucleic acid segment encoding a bispecific antibody derived from any of the sequences listed in Table 3 or portions or fragments thereof.

[0027] The invention provides methods of producing a functional antibody in a subject in need thereof, comprising administering to a subject the AAV particles described herein. The level or amount of the functional antibody in the target cell or tissue after administration to the subject may be from about .001 μg/mL to 100 mg/mL. The functional antibody may be encoded by a single first nucleic acid segment of a viral genome within the AAV particle. The functional antibody may be encoded by two different viral genomes, the two different viral genomes may be packaged in separate capsids.

[0028] The invention provides a pharmaceutical composition comprising an AAV particle described herein in a pharmaceutically acceptable excipient. As a non-limiting example, the pharmaceutically acceptable excipient is saline. As a non-limiting example, the pharmaceutically acceptable excipient is 0.001% pluronic in saline.

[0029] The invention provides methods of producing a functional antibody in a subject in need thereof, comprising administering to a subject the AAV particles described herein by a delivery route such as, but not limited to, enteral (into the intestine), gastroenteral, epidural (into the dura mater), oral (by way of the mouth), transdermal, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal, (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intra-arterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraparenchymal (into brain tissue), intraperitoneal, (infusion or injection into the peritoneum), intravesical infusion, intravitreal (through the eye), intracavernous injection (into a pathologic cavity), intracavitary (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion

through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival, cutaneous, dental (to a tooth or teeth), electro-osmosis, endocervical, endosinusial, endotracheal, extracorporeal, hemodialysis, infiltration, interstitial, intra-abdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracoronal, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the corporus cavernosa of the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within the stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone), intrameningeal (within the meninges), intramyocardial (within the myocardium), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aurus media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique (topical route administration which is then covered by a dressing which occludes the area), ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), soft tissue, subarachnoid, subconjunctival, submucosal, topical, transplacental (through or across the placenta), transtracheal (through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the

ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photopheresis, and spinal.

[0030] The invention provides methods of treating and/or preventing a disease or disorder in a subject comprising administering to the subject an AAV particle described herein. The administration may be at a prophylactically effective dose such as, but not limited to, from about 1 μg/mL to about 500 μg/mL of expressed polypeptide or 1x10e4 to 1x10e16 VG/mL from the pharmaceutical composition. The pharmaceutical composition may be administered at least once. The pharmaceutical composition may be administered daily, weekly, monthly, or yearly. The pharmaceutical composition may be co-administered as part of a combination therapy.

[0031] The invention provides methods of producing an antibody in a subject by administering the AAV particles described herein, where the antibody is not a virus neutralizing antibody.

[0032] The invention provides methods of producing an antibody in a subject by administering the AAV particles described herein, where the antibody is not an HIV or HCV virus neutralizing antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] The foregoing and other objects, features, and advantages will be apparent from the following description of particular embodiments of the invention, as illustrated in the accompanying drawings. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the invention.

[0034] FIG. 1 is a schematic of vectored antibody delivery.

[0035] FIG. 2 is a schematic of a viral genome of the invention.

[0036] FIG. 3 is a schematic of payload regions. Figure discloses SEQ ID NO: 4321.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOSITIONS OF THE INVENTION

[0037] According to the present invention, compositions for delivering functional antibodies and/or antibody-based compositions by adeno-associated viruses (AAVs) are provided. AAV particles of the invention may be provided via any of several routes of administration, to a cell, tissue, organ, or organism, *in vivo*, *ex vivo*, or *in vitro*.

[0038] As used herein, an "AAV particle" is a virus which comprises a viral genome with at least one payload region and at least one inverted terminal repeat (ITR) region.

[0039] As used herein, "viral genome" or "vector genome" refers to the nucleic acid sequence(s) encapsulated in an AAV particle. Viral genomes comprise at least one payload

region encoding polypeptides of the invention, e.g., antibodies, antibody-based compositions or fragments thereof.

[0040] As used herein, a "payload" or "payload region" is any nucleic acid molecule which encodes one or more polypeptides of the invention. At a minimum, a payload region comprises nucleic acid sequences that encode an antibody, an antibody-based composition, or a fragment thereof, but may also optionally comprise one or more functional or regulatory elements to facilitate transcriptional expression and/or polypeptide translation.

[0041] The nucleic acid sequences and polypeptides disclosed herein may be engineered to contain modular elements and/or sequence motifs assembled to enable expression of the antibodies or antibody-based compositions of the invention. In some embodiments, the nucleic acid sequence comprising the payload region may comprise one or more of a promoter region, an intron, a Kozak sequence, an enhancer, or a polyadenylation sequence. Payload regions of the invention typically encode antibodies or antibody based compositions, which may include an antibody heavy chain domain, an antibody light chain domain, both antibody heavy and light chain domains, or fragments of the foregoing in combination with each other or in combination with other polypeptide moieties. In some cases, payload regions may also encode one or more linkers or joining regions between antibody heavy and light chain domains or fragments. The order of expression, structural position, or concatemer count (heavy chain, light chain, or linker) may be different within or among different payload regions. The identity, position and number of linkers expressed by payload regions may also vary.

[0042] The payload regions of the invention may be delivered to one or more target cells, tissues, organs, or organisms within the viral genome of an AAV particle.

Adeno-associated viruses (AAVs) and AAV particles

[0043] Viruses of the Parvoviridae family are small non-enveloped icosahedral capsid viruses characterized by a single stranded DNA genome. Parvoviridae family viruses consist of two subfamilies: Parvovirinae, which infect vertebrates, and Densovirinae, which infect invertebrates. Due to its relatively simple structure, easily manipulated using standard molecular biology techniques, this virus family is useful as a biological tool. The genome of the virus may be modified to contain a minimum of components for the assembly of a functional recombinant virus, or viral particle, which is loaded with or engineered to express or deliver a desired payload, which may be delivered to a target cell, tissue, organ, or organism.

[0044] The parvoviruses and other members of the Parvoviridae family are generally described in Kenneth I. Berns, "Parvoviridae: The Viruses and Their Replication," Chapter 69 in

FIELDS VIROLOGY (3d Ed. 1996), the contents of which are incorporated by reference in their entirety.

[0045] The Parvoviridae family comprises the Dependovirus genus which includes adeno-associated viruses (AAV) capable of replication in vertebrate hosts including, but not limited to, human, primate, bovine, canine, equine, and ovine species.

[0046] The AAV vector genome is a linear, single-stranded DNA (ssDNA) molecule approximately 5,000 nucleotides (nt) in length. The AAV viral genome can comprise a payload region and at least one inverted terminal repeat (ITR) or ITR region. ITRs traditionally flank the coding nucleotide sequences for the non-structural proteins (encoded by Rep genes) and the structural proteins (encoded by capsid genes or Cap genes). While not wishing to be bound by theory, an AAV viral genome typically comprises two ITR sequences. The AAV vector genome comprises a characteristic T-shaped hairpin structure defined by the self-complementary terminal 145 nt of the 5' and 3' ends of the ssDNA which form an energetically stable double stranded region. The double stranded hairpin structures comprise multiple functions including, but not limited to, acting as an origin for DNA replication by functioning as primers for the endogenous DNA polymerase complex of the host viral replication cell.

[0047] In addition to the encoded heterologous payload, AAV vectors may comprise the viral genome, in whole or in part, of any naturally occurring and/or recombinant AAV serotype nucleotide sequence or variant. AAV variants may have sequences of significant homology at the nucleic acid (genome or capsid) and amino acid levels (capsids), to produce constructs which are generally physical and functional equivalents, replicate by similar mechanisms, and assemble by similar mechanisms. Chiorini et al., J. Vir. 71: 6823-33(1997); Srivastava et al., J. Vir. 45:555-64 (1983); Chiorini et al., J. Vir. 73:1309-1319 (1999); Rutledge et al., J. Vir. 72:309-319 (1998); and Wu et al., J. Vir. 74: 8635-47 (2000), the contents of each of which are incorporated herein by reference in their entirety.

[0048] In one embodiment, AAV particles of the present invention are recombinant AAV viral vectors which are replication defective and lacking sequences encoding functional Rep and Cap proteins within their viral genome. These defective AAV vectors may lack most or all parental coding sequences and essentially carry only one or two AAV ITR sequences and the nucleic acid of interest for delivery to a cell, a tissue, an organ, or an organism.

[0049] In one embodiment, the viral genome of the AAV particles of the present invention comprise at least one control element which provides for the replication, transcription, and translation of a coding sequence encoded therein. Not all of the control elements need always be present as long as the coding sequence is capable of being replicated, transcribed, and/or

translated in an appropriate host cell. Non-limiting examples of expression control elements include sequences for transcription initiation and/or termination, promoter and/or enhancer sequences, efficient RNA processing signals such as splicing and polyadenylation signals, sequences that stabilize cytoplasmic mRNA, sequences that enhance translation efficacy (e.g., Kozak consensus sequence), sequences that enhance protein stability, and/or sequences that enhance protein processing and/or secretion.

[0050] According to the present invention, AAV particles for use in therapeutics and/or diagnostics comprise a virus that has been distilled or reduced to the minimum components necessary for transduction of a nucleic acid payload or cargo of interest. In this manner, AAV particles are engineered as vehicles for specific delivery while lacking the deleterious replication and/or integration features found in wild-type viruses.

[0051] AAV vectors of the present invention may be produced recombinantly and may be based on adeno-associated virus (AAV) parent or reference sequences. As used herein, a "vector" is any molecule or moiety which transports, transduces, or otherwise acts as a carrier of a heterologous molecule such as the nucleic acids described herein.

[0052] In addition to single stranded AAV viral genomes (e.g., ssAAVs), the present invention also provides for self-complementary AAV (scAAVs) viral genomes. scAAV vector genomes contain DNA strands which anneal together to form double stranded DNA. By skipping second strand synthesis, scAAVs allow for rapid expression in the cell.

[0053] In one embodiment, the AAV particle of the present invention is an scAAV.

[0054] In one embodiment, the AAV particle of the present invention is an ssAAV.

[0055] Methods for producing and/or modifying AAV particles are disclosed in the art such as pseudotyped AAV vectors (PCT Patent Publication Nos. WO200028004; WO200123001; WO2004112727; WO2005005610; and WO2005072364, the content of each of which is incorporated herein by reference in its entirety).

[0056] AAV particles may be modified to enhance the efficiency of delivery. Such modified AAV particles can be packaged efficiently and be used to successfully infect the target cells at high frequency and with minimal toxicity. In some embodiments, the capsids of the AAV particles are engineered according to the methods described in US Publication Number US20130195801, the contents of which are incorporated herein by reference in their entirety.

[0057] In one embodiment, the AAV particles comprising a payload region encoding the polypeptides of the invention may be introduced into mammalian cells.

AAV serotypes

[0058] AAV particles of the present invention may comprise or be derived from any natural or recombinant AAV serotype. According to the present invention, the AAV particles may utilize or be based on a serotype selected from any of the following AAV1, AAV2, AAV2G9, AAV3, AAV3a, AAV3b, AAV3-3, AAV4, AAV4-4, AAV5, AAV6, AAV6.1, AAV6.2, AAV6.1.2, AAV7, AAV7.2, AAV8, AAV9, AAV9.11, AAV9.13, AAV9.16, AAV9.24, AAV9.45, AAV9.47, AAV9.61, AAV9.68, AAV9.84, AAV9.9, AAV10, AAV11, AAV12, AAV16.3, AAV24.1, AAV27.3, AAV42.12, AAV42-1b, AAV42-2, AAV42-3a, AAV42-3b, AAV42-4, AAV42-5a, AAV42-5b, AAV42-6b, AAV42-8, AAV42-10, AAV42-11, AAV42-12, AAV42-13, AAV42-15, AAV42-aa, AAV43-1, AAV43-12, AAV43-20, AAV43-21, AAV43-23, AAV43-25, AAV43-5, AAV44.1, AAV44.2, AAV44.5, AAV223.1, AAV223.2, AAV223.4, AAV223.5, AAV223.6, AAV223.7, AAV1-7/rh.48, AAV1-8/rh.49, AAV2-15/rh.62, AAV2-3/rh.61, AAV2-4/rh.50, AAV2-5/rh.51, AAV3.1/hu.6, AAV3.1/hu.9, AAV3-9/rh.52, AAV3-11/rh.53, AAV4-8/r11.64, AAV4-9/rh.54, AAV4-19/rh.55, AAV5-3/rh.57, AAV5-22/rh.58, AAV7.3/hu.7, AAV16.8/hu.10, AAV16.12/hu.11, AAV29.3/bb.1, AAV29.5/bb.2, AAV106.1/hu.37, AAV114.3/hu.40, AAV127.2/hu.41, AAV127.5/hu.42, AAV128.3/hu.44, AAV130.4/hu.48, AAV145.1/hu.53, AAV145.5/hu.54, AAV145.6/hu.55, AAV161.10/hu.60, AAV161.6/hu.61, AAV33.12/hu.17, AAV33.4/hu.15, AAV33.8/hu.16, AAV52/hu.19, AAV52.1/hu.20, AAV58.2/hu.25, AAVA3.3, AAVA3.4, AAVA3.5, AAVA3.7, AAVC1, AAVC2, AAVC5, AAV-DJ, AAV-DJ8, AAVF3, AAVF5, AAVH2, AAVrh.72, AAVhu.8, AAVrh.68, AAVrh.70, AAVpi.1, AAVpi.3, AAVpi.2, AAVrh.60, AAVrh.44, AAVrh.65, AAVrh.55, AAVrh.47, AAVrh.69, AAVrh.45, AAVrh.59, AAVhu.12, AAVH6, AAVLK03, AAVH-1/hu.1, AAVH-5/hu.3, AAVLG-10/rh.40, AAVLG-4/rh.38, AAVLG-9/hu.39, AAVN721-8/rh.43, AAVCh.5, AAVCh.5R1, AAVcy.2, AAVcy.3, AAVcy.4, AAVcy.5, AAVCy.5R1, AAVCy.5R2, AAVCy.5R3, AAVCy.5R4, AAVcy.6, AAVhu.1, AAVhu.2, AAVhu.3, AAVhu.4, AAVhu.5, AAVhu.6, AAVhu.7, AAVhu.9, AAVhu.10, AAVhu.11, AAVhu.13, AAVhu.15, AAVhu.16, AAVhu.17, AAVhu.18, AAVhu.20, AAVhu.21, AAVhu.22, AAVhu.23.2, AAVhu.24, AAVhu.25, AAVhu.27, AAVhu.28, AAVhu.29, AAVhu.29R, AAVhu.31, AAVhu.32, AAVhu.34, AAVhu.35, AAVhu.37, AAVhu.39, AAVhu.40, AAVhu.41, AAVhu.42, AAVhu.43, AAVhu.44, AAVhu.44R1, AAVhu.44R2, AAVhu.44R3, AAVhu.45, AAVhu.46, AAVhu.47, AAVhu.48, AAVhu.48R1, AAVhu.48R2, AAVhu.48R3, AAVhu.49, AAVhu.51, AAVhu.52, AAVhu.54, AAVhu.55, AAVhu.56, AAVhu.57, AAVhu.58, AAVhu.60, AAVhu.61, AAVhu.63, AAVhu.64, AAVhu.66, AAVhu.67, AAVhu.14/9, AAVhu.t 19, AAVrh.2, AAVrh.2R, AAVrh.8, AAVrh.8R, AAVrh.10, AAVrh.12, AAVrh.13, AAVrh.13R, AAVrh.14, AAVrh.17, AAVrh.18, AAVrh.19, AAVrh.20,

AAVrh.21, AAVrh.22, AAVrh.23, AAVrh.24, AAVrh.25, AAVrh.31, AAVrh.32, AAVrh.33, AAVrh.34, AAVrh.35, AAVrh.36, AAVrh.37, AAVrh.37R2, AAVrh.38, AAVrh.39, AAVrh.40, AAVrh.46, AAVrh.48, AAVrh.48.1, AAVrh.48.1.2, AAVrh.48.2, AAVrh.49, AAVrh.51, AAVrh.52, AAVrh.53, AAVrh.54, AAVrh.56, AAVrh.57, AAVrh.58, AAVrh.61, AAVrh.64, AAVrh.64R1, AAVrh.64R2, AAVrh.67, AAVrh.73, AAVrh.74, AAVrh8R, AAVrh8R A586R mutant, AAVrh8R R533A mutant, AAAV, BAAV, caprine AAV, bovine AAV, AAVhE1.1, AAVhEr1.5, AAVhER1.14, AAVhEr1.8, AAVhEr1.16, AAVhEr1.18, AAVhEr1.35, AAVhEr1.7, AAVhEr1.36, AAVhEr2.29, AAVhEr2.4, AAVhEr2.16, AAVhEr2.30, AAVhEr2.31, AAVhEr2.36, AAVhER1.23, AAVhEr3.1, AAV2.5T, AAV-PAEC, AAV-LK01, AAV-LK02, AAV-LK03, AAV-LK04, AAV-LK05, AAV-LK06, AAV-LK07, AAV-LK08, AAV-LK09, AAV-LK10, AAV-LK11, AAV-LK12, AAV-LK13, AAV-LK14, AAV-LK15, AAV-LK16, AAV-LK17, AAV-LK18, AAV-LK19, AAV-PAEC2, AAV-PAEC4, AAV-PAEC6, AAV-PAEC7, AAV-PAEC8, AAV-PAEC11, AAV-PAEC12, AAV-2-pre-miRNA-101, AAV-8h, AAV-8b, AAV-h, AAV-b, AAV SM 10-2, AAV Shuffle 100-1, AAV Shuffle 100-3, AAV Shuffle 100-7, AAV Shuffle 10-2, AAV Shuffle 10-6, AAV Shuffle 10-8, AAV Shuffle 100-2, AAV SM 10-1, AAV SM 10-8, AAV SM 100-3, AAV SM 100-10, BNP61 AAV, BNP62 AAV, BNP63 AAV, AAVrh.50, AAVrh.43, AAVrh.62, AAVrh.48, AAVhu.19, AAVhu.11, AAVhu.53, AAV4-8/rh.64, AAVLG-9/hu.39, AAV54.5/hu.23, AAV54.2/hu.22, AAV54.7/hu.24, AAV54.1/hu.21, AAV54.4R/hu.27, AAV46.2/hu.28, AAV46.6/hu.29, AAV128.1/hu.43, true type AAV (ttAAV), UPENN AAV 10, Japanese AAV 10 serotypes, AAV CBr-7.1, AAV CBr-7.10, AAV CBr-7.2, AAV CBr-7.3, AAV CBr-7.4, AAV CBr-7.5, AAV CBr-7.7, AAV CBr-7.8, AAV CBr-B7.3, AAV CBr-B7.4, AAV CBr-E1, AAV CBr-E2, AAV CBr-E3, AAV CBr-E4, AAV CBr-E5, AAV CBr-e5, AAV CBr-E6, AAV CBr-E7, AAV CBr-E8, AAV CHt-1, AAV CHt-2, AAV CHt-3, AAV CHt-6.1, AAV CHt-6.10, AAV CHt-6.5, AAV CHt-6.6, AAV CHt-6.7, AAV CHt-6.8, AAV CHt-P1, AAV CHt-P2, AAV CHt-P5, AAV CHt-P6, AAV CHt-P8, AAV CHt-P9, AAV CKd-1, AAV CKd-10, AAV CKd-2, AAV CKd-3, AAV CKd-4, AAV CKd-6, AAV CKd-7, AAV CKd-8, AAV CKd-B1, AAV CKd-B2, AAV CKd-B3, AAV CKd-B4, AAV CKd-B5, AAV CKd-B6, AAV CKd-B7, AAV CKd-B8, AAV CKd-H1, AAV CKd-H2, AAV CKd-H3, AAV CKd-H4, AAV CKd-H5, AAV CKd-H6, AAV CKd-N3, AAV CKd-N4, AAV CKd-N9, AAV CLg-F1, AAV CLg-F2, AAV CLg-F3, AAV CLg-F4, AAV CLg-F5, AAV CLg-F6, AAV CLg-F7, AAV CLg-F8, AAV CLv-1, AAV CLv1-1, AAV Clv1-10, AAV CLv1-2, AAV CLv-12, AAV CLv1-3, AAV CLv-13, AAV CLv1-4, AAV Clv1-7, AAV Clv1-8, AAV Clv1-9, AAV CLv-2, AAV CLv-3, AAV CLv-4, AAV CLv-6, AAV CLv-8, AAV CLv-D1, AAV CLv-D2, AAV CLv-D3, AAV CLv-D4, AAV CLv-D5, AAV

CLv-D6, AAV CLv-D7, AAV CLv-D8, AAV CLv-E1, AAV CLv-K1, AAV CLv-K3, AAV CLv-K6, AAV CLv-L4, AAV CLv-L5, AAV CLv-L6, AAV CLv-M1, AAV CLv-M11, AAV CLv-M2, AAV CLv-M5, AAV CLv-M6, AAV CLv-M7, AAV CLv-M8, AAV CLv-M9, AAV CLv-R1, AAV CLv-R2, AAV CLv-R3, AAV CLv-R4, AAV CLv-R5, AAV CLv-R6, AAV CLv-R7, AAV CLv-R8, AAV CLv-R9, AAV CSp-1, AAV CSp-10, AAV CSp-11, AAV CSp-2, AAV CSp-3, AAV CSp-4, AAV CSp-6, AAV CSp-7, AAV CSp-8, AAV CSp-8.10, AAV CSp-8.2, AAV CSp-8.4, AAV CSp-8.5, AAV CSp-8.6, AAV CSp-8.7, AAV CSp-8.8, AAV CSp-8.9, AAV CSp-9, AAV.hu.48R3, AAV.VR-355, AAV3B, AAV4, AAV5, AAVF1/HSC1, AAVF11/HSC11, AAVF12/HSC12, AAVF13/HSC13, AAVF14/HSC14, AAVF15/HSC15, AAVF16/HSC16, AAVF17/HSC17, AAVF2/HSC2, AAVF3/HSC3, AAVF4/HSC4, AAVF5/HSC5, AAVF6/HSC6, AAVF7/HSC7, AAVF8/HSC8, AAVF9/HSC9, PHP.B, PHP.A, G2B-26, G2B-13, TH1.1-32, and/or TH1.1-35 and variants thereof.

[0059] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Publication No. US20030138772, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV1 (SEQ ID NO: 6 and 64 of US20030138772), AAV2 (SEQ ID NO: 7 and 70 of US20030138772), AAV3 (SEQ ID NO: 8 and 71 of US20030138772), AAV4 (SEQ ID NO: 63 of US20030138772), AAV5 (SEQ ID NO: 114 of US20030138772), AAV6 (SEQ ID NO: 65 of US20030138772), AAV7 (SEQ ID NO: 1-3 of US20030138772), AAV8 (SEQ ID NO: 4 and 95 of US20030138772), AAV9 (SEQ ID NO: 5 and 100 of US20030138772), AAV10 (SEQ ID NO: 117 of US20030138772), AAV11 (SEQ ID NO: 118 of US20030138772), AAV12 (SEQ ID NO: 119 of US20030138772), AAVrh10 (amino acids 1 to 738 of SEQ ID NO: 81 of US20030138772), AAV16.3 (US20030138772 SEQ ID NO: 10), AAV29.3/bb.1 (US20030138772 SEQ ID NO: 11), AAV29.4 (US20030138772 SEQ ID NO: 12), AAV29.5/bb.2 (US20030138772 SEQ ID NO: 13), AAV1.3 (US20030138772 SEQ ID NO: 14), AAV13.3 (US20030138772 SEQ ID NO: 15), AAV24.1 (US20030138772 SEQ ID NO: 16), AAV27.3 (US20030138772 SEQ ID NO: 17), AAV7.2 (US20030138772 SEQ ID NO: 18), AAVC1 (US20030138772 SEQ ID NO: 19), AAVC3 (US20030138772 SEQ ID NO: 20), AAVC5 (US20030138772 SEQ ID NO: 21), AAVF1 (US20030138772 SEQ ID NO: 22), AAVF3 (US20030138772 SEQ ID NO: 23), AAVF5 (US20030138772 SEQ ID NO: 24), AAVH6 (US20030138772 SEQ ID NO: 25), AAVH2 (US20030138772 SEQ ID NO: 26), AAV42-8 (US20030138772 SEQ ID NO: 27), AAV42-15 (US20030138772 SEQ ID NO: 28), AAV42-5b (US20030138772 SEQ ID NO: 29), AAV42-1b (US20030138772 SEQ ID NO: 30), AAV42-13 (US20030138772 SEQ ID NO: 31), AAV42-3a (US20030138772 SEQ ID NO: 32), AAV42-4 (US20030138772 SEQ ID NO: 33), AAV42-5a (US20030138772 SEQ ID NO: 34),

AAV42-10 (US20030138772 SEQ ID NO: 35), AAV42-3b (US20030138772 SEQ ID NO: 36), AAV42-11 (US20030138772 SEQ ID NO: 37), AAV42-6b (US20030138772 SEQ ID NO: 38), AAV43-1 (US20030138772 SEQ ID NO: 39), AAV43-5 (US20030138772 SEQ ID NO: 40), AAV43-12 (US20030138772 SEQ ID NO: 41), AAV43-20 (US20030138772 SEQ ID NO: 42), AAV43-21 (US20030138772 SEQ ID NO: 43), AAV43-23 (US20030138772 SEQ ID NO: 44), AAV43-25 (US20030138772 SEQ ID NO: 45), AAV44.1 (US20030138772 SEQ ID NO: 46), AAV44.5 (US20030138772 SEQ ID NO: 47), AAV223.1 (US20030138772 SEQ ID NO: 48), AAV223.2 (US20030138772 SEQ ID NO: 49), AAV223.4 (US20030138772 SEQ ID NO: 50), AAV223.5 (US20030138772 SEQ ID NO: 51), AAV223.6 (US20030138772 SEQ ID NO: 52), AAV223.7 (US20030138772 SEQ ID NO: 53), AAVA3.4 (US20030138772 SEQ ID NO: 54), AAVA3.5 (US20030138772 SEQ ID NO: 55), AAVA3.7 (US20030138772 SEQ ID NO: 56), AAVA3.3 (US20030138772 SEQ ID NO: 57), AAV42.12 (US20030138772 SEQ ID NO: 58), AAV44.2 (US20030138772 SEQ ID NO: 59), AAV42-2 (US20030138772 SEQ ID NO: 9), or variants thereof.

[0060] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Publication No. US20150159173, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV2 (SEQ ID NO: 7 and 23 of US20150159173), rh20 (SEQ ID NO: 1 of US20150159173), rh32/33 (SEQ ID NO: 2 of US20150159173), rh39 (SEQ ID NO: 3, 20 and 36 of US20150159173), rh46 (SEQ ID NO: 4 and 22 of US20150159173), rh73 (SEQ ID NO: 5 of US20150159173), rh74 (SEQ ID NO: 6 of US20150159173), AAV6.1 (SEQ ID NO: 29 of US20150159173), rh.8 (SEQ ID NO: 41 of US20150159173), rh.48.1 (SEQ ID NO: 44 of US20150159173), hu.44 (SEQ ID NO: 45 of US20150159173), hu.29 (SEQ ID NO: 42 of US20150159173), hu.48 (SEQ ID NO: 38 of US20150159173), rh54 (SEQ ID NO: 49 of US20150159173), AAV2 (SEQ ID NO: 7 of US20150159173), cy.5 (SEQ ID NO: 8 and 24 of US20150159173), rh.10 (SEQ ID NO: 9 and 25 of US20150159173), rh.13 (SEQ ID NO: 10 and 26 of US20150159173), AAV1 (SEQ ID NO: 11 and 27 of US20150159173), AAV3 (SEQ ID NO: 12 and 28 of US20150159173), AAV6 (SEQ ID NO: 13 and 29 of US20150159173), AAV7 (SEQ ID NO: 14 and 30 of US20150159173), AAV8 (SEQ ID NO: 15 and 31 of US20150159173), hu.13 (SEQ ID NO: 16 and 32 of US20150159173), hu.26 (SEQ ID NO: 17 and 33 of US20150159173), hu.37 (SEQ ID NO: 18 and 34 of US20150159173), hu.53 (SEQ ID NO: 19 and 35 of US20150159173), rh.43 (SEQ ID NO: 21 and 37 of US20150159173), rh2 (SEQ ID NO: 39 of US20150159173), rh.37 (SEQ ID NO: 40 of US20150159173), rh.64 (SEQ ID NO: 43 of US20150159173), rh.48 (SEQ ID NO: 44 of US20150159173), ch.5 (SEQ ID NO 46 of US20150159173), rh.67 (SEQ ID NO:

47 of US20150159173), rh.58 (SEQ ID NO: 48 of US20150159173), or variants thereof including, but not limited to Cy5R1, Cy5R2, Cy5R3, Cy5R4, rh.13R, rh.37R2, rh.2R, rh.8R, rh.48.1, rh.48.2, rh.48.1.2, hu.44R1, hu.44R2, hu.44R3, hu.29R, ch.5R1, rh64R1, rh64R2, AAV6.2, AAV6.1, AAV6.12, hu.48R1, hu.48R2, and hu.48R3.

[0061] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US7198951, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV9 (SEQ ID NO: 1-3 of US7198951), AAV2 (SEQ ID NO: 4 of US7198951), AAV1 (SEQ ID NO: 5 of US7198951), AAV3 (SEQ ID NO: 6 of US7198951), and AAV8 (SEQ ID NO: 7 of US7198951).

[0062] In some embodiments, the AAV serotype may be, or have, a mutation in the AAV9 sequence as described by N Pulicherla et al. (Molecular Therapy 19(6):1070-1078 (2011), herein incorporated by reference in its entirety), such as but not limited to, AAV9.9, AAV9.11, AAV9.13, AAV9.16, AAV9.24, AAV9.45, AAV9.47, AAV9.61, AAV9.68, or AAV9.84.

[0063] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US 6156303, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV3B (SEQ ID NO: 1 and 10 of US 6156303), AAV6 (SEQ ID NO: 2, 7 and 11 of US 6156303), AAV2 (SEQ ID NO: 3 and 8 of US 6156303), AAV3A (SEQ ID NO: 4 and 9, of US 6156303), or derivatives thereof.

[0064] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Publication No. US20140359799, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV8 (SEQ ID NO: 1 of US20140359799), AAVDJ (SEQ ID NO: 2 and 3 of US20140359799), or variants thereof.

[0065] In some embodiments, the serotype may be AAVDJ or a variant thereof, such as AAVDJ8 (or AAV-DJ8), as described by Grimm et al. (Journal of Virology 82(12): 5887-5911 (2008), herein incorporated by reference in its entirety). The amino acid sequence of AAVDJ8 may comprise two or more mutations in order to remove the heparin binding domain (HBD). As a non-limiting example, the AAV-DJ sequence described as SEQ ID NO: 1 in US Patent No. 7588772, the contents of which are herein incorporated by reference in their entirety, may comprise two mutations: (1) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (2) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr). As another non-limiting example, may comprise three mutations: (1) K406R where lysine (K; Lys) at amino acid 406 is changed to arginine (R; Arg), (2) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (3) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr).

[0066] In some embodiments, the AAV serotype may be, or have, a sequence of AAV4 as described in International Publication No. WO1998011244, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV4 (SEQ ID NO: 1-20 of WO19980112 44).

[0067] In some embodiments, the AAV serotype may be, or have, a mutation in the AAV2 sequence to generate AAV2G9 as described in International Publication No. WO2014144229 and herein incorporated by reference in its entirety.

[0068] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2005033321, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV3-3 (SEQ ID NO: 217 of WO2005033321), AAV1 (SEQ ID NO: 219 and 202 of WO2005033321), AAV106.1/hu.37 (SEQ ID NO: 10 of WO2005033321), AAV114.3/hu.40 (SEQ ID NO: 11 of WO2005033321), AAV127.2/hu.41 (SEQ ID NO: 6 and 8 of WO2005033321), AAV128.3/hu.44 (SEQ ID NO: 81 of WO2005033321), AAV130.4/hu.48 (SEQ ID NO: 78 of WO2005033321), AAV145.1/hu.53 (SEQ ID NO: 176 and 177 of WO2005033321), AAV145.6/hu.56 (SEQ ID NO: 168 and 192 of WO2005033321), AAV16.12/hu.11 (SEQ ID NO: 153 and 57 of WO2005033321), AAV16.8/hu.10 (SEQ ID NO: 156 and 56 of WO2005033321), AAV161.10/hu.60 (SEQ ID NO: 170 of WO2005033321), AAV161.6/hu.61 (SEQ ID NO: 174 of WO2005033321), AAV1-7/rh.48 (SEQ ID NO: 32 of WO2005033321), AAV1-8/rh.49 (SEQ ID NO: 103 and 25 of WO2005033321), AAV2 (SEQ ID NO: 211 and 221 of WO2005033321), AAV2-15/rh.62 (SEQ ID NO: 33 and 114 of WO2005033321), AAV2-3/rh.61 (SEQ ID NO: 21 of WO2005033321), AAV2-4/rh.50 (SEQ ID NO: 23 and 108 of WO2005033321), AAV2-5/rh.51 (SEQ ID NO: 104 and 22 of WO2005033321), AAV3.1/hu.6 (SEQ ID NO: 5 and 84 of WO2005033321), AAV3.1/hu.9 (SEQ ID NO: 155 and 58 of WO2005033321), AAV3-11/rh.53 (SEQ ID NO: 186 and 176 of WO2005033321), AAV3-3 (SEQ ID NO: 200 of WO2005033321), AAV33.12/hu.17 (SEQ ID NO: 4 of WO2005033321), AAV33.4/hu.15 (SEQ ID NO: 50 of WO2005033321), AAV33.8/hu.16 (SEQ ID NO: 51 of WO2005033321), AAV3-9/rh.52 (SEQ ID NO: 96 and 18 of WO2005033321), AAV4-19/rh.55 (SEQ ID NO: 117 of WO2005033321), AAV4-4 (SEQ ID NO: 201 and 218 of WO2005033321), AAV4-9/rh.54 (SEQ ID NO: 116 of WO2005033321), AAV5 (SEQ ID NO: 199 and 216 of WO2005033321), AAV52.1/hu.20 (SEQ ID NO: 63 of WO2005033321), AAV52/hu.19 (SEQ ID NO: 133 of WO2005033321), AAV5-22/rh.58 (SEQ ID NO: 27 of WO2005033321), AAV5-3/rh.57 (SEQ ID NO: 105 of WO2005033321), AAV5-3/rh.57 (SEQ ID NO: 26 of WO2005033321), AAV58.2/hu.25 (SEQ ID NO: 49 of WO2005033321), AAV6 (SEQ ID NO: 203 and 220 of WO2005033321), AAV7 (SEQ ID NO:

222 and 213 of WO2005033321), AAV7.3/hu.7 (SEQ ID NO: 55 of WO2005033321), AAV8 (SEQ ID NO: 223 and 214 of WO2005033321), AAVH-1/hu.1 (SEQ ID NO: 46 of WO2005033321), AAVH-5/hu.3 (SEQ ID NO: 44 of WO2005033321), AAVhu.1 (SEQ ID NO: 144 of WO2005033321), AAVhu.10 (SEQ ID NO: 156 of WO2005033321), AAVhu.11 (SEQ ID NO: 153 of WO2005033321), AAVhu.12 (SEQ ID NO: 59 of WO2005033321), AAVhu.13 (SEQ ID NO: 129 of WO2005033321), AAVhu.14/AAV9 (SEQ ID NO: 123 and 3 of WO2005033321), AAVhu.15 (SEQ ID NO: 147 of WO2005033321), AAVhu.16 (SEQ ID NO: 148 of WO2005033321), AAVhu.17 (SEQ ID NO: 83 of WO2005033321), AAVhu.18 (SEQ ID NO: 149 of WO2005033321), AAVhu.19 (SEQ ID NO: 133 of WO2005033321), AAVhu.2 (SEQ ID NO: 143 of WO2005033321), AAVhu.20 (SEQ ID NO: 134 of WO2005033321), AAVhu.21 (SEQ ID NO: 135 of WO2005033321), AAVhu.22 (SEQ ID NO: 138 of WO2005033321), AAVhu.23.2 (SEQ ID NO: 137 of WO2005033321), AAVhu.24 (SEQ ID NO: 136 of WO2005033321), AAVhu.25 (SEQ ID NO: 146 of WO2005033321), AAVhu.27 (SEQ ID NO: 140 of WO2005033321), AAVhu.29 (SEQ ID NO: 132 of WO2005033321), AAVhu.3 (SEQ ID NO: 145 of WO2005033321), AAVhu.31 (SEQ ID NO: 121 of WO2005033321), AAVhu.32 (SEQ ID NO: 122 of WO2005033321), AAVhu.34 (SEQ ID NO: 125 of WO2005033321), AAVhu.35 (SEQ ID NO: 164 of WO2005033321), AAVhu.37 (SEQ ID NO: 88 of WO2005033321), AAVhu.39 (SEQ ID NO: 102 of WO2005033321), AAVhu.4 (SEQ ID NO: 141 of WO2005033321), AAVhu.40 (SEQ ID NO: 87 of WO2005033321), AAVhu.41 (SEQ ID NO: 91 of WO2005033321), AAVhu.42 (SEQ ID NO: 85 of WO2005033321), AAVhu.43 (SEQ ID NO: 160 of WO2005033321), AAVhu.44 (SEQ ID NO: 144 of WO2005033321), AAVhu.45 (SEQ ID NO: 127 of WO2005033321), AAVhu.46 (SEQ ID NO: 159 of WO2005033321), AAVhu.47 (SEQ ID NO: 128 of WO2005033321), AAVhu.48 (SEQ ID NO: 157 of WO2005033321), AAVhu.49 (SEQ ID NO: 189 of WO2005033321), AAVhu.51 (SEQ ID NO: 190 of WO2005033321), AAVhu.52 (SEQ ID NO: 191 of WO2005033321), AAVhu.53 (SEQ ID NO: 186 of WO2005033321), AAVhu.54 (SEQ ID NO: 188 of WO2005033321), AAVhu.55 (SEQ ID NO: 187 of WO2005033321), AAVhu.56 (SEQ ID NO: 192 of WO2005033321), AAVhu.57 (SEQ ID NO: 193 of WO2005033321), AAVhu.58 (SEQ ID NO: 194 of WO2005033321), AAVhu.6 (SEQ ID NO: 84 of WO2005033321), AAVhu.60 (SEQ ID NO: 184 of WO2005033321), AAVhu.61 (SEQ ID NO: 185 of WO2005033321), AAVhu.63 (SEQ ID NO: 195 of WO2005033321), AAVhu.64 (SEQ ID NO: 196 of WO2005033321), AAVhu.66 (SEQ ID NO: 197 of WO2005033321), AAVhu.67 (SEQ ID NO: 198 of WO2005033321), AAVhu.7 (SEQ ID NO: 150 of WO2005033321), AAVhu.8 (SEQ ID NO: 12 of WO2005033321), AAVhu.9 (SEQ ID NO: 155 of WO2005033321),

AAVLG-10/rh.40 (SEQ ID No: 14 of WO2005033321), AAVLG-4/rh.38 (SEQ ID NO: 86 of WO2005033321), AAVLG-4/rh.38 (SEQ ID No: 7 of WO2005033321), AAVN721-8/rh.43 (SEQ ID NO: 163 of WO2005033321), AAVN721-8/rh.43 (SEQ ID NO: 43 of WO2005033321), AAVpi.1 (SEQ ID NO: 28 of WO2005033321), AAVpi.2 (SEQ ID NO: 30 of WO2005033321), AAVpi.3 (SEQ ID NO: 29 of WO2005033321), AAVrh.38 (SEQ ID NO: 86 of WO2005033321), AAVrh.40 (SEQ ID NO: 92 of WO2005033321), AAVrh.43 (SEQ ID NO: 163 of WO2005033321), AAVrh.44 (SEQ ID NO: 34 of WO2005033321), AAVrh.45 (SEQ ID NO: 41 of WO2005033321), AAVrh.47 (SEQ ID NO: 38 of WO2005033321), AAVrh.48 (SEQ ID NO: 115 of WO2005033321), AAVrh.49 (SEQ ID NO: 103 of WO2005033321), AAVrh.50 (SEQ ID NO: 108 of WO2005033321), AAVrh.51 (SEQ ID NO: 104 of WO2005033321), AAVrh.52 (SEQ ID NO: 96 of WO2005033321), AAVrh.53 (SEQ ID NO: 97 of WO2005033321), AAVrh.55 (SEQ ID NO: 37 of WO2005033321), AAVrh.56 (SEQ ID NO: 152 of WO2005033321), AAVrh.57 (SEQ ID NO: 105 of WO2005033321), AAVrh.58 (SEQ ID NO: 106 of WO2005033321), AAVrh.59 (SEQ ID NO: 42 of WO2005033321), AAVrh.60 (SEQ ID NO: 31 of WO2005033321), AAVrh.61 (SEQ ID NO: 107 of WO2005033321), AAVrh.62 (SEQ ID NO: 114 of WO2005033321), AAVrh.64 (SEQ ID NO: 99 of WO2005033321), AAVrh.65 (SEQ ID NO: 35 of WO2005033321), AAVrh.68 (SEQ ID NO: 16 of WO2005033321), AAVrh.69 (SEQ ID NO: 39 of WO2005033321), AAVrh.70 (SEQ ID NO: 20 of WO2005033321), AAVrh.72 (SEQ ID NO: 9 of WO2005033321), or variants thereof including, but not limited to, AAVcy.2, AAVcy.3, AAVcy.4, AAVcy.5, AAVcy.6, AAVrh.12, AAVrh.17, AAVrh.18, AAVrh.19, AAVrh.21, AAVrh.22, AAVrh.23, AAVrh.24, AAVrh.25, AAVrh.25/42 15, AAVrh.31, AAVrh.32, AAVrh.33, AAVrh.34, AAVrh.35, AAVrh.36, AAVrh.37, AAVrh14. Non-limiting examples of variants include SEQ ID NO: 13, 15, 17, 19, 24, 36, 40, 45, 47, 48, 51-54, 60-62, 64-77, 79, 80, 82, 89, 90, 93-95, 98, 100, 101, 109-113, 118-120, 124, 126, 131, 139, 142, 151,154, 158, 161, 162, 165-183, 202, 204-212, 215, 219, 224-236, of WO2005033321, the contents of which are herein incorporated by reference in their entirety.

[0069] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2015168666, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAVrh8R (SEQ ID NO: 9 of WO2015168666), AAVrh8R A586R mutant (SEQ ID NO: 10 of WO2015168666), AAVrh8R R533A mutant (SEQ ID NO: 11 of WO2015168666), or variants thereof.

[0070] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US9233131, the contents of which are herein incorporated by reference

in their entirety, such as, but not limited to, AAVhE1.1 (SEQ ID NO:44 of US9233131), AAVhEr1.5 (SEQ ID NO:45 of US9233131), AAVhER1.14 (SEQ ID NO:46 of US9233131), AAVhEr1.8 (SEQ ID NO:47 of US9233131), AAVhEr1.16 (SEQ ID NO:48 of US9233131), AAVhEr1.18 (SEQ ID NO: 49 of US9233131), AAVhEr1.35 (SEQ ID NO:50 of US9233131), AAVhEr1.7 (SEQ ID NO: 51 of US9233131), AAVhEr1.36 (SEQ ID NO: 52 of US9233131), AAVhEr2.29 (SEQ ID NO:53 of US9233131), AAVhEr2.4 (SEQ ID NO:54 of US9233131), AAVhEr2.16 (SEQ ID NO:55 of US9233131), AAVhEr2.30 (SEQ ID NO:56 of US9233131), AAVhEr2.31 (SEQ ID NO:58 of US9233131), AAVhEr2.36 (SEQ ID NO:57 of US9233131), AAVhER1.23 (SEQ ID NO:53 of US9233131), AAVhEr3.1 (SEQ ID NO:59 of US9233131), AAV2.5T (SEQ ID NO:42 of US9233131), or variants thereof.

[0071] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20150376607, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-PAEC (SEQ ID NO: 1 of US20150376607), AAV-LK01 (SEQ ID NO: 2 of US20150376607), AAV-LK02 (SEQ ID NO: 3 of US20150376607), AAV-LK03 (SEQ ID NO: 4 of US20150376607), AAV-LK04 (SEQ ID NO: 5 of US20150376607), AAV-LK05 (SEQ ID NO: 6 of US20150376607), AAV-LK06 (SEQ ID NO: 7 of US20150376607), AAV-LK07 (SEQ ID NO: 8 of US20150376607), AAV-LK08 (SEQ ID NO: 9 of US20150376607), AAV-LK09 (SEQ ID NO: 10 of US20150376607), AAV-LK10 (SEQ ID NO: 11 of US20150376607), AAV-LK11 (SEQ ID NO: 12 of US20150376607), AAV-LK12 (SEQ ID NO: 13 of US20150376607), AAV-LK13 (SEQ ID NO: 14 of US20150376607), AAV-LK14 (SEQ ID NO: 15 of US20150376607), AAV-LK15 (SEQ ID NO: 16 of US20150376607), AAV-LK16 (SEQ ID NO: 17 of US20150376607), AAV-LK17 (SEQ ID NO: 18 of US20150376607), AAV-LK18 (SEQ ID NO: 19 of US20150376607), AAV-LK19 (SEQ ID NO: 20 of US20150376607), AAV-PAEC2 (SEQ ID NO: 21 of US20150376607), AAV-PAEC4 (SEQ ID NO: 22 of US20150376607), AAV-PAEC6 (SEQ ID NO: 23 of US20150376607), AAV-PAEC7 (SEQ ID NO: 24 of US20150376607), AAV-PAEC8 (SEQ ID NO:25 of US20150376607), AAV-PAEC11 (SEQ ID NO: 26 of US20150376607), AAV-PAEC12 (SEQ ID NO: 27, of US20150376607), or variants thereof.

[0072] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US9163261, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-2-pre-miRNA-101 (SEQ ID NO: 1 of US9163261), or variants thereof.

[0073] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20150376240, the contents of which are herein

incorporated by reference in their entirety, such as, but not limited to, AAV-8h (SEQ ID NO: 6 of US20150376240), AAV-8b (SEQ ID NO: 5 of US20150376240), AAV-h (SEQ ID NO: 2 of US20150376240), AAV-b (SEQ ID NO: 1 of US20150376240), or variants thereof.

[0074] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20160017295, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV SM 10-2 (SEQ ID NO: 22 of US20160017295), AAV Shuffle 100-1 (SEQ ID NO: 23 of US20160017295), AAV Shuffle 100-3 (SEQ ID NO: 24 of US20160017295), AAV Shuffle 100-7 (SEQ ID NO: 25 of US20160017295), AAV Shuffle 10-2 (SEQ ID NO: 34 of US20160017295), AAV Shuffle 10-6 (SEQ ID NO: 35 of US20160017295), AAV Shuffle 10-8 (SEQ ID NO: 36 of US20160017295), AAV Shuffle 100-2 (SEQ ID NO: 37 of US20160017295), AAV SM 10-1 (SEQ ID NO: 38 of US20160017295), AAV SM 10-8 (SEQ ID NO: 39 of US20160017295), AAV SM 100-3 (SEQ ID NO: 40 of US20160017295), AAV SM 100-10 (SEQ ID NO: 41 of US20160017295), or variants thereof.

[0075] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20150238550, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BNP61 AAV (SEQ ID NO: 1 of US20150238550), BNP62 AAV (SEQ ID NO: 3 of US20150238550), BNP63 AAV (SEQ ID NO: 4 of US20150238550), or variants thereof.

[0076] In some embodiments, the AAV serotype may be or may have a sequence as described in United States Patent Publication No. US20150315612, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAVrh.50 (SEQ ID NO: 108 of US20150315612), AAVrh.43 (SEQ ID NO: 163 of US20150315612), AAVrh.62 (SEQ ID NO: 114 of US20150315612), AAVrh.48 (SEQ ID NO: 115 of US20150315612), AAVhu.19 (SEQ ID NO: 133 of US20150315612), AAVhu.11 (SEQ ID NO: 153 of US20150315612), AAVhu.53 (SEQ ID NO: 186 of US20150315612), AAV4-8/rh.64 (SEQ ID NO: 15 of US20150315612), AAVLG-9/hu.39 (SEQ ID NO: 24 of US20150315612), AAV54.5/hu.23 (SEQ ID NO: 60 of US20150315612), AAV54.2/hu.22 (SEQ ID NO: 67 of US20150315612), AAV54.7/hu.24 (SEQ ID NO: 66 of US20150315612), AAV54.1/hu.21 (SEQ ID NO: 65 of US20150315612), AAV54.4R/hu.27 (SEQ ID NO: 64 of US20150315612), AAV46.2/hu.28 (SEQ ID NO: 68 of US20150315612), AAV46.6/hu.29 (SEQ ID NO: 69 of US20150315612), AAV128.1/hu.43 (SEQ ID NO: 80 of US20150315612), or variants thereof.

[0077] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2015121501, the contents of which are herein incorporated by

reference in their entirety, such as, but not limited to, true type AAV (ttAAV) (SEQ ID NO: 2 of WO2015121501), "UPenn AAV10" (SEQ ID NO: 8 of WO2015121501), "Japanese AAV10" (SEQ ID NO: 9 of WO2015121501), or variants thereof.

[0078] According to the present invention, AAV capsid serotype selection or use may be from a variety of species. In one embodiment, the AAV may be an avian AAV (AAAV). The AAAV serotype may be, or have, a sequence as described in United States Patent No. US 9238800, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAAV (SEQ ID NO: 1, 2, 4, 6, 8, 10, 12, and 14 of US9238800), or variants thereof.

[0079] In one embodiment, the AAV may be a bovine AAV (BAAV). The BAAV serotype may be, or have, a sequence as described in United States Patent No. US9193769, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BAAV (SEQ ID NO: 1 and 6 of U9193769), or variants thereof. The BAAV serotype may be or have a sequence as described in United States Patent No. US7427396, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BAAV (SEQ ID NO: 5 and 6 of US7427396), or variants thereof.

[0080] In one embodiment, the AAV may be a caprine AAV. The caprine AAV serotype may be, or have, a sequence as described in United States Patent No. US7427396, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, caprine AAV (SEQ ID NO: 3 of US7427396), or variants thereof.

[0081] In other embodiments, the AAV may be engineered as a hybrid AAV from two or more parental serotypes. In one embodiment, the AAV may be AAV2G9 which comprises sequences from AAV2 and AAV9. The AAV2G9 AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20160017005, the contents of which are herein incorporated by reference in its entirety.

[0082] In one embodiment, the AAV may be a serotype generated by the AAV9 capsid library with mutations in amino acids 390-627 (VP1 numbering) as described by Pulicherla et al. (Molecular Therapy 19(6):1070-1078 (2011), the contents of which are herein incorporated by reference in their entirety. The serotype and corresponding nucleotide and amino acid substitutions may be, but is not limited to, AAV9.1 (G1594C; D532H), AAV6.2 (T1418A and T1436X; V473D and I479K), AAV9.3 (T1238A; F413Y), AAV9.4 (T1250C and A1617T; F417S), AAV9.5 (A1235G, A1314T, A1642G, C1760T; Q412R, T548A, A587V), AAV9.6 (T1231A; F411I), AAV9.9 (G1203A, G1785T; W595C), AAV9.10 (A1500G, T1676C; M559T), AAV9.11 (A1425T, A1702C, A1769T; T568P, Q590L), AAV9.13 (A1369C, A1720T;

N457H, T574S), AAV9.14 (T1340A, T1362C, T1560C, G1713A; L447H), AAV9.16 (A1775T; Q592L), AAV9.24 (T1507C, T1521G; W503R), AAV9.26 (A1337G, A1769C; Y446C, Q590P), AAV9.33 (A1667C; D556A), AAV9.34 (A1534G, C1794T; N512D), AAV9.35 (A1289T, T1450A, C1494T, A1515T, C1794A, G1816A; Q430L, Y484N, N98K, V606I), AAV9.40 (A1694T, E565V), AAV9.41 (A1348T, T1362C; T450S), AAV9.44 (A1684C, A1701T, A1737G; N562H, K567N), AAV9.45 (A1492T, C1804T; N498Y, L602F), AAV9.46 (G1441C, T1525C, T1549G; G481R, W509R, L517V), 9.47 (G1241A, G1358A, A1669G, C1745T; S414N, G453D, K557E, T582I), AAV9.48 (C1445T, A1736T; P482L, Q579L), AAV9.50 (A1638T, C1683T, T1805A; Q546H, L602H), AAV9.53 (G1301A, A1405C, C1664T, G1811T; R134Q, S469R, A555V, G604V), AAV9.54 (C1531A, T1609A; L511I, L537M), AAV9.55 (T1605A; F535L), AAV9.58 (C1475T, C1579A; T492I, H527N), AAV.59 (T1336C; Y446H), AAV9.61 (A1493T; N498I), AAV9.64 (C1531A, A1617T; L511I), AAV9.65 (C1335T, T1530C, C1568A; A523D), AAV9.68 (C1510A; P504T), AAV9.80 (G1441A,,G481R), AAV9.83 (C1402A, A1500T; P468T, E500D), AAV9.87 (T1464C, T1468C; S490P), AAV9.90 (A1196T; Y399F), AAV9.91 (T1316G, A1583T, C1782G, T1806C; L439R, K528I), AAV9.93 (A1273G, A1421G, A1638C, C1712T, G1732A, A1744T, A1832T; S425G, Q474R, Q546H, P571L, G578R, T582S, D611V), AAV9.94 (A1675T; M559L) and AAV9.95 (T1605A; F535L).

[0083] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2016049230, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAVF1/HSC1 (SEQ ID NO: 2 and 20 of WO2016049230), AAVF2/HSC2 (SEQ ID NO: 3 and 21 of WO2016049230), AAVF3/HSC3 (SEQ ID NO: 5 and 22 of WO2016049230), AAVF4/HSC4 (SEQ ID NO: 6 and 23 of WO2016049230), AAVF5/HSC5 (SEQ ID NO: 11 and 25 of WO2016049230), AAVF6/HSC6 (SEQ ID NO: 7 and 24 of WO2016049230), AAVF7/HSC7 (SEQ ID NO: 8 and 27 of WO2016049230), AAVF8/HSC8 (SEQ ID NO: 9 and 28 of WO2016049230), AAVF9/HSC9 (SEQ ID NO: 10 and 29 of WO2016049230), AAVF11/HSC11 (SEQ ID NO: 4 and 26 of WO2016049230), AAVF12/HSC12 (SEQ ID NO: 12 and 30 of WO2016049230), AAVF13/HSC13 (SEQ ID NO: 14 and 31 of WO2016049230), AAVF14/HSC14 (SEQ ID NO: 15 and 32 of WO2016049230), AAVF15/HSC15 (SEQ ID NO: 16 and 33 of WO2016049230), AAVF16/HSC16 (SEQ ID NO: 17 and 34 of WO2016049230), AAVF17/HSC17 (SEQ ID NO: 13 and 35 of WO2016049230), or variants or derivatives thereof.

[0084] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US8734809, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV CBr-E1 (SEQ ID NO: 13 and 87 of

US8734809), AAV CBr-E2 (SEQ ID NO: 14 and 88 of US8734809), AAV CBr-E3 (SEQ ID NO: 15 and 89 of US8734809), AAV CBr-E4 (SEQ ID NO: 16 and 90 of US8734809), AAV CBr-E5 (SEQ ID NO: 17 and 91 of US8734809), AAV CBr-e5 (SEQ ID NO: 18 and 92 of US8734809), AAV CBr-E6 (SEQ ID NO: 19 and 93 of US8734809), AAV CBr-E7 (SEQ ID NO: 20 and 94 of US8734809), AAV CBr-E8 (SEQ ID NO: 21 and 95 of US8734809), AAV CLv-D1 (SEQ ID NO: 22 and 96 of US8734809), AAV CLv-D2 (SEQ ID NO: 23 and 97 of US8734809), AAV CLv-D3 (SEQ ID NO: 24 and 98 of US8734809), AAV CLv-D4 (SEQ ID NO: 25 and 99 of US8734809), AAV CLv-D5 (SEQ ID NO: 26 and 100 of US8734809), AAV CLv-D6 (SEQ ID NO: 27 and 101 of US8734809), AAV CLv-D7 (SEQ ID NO: 28 and 102 of US8734809), AAV CLv-D8 (SEQ ID NO: 29 and 103 of US8734809), AAV CLv-E1 (SEQ ID NO: 13 and 87 of US8734809), AAV CLv-R1 (SEQ ID NO: 30 and 104 of US8734809), AAV CLv-R2 (SEQ ID NO: 31 and 105 of US8734809), AAV CLv-R3 (SEQ ID NO: 32 and 106 of US8734809), AAV CLv-R4 (SEQ ID NO: 33 and 107 of US8734809), AAV CLv-R5 (SEQ ID NO: 34 and 108 of US8734809), AAV CLv-R6 (SEQ ID NO: 35 and 109 of US8734809), AAV CLv-R7 (SEQ ID NO: 36 and 110 of US8734809), AAV CLv-R8 (SEQ ID NO: 37 and 111 of US8734809), AAV CLv-R9 (SEQ ID NO: 38 and 112 of US8734809), AAV CLg-F1 (SEQ ID NO: 39 and 113 of US8734809), AAV CLg-F2 (SEQ ID NO: 40 and 114 of US8734809), AAV CLg-F3 (SEQ ID NO: 41 and 115 of US8734809), AAV CLg-F4 (SEQ ID NO: 42 and 116 of US8734809), AAV CLg-F5 (SEQ ID NO: 43 and 117 of US8734809), AAV CLg-F6 (SEQ ID NO: 43 and 117 of US8734809), AAV CLg-F7 (SEQ ID NO: 44 and 118 of US8734809), AAV CLg-F8 (SEQ ID NO: 43 and 117 of US8734809), AAV CSp-1 (SEQ ID NO: 45 and 119 of US8734809), AAV CSp-10 (SEQ ID NO: 46 and 120 of US8734809), AAV CSp-11 (SEQ ID NO: 47 and 121 of US8734809), AAV CSp-2 (SEQ ID NO: 48 and 122 of US8734809), AAV CSp-3 (SEQ ID NO: 49 and 123 of US8734809), AAV CSp-4 (SEQ ID NO: 50 and 124 of US8734809), AAV CSp-6 (SEQ ID NO: 51 and 125 of US8734809), AAV CSp-7 (SEQ ID NO: 52 and 126 of US8734809), AAV CSp-8 (SEQ ID NO: 53 and 127 of US8734809), AAV CSp-9 (SEQ ID NO: 54 and 128 of US8734809), AAV CHt-2 (SEQ ID NO: 55 and 129 of US8734809), AAV CHt-3 (SEQ ID NO: 56 and 130 of US8734809), AAV CKd-1 (SEQ ID NO: 57 and 131 of US8734809), AAV CKd-10 (SEQ ID NO: 58 and 132 of US8734809), AAV CKd-2 (SEQ ID NO: 59 and 133 of US8734809), AAV CKd-3 (SEQ ID NO: 60 and 134 of US8734809), AAV CKd-4 (SEQ ID NO: 61 and 135 of US8734809), AAV CKd-6 (SEQ ID NO: 62 and 136 of US8734809), AAV CKd-7 (SEQ ID NO: 63 and 137 of US8734809), AAV CKd-8 (SEQ ID NO: 64 and 138 of US8734809), AAV CLv-1 (SEQ ID NO: 35 and 139 of US8734809), AAV CLv-12 (SEQ ID NO: 66 and 140 of US8734809), AAV CLv-13 (SEQ ID

NO: 67 and 141 of US8734809), AAV CLv-2 (SEQ ID NO: 68 and 142 of US8734809), AAV CLv-3 (SEQ ID NO: 69 and 143 of US8734809), AAV CLv-4 (SEQ ID NO: 70 and 144 of US8734809), AAV CLv-6 (SEQ ID NO: 71 and 145 of US8734809), AAV CLv-8 (SEQ ID NO: 72 and 146 of US8734809), AAV CKd-B1 (SEQ ID NO: 73 and 147 of US8734809), AAV CKd-B2 (SEQ ID NO: 74 and 148 of US8734809), AAV CKd-B3 (SEQ ID NO: 75 and 149 of US8734809), AAV CKd-B4 (SEQ ID NO: 76 and 150 of US8734809), AAV CKd-B5 (SEQ ID NO: 77 and 151 of US8734809), AAV CKd-B6 (SEQ ID NO: 78 and 152 of US8734809), AAV CKd-B7 (SEQ ID NO: 79 and 153 of US8734809), AAV CKd-B8 (SEQ ID NO: 80 and 154 of US8734809), AAV CKd-H1 (SEQ ID NO: 81 and 155 of US8734809), AAV CKd-H2 (SEQ ID NO: 82 and 156 of US8734809), AAV CKd-H3 (SEQ ID NO: 83 and 157 of US8734809), AAV CKd-H4 (SEQ ID NO: 84 and 158 of US8734809), AAV CKd-H5 (SEQ ID NO: 85 and 159 of US8734809), AAV CKd-H6 (SEQ ID NO: 77 and 151 of US8734809), AAV CHt-1 (SEQ ID NO: 86 and 160 of US8734809), AAV CLv1-1 (SEQ ID NO: 171 of US8734809), AAV CLv1-2 (SEQ ID NO: 172 of US8734809), AAV CLv1-3 (SEQ ID NO: 173 of US8734809), AAV CLv1-4 (SEQ ID NO: 174 of US8734809), AAV Clv1-7 (SEQ ID NO: 175 of US8734809), AAV Clv1-8 (SEQ ID NO: 176 of US8734809), AAV Clv1-9 (SEQ ID NO: 177 of US8734809), AAV Clv1-10 (SEQ ID NO: 178 of US8734809), AAV.VR-355 (SEQ ID NO: 181 of US8734809), AAV.hu.48R3 (SEQ ID NO: 183 of US8734809), or variants or derivatives thereof.

[0085] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2016065001, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV CHt-P2 (SEQ ID NO: 1 and 51 of WO2016065001), AAV CHt-P5 (SEQ ID NO: 2 and 52 of WO2016065001), AAV CHt-P9 (SEQ ID NO: 3 and 53 of WO2016065001), AAV CBr-7.1 (SEQ ID NO: 4 and 54 of WO2016065001), AAV CBr-7.2 (SEQ ID NO: 5 and 55 of WO2016065001), AAV CBr-7.3 (SEQ ID NO: 6 and 56 of WO2016065001), AAV CBr-7.4 (SEQ ID NO: 7 and 57 of WO2016065001), AAV CBr-7.5 (SEQ ID NO: 8 and 58 of WO2016065001), AAV CBr-7.7 (SEQ ID NO: 9 and 59 of WO2016065001), AAV CBr-7.8 (SEQ ID NO: 10 and 60 of WO2016065001), AAV CBr-7.10 (SEQ ID NO: 11 and 61 of WO2016065001), AAV CKd-N3 (SEQ ID NO: 12 and 62 of WO2016065001), AAV CKd-N4 (SEQ ID NO: 13 and 63 of WO2016065001), AAV CKd-N9 (SEQ ID NO: 14 and 64 of WO2016065001), AAV CLv-L4 (SEQ ID NO: 15 and 65 of WO2016065001), AAV CLv-L5 (SEQ ID NO: 16 and 66 of WO2016065001), AAV CLv-L6 (SEQ ID NO: 17 and 67 of WO2016065001), AAV CLv-K1 (SEQ ID NO: 18 and 68 of WO2016065001), AAV CLv-K3 (SEQ ID NO: 19 and 69 of

WO2016065001), AAV CLv-K6 (SEQ ID NO: 20 and 70 of WO2016065001), AAV CLv-M1 (SEQ ID NO: 21 and 71 of WO2016065001), AAV CLv-M11 (SEQ ID NO: 22 and 72 of WO2016065001), AAV CLv-M2 (SEQ ID NO: 23 and 73 of WO2016065001), AAV CLv-M5 (SEQ ID NO: 24 and 74 of WO2016065001), AAV CLv-M6 (SEQ ID NO: 25 and 75 of WO2016065001), AAV CLv-M7 (SEQ ID NO: 26 and 76 of WO2016065001), AAV CLv-M8 (SEQ ID NO: 27 and 77 of WO2016065001), AAV CLv-M9 (SEQ ID NO: 28 and 78 of WO2016065001), AAV CHt-P1 (SEQ ID NO: 29 and 79 of WO2016065001), AAV CHt-P6 (SEQ ID NO: 30 and 80 of WO2016065001), AAV CHt-P8 (SEQ ID NO: 31 and 81 of WO2016065001), AAV CHt-6.1 (SEQ ID NO: 32 and 82 of WO2016065001), AAV CHt-6.10 (SEQ ID NO: 33 and 83 of WO2016065001), AAV CHt-6.5 (SEQ ID NO: 34 and 84 of WO2016065001), AAV CHt-6.6 (SEQ ID NO: 35 and 85 of WO2016065001), AAV CHt-6.7 (SEQ ID NO: 36 and 86 of WO2016065001), AAV CHt-6.8 (SEQ ID NO: 37 and 87 of WO2016065001), AAV CSp-8.10 (SEQ ID NO: 38 and 88 of WO2016065001), AAV CSp-8.2 (SEQ ID NO: 39 and 89 of WO2016065001), AAV CSp-8.4 (SEQ ID NO: 40 and 90 of WO2016065001), AAV CSp-8.5 (SEQ ID NO: 41 and 91 of WO2016065001), AAV CSp-8.6 (SEQ ID NO: 42 and 92 of WO2016065001), AAV CSp-8.7 (SEQ ID NO: 43 and 93 of WO2016065001), AAV CSp-8.8 (SEQ ID NO: 44 and 94 of WO2016065001), AAV CSp-8.9 (SEQ ID NO: 45 and 95 of WO2016065001), AAV CBr-B7.3 (SEQ ID NO: 46 and 96 of WO2016065001), AAV CBr-B7.4 (SEQ ID NO: 47 and 97 of WO2016065001), AAV3B (SEQ ID NO: 48 and 98 of WO2016065001), AAV4 (SEQ ID NO: 49 and 99 of WO2016065001), AAV5 (SEQ ID NO: 50 and 100 of WO2016065001), or variants or derivatives thereof.

[0086] In one embodiment, the AAV may be a serotype selected from any of those found in Table 1.

[0087] In one embodiment, the AAV may comprise a sequence, fragment or variant thereof, of the sequences in Table 1.

[0088] In one embodiment, the AAV may be encoded by a sequence, fragment or variant as described in Table 1.

Table 1. AAV Serotypes

Serotype	SEQ ID NO	Reference Information
AAV1	1	US20150159173 SEQ ID NO: 11, US20150315612 SEQ ID NO: 202
AAV1	2	US20160017295 SEQ ID NO: 1, US20030138772 SEQ ID NO: 64, US20150159173 SEQ ID NO: 27, US20150315612 SEQ ID NO: 219, US7198951 SEQ ID NO: 5
AAV1	3	US20030138772 SEQ ID NO: 6
AAV1.3	4	US20030138772 SEQ ID NO: 14

AAV10	5	US20030138772 SEQ ID NO: 117
AAV10	6	WO2015121501 SEQ ID NO: 9
AAV10	7	WO2015121501 SEQ ID NO: 8
AAV11	8	US20030138772 SEQ ID NO: 118
AAV12	9	US20030138772 SEQ ID NO: 119
AAV2	10	US20150159173 SEQ ID NO: 7, US20150315612 SEQ ID NO: 211
AAV2	11	US20030138772 SEQ ID NO: 70, US20150159173 SEQ ID NO: 23, US20150315612 SEQ ID NO: 221, US20160017295 SEQ ID NO: 2, US6156303 SEQ ID NO: 4, US7198951 SEQ ID NO: 4, WO2015121501 SEQ ID NO: 1
AAV2	12	US6156303 SEQ ID NO: 8
AAV2	13	US20030138772 SEQ ID NO: 7
AAV2	14	US6156303 SEQ ID NO: 3
AAV2.5T	15	US9233131 SEQ ID NO: 42
AAV223.10	16	US20030138772 SEQ ID NO: 75
AAV223.2	17	US20030138772 SEQ ID NO: 49
AAV223.2	18	US20030138772 SEQ ID NO: 76
AAV223.4	19	US20030138772 SEQ ID NO: 50
AAV223.4	20	US20030138772 SEQ ID NO: 73
AAV223.5	21	US20030138772 SEQ ID NO: 51
AAV223.5	22	US20030138772 SEQ ID NO: 74
AAV223.6	23	US20030138772 SEQ ID NO: 52
AAV223.6	24	US20030138772 SEQ ID NO: 78
AAV223.7	25	US20030138772 SEQ ID NO: 53
AAV223.7	26	US20030138772 SEQ ID NO: 77
AAV29.3	27	US20030138772 SEQ ID NO: 82
AAV29.4	28	US20030138772 SEQ ID NO: 12
AAV29.5	29	US20030138772 SEQ ID NO: 83
AAV29.5 (AAVbb.2)	30	US20030138772 SEQ ID NO: 13
AAV3	31	US20150159173 SEQ ID NO: 12
AAV3	32	US20030138772 SEQ ID NO: 71, US20150159173 SEQ ID NO: 28, US20160017295 SEQ ID NO: 3, US7198951 SEQ ID NO: 6
AAV3	33	US20030138772 SEQ ID NO: 8
AAV3.3b	34	US20030138772 SEQ ID NO: 72
AAV3-3	35	US20150315612 SEQ ID NO: 200
AAV3-3	36	US20150315612 SEQ ID NO: 217
AAV3a	37	US6156303 SEQ ID NO: 5
AAV3a	38	US6156303 SEQ ID NO: 9
AAV3b	39	US6156303 SEQ ID NO: 6
AAV3b	40	US6156303 SEQ ID NO: 10
AAV3b	41	US6156303 SEQ ID NO: 1
AAV4	42	US20140348794 SEQ ID NO: 17
AAV4	43	US20140348794 SEQ ID NO: 5
AAV4	44	US20140348794 SEQ ID NO: 3

AAV4	45	US20140348794 SEQ ID NO: 14
AAV4	46	US20140348794 SEQ ID NO: 15
AAV4	47	US20140348794 SEQ ID NO: 19
AAV4	48	US20140348794 SEQ ID NO: 12
AAV4	49	US20140348794 SEQ ID NO: 13
AAV4	50	US20140348794 SEQ ID NO: 7
AAV4	51	US20140348794 SEQ ID NO: 8
AAV4	52	US20140348794 SEQ ID NO: 9
AAV4	53	US20140348794 SEQ ID NO: 2
AAV4	54	US20140348794 SEQ ID NO: 10
AAV4	55	US20140348794 SEQ ID NO: 11
AAV4	56	US20140348794 SEQ ID NO: 18
AAV4	57	US20030138772 SEQ ID NO: 63, US20160017295 SEQ ID NO: 4, US20140348794 SEQ ID NO: 4
AAV4	58	US20140348794 SEQ ID NO: 16
AAV4	59	US20140348794 SEQ ID NO: 20
AAV4	60	US20140348794 SEQ ID NO: 6
AAV4	61	US20140348794 SEQ ID NO: 1
AAV42.2	62	US20030138772 SEQ ID NO: 9
AAV42.2	63	US20030138772 SEQ ID NO: 102
AAV42.3b	64	US20030138772 SEQ ID NO: 36
AAV42.3B	65	US20030138772 SEQ ID NO: 107
AAV42.4	66	US20030138772 SEQ ID NO: 33
AAV42.4	67	US20030138772 SEQ ID NO: 88
AAV42.8	68	US20030138772 SEQ ID NO: 27
AAV42.8	69	US20030138772 SEQ ID NO: 85
AAV43.1	70	US20030138772 SEQ ID NO: 39
AAV43.1	71	US20030138772 SEQ ID NO: 92
AAV43.12	72	US20030138772 SEQ ID NO: 41
AAV43.12	73	US20030138772 SEQ ID NO: 93
AAV43.20	74	US20030138772 SEQ ID NO: 42
AAV43.20	75	US20030138772 SEQ ID NO: 99
AAV43.21	76	US20030138772 SEQ ID NO: 43
AAV43.21	77	US20030138772 SEQ ID NO: 96
AAV43.23	78	US20030138772 SEQ ID NO: 44
AAV43.23	79	US20030138772 SEQ ID NO: 98
AAV43.25	80	US20030138772 SEQ ID NO: 45
AAV43.25	81	US20030138772 SEQ ID NO: 97
AAV43.5	82	US20030138772 SEQ ID NO: 40
AAV43.5	83	US20030138772 SEQ ID NO: 94
AAV4-4	84	US20150315612 SEQ ID NO: 201
AAV4-4	85	US20150315612 SEQ ID NO: 218
AAV44.1	86	US20030138772 SEQ ID NO: 46
AAV44.1	87	US20030138772 SEQ ID NO: 79
AAV44.5	88	US20030138772 SEQ ID NO: 47

AAV44.5	89	US20030138772 SEQ ID NO: 80
AAV4407	90	US20150315612 SEQ ID NO: 90
AAV5	91	US7427396 SEQ ID NO: 1
AAV5	92	US20030138772 SEQ ID NO: 114
AAV5	93	US20160017295 SEQ ID NO: 5, US7427396 SEQ ID NO: 2, US20150315612 SEQ ID NO: 216
AAV5	94	US20150315612 SEQ ID NO: 199
AAV6	95	US20150159173 SEQ ID NO: 13
AAV6	96	US20030138772 SEQ ID NO: 65, US20150159173 SEQ ID NO: 29, US20160017295 SEQ ID NO: 6, US6156303 SEQ ID NO: 7
AAV6	97	US6156303 SEQ ID NO: 11
AAV6	98	US6156303 SEQ ID NO: 2
AAV6	99	US20150315612 SEQ ID NO: 203
AAV6	100	US20150315612 SEQ ID NO: 220
AAV6.1	101	US20150159173
AAV6.12	102	US20150159173
AAV6.2	103	US20150159173
AAV7	104	US20150159173 SEQ ID NO: 14
AAV7	105	US20150315612 SEQ ID NO: 183
AAV7	106	US20030138772 SEQ ID NO: 2, US20150159173 SEQ ID NO: 30, US20150315612 SEQ ID NO: 181, US20160017295 SEQ ID NO: 7
AAV7	107	US20030138772 SEQ ID NO: 3
AAV7	108	US20030138772 SEQ ID NO: 1, US20150315612 SEQ ID NO: 180
AAV7	109	US20150315612 SEQ ID NO: 213
AAV7	110	US20150315612 SEQ ID NO: 222
AAV8	111	US20150159173 SEQ ID NO: 15
AAV8	112	US20150376240 SEQ ID NO: 7
AAV8	113	US20030138772 SEQ ID NO: 4, US20150315612 SEQ ID NO: 182
AAV8	114	US20030138772 SEQ ID NO: 95, US20140359799 SEQ ID NO: 1, US20150159173 SEQ ID NO: 31, US20160017295 SEQ ID NO: 8, US7198951 SEQ ID NO: 7, US20150315612 SEQ ID NO: 223
AAV8	115	US20150376240 SEQ ID NO: 8
AAV8	116	US20150315612 SEQ ID NO: 214
AAV-8b	117	US20150376240 SEQ ID NO: 5
AAV-8b	118	US20150376240 SEQ ID NO: 3
AAV-8h	119	US20150376240 SEQ ID NO: 6
AAV-8h	120	US20150376240 SEQ ID NO: 4
AAV9	121	US20030138772 SEQ ID NO: 5
AAV9	122	US7198951 SEQ ID NO: 1
AAV9	123	US20160017295 SEQ ID NO: 9
AAV9	124	US20030138772 SEQ ID NO: 100, US7198951 SEQ ID NO: 2
AAV9	125	US7198951 SEQ ID NO: 3
AAV9 (AAVhu.14)	126	US7906111 SEQ ID NO: 3, WO2015038958 SEQ ID NO: 11

AAV9 (AAVhu.14)	127	US7906111 SEQ ID NO: 123, WO2015038958 SEQ ID NO: 2
AAVA3.1	128	US20030138772 SEQ ID NO: 120
AAVA3.3	129	US20030138772 SEQ ID NO: 57
AAVA3.3	130	US20030138772 SEQ ID NO: 66
AAVA3.4	131	US20030138772 SEQ ID NO: 54
AAVA3.4	132	US20030138772 SEQ ID NO: 68
AAVA3.5	133	US20030138772 SEQ ID NO: 55
AAVA3.5	134	US20030138772 SEQ ID NO: 69
AAVA3.7	135	US20030138772 SEQ ID NO: 56
AAVA3.7	136	US20030138772 SEQ ID NO: 67
AAV29.3 (AAVbb.1)	137	US20030138772 SEQ ID NO: 11
AAVC2	138	US20030138772 SEQ ID NO: 61
AAVCh.5	139	US20150159173 SEQ ID NO: 46, US20150315612 SEQ ID NO: 234
AAVcy.2 (AAV13.3)	140	US20030138772 SEQ ID NO: 15
AAV24.1	141	US20030138772 SEQ ID NO: 101
AAVcy.3 (AAV24.1)	142	US20030138772 SEQ ID NO: 16
AAV27.3	143	US20030138772 SEQ ID NO: 104
AAVcy.4 (AAV27.3)	144	US20030138772 SEQ ID NO: 17
AAVcy.5	145	US20150315612 SEQ ID NO: 227
AAV7.2	146	US20030138772 SEQ ID NO: 103
AAVcy.5 (AAV7.2)	147	US20030138772 SEQ ID NO: 18
AAV16.3	148	US20030138772 SEQ ID NO: 105
AAVcy.6 (AAV16.3)	149	US20030138772 SEQ ID NO: 10
AAVcy.5	150	US20150159173 SEQ ID NO: 8
AAVcy.5	151	US20150159173 SEQ ID NO: 24
AAVCy.5R1	152	US20150159173
AAVCy.5R2	153	US20150159173
AAVCy.5R3	154	US20150159173
AAVCy.5R4	155	US20150159173
AAVDJ	156	US20140359799 SEQ ID NO: 3, US7588772 SEQ ID NO: 2
AAVDJ	157	US20140359799 SEQ ID NO: 2, US7588772 SEQ ID NO: 1
AAVDJ-8	158	US7588772; Grimm et al 2008
AAVDJ-8	159	US7588772; Grimm et al 2008
AAVF5	160	US20030138772 SEQ ID NO: 110
AAVH2	161	US20030138772 SEQ ID NO: 26
AAVH6	162	US20030138772 SEQ ID NO: 25
AAVhE1.1	163	US9233131 SEQ ID NO: 44
AAVhEr1.14	164	US9233131 SEQ ID NO: 46
AAVhEr1.16	165	US9233131 SEQ ID NO: 48
AAVhEr1.18	166	US9233131 SEQ ID NO: 49
AAVhEr1.23 (AAVhEr2.29)	167	US9233131 SEQ ID NO: 53
AAVhEr1.35	168	US9233131 SEQ ID NO: 50
AAVhEr1.36	169	US9233131 SEQ ID NO: 52

AAVhEr1.5	170	US9233131 SEQ ID NO: 45
AAVhEr1.7	171	US9233131 SEQ ID NO: 51
AAVhEr1.8	172	US9233131 SEQ ID NO: 47
AAVhEr2.16	173	US9233131 SEQ ID NO: 55
AAVhEr2.30	174	US9233131 SEQ ID NO: 56
AAVhEr2.31	175	US9233131 SEQ ID NO: 58
AAVhEr2.36	176	US9233131 SEQ ID NO: 57
AAVhEr2.4	177	US9233131 SEQ ID NO: 54
AAVhEr3.1	178	US9233131 SEQ ID NO: 59
AAVhu.1	179	US20150315612 SEQ ID NO: 46
AAVhu.1	180	US20150315612 SEQ ID NO: 144
AAVhu.10 (AAV16.8)	181	US20150315612 SEQ ID NO: 56
AAVhu.10 (AAV16.8)	182	US20150315612 SEQ ID NO: 156
AAVhu.11 (AAV16.12)	183	US20150315612 SEQ ID NO: 57
AAVhu.11 (AAV16.12)	184	US20150315612 SEQ ID NO: 153
AAVhu.12	185	US20150315612 SEQ ID NO: 59
AAVhu.12	186	US20150315612 SEQ ID NO: 154
AAVhu.13	187	US20150159173 SEQ ID NO: 16, US20150315612 SEQ ID NO: 71
AAVhu.13	188	US20150159173 SEQ ID NO: 32, US20150315612 SEQ ID NO: 129
AAVhu.136.1	189	US20150315612 SEQ ID NO: 165
AAVhu.140.1	190	US20150315612 SEQ ID NO: 166
AAVhu.140.2	191	US20150315612 SEQ ID NO: 167
AAVhu.145.6	192	US20150315612 SEQ ID No: 178
AAVhu.15	193	US20150315612 SEQ ID NO: 147
AAVhu.15 (AAV33.4)	194	US20150315612 SEQ ID NO: 50
AAVhu.156.1	195	US20150315612 SEQ ID No: 179
AAVhu.16	196	US20150315612 SEQ ID NO: 148
AAVhu.16 (AAV33.8)	197	US20150315612 SEQ ID NO: 51
AAVhu.17	198	US20150315612 SEQ ID NO: 83
AAVhu.17 (AAV33.12)	199	US20150315612 SEQ ID NO: 4
AAVhu.172.1	200	US20150315612 SEQ ID NO: 171
AAVhu.172.2	201	US20150315612 SEQ ID NO: 172
AAVhu.173.4	202	US20150315612 SEQ ID NO: 173
AAVhu.173.8	203	US20150315612 SEQ ID NO: 175
AAVhu.18	204	US20150315612 SEQ ID NO: 52
AAVhu.18	205	US20150315612 SEQ ID NO: 149
AAVhu.19	206	US20150315612 SEQ ID NO: 62
AAVhu.19	207	US20150315612 SEQ ID NO: 133
AAVhu.2	208	US20150315612 SEQ ID NO: 48
AAVhu.2	209	US20150315612 SEQ ID NO: 143
AAVhu.20	210	US20150315612 SEQ ID NO: 63
AAVhu.20	211	US20150315612 SEQ ID NO: 134
AAVhu.21	212	US20150315612 SEQ ID NO: 65
AAVhu.21	213	US20150315612 SEQ ID NO: 135

AAVhu.22	214	US20150315612 SEQ ID NO: 67
AAVhu.22	215	US20150315612 SEQ ID NO: 138
AAVhu.23	216	US20150315612 SEQ ID NO: 60
AAVhu.23.2	217	US20150315612 SEQ ID NO: 137
AAVhu.24	218	US20150315612 SEQ ID NO: 66
AAVhu.24	219	US20150315612 SEQ ID NO: 136
AAVhu.25	220	US20150315612 SEQ ID NO: 49
AAVhu.25	221	US20150315612 SEQ ID NO: 146
AAVhu.26	222	US20150159173 SEQ ID NO: 17, US20150315612 SEQ ID NO: 61
AAVhu.26	223	US20150159173 SEQ ID NO: 33, US20150315612 SEQ ID NO: 139
AAVhu.27	224	US20150315612 SEQ ID NO: 64
AAVhu.27	225	US20150315612 SEQ ID NO: 140
AAVhu.28	226	US20150315612 SEQ ID NO: 68
AAVhu.28	227	US20150315612 SEQ ID NO: 130
AAVhu.29	228	US20150315612 SEQ ID NO: 69
AAVhu.29	229	US20150159173 SEQ ID NO: 42, US20150315612 SEQ ID NO: 132
AAVhu.29	230	US20150315612 SEQ ID NO: 225
AAVhu.29R	231	US20150159173
AAVhu.3	232	US20150315612 SEQ ID NO: 44
AAVhu.3	233	US20150315612 SEQ ID NO: 145
AAVhu.30	234	US20150315612 SEQ ID NO: 70
AAVhu.30	235	US20150315612 SEQ ID NO: 131
AAVhu.31	236	US20150315612 SEQ ID NO: 1
AAVhu.31	237	US20150315612 SEQ ID NO: 121
AAVhu.32	238	US20150315612 SEQ ID NO: 2
AAVhu.32	239	US20150315612 SEQ ID NO: 122
AAVhu.33	240	US20150315612 SEQ ID NO: 75
AAVhu.33	241	US20150315612 SEQ ID NO: 124
AAVhu.34	242	US20150315612 SEQ ID NO: 72
AAVhu.34	243	US20150315612 SEQ ID NO: 125
AAVhu.35	244	US20150315612 SEQ ID NO: 73
AAVhu.35	245	US20150315612 SEQ ID NO: 164
AAVhu.36	246	US20150315612 SEQ ID NO: 74
AAVhu.36	247	US20150315612 SEQ ID NO: 126
AAVhu.37	248	US20150159173 SEQ ID NO: 34, US20150315612 SEQ ID NO: 88
AAVhu.37 (AAV106.1)	249	US20150315612 SEQ ID NO: 10, US20150159173 SEQ ID NO: 18
AAVhu.38	250	US20150315612 SEQ ID NO: 161
AAVhu.39	251	US20150315612 SEQ ID NO: 102
AAVhu.39 (AAVLG-9)	252	US20150315612 SEQ ID NO: 24
AAVhu.4	253	US20150315612 SEQ ID NO: 47
AAVhu.4	254	US20150315612 SEQ ID NO: 141
AAVhu.40	255	US20150315612 SEQ ID NO: 87

AAVhu.40 (AAV114.3)	256	US20150315612 SEQ ID No: 11
AAVhu.41	257	US20150315612 SEQ ID NO: 91
AAVhu.41 (AAV127.2)	258	US20150315612 SEQ ID NO: 6
AAVhu.42	259	US20150315612 SEQ ID NO: 85
AAVhu.42 (AAV127.5)	260	US20150315612 SEQ ID NO: 8
AAVhu.43	261	US20150315612 SEQ ID NO: 160
AAVhu.43	262	US20150315612 SEQ ID NO: 236
AAVhu.43 (AAV128.1)	263	US20150315612 SEQ ID NO: 80
AAVhu.44	264	US20150159173 SEQ ID NO: 45, US20150315612 SEQ ID NO: 158
AAVhu.44 (AAV128.3)	265	US20150315612 SEQ ID NO: 81
AAVhu.44R1	266	US20150159173
AAVhu.44R2	267	US20150159173
AAVhu.44R3	268	US20150159173
AAVhu.45	269	US20150315612 SEQ ID NO: 76
AAVhu.45	270	US20150315612 SEQ ID NO: 127
AAVhu.46	271	US20150315612 SEQ ID NO: 82
AAVhu.46	272	US20150315612 SEQ ID NO: 159
AAVhu.46	273	US20150315612 SEQ ID NO: 224
AAVhu.47	274	US20150315612 SEQ ID NO: 77
AAVhu.47	275	US20150315612 SEQ ID NO: 128
AAVhu.48	276	US20150159173 SEQ ID NO: 38
AAVhu.48	277	US20150315612 SEQ ID NO: 157
AAVhu.48 (AAV130.4)	278	US20150315612 SEQ ID NO: 78
AAVhu.48R1	279	US20150159173
AAVhu.48R2	280	US20150159173
AAVhu.48R3	281	US20150159173
AAVhu.49	282	US20150315612 SEQ ID NO: 209
AAVhu.49	283	US20150315612 SEQ ID NO: 189
AAVhu.5	284	US20150315612 SEQ ID NO: 45
AAVhu.5	285	US20150315612 SEQ ID NO: 142
AAVhu.51	286	US20150315612 SEQ ID NO: 208
AAVhu.51	287	US20150315612 SEQ ID NO: 190
AAVhu.52	288	US20150315612 SEQ ID NO: 210
AAVhu.52	289	US20150315612 SEQ ID NO: 191
AAVhu.53	290	US20150159173 SEQ ID NO: 19
AAVhu.53	291	US20150159173 SEQ ID NO: 35
AAVhu.53 (AAV145.1)	292	US20150315612 SEQ ID NO: 176
AAVhu.54	293	US20150315612 SEQ ID NO: 188
AAVhu.54 (AAV145.5)	294	US20150315612 SEQ ID No: 177
AAVhu.55	295	US20150315612 SEQ ID NO: 187
AAVhu.56	296	US20150315612 SEQ ID NO: 205
AAVhu.56 (AAV145.6)	297	US20150315612 SEQ ID NO: 168
AAVhu.56 (AAV145.6)	298	US20150315612 SEQ ID NO: 192
AAVhu.57	299	US20150315612 SEQ ID NO: 206

AAVhu.57	300	US20150315612 SEQ ID NO: 169
AAVhu.57	301	US20150315612 SEQ ID NO: 193
AAVhu.58	302	US20150315612 SEQ ID NO: 207
AAVhu.58	303	US20150315612 SEQ ID NO: 194
AAVhu.6 (AAV3.1)	304	US20150315612 SEQ ID NO: 5
AAVhu.6 (AAV3.1)	305	US20150315612 SEQ ID NO: 84
AAVhu.60	306	US20150315612 SEQ ID NO: 184
AAVhu.60 (AAV161.10)	307	US20150315612 SEQ ID NO: 170
AAVhu.61	308	US20150315612 SEQ ID NO: 185
AAVhu.61 (AAV161.6)	309	US20150315612 SEQ ID NO: 174
AAVhu.63	310	US20150315612 SEQ ID NO: 204
AAVhu.63	311	US20150315612 SEQ ID NO: 195
AAVhu.64	312	US20150315612 SEQ ID NO: 212
AAVhu.64	313	US20150315612 SEQ ID NO: 196
AAVhu.66	314	US20150315612 SEQ ID NO: 197
AAVhu.67	315	US20150315612 SEQ ID NO: 215
AAVhu.67	316	US20150315612 SEQ ID NO: 198
AAVhu.7	317	US20150315612 SEQ ID NO: 226
AAVhu.7	318	US20150315612 SEQ ID NO: 150
AAVhu.7 (AAV7.3)	319	US20150315612 SEQ ID NO: 55
AAVhu.71	320	US20150315612 SEQ ID NO: 79
AAVhu.8	321	US20150315612 SEQ ID NO: 53
AAVhu.8	322	US20150315612 SEQ ID NO: 12
AAVhu.8	323	US20150315612 SEQ ID NO: 151
AAVhu.9 (AAV3.1)	324	US20150315612 SEQ ID NO: 58
AAVhu.9 (AAV3.1)	325	US20150315612 SEQ ID NO: 155
AAV-LK01	326	US20150376607 SEQ ID NO: 2
AAV-LK01	327	US20150376607 SEQ ID NO: 29
AAV-LK02	328	US20150376607 SEQ ID NO: 3
AAV-LK02	329	US20150376607 SEQ ID NO: 30
AAV-LK03	330	US20150376607 SEQ ID NO: 4
AAV-LK03	331	WO2015121501 SEQ ID NO: 12, US20150376607 SEQ ID NO: 31
AAV-LK04	332	US20150376607 SEQ ID NO: 5
AAV-LK04	333	US20150376607 SEQ ID NO: 32
AAV-LK05	334	US20150376607 SEQ ID NO: 6
AAV-LK05	335	US20150376607 SEQ ID NO: 33
AAV-LK06	336	US20150376607 SEQ ID NO: 7
AAV-LK06	337	US20150376607 SEQ ID NO: 34
AAV-LK07	338	US20150376607 SEQ ID NO: 8
AAV-LK07	339	US20150376607 SEQ ID NO: 35
AAV-LK08	340	US20150376607 SEQ ID NO: 9
AAV-LK08	341	US20150376607 SEQ ID NO: 36
AAV-LK09	342	US20150376607 SEQ ID NO: 10
AAV-LK09	343	US20150376607 SEQ ID NO: 37

AAV-LK10	344	US20150376607 SEQ ID NO: 11
AAV-LK10	345	US20150376607 SEQ ID NO: 38
AAV-LK11	346	US20150376607 SEQ ID NO: 12
AAV-LK11	347	US20150376607 SEQ ID NO: 39
AAV-LK12	348	US20150376607 SEQ ID NO: 13
AAV-LK12	349	US20150376607 SEQ ID NO: 40
AAV-LK13	350	US20150376607 SEQ ID NO: 14
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AAV-LK15	354	US20150376607 SEQ ID NO: 16
AAV-LK15	355	US20150376607 SEQ ID NO: 43
AAV-LK16	356	US20150376607 SEQ ID NO: 17
AAV-LK16	357	US20150376607 SEQ ID NO: 44
AAV-LK17	358	US20150376607 SEQ ID NO: 18
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AAV-PAEC12	368	US20150376607 SEQ ID NO: 27
AAV-PAEC12	369	US20150376607 SEQ ID NO: 51
AAV-PAEC13	370	US20150376607 SEQ ID NO: 28
AAV-PAEC13	371	US20150376607 SEQ ID NO: 49
AAV-PAEC2	372	US20150376607 SEQ ID NO: 21
AAV-PAEC2	373	US20150376607 SEQ ID NO: 56
AAV-PAEC4	374	US20150376607 SEQ ID NO: 22
AAV-PAEC4	375	US20150376607 SEQ ID NO: 55
AAV-PAEC6	376	US20150376607 SEQ ID NO: 23
AAV-PAEC6	377	US20150376607 SEQ ID NO: 52
AAV-PAEC7	378	US20150376607 SEQ ID NO: 24
AAV-PAEC7	379	US20150376607 SEQ ID NO: 53
AAV-PAEC8	380	US20150376607 SEQ ID NO: 25
AAV-PAEC8	381	US20150376607 SEQ ID NO: 50
AAVpi.1	382	US20150315612 SEQ ID NO: 28
AAVpi.1	383	US20150315612 SEQ ID NO: 93
AAVpi.2	384	US20150315612 SEQ ID NO: 30
AAVpi.2	385	US20150315612 SEQ ID NO: 95
AAVpi.3	386	US20150315612 SEQ ID NO: 29
AAVpi.3	387	US20150315612 SEQ ID NO: 94
AAVrh.10	388	US20150159173 SEQ ID NO: 9

AAVrh.10	389	US20150159173 SEQ ID NO: 25
AAV44.2	390	US20030138772 SEQ ID NO: 59
AAVrh.10 (AAV44.2)	391	US20030138772 SEQ ID NO: 81
AAV42.1B	392	US20030138772 SEQ ID NO: 90
AAVrh.12 (AAV42.1b)	393	US20030138772 SEQ ID NO: 30
AAVrh.13	394	US20150159173 SEQ ID NO: 10
AAVrh.13	395	US20150159173 SEQ ID NO: 26
AAVrh.13	396	US20150315612 SEQ ID NO: 228
AAVrh.13R	397	US20150159173
AAV42.3A	398	US20030138772 SEQ ID NO: 87
AAVrh.14 (AAV42.3a)	399	US20030138772 SEQ ID NO: 32
AAV42.5A	400	US20030138772 SEQ ID NO: 89
AAVrh.17 (AAV42.5a)	401	US20030138772 SEQ ID NO: 34
AAV42.5B	402	US20030138772 SEQ ID NO: 91
AAVrh.18 (AAV42.5b)	403	US20030138772 SEQ ID NO: 29
AAV42.6B	404	US20030138772 SEQ ID NO: 112
AAVrh.19 (AAV42.6b)	405	US20030138772 SEQ ID NO: 38
AAVrh.2	406	US20150159173 SEQ ID NO: 39
AAVrh.2	407	US20150315612 SEQ ID NO: 231
AAVrh.20	408	US20150159173 SEQ ID NO: 1
AAV42.10	409	US20030138772 SEQ ID NO: 106
AAVrh.21 (AAV42.10)	410	US20030138772 SEQ ID NO: 35
AAV42.11	411	US20030138772 SEQ ID NO: 108
AAVrh.22 (AAV42.11)	412	US20030138772 SEQ ID NO: 37
AAV42.12	413	US20030138772 SEQ ID NO: 113
AAVrh.23 (AAV42.12)	414	US20030138772 SEQ ID NO: 58
AAV42.13	415	US20030138772 SEQ ID NO: 86
AAVrh.24 (AAV42.13)	416	US20030138772 SEQ ID NO: 31
AAV42.15	417	US20030138772 SEQ ID NO: 84
AAVrh.25 (AAV42.15)	418	US20030138772 SEQ ID NO: 28
AAVrh.2R	419	US20150159173
AAVrh.31 (AAV223.1)	420	US20030138772 SEQ ID NO: 48
AAVC1	421	US20030138772 SEQ ID NO: 60
AAVrh.32 (AAVC1)	422	US20030138772 SEQ ID NO: 19
AAVrh.32/33	423	US20150159173 SEQ ID NO: 2
AAVrh.33 (AAVC3)	424	US20030138772 SEQ ID NO: 20
AAVC5	425	US20030138772 SEQ ID NO: 62
AAVrh.34 (AAVC5)	426	US20030138772 SEQ ID NO: 21
AAVF1	427	US20030138772 SEQ ID NO: 109
AAVrh.35 (AAVF1)	428	US20030138772 SEQ ID NO: 22
AAVF3	429	US20030138772 SEQ ID NO: 111
AAVrh.36 (AAVF3)	430	US20030138772 SEQ ID NO: 23
AAVrh.37	431	US20030138772 SEQ ID NO: 24
AAVrh.37	432	US20150159173 SEQ ID NO: 40
AAVrh.37	433	US20150315612 SEQ ID NO: 229

AAVrh.37R2	434	US20150159173
AAVrh.38 (AAVLG-4)	435	US20150315612 SEQ ID NO: 7
AAVrh.38 (AAVLG-4)	436	US20150315612 SEQ ID NO: 86
AAVrh.39	437	US20150159173 SEQ ID NO: 20, US20150315612 SEQ ID NO: 13
AAVrh.39	438	US20150159173 SEQ ID NO: 3, US20150159173 SEQ ID NO: 36, US20150315612 SEQ ID NO: 89
AAVrh.40	439	US20150315612 SEQ ID NO: 92
AAVrh.40 (AAVLG-10)	440	US20150315612 SEQ ID No: 14
AAVrh.43 (AAVN721-8)	441	US20150315612 SEQ ID NO: 43, US20150159173 SEQ ID NO: 21
AAVrh.43 (AAVN721-8)	442	US20150315612 SEQ ID NO: 163, US20150159173 SEQ ID NO: 37
AAVrh.44	443	US20150315612 SEQ ID NO: 34
AAVrh.44	444	US20150315612 SEQ ID NO: 111
AAVrh.45	445	US20150315612 SEQ ID NO: 41
AAVrh.45	446	US20150315612 SEQ ID NO: 109
AAVrh.46	447	US20150159173 SEQ ID NO: 22, US20150315612 SEQ ID NO: 19
AAVrh.46	448	US20150159173 SEQ ID NO: 4, US20150315612 SEQ ID NO: 101
AAVrh.47	449	US20150315612 SEQ ID NO: 38
AAVrh.47	450	US20150315612 SEQ ID NO: 118
AAVrh.48	451	US20150159173 SEQ ID NO: 44, US20150315612 SEQ ID NO: 115
AAVrh.48.1	452	US20150159173
AAVrh.48.1.2	453	US20150159173
AAVrh.48.2	454	US20150159173
AAVrh.48 (AAV1-7)	455	US20150315612 SEQ ID NO: 32
AAVrh.49 (AAV1-8)	456	US20150315612 SEQ ID NO: 25
AAVrh.49 (AAV1-8)	457	US20150315612 SEQ ID NO: 103
AAVrh.50 (AAV2-4)	458	US20150315612 SEQ ID NO: 23
AAVrh.50 (AAV2-4)	459	US20150315612 SEQ ID NO: 108
AAVrh.51 (AAV2-5)	460	US20150315612 SEQ ID NO: 22
AAVrh.51 (AAV2-5)	461	US20150315612 SEQ ID NO: 104
AAVrh.52 (AAV3-9)	462	US20150315612 SEQ ID NO: 18
AAVrh.52 (AAV3-9)	463	US20150315612 SEQ ID NO: 96
AAVrh.53	464	US20150315612 SEQ ID NO: 97
AAVrh.53 (AAV3-11)	465	US20150315612 SEQ ID NO: 17
AAVrh.53 (AAV3-11)	466	US20150315612 SEQ ID NO: 186
AAVrh.54	467	US20150315612 SEQ ID NO: 40
AAVrh.54	468	US20150159173 SEQ ID NO: 49, US20150315612 SEQ ID NO: 116
AAVrh.55	469	US20150315612 SEQ ID NO: 37
AAVrh.55 (AAV4-19)	470	US20150315612 SEQ ID NO: 117
AAVrh.56	471	US20150315612 SEQ ID NO: 54
AAVrh.56	472	US20150315612 SEQ ID NO: 152
AAVrh.57	473	US20150315612 SEQ ID NO: 26
AAVrh.57	474	US20150315612 SEQ ID NO: 105

AAVrh.58	475	US20150315612 SEQ ID NO: 27
AAVrh.58	476	US20150159173 SEQ ID NO: 48, US20150315612 SEQ ID NO: 106
AAVrh.58	477	US20150315612 SEQ ID NO: 232
AAVrh.59	478	US20150315612 SEQ ID NO: 42
AAVrh.59	479	US20150315612 SEQ ID NO: 110
AAVrh.60	480	US20150315612 SEQ ID NO: 31
AAVrh.60	481	US20150315612 SEQ ID NO: 120
AAVrh.61	482	US20150315612 SEQ ID NO: 107
AAVrh.61 (AAV2-3)	483	US20150315612 SEQ ID NO: 21
AAVrh.62 (AAV2-15)	484	US20150315612 SEQ ID NO: 33
AAVrh.62 (AAV2-15)	485	US20150315612 SEQ ID NO: 114
AAVrh.64	486	US20150315612 SEQ ID NO: 15
AAVrh.64	487	US20150159173 SEQ ID NO: 43, US20150315612 SEQ ID NO: 99
AAVrh.64	488	US20150315612 SEQ ID NO: 233
AAVRh.64R1	489	US20150159173
AAVRh.64R2	490	US20150159173
AAVrh.65	491	US20150315612 SEQ ID NO: 35
AAVrh.65	492	US20150315612 SEQ ID NO: 112
AAVrh.67	493	US20150315612 SEQ ID NO: 36
AAVrh.67	494	US20150315612 SEQ ID NO: 230
AAVrh.67	495	US20150159173 SEQ ID NO: 47, US20150315612 SEQ ID NO: 113
AAVrh.68	496	US20150315612 SEQ ID NO: 16
AAVrh.68	497	US20150315612 SEQ ID NO: 100
AAVrh.69	498	US20150315612 SEQ ID NO: 39
AAVrh.69	499	US20150315612 SEQ ID NO: 119
AAVrh.70	500	US20150315612 SEQ ID NO: 20
AAVrh.70	501	US20150315612 SEQ ID NO: 98
AAVrh.71	502	US20150315612 SEQ ID NO: 162
AAVrh.72	503	US20150315612 SEQ ID NO: 9
AAVrh.73	504	US20150159173 SEQ ID NO: 5
AAVrh.74	505	US20150159173 SEQ ID NO: 6
AAVrh.8	506	US20150159173 SEQ ID NO: 41
AAVrh.8	507	US20150315612 SEQ ID NO: 235
AAVrh.8R	508	US20150159173, WO2015168666 SEQ ID NO: 9
AAVrh.8R A586R mutant	509	WO2015168666 SEQ ID NO: 10
AAVrh.8R R533A mutant	510	WO2015168666 SEQ ID NO: 11
BAAV (bovine AAV)	511	US9193769 SEQ ID NO: 8
BAAV (bovine AAV)	512	US9193769 SEQ ID NO: 10
BAAV (bovine AAV)	513	US9193769 SEQ ID NO: 4
BAAV (bovine AAV)	514	US9193769 SEQ ID NO: 2
BAAV (bovine AAV)	515	US9193769 SEQ ID NO: 6
BAAV (bovine AAV)	516	US9193769 SEQ ID NO: 1
BAAV (bovine AAV)	517	US9193769 SEQ ID NO: 5

BAAV (bovine AAV)	518	US9193769 SEQ ID NO: 3
BAAV (bovine AAV)	519	US9193769 SEQ ID NO: 11
BAAV (bovine AAV)	520	US7427396 SEQ ID NO: 5
BAAV (bovine AAV)	521	US7427396 SEQ ID NO: 6
BAAV (bovine AAV)	522	US9193769 SEQ ID NO: 7
BAAV (bovine AAV)	523	US9193769 SEQ ID NO: 9
BNP61 AAV	524	US20150238550 SEQ ID NO: 1
BNP61 AAV	525	US20150238550 SEQ ID NO: 2
BNP62 AAV	526	US20150238550 SEQ ID NO: 3
BNP63 AAV	527	US20150238550 SEQ ID NO: 4
caprine AAV	528	US7427396 SEQ ID NO: 3
caprine AAV	529	US7427396 SEQ ID NO: 4
true type AAV (ttAAV)	530	WO2015121501 SEQ ID NO: 2
AAAV (Avian AAV)	531	US9238800 SEQ ID NO: 12
AAAV (Avian AAV)	532	US9238800 SEQ ID NO: 2
AAAV (Avian AAV)	533	US9238800 SEQ ID NO: 6
AAAV (Avian AAV)	534	US9238800 SEQ ID NO: 4
AAAV (Avian AAV)	535	US9238800 SEQ ID NO: 8
AAAV (Avian AAV)	536	US9238800 SEQ ID NO: 14
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AAAV (Avian AAV)	538	US9238800 SEQ ID NO: 15
AAAV (Avian AAV)	539	US9238800 SEQ ID NO: 5
AAAV (Avian AAV)	540	US9238800 SEQ ID NO: 9
AAAV (Avian AAV)	541	US9238800 SEQ ID NO: 3
AAAV (Avian AAV)	542	US9238800 SEQ ID NO: 7
AAAV (Avian AAV)	543	US9238800 SEQ ID NO: 11
AAAV (Avian AAV)	544	US9238800 SEQ ID NO: 13
AAAV (Avian AAV)	545	US9238800 SEQ ID NO: 1
AAV Shuffle 100-1	546	US20160017295 SEQ ID NO: 23
AAV Shuffle 100-1	547	US20160017295 SEQ ID NO: 11
AAV Shuffle 100-2	548	US20160017295 SEQ ID NO: 37
AAV Shuffle 100-2	549	US20160017295 SEQ ID NO: 29
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AAV CLv-M7	843	WO2016065001 SEQ ID NO: 76
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AAV CSp-8.4	857	WO2016065001 SEQ ID NO: 90
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AAV CSp-8.9	862	WO2016065001 SEQ ID NO: 95
AAV CBr-B7.3	863	WO2016065001 SEQ ID NO: 96
AAV CBr-B7.4	864	WO2016065001 SEQ ID NO: 97
AAV3B	865	WO2016065001 SEQ ID NO: 98
AAV4	866	WO2016065001 SEQ ID NO: 99
AAV5	867	WO2016065001 SEQ ID NO: 100
AAVPHP.B or G2B-26	868	WO2015038958 SEQ ID NO: 8 and 13, GenBankALU85156.1
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AAVG2B-13	870	WO2015038958 SEQ ID NO: 12
AAVTH1.1-32	871	WO2015038958 SEQ ID NO: 14
AAVTH1.1-35	872	WO2015038958 SEQ ID NO: 15

[0089] Each of the patents, applications and/or publications listed in Table 1 are hereby incorporated by reference in their entirety.

[0090] In one embodiment, the AAV serotype may be, or may have a sequence as described in International Patent Publication WO2015038958, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV9 (SEQ ID NO: 2 and 11 of WO2015038958, herein SEQ ID NO: 127 and 126 respectively), PHP.B (SEQ ID NO: 8 and 9 of WO2015038958, herein SEQ ID NO: 868 and 869 respectively), G2B-13 (SEQ ID NO: 12 of WO2015038958, herein SEQ ID NO: 870), G2B-26 (SEQ ID NO: 13 of WO2015038958, herein SEQ ID NO: 868 and 869 respectively), TH1.1-32 (SEQ ID NO: 14 of WO2015038958, herein SEQ ID NO: 871), TH1.1-35 (SEQ ID NO: 15 of WO2015038958, herein SEQ ID NO: 872) or variants thereof. Further, any of the targeting peptides or amino acid inserts described in WO2015038958, may be inserted into any parent AAV serotype, such as, but not limited to, AAV9 (SEQ ID NO: 126 for the DNA sequence and SEQ ID NO: 127 for the amino acid sequence). In one embodiment, the amino acid insert is inserted between amino acids 586-592 of the parent AAV (e.g., AAV9). In another embodiment, the amino acid insert is inserted between amino acids 588-589 of the parent AAV sequence. The amino acid insert may be, but is not limited to, any of the following amino acid sequences, TLAVPFK (SEQ ID NO: 1 of WO2015038958; herein SEQ ID NO: 873), KFPVALT (SEQ ID NO: 3 of WO2015038958; herein SEQ ID NO: 874), LAVPFK (SEQ ID NO: 31 of WO2015038958; herein SEQ ID NO: 875), AVPFK (SEQ ID NO: 32 of WO2015038958; herein SEQ ID NO: 876), VPFK (SEQ ID NO: 33 of WO2015038958; herein SEQ ID NO: 877), TLAVPF (SEQ ID NO: 34 of WO2015038958; herein SEQ ID NO: 878), TLAVP (SEQ ID NO: 35 of WO2015038958; herein SEQ ID NO: 879), TLAV (SEQ ID NO: 36 of WO2015038958; herein SEQ ID NO: 880), SVSKPFL (SEQ ID NO: 28 of WO2015038958; herein SEQ ID NO: 881), FTLTTPK (SEQ ID NO: 29 of WO2015038958; herein SEQ ID NO: 882), MNATKNV (SEQ ID NO: 30 of WO2015038958; herein SEQ ID NO: 883), QSSQTPR (SEQ ID NO: 54 of WO2015038958; herein SEQ ID NO: 884), ILGTGTS (SEQ ID NO: 55 of WO2015038958; herein SEQ ID NO: 885), TRTNPEA (SEQ ID NO: 56 of WO2015038958; herein SEQ ID NO: 886), NGGTSSS (SEQ ID NO: 58 of WO2015038958; herein SEQ ID NO: 887), or YTLSQGW (SEQ ID NO: 60 of WO2015038958; herein SEQ ID NO: 888). Non-limiting examples of nucleotide sequences that may encode the amino acid inserts include the following, AAGTTTCCTGTGGCGTTGACT (SEQ ID NO: 3 of WO2015038958; herein SEQ ID NO: 889), ACTTTGGCGGTGCCTTTTAAG (SEQ ID NO: 24 and 49 of WO2015038958; herein SEQ ID NO: 890), AGTGTGAGTAAGCCTTTTTTG (SEQ ID NO: 25 of WO2015038958; herein SEQ ID NO: 891), TTTACGTTGACGACGCCTAAG (SEQ ID NO: 26 of WO2015038958; herein SEQ ID NO: 892), ATGAATGCTACGAAGAATGTG (SEQ ID NO: 27 of WO2015038958;

herein SEQ ID NO: 893), CAGTCGTCGCAGACGCCTAGG (SEQ ID NO: 48 of WO2015038958; herein SEQ ID NO: 894), ATTCTGGGGACTGGTACTTCG (SEQ ID NO: 50 and 52 of WO2015038958; herein SEQ ID NO: 895), ACGCGGACTAATCCTGAGGCT (SEQ ID NO: 51 of WO2015038958; herein SEQ ID NO: 896), AATGGGGGGACTAGTAGTTCT (SEQ ID NO: 53 of WO2015038958; herein SEQ ID NO: 897), or TATACTTTGTCGCAGGGTTGG (SEQ ID NO: 59 of WO2015038958; herein SEQ ID NO: 898).

Viral Genome Component: Inverted Terminal Repeats (ITRs)

[0091] The AAV particles of the present invention comprise a viral genome with at least one ITR region and a payload region. In one embodiment, the viral genome has two ITRs. These two ITRs flank the payload region at the 5' and 3' ends. The ITRs function as origins of replication comprising recognition sites for replication. ITRs comprise sequence regions which can be complementary and symmetrically arranged. ITRs incorporated into viral genomes of the invention may be comprised of naturally occurring polynucleotide sequences or recombinantly derived polynucleotide sequences.

[0092] The ITRs may be derived from the same serotype as the capsid, selected from any of the serotypes listed in Table 1, or a derivative thereof. The ITR may be of a different serotype than the capsid. In one embodiment, the AAV particle has more than one ITR. In a non-limiting example, the AAV particle has a viral genome comprising two ITRs. In one embodiment, the ITRs are of the same serotype as one another. In another embodiment, the ITRs are of different serotypes. Non-limiting examples include zero, one or both of the ITRs having the same serotype as the capsid. In one embodiment both ITRs of the viral genome of the AAV particle are AAV2 ITRs.

[0093] Independently, each ITR may be about 100 to about 150 nucleotides in length. An ITR may be about 100-105 nucleotides in length, 106-110 nucleotides in length, 111-115 nucleotides in length, 116-120 nucleotides in length, 121-125 nucleotides in length, 126-130 nucleotides in length, 131-135 nucleotides in length, 136-140 nucleotides in length, 141-145 nucleotides in length or 146-150 nucleotides in length. In one embodiment, the ITRs are 140-142 nucleotides in length. Non-limiting examples of ITR length are 102, 140, 141, 142, 145 nucleotides in length, and those having at least 95% identity thereto.

Viral Genome Component: Promoters

[0094] In one embodiment, the payload region of the viral genome comprises at least one element to enhance the transgene target specificity and expression (See e.g., Powell et al. Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene

Therapy, 2015; the contents of which are herein incorporated by reference in its entirety). Non-limiting examples of elements to enhance the transgene target specificity and expression include promoters, endogenous miRNAs, post-transcriptional regulatory elements (PREs), polyadenylation (PolyA) signal sequences and upstream enhancers (USEs), CMV enhancers and introns.

[0095] A person skilled in the art may recognize that expression of the polypeptides of the invention in a target cell may require a specific promoter, including but not limited to, a promoter that is species specific, inducible, tissue-specific, or cell cycle-specific (Parr et al., *Nat. Med.*3:1145-9 (1997); the contents of which are herein incorporated by reference in their entirety).

[0096] In one embodiment, the promoter is deemed to be efficient when it drives expression of the polypeptide(s) encoded in the payload region of the viral genome of the AAV particle.

[0097] In one embodiment, the promoter is a promoter deemed to be efficient when it drives expression in the cell being targeted.

[0098] In one embodiment, the promoter drives expression of the polypeptides of the invention (e.g., a functional antibody) for a period of time in targeted tissues. Expression driven by a promoter may be for a period of 1 hour, 2, hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 3 weeks, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years or more than 10 years. Expression may be for 1-5 hours, 1-12 hours, 1-2 days, 1-5 days, 1-2 weeks, 1-3 weeks, 1-4 weeks, 1-2 months, 1-4 months, 1-6 months, 2-6 months, 3-6 months, 3-9 months, 4-8 months, 6-12 months, 1-2 years, 1-5 years, 2-5 years, 3-6 years, 3-8 years, 4-8 years, or 5-10 years.

[0099] In one embodiment, the promoter drives expression of the polypeptides of the invention (e.g., a functional antibody) for at least 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, 3 years 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, 15 years, 16 years, 17 years, 18 years, 19 years, 20 years, 21 years, 22 years, 23 years, 24 years, 25 years, 26 years, 27 years, 28 years, 29 years, 30 years, 31 years, 32 years, 33 years, 34

years, 35 years, 36 years, 37 years, 38 years, 39 years, 40 years, 41 years, 42 years, 43 years, 44 years, 45 years, 46 years, 47 years, 48 years, 49 years, 50 years, 55 years, 60 years, 65 years, or more than 65 years.

[00100] Promoters may be naturally occurring or non-naturally occurring. Non-limiting examples of promoters include viral promoters, plant promoters and mammalian promoters. In some embodiments, the promoters may be human promoters. In some embodiments, the promoter may be truncated.

[00101] Promoters which drive or promote expression in most tissues include, but are not limited to, human elongation factor 1α-subunit (EF1α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β-actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC). Tissue-specific expression elements can be used to restrict expression to certain cell types such as, but not limited to, muscle specific promoters, B cell promoters, monocyte promoters, leukocyte promoters, macrophage promoters, pancreatic acinar cell promoters, endothelial cell promoters, lung tissue promoters, astrocyte promoters, or nervous system promoters which can be used to restrict expression to neurons, astrocytes, or oligodendrocytes.

[00102] Non-limiting examples of muscle-specific promoters include mammalian muscle creatine kinase (MCK) promoter, mammalian desmin (DES) promoter, mammalian troponin I (TNNI2) promoter, and mammalian skeletal alpha-actin (ASKA) promoter (see, e.g. U.S. Patent Publication US20110212529, the contents of which are herein incorporated by reference in their entirety)

[00103] Non-limiting examples of tissue-specific expression elements for neurons include neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF-β), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light (NFL) or heavy (NFH), β-globin minigene nβ2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2) promoters. Non-limiting examples of tissue-specific expression elements for astrocytes include glial fibrillary acidic protein (GFAP) and EAAT2 promoters. A non-limiting example of a tissue-specific expression element for oligodendrocytes includes the myelin basic protein (MBP) promoter.

[00104] In one embodiment, the promoter may be less than 1 kb. The promoter may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740,

750, 760, 770, 780, 790, 800, or more than 800 nucleotides. The promoter may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800, or 700-800.

[00105] In one embodiment, the promoter may be a combination of two or more components of the same or different starting or parental promoters such as, but not limited to, CMV and CBA. Each component may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, or more than 800. Each component may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800 or 700-800. In one embodiment, the promoter is a combination of a 382 nucleotide CMV-enhancer sequence and a 260 nucleotide CBA-promoter sequence.

[00106] In one embodiment, the viral genome comprises a ubiquitous promoter. Non-limiting examples of ubiquitous promoters include CMV, CBA (including derivatives CAG, CBh, etc.), EF-1α, PGK, UBC, GUSB (hGBp), and UCOE (promoter of HNRPA2B1-CBX3).

Yu et al. (Molecular Pain 2011, 7:63; the contents of which are herein incorporated by reference in their entirety) evaluated the expression of eGFP under the CAG, EFIα, PGK and UBC promoters in rat DRG cells and primary DRG cells using lentiviral vectors and found that UBC showed weaker expression than the other 3 promoters and only 10-12% glial expression was seen for all promoters. Soderblom et al. (E. Neuro 2015; the contents of which are herein incorporated by reference in its entirety) evaluated the expression of eGFP in AAV8 with CMV and UBC promoters and AAV2 with the CMV promoter after injection in the motor cortex. Intranasal administration of a plasmid containing a UBC or EFIα promoter showed a sustained airway expression greater than the expression with the CMV promoter (See e.g., Gill et al., Gene Therapy 2001, Vol. 8, 1539-1546; the contents of which are herein incorporated by reference in their entirety). Husain et al. (Gene Therapy 2009; the contents of which are herein incorporated by reference in its entirety) evaluated an HβH construct with a hGUSB promoter, a HSV-1LAT promoter and an NSE promoter and found that the HβH construct showed weaker expression than NSE in mouse brain. Passini and Wolfe (J. Virol. 2001, 12382-12392, the contents of which are herein incorporated by reference in its entirety) evaluated the long-term effects of the HβH vector following an intraventricular injection in neonatal mice and found that there was

sustained expression for at least 1 year. Low expression in all brain regions was found by Xu et al. (Gene Therapy 2001, 8, 1323-1332; the contents of which are herein incorporated by reference in their entirety) when NFL and NFH promoters were used as compared to the CMV-lacZ, CMV-luc, EF, GFAP, hENK, nAChR, PPE, PPE + wpre, NSE (0.3 kb), NSE (1.8 kb) and NSE (1.8 kb + wpre). Xu et al. found that the promoter activity in descending order was NSE (1.8 kb), EF, NSE (0.3 kb), GFAP, CMV, hENK, PPE, NFL and NFH. NFL is a 650nucleotide promoter and NFH is a 920 nucleotide promoter which are both absent in the liver but NFH is abundant in the sensory proprioceptive neurons, brain and spinal cord and NFH is present in the heart. Scn8a is a 470 nucleotide promoter which expresses throughout the DRG, spinal cord and brain with particularly high expression seen in the hippocampal neurons and cerebellar Purkinje cells, cortex, thalamus, and hypothalamus (See e.g., Drews et al. *Identification of evolutionary conserved, functional noncoding elements in the promoter region of the sodium channel gene SCN8A,* Mamm Genome (2007) 18:723-731; and Raymond et al. *Expression of Alternatively Spliced Sodium Channel α-subunit genes,* Journal of Biological Chemistry (2004) 279(44) 46234-46241; the contents of each of which are herein incorporated by reference in their entireties).

[00107] Any of promoters taught by the aforementioned Yu, Soderblom, Gill, Husain, Passini, Xu, Drews, or Raymond may be used in the present inventions.

[00108] In one embodiment, the promoter is not cell specific.

[00109] In one embodiment, the promoter is a ubiquitin c (UBC) promoter. The UBC promoter may have a size of 300-350 nucleotides. As a non-limiting example, the UBC promoter is 332 nucleotides.

[00110] In one embodiment, the promoter is a β-glucuronidase (GUSB) promoter. The GUSB promoter may have a size of 350-400 nucleotides. As a non-limiting example, the GUSB promoter is 378 nucleotides.

[00111] In one embodiment, the promoter is a neurofilament light (NFL) promoter. The NFL promoter may have a size of 600-700 nucleotides. As a non-limiting example, the NFL promoter is 650 nucleotides.

[00112] In one embodiment, the promoter is a neurofilament heavy (NFH) promoter. The NFH promoter may have a size of 900-950 nucleotides. As a non-limiting example, the NFH promoter is 920 nucleotides.

[00113] In one embodiment, the promoter is a scn8a promoter. The scn8a promoter may have a size of 450-500 nucleotides. As a non-limiting example, the scn8a promoter is 470 nucleotides.

[00114] In one embodiment, the promoter is a phosphoglycerate kinase 1 (PGK) promoter.

[00115] In one embodiment, the promoter is a chicken β-actin (CBA) promoter.

[00116] In one embodiment, the promoter is a cytomegalovirus (CMV) promoter.

[00117] In one embodiment, the promoter is a liver or a skeletal muscle promoter. Non-limiting examples of liver promoters include human α-1-antitrypsin (hAAT) and thyroxine binding globulin (TBG). Non-limiting examples of skeletal muscle promoters include Desmin, MCK or synthetic C5-12.

[00118] In one embodiment, the promoter is a RNA pol III promoter. As a non-limiting example, the RNA pol III promoter is U6. As a non-limiting example, the RNA pol III promoter is H1.

[00119] In one embodiment, the viral genome comprises two promoters. As a non-limiting example, the promoters are an EF1α promoter and a CMV promoter.

[00120] In one embodiment, the viral genome comprises an enhancer element, a promoter and/or a 5'UTR intron. The enhancer element, also referred to herein as an "enhancer," may be, but is not limited to, a CMV enhancer, the promoter may be, but is not limited to, a CMV, CBA, UBC, GUSB, NSE, Synapsin, MeCP2, and GFAP promoter and the 5'UTR/intron may be, but is not limited to, SV40, and CBA-MVM. As a non-limiting example, the enhancer, promoter and/or intron used in combination may be: (1) CMV enhancer, CMV promoter, SV40 5'UTR intron; (2) CMV enhancer, CBA promoter, SV 40 5'UTR intron; (3) CMV enhancer, CBA promoter, CBA-MVM 5'UTR intron; (4) UBC promoter; (5) GUSB promoter; (6) NSE promoter; (7) Synapsin promoter; (8) MeCP2 promoter; and (9) GFAP promoter.

[00121] In one embodiment, the viral genome comprises an engineered promoter.

[00122] In another embodiment, the viral genome comprises a promoter from a naturally expressed protein.

Viral Genome Component: Untranslated Regions (UTRs)

[00011] By definition, wild type untranslated regions (UTRs) of a gene are transcribed but not translated. Generally, the 5' UTR starts at the transcription start site and ends at the start codon and the 3' UTR starts immediately following the stop codon and continues until the termination signal for transcription.

[00012] Features typically found in abundantly expressed genes of specific target organs may be engineered into UTRs to enhance the stability and protein production. As a non-limiting example, a 5' UTR from mRNA normally expressed in the liver (e.g., albumin, serum amyloid A, Apolipoprotein A/B/E, transferrin, alpha fetoprotein, erythropoietin, or Factor VIII) may be used in the viral genomes of the AAV particles of the invention to enhance expression in hepatic cell lines or liver.

[00013] While not wishing to be bound by theory, wild-type 5′ untranslated regions (UTRs) include features which play roles in translation initiation. Kozak sequences, which are commonly known to be involved in the process by which the ribosome initiates translation of many genes, are usually included in 5' UTRs. Kozak sequences have the consensus CCR(A/G)CCAUGG, where R is a purine (adenine or guanine) three bases upstream of the start codon (ATG), which is followed by another 'G'.

[00014] In one embodiment, the 5'UTR in the viral genome includes a Kozak sequence.

[00015] In one embodiment, the 5'UTR in the viral genome does not include a Kozak sequence.

[00016] While not wishing to be bound by theory, wild-type 3′ UTRs are known to have stretches of Adenosines and Uridines embedded therein. These AU rich signatures are particularly prevalent in genes with high rates of turnover. Based on their sequence features and functional properties, the AU rich elements (AREs) can be separated into three classes (Chen et al, 1995, the contents of which are herein incorporated by reference in its entirety): Class I AREs, such as, but not limited to, c-Myc and MyoD, contain several dispersed copies of an AUUUA motif within U-rich regions. Class II AREs, such as, but not limited to, GM-CSF and TNF-a, possess two or more overlapping UUAUUUA(U/A)(U/A) nonamers. Class III ARES, such as, but not limited to, c-Jun and Myogenin, are less well defined. These U rich regions do not contain an AUUUA motif. Most proteins binding to the AREs are known to destabilize the messenger, whereas members of the ELAV family, most notably HuR, have been documented to increase the stability of mRNA. HuR binds to AREs of all the three classes. Engineering the HuR specific binding sites into the 3′ UTR of nucleic acid molecules will lead to HuR binding and thus, stabilization of the message *in vivo*.

[00017] Introduction, removal or modification of 3′ UTR AU rich elements (AREs) can be used to modulate the stability of polynucleotides. When engineering specific polynucleotides, e.g., payload regions of viral genomes, one or more copies of an ARE can be introduced to make polynucleotides less stable and thereby curtail translation and decrease production of the resultant protein. Likewise, AREs can be identified and removed or mutated to increase the intracellular stability and thus increase translation and production of the resultant protein.

[00018] In one embodiment, the 3' UTR of the viral genome may include an oligo(dT) sequence for templated addition of a poly-A tail.

[00019] In one embodiment, the viral genome may include at least one miRNA seed, binding site or full sequence. microRNAs (or miRNA or miR) are 19-25 nucleotide noncoding RNAs that bind to the sites of nucleic acid targets and down-regulate gene expression either by

reducing nucleic acid molecule stability or by inhibiting translation. A microRNA sequence comprises a "seed" region, i.e., a sequence in the region of positions 2-8 of the mature microRNA, which sequence has perfect Watson-Crick complementarity to the miRNA target sequence of the nucleic acid.

[00020] In one embodiment, the viral genome may be engineered to include, alter or remove at least one miRNA binding site, sequence, or seed region.

[00021] Any UTR from any gene known in the art may be incorporated into the viral genome of the AAV particle. These UTRs, or portions thereof, may be placed in the same orientation as in the gene from which they were selected or they may be altered in orientation or location. In one embodiment, the UTR used in the viral genome of the AAV particle may be inverted, shortened, lengthened, made with one or more other 5′ UTRs or 3′ UTRs known in the art. As used herein, the term "altered" as it relates to a UTR, means that the UTR has been changed in some way in relation to a reference sequence. For example, a 3′ or 5′ UTR may be altered relative to a wild type or native UTR by the change in orientation or location as taught above or may be altered by the inclusion of additional nucleotides, deletion of nucleotides, swapping or transposition of nucleotides.

[00022] In one embodiment, the viral genome of the AAV particle comprises at least one artificial UTRs which is not a variant of a wild type UTR.

[00023] In one embodiment, the viral genome of the AAV particle comprises UTRs which have been selected from a family of transcripts whose proteins share a common function, structure, feature or property.

Viral Genome Component: Polyadenylation Sequence

[00123] In one embodiment, the viral genome of the AAV particles of the present invention comprise at least one polyadenylation sequence. The viral genome of the AAV particle may comprise a polyadenylation sequence between the 3' end of the payload coding sequence and the 5' end of the 3'ITR.

[00124] In one embodiment, the polyadenylation sequence or "polyA sequence" may range from absent to about 500 nucleotides in length. The polyadenylation sequence may be, but is not limited to, 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, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140,

141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, and 500 nucleotides in length.

[00125] In one embodiment, the polyadenylation sequence is 50-100 nucleotides in length.

[00126] In one embodiment, the polyadenylation sequence is 50-150 nucleotides in length.

[00127] In one embodiment, the polyadenylation sequence is 50-160 nucleotides in length.

[00128] In one embodiment, the polyadenylation sequence is 50-200 nucleotides in length.

[00129] In one embodiment, the polyadenylation sequence is 60-100 nucleotides in length.

[00130] In one embodiment, the polyadenylation sequence is 60-150 nucleotides in length.

[00131] In one embodiment, the polyadenylation sequence is 60-160 nucleotides in length.

[00132] In one embodiment, the polyadenylation sequence is 60-200 nucleotides in length.

[00133] In one embodiment, the polyadenylation sequence is 70-100 nucleotides in length.

[00134] In one embodiment, the polyadenylation sequence is 70-150 nucleotides in length.

[00135] In one embodiment, the polyadenylation sequence is 70-160 nucleotides in length.

[00136] In one embodiment, the polyadenylation sequence is 70-200 nucleotides in length.

[00137] In one embodiment, the polyadenylation sequence is 80-100 nucleotides in length.

[00138] In one embodiment, the polyadenylation sequence is 80-150 nucleotides in length.

[00139] In one embodiment, the polyadenylation sequence is 80-160 nucleotides in length.

[00140] In one embodiment, the polyadenylation sequence is 80-200 nucleotides in length.

[00141] In one embodiment, the polyadenylation sequence is 90-100 nucleotides in length.

[00142] In one embodiment, the polyadenylation sequence is 90-150 nucleotides in length.

[00143] In one embodiment, the polyadenylation sequence is 90-160 nucleotides in length.

[00144] In one embodiment, the polyadenylation sequence is 90-200 nucleotides in length.

Viral Genome Component: Linkers

[00145] Viral genomes of the invention may be engineered with one or more spacer or linker regions to separate coding or non-coding regions.

[00146] In one embodiment, the payload region of the AAV particle may optionally encode one or more linker sequences. In some cases, the linker may be a peptide linker that may be used to connect the polypeptides encoded by the payload region (i.e., light and heavy antibody chains during expression). Some peptide linkers may be cleaved after expression to separate heavy and light chain domains, allowing assembly of mature antibodies or antibody fragments. Linker cleavage may be enzymatic. In some cases, linkers comprise an enzymatic cleavage site to facilitate intracellular or extracellular cleavage. Some payload regions encode linkers that interrupt polypeptide synthesis during translation of the linker sequence from an mRNA transcript. Such linkers may facilitate the translation of separate protein domains (e.g., heavy and light chain antibody domains) from a single transcript. In some cases, two or more linkers are encoded by a payload region of the viral genome. Non-limiting examples of linkers that may be encoded by the payload region of an AAV particle viral genome are given in Table 2.

Table 2. Linkers

Linker No.	Description	SEQ ID NO or SEQUENCE
L1	Internal ribosome entry site (IRES)	899
L2	Foot and mouth disease virus 2A (F2A)	900
L3	Porcine teschovirus-1 virus 2A (P2A)	901
L4	Furin cleavage site (F)	902
L5	5xG4S (SEQ ID NO: 4321)	903
L6	1,4-alpha-glucan-branching enzyme	CHP
L7	1,4-alpha-glucan-branching enzyme	904
L8	1,4-beta-N-acetylmuramidase	FKK
L9	1,4-beta-N-acetylmuramidase	905
L10	1,4-beta-N-acetylmuramidase	906
L11	1,4-beta-N-acetylmuramidase	907
L12	1,4-beta-N-acetylmuramidase	908
L13	1,4-beta-N-acetylmuramidase	909
L14	1,4-beta-N-acetylmuramidase	910
L15	1,4-beta-N-acetylmuramidase	911
L16	1,4-beta-N-acetylmuramidase	912
L17	1,4-beta-N-acetylmuramidase	913
L18	1,4-beta-N-acetylmuramidase	914

L19	150aa long hypothetical transcriptional regulator	915
L20	150aa long hypothetical transcriptional regulator	916
L21	1-deoxy-D-xylulose 5-phosphate reductoisomerase	917
L22	1-deoxy-D-xylulose 5-phosphate reductoisomerase	918
L23	1-deoxy-D-xylulose 5-phosphate reductoisomerase	919
L24	1-deoxy-D-xylulose 5-phosphate reductoisomerase	920
L25	235aa long hypothetical biotin-[acetyl-CoA-carboxylase] ligase	921
L26	235aa long hypothetical biotin-[acetyl-CoA-carboxylase] ligase	922
L27	235aa long hypothetical biotin-[acetyl-CoA-carboxylase] ligase	923
L28	2-dehydropantoate 2-reductase	924
L29	2-dehydropantoate 2-reductase	925
L30	2-dehydropantoate 2-reductase	926
L31	2-dehydropantoate 2-reductase	927
L32	2-dehydropantoate 2-reductase	928
L33	2-dehydropantoate 2-reductase	929
L34	2-dehydropantoate 2-reductase, putative	930
L35	2-dehydropantoate 2-reductase, putative	931
L36	4-alpha-glucanotransferase	932
L37	4-alpha-glucanotransferase	933
L38	4-alpha-glucanotransferase	934
L39	4-diphosphocytidyl-2C-methyl-D-erythritol kinase	HAA
L40	4-diphosphocytidyl-2C-methyl-D-erythritol kinase	935
L41	4-diphosphocytidyl-2C-methyl-D-erythritol kinase	936
L42	4-diphosphocytidyl-2C-methyl-D-erythritol kinase	937
L43	4-diphosphocytidyl-2C-methyl-D-erythritol kinase	938
L44	4-hydroxyphenylpyruvate dioxygenase	939
L45	5-13 amino acids from the N termini of human Ck and CH1 domains linker	940
L46	5-13 amino acids from the N termini of human Ck and CH1 domains linker	ERK
L47	5-13 amino acids from the N termini of human Ck and CH1 domains linker	941
L48	5-13 amino acids from the N termini of human Ck and CH1 domains linker	942
L49	5-13 amino acids from the N termini of human Ck and CH1 domains linker	943
L50	5-13 amino acids from the N termini of human Ck and CH1 domains linker	944
L51	5'-exonuclease	945
L52	5-methyltetrahydropteroyltriglutamate--homocysteinemethyltransferase	ARL
L53	5-methyltetrahydropteroyltriglutamate--homocysteinemethyltransferase	946
L54	5-methyltetrahydropteroyltriglutamate--homocysteinemethyltransferase	947
L55	5-methyltetrahydropteroyltriglutamate--homocysteinemethyltransferase	948
L56	5-methyltetrahydropteroyltriglutamate--homocysteinemethyltransferase	949
L57	5'-nucleotidase	950
L58	5'-nucleotidase	951
L59	5'-nucleotidase	952
L60	5'-nucleotidase	953
L61	704aa long hypothetical glycosyltransferase	954
L62	704aa long hypothetical glycosyltransferase	955
L63	80 kDa nuclear cap binding protein	956
L64	80 kDa nuclear cap binding protein	957
L65	80 kDa nuclear cap binding protein	958
L66	80 kDa nuclear cap binding protein	959
L67	Acetaldehyde dehydrogenase (acylating)	960
L68	Acetaldehyde dehydrogenase (acylating)	961
L69	Acetolactate synthase isozyme III small subunit	962
L70	Acetylcholine receptor protein, alpha chain	963
L71	Acetylcholine receptor protein, beta chain	964
L72	Aconitate hydratase 2	965
L73	Aconitate hydratase 2	966
L74	Aconitate hydratase 2	967
L75	Aconitate hydratase 2	968
L76	Aconitate hydratase 2	969

L77	Acriflavine resistance protein B	DWY
L78	Acriflavine resistance protein B	GGS
L79	Acriflavine resistance protein B	IDQ
L80	Acriflavine resistance protein B	NKV
L81	Acriflavine resistance protein B	SEA
L82	Acriflavine resistance protein B	970
L83	Acriflavine resistance protein B	971
L84	Acriflavine resistance protein B	972
L85	Acriflavine resistance protein B	973
L86	Acriflavine resistance protein B	974
L87	Acriflavine resistance protein B	975
L88	Acriflavine resistance protein B	976
L89	Acriflavine resistance protein B	977
L90	Acriflavine resistance protein B	978
L91	Acriflavine resistance protein B	979
L92	Acriflavine resistance protein B	980
L93	Acriflavine resistance protein B	981
L94	Acriflavine resistance protein B	982
L95	Acriflavine resistance protein B	983
L96	Acriflavine resistance protein B	984
L97	Acriflavine resistance protein B	985
L98	Acriflavine resistance protein B	986
L99	Acriflavine resistance protein B	987
L100	Acriflavine resistance protein B	988
L101	Acriflavine resistance protein B	989
L102	Acriflavine resistance protein B	990
L103	Acriflavine resistance protein B	991
L104	Acriflavine resistance protein B	992
L105	Acriflavine resistance protein B	993
L106	Acyl-CoA thioesterase II	994
L107	Acyl-CoA thioesterase II	995
L108	Acyl-CoA thioesterase II	996
L109	Acyl-CoA thioesterase II	997
L110	Acyl-CoA thioesterase II	998
L111	Acyl-coenzyme A thioesterase 4	999
L112	Acyl-coenzyme A thioesterase 4	1000
L113	Acyl-coenzyme A thioesterase 4	1001
L114	Acyl-coenzyme A thioesterase 4	1002
L115	Acyl-coenzyme A thioesterase 4	1003
L116	Adenine glycosylase	1004
L117	Adenylate cyclase	1005
L118	Aerolysin	1006
L119	Aerolysin	1007
L120	Agglutinin	DWK
L121	Agglutinin isolectin 1	1008
L122	Agglutinin isolectin 1	1009
L123	Aldehyde ferredoxin oxidoreductase	1010
L124	Aldehyde oxidoreductase	1011
L125	Aldehyde oxidoreductase	1012
L126	Aldehyde oxidoreductase	1013
L127	Aldehyde oxidoreductase	1014
L128	Aldehyde oxidoreductase	1015
L129	Alkyl hydroperoxide reductase subunit F	1016
L130	Alkyl hydroperoxide reductase subunit F	1017
L131	Alkyl hydroperoxide reductase subunit F	1018
L132	Alkyl hydroperoxide reductase subunit F	1019
L133	Alkyl hydroperoxide reductase subunit F	1020
L134	Alkyl hydroperoxide reductase subunit F	1021

L135	Alkyl hydroperoxide reductase subunit F	1022
L136	Alkyl hydroperoxide reductase subunit F	1023
L137	Alkyl hydroperoxide reductase subunit F	1024
L138	Alkyl hydroperoxide reductase subunit F	1025
L139	Allantoicase	1026
L140	Allantoicase	1027
L141	Alliin lyase 1	SAV
L142	Alliin lyase 1	1028
L143	Alliin lyase 1	1029
L144	Alliin lyase 1	1030
L145	Alliin lyase 1	1031
L146	Alpha amylase	1032
L147	Alpha amylase	1033
L148	Alpha-actinin 1	1034
L149	Alpha-actinin 1	1035
L150	Alpha-adaptin C	1036
L151	Alpha-amylase	1037
L152	Alpha-glucuronidase	LSD
L153	Alpha-glucuronidase	1038
L154	Alpha-glucuronidase	1039
L155	Alpha-glucuronidase	1040
L156	Alpha-glucuronidase	1041
L157	Alpha-glucuronidase	1042
L158	Alpha-glucuronidase	1043
L159	Alpha-glucuronidase	1044
L160	Alpha-glucuronidase	1045
L161	Alpha-glucuronidase	1046
L162	Alpha-glucuronidase	1047
L163	Alpha-glucuronidase	1048
L164	Alpha-glucuronidase	1049
L165	Alpha-glucuronidase	1050
L166	Alpha-glucuronidase	1051
L167	Alpha-glucuronidase	1052
L168	Alpha-glucuronidase	1053
L169	Alpha-glucuronidase	1054
L170	Alpha-glucuronidase	1055
L171	Alpha-glucuronidase	1056
L172	Alpha-glucuronidase	1057
L173	Alpha-glucuronidase	1058
L174	Alpha-L-arabinofuranosidase B	1059
L175	Alpha-mannosidase	1060
L176	Alr2269 protein	1061
L177	AMP nucleosidase	1062
L178	AMP nucleosidase	1063
L179	AMP nucleosidase	1064
L180	Angiopoietin-1 receptor	DAG
L181	Angiopoietin-1 receptor	NSG
L182	Angiopoietin-1 receptor	TSA
L183	Angiopoietin-1 receptor	VPR
L184	Angiopoietin-1 receptor	1065
L185	Angiopoietin-1 receptor	1066
L186	Angiopoietin-1 receptor	1067
L187	Angiopoietin-1 receptor	1068
L188	Angiopoietin-1 receptor	1069
L189	Angiopoietin-1 receptor	1070
L190	Angiopoietin-1 receptor	1071
L191	Angiopoietin-1 receptor	1072
L192	Angiopoietin-1 receptor	1073

L193	Angiopoietin-1 receptor	1074
L194	Angiopoietin-1 receptor	1075
L195	Angiopoietin-1 receptor	1076
L196	Angiopoietin-1 receptor	1077
L197	Angiopoietin-1 receptor	1078
L198	Angiopoietin-1 receptor	1079
L199	Angiopoietin-1 receptor	1080
L200	Angiopoietin-1 receptor	1081
L201	Angiopoietin-1 receptor	1082
L202	Angiopoietin-1 receptor	1083
L203	Angiopoietin-1 receptor	1084
L204	Angiopoietin-1 receptor	1085
L205	Annexin A2	QNK
L206	Annexin A2	1086
L207	Annexin A2	1087
L208	Anthranilate phosphoribosyltransferase	1088
L209	AP-2 complex subunit beta-2	1089
L210	Archaeosine tRNA-guanine transglycosylase	LGI
L211	Archaeosine tRNA-guanine transglycosylase	1090
L212	Archaeosine tRNA-guanine transglycosylase	1091
L213	Archaeosine tRNA-guanine transglycosylase	1092
L214	Archaeosine tRNA-guanine transglycosylase	1093
L215	Archaeosine tRNA-guanine transglycosylase	1094
L216	Archaeosine tRNA-guanine transglycosylase	1095
L217	Archaeosine tRNA-guanine transglycosylase	1096
L218	Archeal exosome RNA binding protein rrp4	1097
L219	Archeal exosome RNA binding protein rrp4	1098
L220	Archeal exosome RNA binding protein rrp4	1099
L221	Arginyl-tRNA synthetase	IDY
L222	Arginyl-tRNA synthetase	1100
L223	Arginyl-tRNA synthetase	1101
L224	Arginyl-tRNA synthetase	1102
L225	Arrestin	1103
L226	Arrestin	1104
L227	Arsenite oxidase	1105
L228	Artificial linker	PGS
L229	Artificial linker	ATK
L230	Artificial linker	ASK
L231	Artificial linker	1106
L232	Artificial linker	1107
L233	Artificial linker	1108
L234	Artificial linker	1109
L235	Artificial linker	1110
L236	Artificial linker	1111
L237	ATP phosphoribosyltransferase	ANR
L238	ATP-dependent DNA helicase	YDP
L239	ATP-dependent DNA helicase	1112
L240	ATP-dependent DNA helicase	1113
L241	ATP-dependent DNA helicase	1114
L242	ATP-dependent DNA helicase	1115
L243	ATP-dependent DNA helicase	1116
L244	ATP-dependent DNA helicase	1117
L245	ATP-dependent DNA helicase	1118
L246	ATP-dependent DNA helicase	1119
L247	AT-rich DNA-binding protein	1120
L248	AT-rich DNA-binding protein	1121
L249	Axonin-1	DEG
L250	Axonin-1	ECF

L251	Axonin-1	1122
L252	Axonin-1	1123
L253	Axonin-1	1124
L254	Axonin-1	1125
L255	Axonin-1	1126
L256	Axonin-1	1127
L257	Axonin-1	1128
L258	Bacilysin biosynthesis protein BacB	1129
L259	Bacilysin biosynthesis protein BacB	1130
L260	Bacilysin biosynthesis protein BacB	1131
L261	Bacilysin biosynthesis protein BacB	1132
L262	Bacilysin biosynthesis protein BacB	1133
L263	Bacteriophage Mu transposase	1134
L264	Bacteriophage Mu transposase	1135
L265	Benzoyl-CoA-dihydrodiol lyase	1136
L266	Benzoyl-CoA-dihydrodiol lyase	1137
L267	Benzoyl-CoA-dihydrodiol lyase	1138
L268	Benzoyl-CoA-dihydrodiol lyase	1139
L269	Benzoyl-CoA-dihydrodiol lyase	1140
L270	Benzoylformate decarboxylase	1141
L271	Benzoylformate decarboxylase	1142
L272	Benzoylformate decarboxylase	1143
L273	Beta-amylase	1144
L274	Beta-galactosidase	AIS
L275	Beta-galactosidase	1145
L276	Beta-galactosidase	1146
L277	Beta-galactosidase	1147
L278	Beta-galactosidase	1148
L279	Beta-galactosidase	1149
L280	Beta-galactosidase	1150
L281	Beta-galactosidase	1151
L282	Beta-galactosidase	1152
L283	Beta-galactosidase	1153
L284	Beta-galactosidase	1154
L285	Beta-galactosidase	1155
L286	Beta-galactosidase	1156
L287	Beta-galactosidase	1157
L288	Beta-galactosidase	1158
L289	Beta-galactosidase	1159
L290	Beta-galactosidase	1160
L291	Beta-galactosidase	1161
L292	Beta-galactosidase	1162
L293	Beta-galactosidase	1163
L294	Beta-galactosidase	1164
L295	Beta-galactosidase	1165
L296	Beta-galactosidase	1166
L297	Beta-N-acetylhexosaminidase	QRE
L298	Beta-N-acetylhexosaminidase	1167
L299	Beta-N-acetylhexosaminidase	1168
L300	Beta-N-acetylhexosaminidase	1169
L301	Bifunctional NMN adenylyltransferase/Nudix hydrolase	1170
L302	Bifunctional purine biosynthesis protein PURH	1171
L303	Biliverdin reductase A	EHV
L304	Biliverdin reductase A	LME
L305	Biliverdin reductase A	1172
L306	Biliverdin reductase A	1173
L307	Biodegradative arginine decarboxylase	TVQ
L308	Biodegradative arginine decarboxylase	1174

L309	Biodegradative arginine decarboxylase	1175
L310	Biodegradative arginine decarboxylase	1176
L311	Biodegradative arginine decarboxylase	1177
L312	Biodegradative arginine decarboxylase	1178
L313	Biodegradative arginine decarboxylase	1179
L314	Biodegradative arginine decarboxylase	1180
L315	Biodegradative arginine decarboxylase	1181
L316	Biodegradative arginine decarboxylase	1182
L317	Biodegradative arginine decarboxylase	1183
L318	Biodegradative arginine decarboxylase	1184
L319	Biodegradative arginine decarboxylase	1185
L320	Biotin carboxylase	1186
L321	Bowman-Birk trypsin inhibitor	1187
L322	Bpt4 gene 59 helicase assembly protein	KQI
L323	BRCA1-associated RING domain protein 1	1188
L324	BRCA1-associated RING domain protein 1	1189
L325	BRCA1-associated RING domain protein 1	1190
L326	Breast cancer 2	1191
L327	Breast cancer 2	1192
L328	Breast cancer 2	1193
L329	Breast cancer 2	1194
L330	Breast cancer 2	1195
L331	Breast cancer 2	1196
L332	Butyrate response factor 2	1197
L333	C4b-binding protein	YKR
L334	C4b-binding protein	1198
L335	C5a peptidase	1199
L336	C5a peptidase	1200
L337	C5a peptidase	1201
L338	C5a peptidase	1202
L339	C5a peptidase	1203
L340	C5a peptidase	1204
L341	C5a peptidase	1205
L342	C5a peptidase	1206
L343	C5a peptidase	1207
L344	C5a peptidase	1208
L345	C5a peptidase	1209
L346	C5a peptidase	1210
L347	C5a peptidase	1211
L348	Calcium-binding protein	1212
L349	CarA	1213
L350	CarA	1214
L351	Carbamoyl phosphate synthetase (small chain)	1215
L352	Carbamoyl phosphate synthetase (small chain)	1216
L353	Carbamoyl phosphate synthetase (small chain)	1217
L354	Carbamoyl phosphate synthetase (small chain)	1218
L355	Carbamoyl phosphate synthetase (small chain)	1219
L356	Carbon monoxide dehydrogenase/acetyl-CoA synthase subunitalpha	1220
L357	Carboxypeptidase Gp180 residues 503-882	HRG
L358	Catabolite activation-like protein	1221
L359	Catabolite activation-like protein	1222
L360	Catechol 2,3-dioxygenase	1223
L361	Cation-independent mannose 6-phosphate receptor	1224
L362	CD3 epsilon and gamma ectodomain fragment complex	1225
L363	CD3 epsilon and gamma ectodomain fragment complex	1226
L364	Cell filamentation protein	SNP
L365	Cell filamentation protein	1227
L366	Cell filamentation protein	1228

L367	Cellular coagulation factor XIII zymogen	DIT
L368	Cellular coagulation factor XIII zymogen	NSD
L369	Cellular coagulation factor XIII zymogen	TDT
L370	Cellular coagulation factor XIII zymogen	1229
L371	Cellular coagulation factor XIII zymogen	1230
L372	Cellular coagulation factor XIII zymogen	1231
L373	Cellular coagulation factor XIII zymogen	1232
L374	Cellular coagulation factor XIII zymogen	1233
L375	Cellular coagulation factor XIII zymogen	1234
L376	Cellular coagulation factor XIII zymogen	1235
L377	Cellular coagulation factor XIII zymogen	1236
L378	Cellular coagulation factor XIII zymogen	1237
L379	Cellular coagulation factor XIII zymogen	1238
L380	Cellular coagulation factor XIII zymogen	1239
L381	Cellular coagulation factor XIII zymogen	1240
L382	Cellular coagulation factor XIII zymogen	1241
L383	Cellular coagulation factor XIII zymogen	1242
L384	Cellular coagulation factor XIII zymogen	1243
L385	Cellular coagulation factor XIII zymogen	1244
L386	Cellular coagulation factor XIII zymogen	1245
L387	Cellular coagulation factor XIII zymogen	1246
L388	Cellular coagulation factor XIII zymogen	1247
L389	Cellulase	1248
L390	Cellulase	1249
L391	Cellulase	1250
L392	Cellulase	1251
L393	Cellulase	1252
L394	Cellulase	1253
L395	Cellulase	1254
L396	Cellulase	1255
L397	Cellulase	1256
L398	Cellulase linker	1257
L399	Cellulase linker	1258
L400	Cellulase linker	1259
L401	Cellulase linker	1260
L402	Chaperone protein FimC	KLR
L403	Chaperone protein FimC	QAA
L404	Chaperone protein FimC	1261
L405	Chaperone protein FimC	1262
L406	Chaperone protein HscB	RHP
L407	Chaperone protein HscB	1263
L408	CheB methylesterase	1264
L409	CheB methylesterase	1265
L410	CheB methylesterase	1266
L411	Chelatase, putative	1267
L412	Chemotaxis receptor methyltransferase cheR	1268
L413	Chemotaxis receptor methyltransferase cheR	1269
L414	Chemotaxis receptor methyltransferase cheR	1270
L415	Cholesterol oxidase	1271
L416	Cholesterol oxidase	1272
L417	Cholesterol oxidase	1273
L418	Cholesterol oxidase	1274
L419	Cholesterol oxidase	1275
L420	Cholesterol oxidase	1276
L421	Cholesterol oxidase	1277
L422	Cholesterol oxidase	1278
L423	Cholesterol oxidase	1279
L424	Cholesterol oxidase	1280

L425	Cholesterol oxidase	1281
L426	Cholesterol oxidase	1282
L427	Chromatin structure-remodeling complex protein RSC4	KNL
L428	Chromatin structure-remodeling complex protein RSC4	1283
L429	Chromatin structure-remodeling complex protein RSC4	1284
L430	Chromatin structure-remodeling complex protein RSC4	1285
L431	Chromodomain-helicase-DNA-binding protein 1	1286
L432	Chromodomain-helicase-DNA-binding protein 1	1287
L433	Cleavable disulfide	1288
L434	Cleavable disulfide	1289
L435	Cleavable disulfide	1290
L436	Cleavable disulfide	1291
L437	Cleavable disulfide	1292
L438	Cleavable disulfide	1293
L439	Cleavable disulfide	1294
L440	Cleavable disulfide	1295
L441	Cleavable disulfide	1296
L442	Cleavable disulfide	1297
L443	Cleavable disulfide	1298
L444	Colicin Ia	1299
L445	Collagen adhesin	1300
L446	Complement C3 beta chain	1301
L447	Complement C3 beta chain	1302
L448	Complement C3 beta chain	1303
L449	Complement C3 beta chain	1304
L450	Complement decay-accelerating factor	EIY
L451	Complement factor H	KRP
L452	Complement receptor type 2	1305
L453	Conserved hypothetical protein	1306
L454	Conserved hypothetical protein MTH1747	DIR
L455	Conserved hypothetical protein MTH1747	1307
L456	Conserved hypothetical protein MTH1747	1308
L457	Conserved hypothetical protein MTH1747	1309
L458	Conserved hypothetical protein MTH1747	1310
L459	Conserved hypothetical protein MTH1747	1311
L460	Conserved hypothetical protein MTH1747	1312
L461	Conserved hypothetical protein MTH1747	1313
L462	Conserved protein (MTH177)	1314
L463	Creatine amidinohydrolase	1315
L464	Cruciferin	1316
L465	Cruciferin	1317
L466	Cruciferin	1318
L467	Cruciferin	1319
L468	Cruciferin	1320
L469	Cruciferin	1321
L470	Cruciferin	1322
L471	CSL3	1323
L472	CSL3	1324
L473	CTP synthase	1325
L474	CTP synthase	1326
L475	Cullin homolog	HKN
L476	Cullin homolog	1327
L477	Cullin homolog	1328
L478	Cullin homolog	1329
L479	Cullin homolog	1330
L480	Cullin homolog	1331
L481	Cyclin A2	1332
L482	Cysteine-rich secretory protein	1333

L483	Cytidine deaminase	1334
L484	Cytidine deaminase	1335
L485	Cytidine deaminase	1336
L486	Cytochrome b-c1 complex subunit Rieske, mitochondrial	1337
L487	Cytochrome c oxidase subunit 2	QAV
L488	Cytochrome c oxidase subunit 2	1338
L489	Cytochrome c oxidase subunit 2	1339
L490	Cytochrome c oxidase subunit 2	1340
L491	Cytochrome c oxidase subunit 2	1341
L492	Cytochrome c4	GGK
L493	Cytochrome c4	QGM
L494	D-aminopeptidase	1342
L495	DDMC	1343
L496	DDMC	1344
L497	Deltex protein	1345
L498	Deoxyuridine 5'-triphosphate nucleotidohydrolase	1346
L499	Diaminopimelate epimerase	1347
L500	Diaminopimelate epimerase	1348
L501	Diaminopimelate epimerase	1349
L502	Di-heme peroxidase	SGC
L503	Di-heme peroxidase	1350
L504	Dihydropyrimidine dehydrogenase	1351
L505	Dihydropyrimidine dehydrogenase	1352
L506	Dihydropyrimidine dehydrogenase	1353
L507	Dihydropyrimidine dehydrogenase	1354
L508	Dihydropyrimidine dehydrogenase	1355
L509	Dihydropyrimidine dehydrogenase	1356
L510	Dihydropyrimidine dehydrogenase	1357
L511	Dihydropyrimidine dehydrogenase	1358
L512	Dihydropyrimidine dehydrogenase	1359
L513	Dihydropyrimidine dehydrogenase	1360
L514	Dihydropyrimidine dehydrogenase	1361
L515	Dihydropyrimidine dehydrogenase	1362
L516	Dihydropyrimidine dehydrogenase	1363
L517	Dihydropyrimidine dehydrogenase	1364
L518	Dihydropyrimidine dehydrogenase	1365
L519	Dihydropyrimidine dehydrogenase	1366
L520	Dihydropyrimidine dehydrogenase	1367
L521	Dihydropyrimidine dehydrogenase	1368
L522	Dihydropyrimidine dehydrogenase	1369
L523	Dihydropyrimidine dehydrogenase	1370
L524	Dihydropyrimidine dehydrogenase	1371
L525	Dihydropyrimidine dehydrogenase	1372
L526	Dihydropyrimidine dehydrogenase	1373
L527	Dihydropyrimidine dehydrogenase	1374
L528	Dihydropyrimidine dehydrogenase	1375
L529	Dihydropyrimidine dehydrogenase	1376
L530	Dihydropyrimidine dehydrogenase	1377
L531	Dihydropyrimidine dehydrogenase	1378
L532	Dihydropyrimidine dehydrogenase	1379
L533	Dihydropyrimidine dehydrogenase	1380
L534	Dihydropyrimidine dehydrogenase	1381
L535	Discoidin-I subunit A	1382
L536	Discoidin-I subunit A	1383
L537	Discoidin-I subunit A	1384
L538	Dissimilatory copper-containing nitritereductase	1385
L539	D-lactate dehydrogenase	DTF
L540	D-lactate dehydrogenase	1386

L541	D-lactate dehydrogenase	1387
L542	D-lactate dehydrogenase	1388
L543	D-lactate dehydrogenase	1389
L544	D-lactate dehydrogenase	1390
L545	D-lactate dehydrogenase	1391
L546	DNA damage-binding protein 1	LCA
L547	DNA damage-binding protein 1	1392
L548	DNA damage-binding protein 1	1393
L549	DNA damage-binding protein 1	1394
L550	DNA damage-binding protein 1	1395
L551	DNA damage-binding protein 1	1396
L552	DNA damage-binding protein 1	1397
L553	DNA damage-binding protein 1	1398
L554	DNA damage-binding protein 1	1399
L555	DNA damage-binding protein 1	1400
L556	DNA damage-binding protein 1	1401
L557	DNA damage-binding protein 1	1402
L558	DNA damage-binding protein 1	1403
L559	DNA damage-binding protein 1	1404
L560	DNA damage-binding protein 1	1405
L561	DNA damage-binding protein 1	1406
L562	DNA damage-binding protein 1	1407
L563	DNA damage-binding protein 1	1408
L564	DNA damage-binding protein 1	1409
L565	DNA damage-binding protein 1	1410
L566	DNA damage-binding protein 1	1411
L567	DNA damage-binding protein 1	1412
L568	DNA damage-binding protein 1	1413
L569	DNA gyrase B	ALS
L570	DNA gyrase B	1414
L571	DNA gyrase B	1415
L572	DNA gyrase B	1416
L573	DNA gyrase B	1417
L574	DNA gyrase B	1418
L575	DNA gyrase B	1419
L576	DNA gyrase B	1420
L577	DNA gyrase B	1421
L578	DNA gyrase B	1422
L579	DNA gyrase B	1423
L580	DNA gyrase B	1424
L581	DNA ligase	1425
L582	DNA ligase	1426
L583	DNA ligase	1427
L584	DNA ligase	1428
L585	DNA ligase	1429
L586	DNA mismatch repair protein MutS	MDA
L587	DNA mismatch repair protein MutS	SII
L588	DNA mismatch repair protein MutS	1430
L589	DNA mismatch repair protein MutS	1431
L590	DNA mismatch repair protein MutS	1432
L591	DNA mismatch repair protein MutS	1433
L592	DNA mismatch repair protein MutS	1434
L593	DNA polymerase	FSP
L594	DNA polymerase	RQF
L595	DNA polymerase	1435
L596	DNA polymerase	1436
L597	DNA polymerase	1437
L598	DNA polymerase	1438

L599	DNA polymerase	1439
L600	DNA polymerase	1440
L601	DNA polymerase	1441
L602	DNA polymerase	1442
L603	DNA polymerase alpha subunit B	1443
L604	DNA polymerase alpha subunit B	1444
L605	DNA polymerase alpha subunit B	1445
L606	DNA polymerase alpha subunit B	1446
L607	DNA polymerase alpha subunit B	1447
L608	DNA polymerase alpha subunit B	1448
L609	DNA polymerase alpha subunit B	1449
L610	DNA polymerase alpha subunit B	1450
L611	DNA polymerase alpha subunit B	1451
L612	DNA polymerase alpha subunit B	1452
L613	DNA polymerase eta	ALS
L614	DNA polymerase eta	1453
L615	DNA polymerase eta	1454
L616	DNA polymerase eta	1455
L617	DNA polymerase eta	1456
L618	DNA polymerase eta	1457
L619	DNA polymerase I	AGV
L620	DNA polymerase I	ELE
L621	DNA polymerase I	1458
L622	DNA primase	DHK
L623	DNA primase	1459
L624	DNA primase	1460
L625	DNA primase	1461
L626	DNA primase	1462
L627	DNA primase	1463
L628	DNA primase	1464
L629	DNA primase	1465
L630	DNA primase/helicase	AGY
L631	DNA primase/helicase	1466
L632	DNA primase/helicase	1467
L633	DNA primase/helicase	1468
L634	DNA primase/helicase	1469
L635	DNA primase/helicase	1470
L636	DNA primase/helicase	1471
L637	DNA primase/helicase	1472
L638	DNA primase/helicase	1473
L639	DNA primase/helicase	1474
L640	DNA primase/helicase	1475
L641	DNA topoisomerase 2	EES
L642	DNA topoisomerase 2	IPI
L643	DNA topoisomerase 2	KEL
L644	DNA topoisomerase 2	1476
L645	DNA topoisomerase 2	1477
L646	DNA topoisomerase 2	1478
L647	DNA topoisomerase 2	1479
L648	DNA topoisomerase 2	1480
L649	DNA topoisomerase 2	1481
L650	DNA topoisomerase 2	1482
L651	DNA topoisomerase 2	1483
L652	DNA topoisomerase 2	1484
L653	DNA topoisomerase I	1485
L654	DNA topoisomerase I	1486
L655	DNA topoisomerase I	1487
L656	DNA topoisomerase II, alpha isozyme	PDL

L657	DNA topoisomerase II, alpha isozyme	1488
L658	DNA topoisomerase II, alpha isozyme	1489
L659	DNA topoisomerase II, alpha isozyme	1490
L660	DNA topoisomerase II, alpha isozyme	1491
L661	DNA topoisomerase II, alpha isozyme	1492
L662	DNA topoisomerase II, alpha isozyme	1493
L663	DNA topoisomerase II, alpha isozyme	1494
L664	DNA topoisomerase II, alpha isozyme	1495
L665	DNA topoisomerase VI A subunit	1496
L666	DNA topoisomerase VI A subunit	1497
L667	DNA topoisomerase VI A subunit	1498
L668	DNA topoisomerase VI A subunit	1499
L669	DNA topoisomerase VI A subunit	1500
L670	DNA topoisomerase VI A subunit	1501
L671	DNA-3-methyladenine glycosylase 2	1502
L672	DNA-binding response regulator MtrA	1503
L673	DNA-directed RNA polymerase beta chain	1504
L674	DNA-directed RNA polymerase beta chain	1505
L675	DNA-directed RNA polymerase beta chain	1506
L676	DNA-directed RNA polymerase beta chain	1507
L677	DNA-directed RNA polymerase beta chain	1508
L678	DNA-directed RNA polymerase beta chain	1509
L679	DNA-directed RNA polymerase beta chain	1510
L680	DNA-directed RNA polymerase beta chain	1511
L681	DNA-directed RNA polymerase II 14.2 kDa polypeptide	1512
L682	DNA-directed RNA polymerase II 14.2 kDa polypeptide	1513
L683	DNA-directed RNA polymerase, subunit E' (rpoe1)	1514
L684	DNA-directed RNA polymerase, subunit E' (rpoe1)	1515
L685	DNA-directed RNA polymerases I, II, and III 27 kDa polypeptide	ITP
L686	DNA-directed RNA polymerases I, II, and III 27 kDa polypeptide	1516
L687	DNA-directed RNA polymerases I, II, and III 27 kDa polypeptide	1517
L688	DNA-directed RNA polymerases I, II, and III 27 kDa polypeptide	1518
L689	DNA-directed RNA polymerases I, II, and III 27 kDa polypeptide	1519
L690	Drosophila neuroglian	1520
L691	Dystroglycan	1521
L692	Dystrophin	1522
L693	Dystrophin	1523
L694	Dystrophin	1524
L695	Dystrophin	1525
L696	Dystrophin	1526
L697	Dystrophin	1527
L698	Dystrophin	1528
L699	E2A DNA-binding protein	1529
L700	E2A DNA-binding protein	1530
L701	E3 sumo-protein ligase SIZ1	1531
L702	E3 sumo-protein ligase SIZ1	1532
L703	E3 sumo-protein ligase SIZ1	1533
L704	Early switch protein xol-1 2.2k splice form	1534
L705	EGF-like module containing mucin-like hormonereceptor-like 2 precursor	1535
L706	EGF-like module containing mucin-like hormonereceptor-like 2 precursor	1536
L707	Elongation factor 1-gamma 1	1537
L708	Elongation factor 1-gamma 1	1538
L709	Elongation factor g	1539
L710	Elongation factor G	1540
L711	Elongation factor G	1541
L712	Elongation factor G	1542
L713	Elongation factor G	1543
L714	Elongation factor G	1544

L715	Elongation factor G	1545
L716	Elongation factor G	1546
L717	Elongation factor G	1547
L718	Elongation factor G	1548
L719	Elongation factor P	1549
L720	Elongation factor Ts	1550
L721	Elongation factor Ts	1551
L722	Elongation factor Ts	1552
L723	Elongation factor Tu (ef-Tu)	1553
L724	Endoglucanase	1554
L725	Endonuclease PI-SceI	1555
L726	Endonuclease PI-SceI	1556
L727	Endonuclease PI-SceI	1557
L728	Endonuclease PI-SceI	1558
L729	Endonuclease PI-SceI	1559
L730	Endonuclease PI-SceI	1560
L731	Endonuclease PI-SceI	1561
L732	Endonuclease PI-SceI	1562
L733	Endonuclease PI-SceI	1563
L734	Enterobactin synthetase component F	1564
L735	Enterobactin synthetase component F	1565
L736	Enterobactin synthetase component F	1566
L737	Enterobactin synthetase component F	1567
L738	Enterobactin synthetase component F	1568
L739	Enterobactin synthetase component F	1569
L740	Enterobactin synthetase component F	1570
L741	Enterobactin synthetase component F	1571
L742	Enterobactin synthetase component F	1572
L743	Enterochelin esterase	1573
L744	Epo receptor	EVV
L745	Epo receptor	1574
L746	Erythrocyte binding antigen region II	1575
L747	Erythrocyte binding antigen region II	1576
L748	Erythrocyte binding antigen region II	1577
L749	Erythrocyte binding antigen region II	1578
L750	Erythrocyte binding antigen region II	1579
L751	E-selectin	1580
L752	Esterase EstA	SAP
L753	Esterase EstA	1581
L754	Esterase EstA	1582
L755	Eukaryotic peptide chain release factor GTP-binding subunit	1583
L756	Exonuclease I	RQP
L757	Exonuclease I	1584
L758	FascIclIn I	SDP
L759	FascIclIn I	1585
L760	Fibrillin-1	1586
L761	Fibrillin-1	1587
L762	Fibrillin-1	1588
L763	Fibrillin-1	1589
L764	Fibrillin-1	1590
L765	Fibronectin	1591
L766	Fibronectin	1592
L767	Fibronectin	1593
L768	Flagellar hook protein FlgE	1594
L769	Flagellar hook protein FlgE	1595
L770	Flagellar hook protein FlgE	1596
L771	Flagellar hook protein FlgE	1597
L772	Flagellar hook protein FlgE	1598

L773	Flagellar hook protein FlgE	1599
L774	Flagellar hook protein FlgE	1600
L775	Flavohemoprotein	1601
L776	Flexible G/S rich linker	G
L777	Flexible G/S rich linker	S
L778	Flexible G/S rich linker	GG
L779	Flexible G/S rich linker	GS
L780	Flexible G/S rich linker	GGS
L781	Flexible G/S rich linker	GGG
L782	Flexible G/S rich linker	1602
L783	Flexible G/S rich linker	1603
L784	Flexible G/S rich linker	1604
L785	Flexible G/S rich linker	1605
L786	Flexible G/S rich linker	1606
L787	Flexible G/S rich linker	1607
L788	Flexible G/S rich linker	1608
L789	Flexible G/S rich linker	1609
L790	Flexible G/S rich linker	1610
L791	Flexible G/S rich linker	1611
L792	Flexible G/S rich linker	1612
L793	Flexible G/S rich linker	1613
L794	Flexible G/S rich linker	1614
L795	Flexible G/S rich linker	1615
L796	Focal adhesion kinase 1	1616
L797	FolC bifunctional protein	1617
L798	FolC bifunctional protein	1618
L799	FolC bifunctional protein	1619
L800	FolC bifunctional protein	1620
L801	FolC bifunctional protein	1621
L802	FolC bifunctional protein	1622
L803	FolC bifunctional protein	1623
L804	FolC bifunctional protein	1624
L805	Follistatin	1625
L806	Formate dehydrogenase (large subunit)	YDK
L807	Formate dehydrogenase (large subunit)	1626
L808	Formate dehydrogenase (large subunit)	1627
L809	Formate dehydrogenase (large subunit)	1628
L810	Formate dehydrogenase (large subunit)	1629
L811	Formate dehydrogenase (large subunit)	1630
L812	Formate dehydrogenase (large subunit)	1631
L813	Formate dehydrogenase (large subunit)	1632
L814	Formate dehydrogenase (large subunit)	1633
L815	Formate dehydrogenase (large subunit)	1634
L816	Formate dehydrogenase (large subunit)	1635
L817	Formate dehydrogenase (large subunit)	1636
L818	Formate dehydrogenase (large subunit)	1637
L819	Formate dehydrogenase, nitrate-inducible major subunit	1638
L820	Formate dehydrogenase, nitrate-inducible, major subunit	1639
L821	Formate dehydrogenase, nitrate-inducible, major subunit	1640
L822	Formate dehydrogenase, nitrate-inducible, major subunit	1641
L823	Formate dehydrogenase, nitrate-inducible, major subunit	1642
L824	Formate dehydrogenase, nitrate-inducible, major subunit	1643
L825	Formate dehydrogenase, nitrate-inducible, major subunit	1644
L826	Formate dehydrogenase, nitrate-inducible, major subunit	1645
L827	Formate dehydrogenase, nitrate-inducible, major subunit	1646
L828	Formate dehydrogenase, nitrate-inducible, major subunit	1647
L829	Formate dehydrogenase, nitrate-inducible, major subunit	1648
L830	Formate dehydrogenase, nitrate-inducible, major subunit	1649

L831	Formate dehydrogenase, nitrate-inducible, major subunit	1650
L832	Formate dehydrogenase, nitrate-inducible, major subunit	1651
L833	Fumarylacetoacetate hydrolase	1652
L834	Galactose oxidase	GSV
L835	Galactose oxidase	GWK
L836	Galactose oxidase	IAE
L837	Galactose oxidase	KRQ
L838	Galactose oxidase	QDT
L839	Galactose oxidase	TPN
L840	Galactose oxidase	1653
L841	Galactose oxidase	1654
L842	Galactose oxidase	1655
L843	Galactose oxidase	1656
L844	Galactose oxidase	1657
L845	Galactose oxidase	1658
L846	Galactose oxidase	1659
L847	Galactose oxidase	1660
L848	Galactose oxidase	1661
L849	Galactose oxidase	1662
L850	Galactose oxidase	1663
L851	Galactose oxidase	1664
L852	Galactose oxidase	1665
L853	Galactose oxidase	1666
L854	Galactose oxidase	1667
L855	Galactose oxidase	1668
L856	Galactose oxidase	1669
L857	Galactose oxidase	1670
L858	Galactose oxidase	1671
L859	Galactose oxidase	1672
L860	Galactose oxidase	1673
L861	Galactose oxidase	1674
L862	Galactose oxidase	1675
L863	Galactose oxidase	1676
L864	Gamma B-crystallin	1677
L865	Gamma-delta T-cell receptor	1678
L866	Gelation factor	DSS
L867	Gelation factor	1679
L868	Gelation factor	1680
L869	Gelation factor	1681
L870	Gene activator alpha	1682
L871	Gingipain R	1683
L872	Glucodextranase	1684
L873	Glucodextranase	1685
L874	Glucodextranase	1686
L875	Glucosamine-fructose-6-phosphate aminotransferase	YEQ
L876	Glucosamine-fructose-6-phosphate aminotransferase	1687
L877	Glucosamine-fructose-6-phosphate aminotransferase	1688
L878	Glucosamine-fructose-6-phosphate aminotransferase	1689
L879	Glucosamine-fructose-6-phosphate aminotransferase	1690
L880	Glucosamine-fructose-6-phosphate aminotransferase	1691
L881	Glucosamine-fructose-6-phosphate aminotransferase	1692
L882	Glucosamine-fructose-6-phosphate aminotransferase	1693
L883	Glucosamine-fructose-6-phosphate aminotransferase	1694
L884	Glucosamine-fructose-6-phosphate aminotransferase	1695
L885	Glucosamine-fructose-6-phosphate aminotransferase	1696
L886	Glucose-1-phosphate adenylyltransferase small subunit	1697
L887	Glucose-1-phosphate adenylyltransferase small subunit	1698
L888	Glucose-6-phosphate isomerase	KNA

L889	Glucose-6-phosphate isomerase	VGF
L890	Glucose-6-phosphate isomerase	1699
L891	Glucose-6-phosphate isomerase	1700
L892	Glucose-6-phosphate isomerase, conjectural	1701
L893	Glutamate dehydrogenase	1702
L894	Glutamate dehydrogenase	1703
L895	Glutamate receptor interacting protein	1704
L896	Glutamate synthase [NADPH] large chain	1705
L897	Glutamate synthase [NADPH] large chain	1706
L898	Glutamate synthase [NADPH] large chain	1707
L899	Glutamate synthase [NADPH] large chain	1708
L900	Glutamate synthase [NADPH] large chain	1709
L901	Glutamate synthase [NADPH] large chain	1710
L902	Glutamate synthase [NADPH] large chain	1711
L903	Glutamine synthetase	1712
L904	Glutamine synthetase	1713
L905	Glutamyl-tRNA synthetase	1714
L906	Glutamyl-tRNA synthetase	1715
L907	Glutamyl-tRNA synthetase	1716
L908	Glutamyl-tRNA synthetase	1717
L909	Glutamyl-tRNA synthetase	1718
L910	Glutamyl-tRNA synthetase	1719
L911	Glutamyl-tRNA synthetase	1720
L912	Glutamyl-tRNA synthetase	1721
L913	Glutaredoxin 2	1722
L914	Glutathione S-transferase	1723
L915	Glutathione S-transferase	1724
L916	Glutathione S-transferase	1725
L917	Glutathione S-transferase 1-6	1726
L918	Glutathione S-transferase A1	1727
L919	Glutathlone S-transferase I	NKP
L920	Glutathlone S-transferase I	1728
L921	Glutathione synthetase	1729
L922	Glutathione transferase GST1-4	1730
L923	Glutathione transferase GST1-4	1731
L924	Glutathione transferase sigma class	1732
L925	Glycerol-3-phosphate dehydrogenase [NAD(P)+]	1733
L926	Glycine cleavage system transcriptionalrepressor, putative	1734
L927	Glycolipid-anchored surface protein 2	1735
L928	Glycolipid-anchored surface protein 2	1736
L929	Glycyl-tRNA synthetase	KFA
L930	Glycyl-tRNA synthetase	1737
L931	Glycyl-tRNA synthetase	1738
L932	Glycyl-tRNA synthetase	1739
L933	Glycyl-tRNA synthetase	1740
L934	Glycyl-tRNA synthetase	1741
L935	Glycyl-tRNA synthetase	1742
L936	Glycyl-tRNA synthetase	1743
L937	Glycyl-tRNA synthetase	1744
L938	Glycyl-tRNA synthetase	1745
L939	Growth hormone receptor	1746
L940	Growth hormone receptor	1747
L941	Harmonin	1748
L942	HasR protein	1749
L943	HasR protein	1750
L944	Hemin transport protein HemS	1751
L945	Hemin transport protein HemS	1752
L946	Hemin transport protein HemS	1753

L947	Hemoglobin	1754
L948	Hemolytic lectin CEL-iii	1755
L949	Hepatocyte nuclear factor 6	1756
L950	Histidyl-tRNA synthetase	1757
L951	HNH homing endonuclease	1758
L952	HNH homing endonuclease	1759
L953	HNH homing endonuclease	1760
L954	Homoserine dehydrogenase	1761
L955	Homoserine kinase	1762
L956	Homoserine kinase	1763
L957	Homoserine kinase	1764
L958	Homoserine kinase	1765
L959	HTH-type transcriptional regulator MqsA (Ygit/B3021)	1766
L960	HTH-type transcriptional repressor YvoA	1767
L961	HTH-type transcriptional repressor YvoA	1768
L962	Human IgG1 middle hinge linker	1769
L963	Human IgG1 upper hinge linker	1770
L964	Human IgG3 middle hinge linker	1771
L965	Human IgG3m15 middle hinge linker	1772
L966	Human IgG4 lower hinge linker	1773
L967	Human IgG4 middle hinge linker	1774
L968	Human IgG4 upper hinge linker	1775
L969	Hybrid cluster protein	1776
L970	Hybrid cluster protein	1777
L971	Hybrid cluster protein	1778
L972	Hybrid cluster protein	1779
L973	Hybrid cluster protein	1780
L974	Hypothetical conserved protein, GK1056	1781
L975	Hypothetical membrane spanning protein	1782
L976	Hypothetical methylmalonyl-CoA decarboxylase alpha subunit	1783
L977	Hypothetical methylmalonyl-CoA decarboxylase alpha subunit	1784
L978	Hypothetical methylmalonyl-CoA decarboxylase alpha subunit	1785
L979	Hypothetical methylmalonyl-CoA decarboxylase alpha subunit	1786
L980	Hypothetical methylmalonyl-CoA decarboxylase alpha subunit	1787
L981	Hypothetical methylmalonyl-CoA decarboxylase alpha subunit	1788
L982	Hypothetical methylmalonyl-CoA decarboxylase alpha subunit	1789
L983	Hypothetical protein	AEP
L984	Hypothetical protein	1790
L985	Hypothetical protein APE0525	PTL
L986	Hypothetical protein APE0525	1791
L987	Hypothetical protein LOC449832	1792
L988	Hypothetical protein LOC449832	1793
L989	Hypothetical protein PA4388	1794
L990	Hypothetical protein PA5201	ASE
L991	Hypothetical protein PA5201	QDP
L992	Hypothetical protein PA5201	VKL
L993	Hypothetical protein PA5201	1795
L994	Hypothetical protein PA5201	1796
L995	Hypothetical protein PA5201	1797
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L999	Hypothetical protein PA5201	1801
L1000	Hypothetical protein PA5201	1802
L1001	Hypothetical protein PA5201	1803
L1002	Hypothetical protein PA5201	1804
L1003	Hypothetical protein PA5201	1805
L1004	Hypothetical protein PA5201	1806

L1005	Hypothetical protein PA5201	1807
L1006	Hypothetical protein PA5201	1808
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L1008	Hypothetical protein PA5201	1810
L1009	Hypothetical protein PA5201	1811
L1010	Hypothetical protein PA5201	1812
L1011	Hypothetical protein PA5201	1813
L1012	Hypothetical protein PA5201	1814
L1013	Hypothetical protein PH0495	ASN
L1014	Hypothetical protein PH0495	1815
L1015	Hypothetical protein PH0495	1816
L1016	Hypothetical protein PH0495	1817
L1017	Hypothetical protein PH0495	1818
L1018	Hypothetical protein PH0510	1819
L1019	Hypothetical protein PH0510	1820
L1020	Hypothetical protein PH1313	1821
L1021	Hypothetical protein PH1313	1822
L1022	Hypothetical protein SLR0953	1823
L1023	Hypothetical protein SLR0953	1824
L1024	Hypothetical protein SLR0953	1825
L1025	Hypothetical protein SLR0953	1826
L1026	Hypothetical protein SLR0953	1827
L1027	Hypothetical protein YIGZ	1828
L1028	Hypothetical protein YIGZ	1829
L1029	Hypothetical protein YJIA	1830
L1030	Hypothetical protein YJIA	1831
L1031	Hypothetical protein YJIA	1832
L1032	Hypothetical protein YJIA	1833
L1033	Hypothetical protein YJIA	1834
L1034	Hypothetical tRNA/rRNA methyltransferase YJFH	1835
L1035	Hypothetical tRNA/rRNA methyltransferase YJFH	1836
L1036	IclR transcriptional regulator	1837
L1037	IclR transcriptional regulator	1838
L1038	IclR transcriptional regulator	1839
L1039	IclR transcriptional regulator	1840
L1040	Integrase	1841
L1041	Interferon, alpha-inducible protein (clone IFI-15k)	1842
L1042	Interleukin-1 receptor, type I	AIF
L1043	Interleukin-1 receptor, type I	1843
L1044	Interleukin-1 receptor, type I	1844
L1045	Interleukin-1 receptor, type I	1845
L1046	Interleukin-12 subunit p40	FFI
L1047	Interleukin-12 subunit p40	1846
L1048	Interleukin-12 subunit p40	1847
L1049	Interleukin-12 subunit p40	1848
L1050	Interleukin-12 subunit p40	1849
L1051	Interleukin-12 subunit p40	1850
L1052	Interleukin-12 subunit p40	1851
L1053	Interleukin-12 subunit p40	1852
L1054	Interleukin-2 receptor alpha chain	1853
L1055	Interleukin-2 receptor alpha chain	1854
L1056	Internalin B	VTQ
L1057	Internalin B	1855
L1058	Internalin B	1856
L1059	Internalin B	1857
L1060	Internalin B	1858
L1061	Internalin B	1859
L1062	Internalin B	1860

L1063	Internalin B	1861
L1064	Internalin B	1862
L1065	Internalin B	1863
L1066	Internalin B	1864
L1067	Internalin B	1865
L1068	Internalin B	1866
L1069	Intimin	SLV
L1070	Intimin	1867
L1071	Intimin	1868
L1072	Intimin	1869
L1073	Intron-encoded DNA endonuclease I-anil	1870
L1074	Intron-encoded DNA endonuclease I-anil	1871
L1075	Invasin	KST
L1076	Invasin	1872
L1077	Invasin	1873
L1078	Invasin	1874
L1079	Invasin	1875
L1080	Invasin	1876
L1081	Invasin	1877
L1082	Invasin	1878
L1083	Invasin	1879
L1084	Invasin	1880
L1085	Invasin	1881
L1086	Invasin	1882
L1087	Invasin	1883
L1088	Iron hydrogenase 1	GAE
L1089	Iron hydrogenase 1	1884
L1090	Iron hydrogenase 1	1885
L1091	Iron hydrogenase 1	1886
L1092	Iron hydrogenase 1	1887
L1093	Iron hydrogenase 1	1888
L1094	Iron hydrogenase 1	1889
L1095	Iron hydrogenase 1	1890
L1096	Iron hydrogenase 1	1891
L1097	Iron hydrogenase 1	1892
L1098	Iron hydrogenase 1	1893
L1099	Iron hydrogenase 1	1894
L1100	Iron hydrogenase 1	1895
L1101	Iron hydrogenase 1	1896
L1102	Iron transport protein	1897
L1103	Isoflavanone 4'-O-methyltransferase	1898
L1104	Isoflavanone 4'-O-methyltransferase	1899
L1105	Junctional adhesion molecule 1	1900
L1106	Junctional adhesion molecule 1	1901
L1107	Junctional adhesion molecule 1	1902
L1108	Kanamycin nucleotidyltransferase	1903
L1109	Kanamycin nucleotidyltransferase	1904
L1110	Kanamycin nucleotidyltransferase	1905
L1111	Kanamycin nucleotidyltransferase	1906
L1112	Kelch-like protein 11	1907
L1113	Kexin	ISE
L1114	Kexin	1908
L1115	Kexin	1909
L1116	Kexin	1910
L1117	Kexin	1911
L1118	Kexin	1912
L1119	Kexin	1913
L1120	Kexin	1914

L1121	Ku70	1915
L1122	Ku70	1916
L1123	Ku70	1917
L1124	Ku70	1918
L1125	Ku80	1919
L1126	Laccase-1	1920
L1127	Laccase-1	1921
L1128	Laccase-1	1922
L1129	Laccase-1	1923
L1130	Laminin	DKC
L1131	L-aspartate dehydrogenase	SAS
L1132	L-aspartate dehydrogenase	1924
L1133	L-aspartate dehydrogenase	1925
L1134	Leucine dehydrogenase	1926
L1135	Leucine dehydrogenase	1927
L1136	Light chain of HyHel10 antibody fragment (fab)	1928
L1137	Lin2111 protein	1929
L1138	Lin2111 protein	1930
L1139	Lipopolysaccharide-responsive and beige-like anchor protein	1931
L1140	Lipopolysaccharide-responsive and beige-like anchor protein	1932
L1141	Lipovitellin (LV-1N, LV-1C)	1933
L1142	Lipovitellin (LV-1N, LV-1C)	1934
L1143	Lipovitellin (LV-1N, LV-1C)	1935
L1144	Lipovitellin (LV-1N, LV-1C)	1936
L1145	Lipovitellin (LV-1N, LV-1C)	1937
L1146	Lipoxygenase-1	1938
L1147	Lipoxygenase-1	1939
L1148	Low affinity immunoglobulin gamma Fc region receptor II-A	1940
L1149	Luciferase	1941
L1150	LysR-type regulatory protein	1942
L1151	Macrolide-specific efflux protein MacA	ATE
L1152	Macrolide-specific efflux protein MacA	1943
L1153	Macrolide-specific efflux protein MacA	1944
L1154	Magnesium transporter, putative	1945
L1155	Main hemagglutinin component	1946
L1156	Major centromere autoantigen B	1947
L1157	Major surface antigen p30	1948
L1158	Major surface antigen p30	1949
L1159	Major vault protein	1950
L1160	Major vault protein	1951
L1161	Maltose phosphorylase	1952
L1162	Maltose phosphorylase	1953
L1163	Maltose phosphorylase	1954
L1164	Maltose phosphorylase	1955
L1165	Maltose phosphorylase	1956
L1166	Manganese-dependent inorganic pyrophosphatase	1957
L1167	Manganese-dependent inorganic pyrophosphatase	1958
L1168	Mannan-binding lectin	1959
L1169	Mannan-binding lectin	1960
L1170	Mannan-binding lectin	1961
L1171	Mannitol dehydrogenase	HNA
L1172	Mannitol dehydrogenase	1962
L1173	Membrane cofactor protein	RET
L1174	Membrane cofactor protein	1963
L1175	Membrane-associated prostaglandin E synthase-2	1964
L1176	Membrane-associated prostaglandin E synthase-2	1965
L1177	Membrane-associated prostaglandin E synthase-2	1966
L1178	Membrane-associated prostaglandin E synthase-2	1967

L1179	Membrane-associated prostaglandin E synthase-2	1968
L1180	Membrane-bound lytic murein transglycosylase A	1969
L1181	Methionyl-tRNA synthetase	1970
L1182	Methyl-accepting chemotaxis protein	VRP
L1183	Methyl-accepting chemotaxis protein	1971
L1184	Methyl-accepting chemotaxis protein	1972
L1185	Methyl-accepting chemotaxis protein	1973
L1186	Methyl-coenzyme M reductase	1974
L1187	Methyl-coenzyme M reductase	1975
L1188	Methyl-coenzyme M reductase	1976
L1189	Methyl-coenzyme M reductase	1977
L1190	Methylene tetrahydromethanopterin dehydrogenase	1978
L1191	Methylene tetrahydromethanopterin dehydrogenase	1979
L1192	Mg2+ transporter MgtE	1980
L1193	Mg2+ transporter MgtE	1981
L1194	Mg2+ transporter MgtE	1982
L1195	Mitochondrial aconitase	1983
L1196	Mitochondrial aconitase	1984
L1197	Modification methylase TaqI	EGK
L1198	Modification methylase TaqI	PAT
L1199	Modification methylase TaqI	1985
L1200	Modification methylase TaqI	1986
L1201	Modification methylase TaqI	1987
L1202	Modification methylase TaqI	1988
L1203	Modification methylase TaqI	1989
L1204	Modification methylase TaqI	1990
L1205	Modification methylase TaqI	1991
L1206	Modification methylase TaqI	1992
L1207	Multidrug-efflux transporter 1 regulator	1993
L1208	Muramoyl-pentapeptide carboxypeptidase	1994
L1209	MutL	1995
L1210	MutL	1996
L1211	MutL	1997
L1212	MutL	1998
L1213	MutL	1999
L1214	MutL	2000
L1215	MutL	2001
L1216	MutL	2002
L1217	MutL	2003
L1218	MutM (Fpg) protein	2004
L1219	MutM (Fpg) protein	2005
L1220	MutM (Fpg) protein	2006
L1221	MutM (Fpg) protein	2007
L1222	Myotubularin-related protein 2	THW
L1223	Myotubularin-related protein 2	2008
L1224	Myotubularin-related protein 2	2009
L1225	Myotubularin-related protein 2	2010
L1226	Myotubularin-related protein 2	2011
L1227	Myotubularin-related protein 2	2012
L1228	N utilization substance protein A	EIP
L1229	N utilization substance protein A	2013
L1230	N utilization substance protein A	2014
L1231	N utilization substance protein A	2015
L1232	N-acetylglucosamine kinase	CAY
L1233	N-acetylglucosamine kinase	ISP
L1234	N-acetylglucosamine kinase	2016
L1235	N-acyl-D-glutamate deacylase	2017
L1236	N-acyl-D-glutamate deacylase	2018

L1237	N-acyl-D-glutamate deacylase	2019
L1238	N-acyl-D-glutamate deacylase	2020
L1239	N-acyl-D-glutamate deacylase	2021
L1240	N-acyl-D-glutamate deacylase	2022
L1241	N-acyl-D-glutamate deacylase	2023
L1242	NAD-dependent malic enzyme	2024
L1243	NAD-dependent malic enzyme	2025
L1244	NADH peroxidase	ADT
L1245	NADH peroxidase	AVG
L1246	NADH peroxidase	TLI
L1247	NADH peroxidase	2026
L1248	NADH peroxidase	2027
L1249	NADH peroxidase	2028
L1250	NADH peroxidase	2029
L1251	NADH peroxidase	2030
L1252	NADH peroxidase	2031
L1253	NADH pyrophosphatase	2032
L1254	Naphthalene 1,2-dioxygenase alpha subunit	2033
L1255	Naphthalene 1,2-dioxygenase alpha subunit	2034
L1256	NEDD8-activating enzyme E1 catalytic subunit	2035
L1257	NEDD8-activating enzyme E1 regulatory subunit	2036
L1258	NEDD8-activating enzyme E1 regulatory subunit	2037
L1259	NEDD8-activating enzyme E1 regulatory subunit	2038
L1260	Nei endonuclease VIII-Like 1	2039
L1261	Nei endonuclease VIII-Like 1	2040
L1262	Nei endonuclease VIII-Like 1	2041
L1263	Nei endonuclease VIII-Like 1	2042
L1264	Neural cell adhesion molecule 2	2043
L1265	Neural cell adhesion molecule 2	2044
L1266	Neural cell adhesion molecule 2	2045
L1267	Neural cell adhesion molecule 2	2046
L1268	Neural cell adhesion molecule 2	2047
L1269	Neuroplastin	2048
L1270	Neuroplastin	2049
L1271	Neuroplastin	2050
L1272	Neutrophil cytosol factor 1	2051
L1273	Nickel responsive regulator	2052
L1274	NifU-like protein 2, chloroplast	2053
L1275	Nitric oxide reductase	ILM
L1276	Nitric oxide reductase	2054
L1277	Nitric oxide reductase	2055
L1278	Nitric oxide reductase	2056
L1279	Nitric oxide reductase	2057
L1280	Nitric oxide reductase	2058
L1281	NK receptor	2059
L1282	Nuclear factor of activated t-cells, cytoplasmic2	2060
L1283	Nucleolin RBD12	2061
L1284	O-GlcNAcase NagJ	2062
L1285	Orange carotenoid protein	EGV
L1286	Orange carotenoid protein	2063
L1287	Orange carotenoid protein	2064
L1288	Orn/Lys/Arg decarboxylase family protein	LEL
L1289	Orn/Lys/Arg decarboxylase family protein	2065
L1290	Orn/Lys/Arg decarboxylase family protein	2066
L1291	Orn/Lys/Arg decarboxylase family protein	2067
L1292	Orn/Lys/Arg decarboxylase family protein	2068
L1293	Orn/Lys/Arg decarboxylase family protein	2069
L1294	Orn/Lys/Arg decarboxylase family protein	2070

L1295	Orn/Lys/Arg decarboxylase family protein	2071
L1296	Osteoclast-stimulating factor 1	2072
L1297	Oxygen-independent coproporphyrinogen III oxidase	2073
L1298	Oxygen-independent coproporphyrinogen III oxidase	2074
L1299	Oxygen-independent coproporphyrinogen III oxidase	2075
L1300	Oxygen-independent coproporphyrinogen III oxidase	2076
L1301	Oxygen-independent coproporphyrinogen III oxidase	2077
L1302	Oxygen-independent coproporphyrinogen III oxidase	2078
L1303	Oxygen-independent coproporphyrinogen III oxidase	2079
L1304	Oxygen-independent coproporphyrinogen III oxidase	2080
L1305	Oxygen-independent coproporphyrinogen III oxidase	2081
L1306	Oxygen-independent coproporphyrinogen III oxidase	2082
L1307	Paraneoplastic encephalomyelitis antigen HuD	2083
L1308	Paraneoplastic encephalomyelitis antigen HuD	2084
L1309	Penicillin binding protein 4	2085
L1310	Penicillin binding protein 4	2086
L1311	Penicillin binding protein 4	2087
L1312	Penicillin binding protein 4	2088
L1313	Penicillin binding protein 4	2089
L1314	Penicillin binding protein 4	2090
L1315	Penicillin binding protein 4	2091
L1316	Peptide-N(4)-(N-acetyl-beta-D-glucosaminyl)asparagine amidase F	DGV
L1317	Peptide-N(4)-(N-acetyl-beta-D-glucosaminyl)asparagine amidase F	2092
L1318	Peptide-N(4)-(N-acetyl-beta-D-glucosaminyl)asparagine amidase F	2093
L1319	Peptide-N(4)-(N-acetyl-beta-D-glucosaminyl)asparagine amidase F	2094
L1320	Peroxisomal primary amine oxidase	2095
L1321	Peroxisomal primary amine oxidase	2096
L1322	Peroxisome biogenesis factor 1	2097
L1323	Pesticidial crystal protein Cry2Aa	2098
L1324	Pesticidial crystal protein Cry2Aa	2099
L1325	Pesticidial crystal protein Cry2Aa	2100
L1326	Phase 1 flagellin	DLT
L1327	Phase 1 flagellin	2101
L1328	Phase 1 flagellin	2102
L1329	Phase 1 flagellin	2103
L1330	Phase 1 flagellin	2104
L1331	Phase 1 flagellin	2105
L1332	Phase 1 flagellin	2106
L1333	Phase 1 flagellin	2107
L1334	Phase 1 flagellin	2108
L1335	Phase 1 flagellin	2109
L1336	Phase 1 flagellin	2110
L1337	Phase 1 flagellin	2111
L1338	Phase 1 flagellin	2112
L1339	Phenylalanyl-tRNA synthetase beta chain	LGL
L1340	Phenylalanyl-tRNA synthetase beta chain	2113
L1341	Phenylalanyl-tRNA synthetase beta chain	2114
L1342	Phenylalanyl-tRNA synthetase beta chain	2115
L1343	Phenylalanyl-tRNA synthetase beta chain	2116
L1344	Phenylalanyl-tRNA synthetase beta chain	2117
L1345	Phenylalanyl-tRNA synthetase beta chain	2118
L1346	Phenylalanyl-tRNA synthetase beta chain	2119
L1347	Phenylalanyl-tRNA synthetase beta chain	2120
L1348	Phenylalanyl-tRNA synthetase beta chain	2121
L1349	Phenylalanyl-tRNA synthetase beta chain	2122
L1350	Phenylalanyl-tRNA synthetase beta chain	2123
L1351	Phenylalanyl-tRNA synthetase beta chain	2124
L1352	Phenylalanyl-tRNA synthetase beta chain	2125

L1353	Phosphatase	2126
L1354	Phosphatase	2127
L1355	Phosphatase	2128
L1356	Phosphatidylinositol transfer protein Sec14p	YGT
L1357	Phosphatidylinositol transfer protein Sec14p	2129
L1358	Phosphatidylinositol transfer protein Sec14p	2130
L1359	Phosphatidylserine synthase	2131
L1360	Phosphatidylserine synthase	2132
L1361	Phosphatidylserine synthase	2133
L1362	Phosphoglycolate phosphatase	2134
L1363	Phosphoglycolate phosphatase	2135
L1364	Phosphoglycolate phosphatase	2136
L1365	Phosphoglycolate phosphatase	2137
L1366	Phospholipase D	2138
L1367	Phospholipase D	2139
L1368	Phospholipase D	2140
L1369	Phosphoribosylamine--glycine ligase	2141
L1370	Phosphoribosylamine--glycine ligase	2142
L1371	Phosphotransferase system, enzyme I	2143
L1372	Photosystem II d1 protease	2144
L1373	Photosystem II d1 protease	2145
L1374	Photosystem II d1 protease	2146
L1375	Photosystem II d1 protease	2147
L1376	Photosystem II d1 protease	2148
L1377	Phthalate dioxygenase reductase	2149
L1378	P-hydroxybenzoate hydroxylase	DGL
L1379	P-hydroxybenzoate hydroxylase	IDL
L1380	P-hydroxybenzoate hydroxylase	RLK
L1381	P-hydroxybenzoate hydroxylase	2150
L1382	P-hydroxybenzoate hydroxylase	2151
L1383	P-hydroxybenzoate hydroxylase	2152
L1384	P-hydroxybenzoate hydroxylase	2153
L1385	P-hydroxybenzoate hydroxylase	2154
L1386	P-hydroxybenzoate hydroxylase	2155
L1387	P-hydroxybenzoate hydroxylase	2156
L1388	P-hydroxybenzoate hydroxylase	2157
L1389	P-hydroxybenzoate hydroxylase	2158
L1390	P-hydroxybenzoate hydroxylase	2159
L1391	P-hydroxybenzoate hydroxylase	2160
L1392	P-hydroxybenzoate hydroxylase	2161
L1393	P-hydroxybenzoate hydroxylase	2162
L1394	P-hydroxybenzoate hydroxylase	2163
L1395	P-hydroxybenzoate hydroxylase	2164
L1396	P-hydroxybenzoate hydroxylase	2165
L1397	P-hydroxybenzoate hydroxylase	2166
L1398	Phytase	LNF
L1399	Phytase	QSN
L1400	Phytase	2167
L1401	Phytase	2168
L1402	Phytase	2169
L1403	Phytase	2170
L1404	Phytase	2171
L1405	Phytase	2172
L1406	Phytase	2173
L1407	Phytase	2174
L1408	Pirin	LKS
L1409	Pirin	SGE
L1410	Pirin	2175

L1411	Pirin	2176
L1412	Pirin	2177
L1413	Pirin	2178
L1414	Pirin	2179
L1415	Pirin	2180
L1416	Poly(A) polymerase	2181
L1417	Poly(A) polymerase	2182
L1418	Poly(A) polymerase	2183
L1419	Poly(A) polymerase	2184
L1420	Poly(A) polymerase	2185
L1421	Poly(A) polymerase	2186
L1422	Poly(A) polymerase	2187
L1423	Poly(A) polymerase	2188
L1424	Poly(A) polymerase	2189
L1425	Poly(A) polymerase	2190
L1426	Poly(A) polymerase	2191
L1427	Poly(A) polymerase	2192
L1428	Poly(rC)-binding protein 2	2193
L1429	Polymerase x	2194
L1430	Polymerase x	2195
L1431	Polypeptide N-acetylgalactosaminyltransferase 2	2196
L1432	Polypeptide N-acetylgalactosaminyltransferase 2	2197
L1433	Polyphosphate kinase	2198
L1434	Polyphosphate kinase	2199
L1435	Polyphosphate kinase	2200
L1436	Polypyrimidine tract-binding protein	2201
L1437	Porcine pancreatic spasmolytic polypeptide	2202
L1438	Possible 3-mercaptopyruvate sulfurtransferase	LFR
L1439	Possible 3-mercaptopyruvate sulfurtransferase	YGM
L1440	Possible 3-mercaptopyruvate sulfurtransferase	2203
L1441	Possible 3-mercaptopyruvate sulfurtransferase	2204
L1442	Possible 3-mercaptopyruvate sulfurtransferase	2205
L1443	Postsynaptic density protein 95	2206
L1444	Postsynaptic density protein 95	2207
L1445	Predicted sugar phosphatases of the HAD superfamily	IAI
L1446	Predicted sugar phosphatases of the HAD superfamily	2208
L1447	Predicted sugar phosphatases of the HAD superfamily	2209
L1448	Predicted sugar phosphatases of the HAD superfamily	2210
L1449	Predicted sugar phosphatases of the HAD superfamily	2211
L1450	Predicted sugar phosphatases of the HAD superfamily	2212
L1451	Predicted sugar phosphatases of the HAD superfamily	2213
L1452	Predicted sugar phosphatases of the HAD superfamily	2214
L1453	Predicted sugar phosphatases of the HAD superfamily	2215
L1454	Preprotein translocase SecA	ITF
L1455	Preprotein translocase SecA	LID
L1456	Preprotein translocase SecA	2216
L1457	Preprotein translocase SecA	2217
L1458	Preprotein translocase SecA	2218
L1459	Preprotein translocase SecA	2219
L1460	Preprotein translocase SecA	2220
L1461	Preprotein translocase SecA	2221
L1462	Preprotein translocase SecA	2222
L1463	Preprotein translocase SecA	2223
L1464	Preprotein translocase SecA	2224
L1465	Preprotein translocase SecA	2225
L1466	Preprotein translocase SecA	2226
L1467	Preprotein translocase SecA	2227
L1468	Preprotein translocase SecA	2228

L1469	Preprotein translocase SecA	2229
L1470	Preprotein translocase SecA	2230
L1471	Preprotein translocase SecA	2231
L1472	Preprotein translocase SecA	2232
L1473	PrfA	ING
L1474	Probable 16s rRNA-processing protein RimM	2233
L1475	Probable biphenyl-2,3-diol 1,2-dioxygenase BphC	2234
L1476	Probable chorismate mutase	LLA
L1477	Probable chorismate mutase	2235
L1478	Probable chorismate mutase	2236
L1479	Probable ferredoxin-dependent nitrite reductase NirA	VPL
L1480	Probable ferredoxin-dependent nitrite reductase NirA	WGI
L1481	Probable ferredoxin-dependent nitrite reductase NirA	2237
L1482	Probable ferredoxin-dependent nitrite reductase NirA	2238
L1483	Probable ferredoxin-dependent nitrite reductase NirA	2239
L1484	Probable ferredoxin-dependent nitrite reductase NirA	2240
L1485	Probable ferredoxin-dependent nitrite reductase NirA	2241
L1486	Probable ferredoxin-dependent nitrite reductase NirA	2242
L1487	Probable ferredoxin-dependent nitrite reductase NirA	2243
L1488	Probable ferredoxin-dependent nitrite reductase NirA	2244
L1489	Probable ferredoxin-dependent nitrite reductase NirA	2245
L1490	Probable ferredoxin-dependent nitrite reductase NirA	2246
L1491	Probable ferredoxin-dependent nitrite reductase NirA	2247
L1492	Probable ferredoxin-dependent nitrite reductase NirA	2248
L1493	Probable galactokinase	2249
L1494	Probable galactokinase	2250
L1495	Probable galactokinase	2251
L1496	Probable galactokinase	2252
L1497	Probable galactokinase	2253
L1498	Probable galactokinase	2254
L1499	Probable galactokinase	2255
L1500	Probable galactokinase	2256
L1501	Probable galactokinase	2257
L1502	Probable galactokinase	2258
L1503	Probable galactokinase	2259
L1504	Probable galactokinase	2260
L1505	Probable glutathione S-transferase	2261
L1506	Probable GST-related protein	2262
L1507	Probable HPr(Ser) kinase/phosphatase	2263
L1508	Probable thiosulfate sulfur transferase	2264
L1509	Probable thiosulfate sulfur transferase	2265
L1510	Probable thiosulfate sulfur transferase	2266
L1511	Probable thiosulfate sulfur transferase	2267
L1512	Probable thiosulfate sulfur transferase	2268
L1513	Probable thiosulfate sulfur transferase	2269
L1514	Probable thiosulfate sulfur transferase	2270
L1515	Probable thiosulfate sulfur transferase	2271
L1516	Probable tRNA pseudouridine synthase D	2272
L1517	Probable tRNA pseudouridine synthase D	2273
L1518	Probable tRNA pseudouridine synthase D	2274
L1519	Probable tRNA pseudouridine synthase D	2275
L1520	Probable tRNA pseudouridine synthase D	2276
L1521	Probable tRNA pseudouridine synthase D	2277
L1522	Programed cell death protein 8	SKE
L1523	Programed cell death protein 8	TLQ
L1524	Programed cell death protein 8	2278
L1525	Programed cell death protein 8	2279
L1526	Programed cell death protein 8	2280

L1527	Programed cell death protein 8	2281
L1528	Programed cell death protein 8	2282
L1529	Programed cell death protein 8	2283
L1530	Programed cell death protein 8	2284
L1531	Programed cell death protein 8	2285
L1532	Programed cell death protein 8	2286
L1533	Programed cell death protein 8	2287
L1534	Programed cell death protein 8	2288
L1535	Programed cell death protein 8	2289
L1536	Programed cell death protein 8	2290
L1537	Programed cell death protein 8	2291
L1538	Programed cell death protein 8	2292
L1539	Programed cell death protein 8	2293
L1540	Programed cell death protein 8	2294
L1541	Programed cell death protein 8	2295
L1542	Proline oxidase	2296
L1543	Prolyl-tRNA synthetase	2297
L1544	Prostaglandin G/H synthase 1	PEI
L1545	Prostaglandin G/H synthase 1	2298
L1546	Protease	2299
L1547	Protease	2300
L1548	Protease	2301
L1549	Protease DegS	2302
L1550	Protease DegS	2303
L1551	Protease DegS	2304
L1552	Protease DegS	2305
L1553	Protease III	NAR
L1554	Protease III	RNP
L1555	Protease III	2306
L1556	Protease III	2307
L1557	Protease III	2308
L1558	Protease III	2309
L1559	Protease III	2310
L1560	Protease III	2311
L1561	Protease III	2312
L1562	Protease III	2313
L1563	Protease III	2314
L1564	Protease III	2315
L1565	Protease III	2316
L1566	Protease III	2317
L1567	Protease III	2318
L1568	Protease III	2319
L1569	Protease III	2320
L1570	Protease III	2321
L1571	Protease III	2322
L1572	Protease III	2323
L1573	Protease III	2324
L1574	Protease III	2325
L1575	Protection of telomeres 1	2326
L1576	Protection of telomeres 1	2327
L1577	Protein (CD58)	2328
L1578	Protein (CRP1)	2329
L1579	Protein (DNA polymerase)	2330
L1580	Protein (DNA polymerase)	2331
L1581	Protein (DNA polymerase)	2332
L1582	Protein (electron transfer flavoprotein)	2333
L1583	Protein (electron transfer flavoprotein)	2334
L1584	Protein (Ffh)	2335

L1585	Protein (Ffh)	2336
L1586	Protein (Ffh)	2337
L1587	Protein (Ffh)	2338
L1588	Protein (Ffh)	2339
L1589	Protein (FokI restriction endonuclease)	2340
L1590	Protein (FokI restriction endonuclease)	2341
L1591	Protein (FokI restriction endonuclease)	2342
L1592	Protein (FokI restriction endonuclease)	2343
L1593	Protein (FokI restriction endonuclease)	2344
L1594	Protein (FokI restriction endonuclease)	2345
L1595	Protein (FokI restriction endonuclease)	2346
L1596	Protein (FokI restriction endonuclease)	2347
L1597	Protein (FokI restriction endonuclease)	2348
L1598	Protein (neural cell adhesion molecule)	2349
L1599	Protein (neural cell adhesion molecule)	2350
L1600	Protein (neural cell adhesion molecule)	2351
L1601	Protein (nine-haem cytochrome c)	FTH
L1602	Protein (nine-haem cytochrome c)	2352
L1603	Protein (nine-haem cytochrome c)	2353
L1604	Protein (nine-haem cytochrome c)	2354
L1605	Protein (nine-haem cytochrome c)	2355
L1606	Protein (nine-haem cytochrome c)	2356
L1607	Protein (nine-haem cytochrome c)	2357
L1608	Protein (nine-haem cytochrome c)	2358
L1609	Protein (nine-haem cytochrome c)	2359
L1610	Protein (protease/helicase NS3)	2360
L1611	Protein (protease/helicase NS3)	2361
L1612	Protein (protease/helicase NS3)	2362
L1613	Protein (protease/helicase NS3)	2363
L1614	Protein disulfide oxidoreductase	2364
L1615	Protein disulfide oxidoreductase	2365
L1616	Protein disulfide-isomerase A4	2366
L1617	Protein kinase PKR	2367
L1618	Protein kinase PKR	2368
L1619	Protein TolB	VNK
L1620	Protein TolB	2369
L1621	Protein TolB	2370
L1622	Protein TolB	2371
L1623	Protein TolB	2372
L1624	Protein TolB	2373
L1625	Protein TolB	2374
L1626	Protein translation elongation factor 1A	2375
L1627	Protein transport protein Sec24	DRN
L1628	Protein transport protein Sec24	2376
L1629	Protein transport protein Sec24	2377
L1630	Protein transport protein Sec24	2378
L1631	Protein transport protein Sec24	2379
L1632	Protein transport protein Sec24	2380
L1633	Protein transport protein Sec24	2381
L1634	Protein transport protein Sec24	2382
L1635	Protein transport protein Sec24	2383
L1636	Pseudouridine synthase CBF5	AIQ
L1637	Pseudouridine synthase CBF5	2384
L1638	Pseudouridine synthase CBF5	2385
L1639	Putative acetylglutamate synthase	2386
L1640	Putative acetylglutamate synthase	2387
L1641	Putative acetylglutamate synthase	2388
L1642	Putative family 31 glucosidase YicI	2389

L1643	Putative family 31 glucosidase YicI	2390
L1644	Putative family 31 glucosidase YicI	2391
L1645	Putative glutathione transferase	2392
L1646	Putative glutathione transferase	2393
L1647	Putative glutathione transferase	2394
L1648	Putative GNTR-family transcriptional regulator	2395
L1649	Putative GNTR-family transcriptional regulator	2396
L1650	Putative GNTR-family transcriptional regulator	2397
L1651	Putative HTH-type transcriptional regulator PH0061	2398
L1652	Putative HTH-type transcriptional regulator PH1519	2399
L1653	Putative HTH-type transcriptional regulator PH1519	2400
L1654	Putative metallopeptidase	2401
L1655	Putative N-acetylmannosamine kinase	2402
L1656	Putative N-acetylmannosamine kinase	2403
L1657	Putative N-acetylmannosamine kinase	2404
L1658	Putative NADP oxidoreductase BF3122	2405
L1659	Putative NADP oxidoreductase BF3122	2406
L1660	Putative NADP oxidoreductase BF3122	2407
L1661	Putative NADP oxidoreductase BF3122	2408
L1662	Putative oxidoreductase	2409
L1663	Putative secreted alpha-galactosidase	PLP
L1664	Putative secreted alpha-galactosidase	TNG
L1665	Putative secreted alpha-galactosidase	2410
L1666	Putative secreted alpha-galactosidase	2411
L1667	Putative secreted alpha-galactosidase	2412
L1668	Putative tagatose-6-phosphate ketose/aldose isomerase	DKA
L1669	Putative tagatose-6-phosphate ketose/aldose isomerase	2413
L1670	Putative tagatose-6-phosphate ketose/aldose isomerase	2414
L1671	Putative tagatose-6-phosphate ketose/aldose isomerase	2415
L1672	Putative transcriptional regulator GntR	2416
L1673	Putative transcriptional repressor (TetR/AcrR family)	KFR
L1674	Putative transcriptional repressor (TetR/AcrR family)	2417
L1675	Putative uncharacterized protein	2418
L1676	Putative uncharacterized protein	2419
L1677	Putative uncharacterized protein	2420
L1678	Putative uncharacterized protein	2421
L1679	Putative uncharacterized protein	2422
L1680	Putative uncharacterized protein	2423
L1681	Putative uncharacterized protein	2424
L1682	Putative uncharacterized protein	2425
L1683	Putative uncharacterized protein	2426
L1684	Pyruvate decarboxylase	CAA
L1685	Pyruvate decarboxylase	2427
L1686	Pyruvate decarboxylase	2428
L1687	Pyruvate decarboxylase	2429
L1688	Pyruvate decarboxylase	2430
L1689	Pyruvate decarboxylase	2431
L1690	Pyruvate dehydrogenase [lipoamide] kinase isozyme 2, mitochondrial	YVP
L1691	Pyruvate dehydrogenase [lipoamide] kinase isozyme 2, mitochondrial	2432
L1692	Pyruvate dehydrogenase [lipoamide] kinase isozyme 2, mitochondrial	2433
L1693	Pyruvate dehydrogenase E1 component subunit beta, mitochondrial	2434
L1694	Pyruvate dehydrogenase E1 component subunit beta, mitochondrial	2435
L1695	Pyruvate dehydrogenase E1 component subunit beta, mitochondrial	2436
L1696	Pyruvate phosphate dikinase	FNP
L1697	Pyruvate phosphate dikinase	SAL
L1698	Pyruvate phosphate dikinase	2437
L1699	Pyruvate phosphate dikinase	2438
L1700	Pyruvate phosphate dikinase	2439

L1701	Pyruvate phosphate dikinase	2440
L1702	Pyruvate phosphate dikinase	2441
L1703	Pyruvate phosphate dikinase	2442
L1704	Pyruvate phosphate dikinase	2443
L1705	Pyruvate phosphate dikinase	2444
L1706	Pyruvate phosphate dikinase	2445
L1707	Pyruvate phosphate dikinase	2446
L1708	Pyruvate-ferredoxin oxidoreductase	VRL
L1709	Pyruvate-ferredoxin oxidoreductase	2447
L1710	Pyruvate-ferredoxin oxidoreductase	2448
L1711	Pyruvate-ferredoxin oxidoreductase	2449
L1712	Pyruvate-ferredoxin oxidoreductase	2450
L1713	Pyruvate-ferredoxin oxidoreductase	2451
L1714	Pyruvate-ferredoxin oxidoreductase	2452
L1715	Pyruvate-ferredoxin oxidoreductase	2453
L1716	Pyruvate-ferredoxin oxidoreductase	2454
L1717	Pyruvate-ferredoxin oxidoreductase	2455
L1718	Pyruvate-ferredoxin oxidoreductase	2456
L1719	Pyruvate-ferredoxin oxidoreductase	2457
L1720	Pyruvate-ferredoxin oxidoreductase	2458
L1721	Pyruvate-ferredoxin oxidoreductase	2459
L1722	Pyruvate-ferredoxin oxidoreductase	2460
L1723	Pyruvate-ferredoxin oxidoreductase	2461
L1724	Pyruvate-ferredoxin oxidoreductase	2462
L1725	Pyruvate-ferredoxin oxidoreductase	2463
L1726	Pyruvate-ferredoxin oxidoreductase	2464
L1727	Pyruvate-ferredoxin oxidoreductase	2465
L1728	Quinohemoprotein amine dehydrogenase 60 kDa subunit	2466
L1729	Quinohemoprotein amine dehydrogenase 60 kDa subunit	2467
L1730	Quinohemoprotein amine dehydrogenase 60 kDa subunit	2468
L1731	Quinohemoprotein amine dehydrogenase 60 kDa subunit	2469
L1732	Quinohemoprotein amine dehydrogenase 60 kDa subunit	2470
L1733	Quinohemoprotein amine dehydrogenase 60 kDa subunit	2471
L1734	Quinohemoprotein amine dehydrogenase 60 kDa subunit	2472
L1735	Quinohemoprotein amine dehydrogenase 60 kDa subunit	2473
L1736	Quinohemoprotein amine dehydrogenase 60 kDa subunit	2474
L1737	Quinohemoprotein amine dehydrogenase 60 kDa subunit	2475
L1738	Rag1	2476
L1739	Rag1	2477
L1740	Receptor-type tyrosine-protein phosphatase Mu	2478
L1741	Receptor-type tyrosine-protein phosphatase Mu	2479
L1742	RecG	2480
L1743	RecG	2481
L1744	RecG	2482
L1745	RecG	2483
L1746	RecG	2484
L1747	RecG	2485
L1748	RecG	2486
L1749	RecG	2487
L1750	RecG	2488
L1751	RecG	2489
L1752	RecG	2490
L1753	RecG	2491
L1754	Recombination endonuclease VII	2492
L1755	Recombining binding protein suppressor of hairless	2493
L1756	Restriction endonuclease	ERV
L1757	Restriction endonuclease	2494
L1758	Restriction endonuclease	2495

L1759	Restriction endonuclease	2496
L1760	Retinaldehyde-binding protein 1	QYP
L1761	Retinaldehyde-binding protein 1	2497
L1762	Retinaldehyde-binding protein 1	2498
L1763	Retinoblastoma pocket	2499
L1764	RfcS	ITD
L1765	RfcS	LTE
L1766	RfcS	2500
L1767	RfcS	2501
L1768	RfcS	2502
L1769	RfcS	2503
L1770	RfcS	2504
L1771	Rhamnogalacturonase B	2505
L1772	Rhamnogalacturonase B	2506
L1773	Rhamnogalacturonase B	2507
L1774	Rhamnogalacturonase B	2508
L1775	Rhamnogalacturonase B	2509
L1776	Rhodniin	2510
L1777	Rhodniin	2511
L1778	Riboflavin synthase	2512
L1779	Ribonuclease D	2513
L1780	Ribonuclease D	2514
L1781	Ribonuclease D	2515
L1782	Ribonuclease TTHA0252	2516
L1783	Ribonuclease TTHA0252	2517
L1784	Ribonuclease TTHA0252	2518
L1785	Ribonuclease TTHA0252	2519
L1786	Ribonuclease TTHA0252	2520
L1787	Ribonuclease TTHA0252	2521
L1788	Ribonucleotide reductase r1 protein	2522
L1789	Ribonucleotide reductase r1 protein	2523
L1790	Ribonucleotide reductase r1 protein	2524
L1791	Ribonucleotide reductase r1 protein	2525
L1792	Ribonucleotide reductase r1 protein	2526
L1793	Ribonucleotide reductase r1 protein	2527
L1794	Ribosome maturation factor RimM	2528
L1795	Ribulose-1,5 bisphosphate carboxylase/oxygenase large subunit N-methyltransferase	RHA
L1796	Ribulose-1,5 bisphosphate carboxylase/oxygenase large subunit N-methyltransferase	2529
L1797	Rigid extended P-rich	2530
L1798	Rigid extended P-rich	2531
L1799	Rigid extended P-rich	2532
L1800	Rigid extended P-rich	2533
L1801	Rigid extended P-rich	2534
L1802	Rigid extended P-rich	2535
L1803	Rigid extended P-rich	2536
L1804	Rigid extended P-rich	2537
L1805	Rigid extended P-rich	2538
L1806	Rigid extended P-rich	2539
L1807	Rigid extended P-rich	2540
L1808	Rigid extended P-rich	2541
L1809	Rigid extended P-rich	2542
L1810	Rigid extended P-rich	2543
L1811	Rigid extended P-rich	2544
L1812	Rigid helical	2545
L1813	Rigid helical	2546
L1814	Rigid helical	2547

L1815	Rigid helical	2548
L1816	Rigid helical	2549
L1817	Rigid helical	2550
L1818	Rigid helical	2551
L1819	Rigid helical	2552
L1820	RNA binding domain of rho transcription termination factor	2553
L1821	RNA binding protein ZFa	2554
L1822	Rob transcription factor	2555
L1823	Rob transcription factor	2556
L1824	RP2 lipase	2557
L1825	Rubrerythrin	2558
L1826	S-adenosylmethionine synthetase	2559
L1827	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	QFD
L1828	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2560
L1829	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2561
L1830	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2562
L1831	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2563
L1832	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2564
L1833	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2565
L1834	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2566
L1835	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2567
L1836	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2568
L1837	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2569
L1838	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2570
L1839	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2571
L1840	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2572
L1841	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2573
L1842	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2574
L1843	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2575
L1844	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2576
L1845	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2577
L1846	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2578
L1847	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2579
L1848	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2580
L1849	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2581
L1850	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2582
L1851	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2583
L1852	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	2584
L1853	Scavenger mRNA-decapping enzyme DcpS	ETG
L1854	Scavenger mRNA-decapping enzyme DcpS	NIT
L1855	Scavenger mRNA-decapping enzyme DcpS	2585
L1856	Scavenger mRNA-decapping enzyme DcpS	2586
L1857	Sec18p (residues 22 - 210)	2587
L1858	Sec18p (residues 22 - 210)	2588
L1859	Sensor protein	2589
L1860	Sensor protein	2590
L1861	Septum site-determining protein MinC	2591
L1862	Serine acetyltransferase	2592
L1863	Serine protease/NTPase/helicase NS3	2593
L1864	Serine protease/NTPase/helicase NS3	2594
L1865	Serine protease/NTPase/helicase NS3	2595
L1866	Serine rich linker	2596
L1867	Serine rich linker	2597
L1868	Serine rich linker	2598
L1869	Serine rich linker	2599
L1870	Serine rich linker	2600
L1871	Serine rich linker	2601
L1872	Serine rich linker	2602

L1873	Seryl-tRNA synthetase	2603
L1874	Sialidase	2604
L1875	Sialidase B	SLT
L1876	Sialidase B	VRE
L1877	Sialidase B	2605
L1878	Sialidase B	2606
L1879	Sialidase B	2607
L1880	Sialidase B	2608
L1881	Sialidase B	2609
L1882	Sialidase B	2610
L1883	Signal peptidase I	SRR
L1884	Signal peptidase I	2611
L1885	Signal peptidase I	2612
L1886	Signal peptidase I	2613
L1887	Signal peptidase I	2614
L1888	Signal peptidase I	2615
L1889	Signal peptidase I	2616
L1890	Signal peptidase I	2617
L1891	Signal peptidase I	2618
L1892	Signal peptidase I	2619
L1893	Signal peptidase I	2620
L1894	Signal recognition particle protein	2621
L1895	Signal transducer and activator of transcription1-alpha/beta	NDE
L1896	Signal transducer and activator of transcription1-alpha/beta	SSF
L1897	Signal transducer and activator of transcription1-alpha/beta	2622
L1898	Signal transducer and activator of transcription1-alpha/beta	2623
L1899	Signal transducer and activator of transcription1-alpha/beta	2624
L1900	Signal transducer and activator of transcription1-alpha/beta	2625
L1901	Signal transduction protein CBL	2626
L1902	Signal transduction protein CBL	2627
L1903	Similar to RAD54-like	AKP
L1904	Similar to RAD54-like	EYF
L1905	Similar to RAD54-like	RFE
L1906	Similar to RAD54-like	2628
L1907	Similar to RAD54-like	2629
L1908	Similar to RAD54-like	2630
L1909	Similar to RAD54-like	2631
L1910	Similar to RAD54-like	2632
L1911	Similar to RAD54-like	2633
L1912	Similar to RAD54-like	2634
L1913	Similar to RAD54-like	2635
L1914	Similar to RAD54-like	2636
L1915	Similar to RAD54-like	2637
L1916	SKD1 protein	LMQ
L1917	SKD1 protein	2638
L1918	SKD1 protein	2639
L1919	SKD1 protein	2640
L1920	SKD1 protein	2641
L1921	SKD1 protein	2642
L1922	Sll1358 protein	2643
L1923	Sll1358 protein	2644
L1924	Sll1358 protein	2645
L1925	Sll1358 protein	2646
L1926	Soluble IFN alpha/beta receptor	2647
L1927	Soluble IFN alpha/beta receptor	2648
L1928	Sporozoite-specific SAG protein	2649
L1929	Staphylococcal accessory regulator a homologue	2650
L1930	Staphylococcal nuclease domain-containing protein 1	2651

L1931	Staphylococcal nuclease domain-containing protein 1	2652
L1932	Staphylococcal nuclease domain-containing protein 1	2653
L1933	Staphylococcal nuclease domain-containing protein 1	2654
L1934	Staphylococcal nuclease domain-containing protein 1	2655
L1935	Staphylococcal nuclease domain-containing protein 1	2656
L1936	Stat protein	2657
L1937	Stat protein	2658
L1938	Stat protein	2659
L1939	Stat protein	2660
L1940	Stat protein	2661
L1941	Stat protein	2662
L1942	Stat protein	2663
L1943	Stat protein	2664
L1944	Stat protein	2665
L1945	Stat protein	2666
L1946	Stat protein	2667
L1947	Stat protein	2668
L1948	Stat protein	2669
L1949	Stat protein	2670
L1950	Stat protein	2671
L1951	Subtilisin-like protease	2672
L1952	Succinyl-CoA ligase [GDP-forming] alpha-chain, mitochondrial	2673
L1953	Succinyl-CoA ligase [GDP-forming] alpha-chain, mitochondrial	2674
L1954	Succinyl-CoA ligase [GDP-forming] alpha-chain, mitochondrial	2675
L1955	Succinyl-CoA ligase [GDP-forming] alpha-chain, mitochondrial	2676
L1956	Succinyl-CoA ligase [GDP-forming] alpha-chain, mitochondrial	2677
L1957	Succinyl-CoA ligase [GDP-forming] alpha-chain, mitochondrial	2678
L1958	Succinyl-CoA synthetase beta chain	ADG
L1959	Succinyl-CoA synthetase beta chain	RQP
L1960	Succinyl-CoA synthetase beta chain	2679
L1961	Succinyl-CoA synthetase beta chain	2680
L1962	Succinyl-CoA synthetase beta chain	2681
L1963	Succinyl-CoA synthetase beta chain	2682
L1964	Succinyl-CoA synthetase beta chain	2683
L1965	Succinyl-CoA synthetase beta chain	2684
L1966	Succinyl-CoA:3-ketoacid-coenzyme A transferase	2685
L1967	Sulfurtransferase	2686
L1968	Superantigen SMEZ-2	2687
L1969	Superoxide dismutase 1 copper chaperone	2688
L1970	Surface layer protein	2689
L1971	Surface layer protein	2690
L1972	Surface layer protein	2691
L1973	Surface layer protein	2692
L1974	Surface layer protein	2693
L1975	Surface layer protein	2694
L1976	Surface layer protein	2695
L1977	Surface layer protein	2696
L1978	T lymphocyte activation antigen	2697
L1979	T lymphocyte activation antigen	2698
L1980	T-cell receptor alpha chain C region	2699
L1981	Terminal oxygenase component of carbazole	2700
L1982	Tetanus neurotoxin	2701
L1983	Tetracycline repressor protein class D	2702
L1984	The GTP-binding protein Obg	2703
L1985	The GTP-binding protein Obg	2704
L1986	The GTP-binding protein Obg	2705
L1987	The GTP-binding protein Obg	2706
L1988	Thioredoxin domain-containing protein 4	2707

L1989	Thioredoxin domain-containing protein 4	2708
L1990	Thiosulfate sulfurtransferase	IDP
L1991	Thiosulfate sulfurtransferase	2709
L1992	Thiosulfate sulfurtransferase	2710
L1993	Thiosulfate sulfurtransferase	2711
L1994	Thiosulfate sulfurtransferase	2712
L1995	Threonyl-tRNA synthetase	2713
L1996	Threonyl-tRNA synthetase	2714
L1997	Threonyl-tRNA synthetase	2715
L1998	Threonyl-tRNA synthetase	2716
L1999	Threonyl-tRNA synthetase	2717
L2000	Threonyl-tRNA synthetase	2718
L2001	Threonyl-tRNA synthetase	2719
L2002	Threonyl-tRNA synthetase	2720
L2003	Threonyl-tRNA synthetase	2721
L2004	Threonyl-tRNA synthetase 1	2722
L2005	Threonyl-tRNA synthetase 1	2723
L2006	Threonyl-tRNA synthetase 1	2724
L2007	Threonyl-tRNA synthetase 1	2725
L2008	Threonyl-tRNA synthetase 1	2726
L2009	Threonyl-tRNA synthetase 1	2727
L2010	Threonyl-tRNA synthetase 1	2728
L2011	Threonyl-tRNA synthetase 1	2729
L2012	Thrombospondin 1	2730
L2013	Tick-borne encephalitis virus glycoprotein	2731
L2014	Titin	2732
L2015	Titin	2733
L2016	TLR1789 protein	2734
L2017	TLR1789 protein	2735
L2018	Topoisomerase I	2736
L2019	Topoisomerase I	2737
L2020	Toxic shock syndrome toxin-1	2738
L2021	Toxic shock syndrome toxin-1	2739
L2022	Toxic shock syndrome toxin-1	2740
L2023	Toxic shock syndrome toxin-1	2741
L2024	T-plasminogen activator F1-G	VPV
L2025	T-plasminogen activator F1-G	2742
L2026	TpsB transporter FhaC	2743
L2027	TpsB transporter FhaC	2744
L2028	TpsB transporter FhaC	2745
L2029	Transcarbamylase	2746
L2030	Transcarbamylase	2747
L2031	Transcription antiterminator LicT	2748
L2032	Transcription elongation factor GreB	2749
L2033	Transcription initiation factor IIa gamma chain	2750
L2034	Transcription initiation factor IIb	2751
L2035	Transcription initiation factor IIb	2752
L2036	Transcriptional regulator (NtrC family)	2753
L2037	Transcriptional regulator AefR	2754
L2038	Transcriptional regulator AefR	2755
L2039	Transcriptional regulator AefR	2756
L2040	Transcriptional regulator AefR	2757
L2041	Transcriptional regulator AefR	2758
L2042	Transcriptional regulator, AsnC family	2759
L2043	Transcriptional regulator, AsnC family	2760
L2044	Transcriptional regulator, AsnC family	2761
L2045	Transcriptional regulator, biotin repressor family	2762
L2046	Transcriptional regulator, Crp/Fnr family	2763

L2047	Transcriptional regulator, GntR family	2764
L2048	Transcriptional regulator, HTH_3 family	2765
L2049	Transcriptional regulator, HTH_3 family	2766
L2050	Transcriptional regulator, HTH_3 family	2767
L2051	Transcriptional regulator, HTH_3 family	2768
L2052	Transcriptional regulator, HTH_3 family	2769
L2053	Transcriptional regulator, laci family	2770
L2054	Transcriptional regulatory protein ZraR	2771
L2055	Transcriptional regulatory protein ZraR	2772
L2056	Transcriptional regulatory protein ZraR	2773
L2057	Transcriptional regulatory protein ZraR	2774
L2058	Transcriptional regulatory protein ZraR	2775
L2059	Transcriptional regulatory protein ZraR	2776
L2060	Transcriptional regulatory protein ZraR	2777
L2061	Transferrin receptor protein	VSN
L2062	Transferrin receptor protein	2778
L2063	Transferrin receptor protein	2779
L2064	Transferrin receptor protein	2780
L2065	Transferrin receptor protein	2781
L2066	Translation initiation factor 5A	2782
L2067	Translation initiation factor 5A	2783
L2068	Translation initiation factor 5A	2784
L2069	Translation initiation factor IF2/eIF5b	2785
L2070	Translation initiation factor IF2/eIF5b	2786
L2071	Transposable element mariner, complete CDS	2787
L2072	Tricorn protease	2788
L2073	Tricorn protease	2789
L2074	Tricorn protease	2790
L2075	Trigger factor	2791
L2076	Trigger factor	2792
L2077	Trigger factor	2793
L2078	TRNA CCA-adding enzyme	RRI
L2079	TRNA CCA-adding enzyme	2794
L2080	TRNA CCA-adding enzyme	2795
L2081	TRNA CCA-adding enzyme	2796
L2082	TRNA CCA-adding enzyme	2797
L2083	TRNA nucleotidyltransferase	2798
L2084	TRNA-splicing endonuclease	2799
L2085	Tt1467 protein	LEA
L2086	Tt1467 protein	2800
L2087	Tumor suppressor p53-binding protein 1	2801
L2088	Tumor suppressor p53-binding protein 1	2802
L2089	Tumor suppressor p53-binding protein 1	2803
L2090	Tumor suppressor p53-binding protein 1	2804
L2091	Type A flavoprotein FprA	2805
L2092	Type A flavoprotein FprA	2806
L2093	Type A flavoprotein FprA	2807
L2094	Type A flavoprotein FprA	2808
L2095	Type A flavoprotein FprA	2809
L2096	Type I restriction enzyme specificity protein MG438	QMH
L2097	Type I restriction enzyme specificity protein MG438	2810
L2098	Type I restriction enzyme specificity protein MG438	2811
L2099	Type I restriction-modification enzyme, S subunit	2812
L2100	Type I restriction-modification enzyme, S subunit	2813
L2101	Type I site-specific restriction-modification system, R (restriction) subunit	2814
L2102	Type I site-specific restriction-modification system, R (restriction) subunit	2815
L2103	Type I site-specific restriction-modification system, R (restriction) subunit	2816
L2104	Type II DNA topoisomerase VI subunit B	2817

L2105	Type II DNA topoisomerase VI subunit B	2818
L2106	Type II DNA topoisomerase VI subunit B	2819
L2107	Type II DNA topoisomerase VI subunit B	2820
L2108	Type II DNA topoisomerase VI subunit B	2821
L2109	Type II DNA topoisomerase VI subunit B	2822
L2110	Type II DNA topoisomerase VI subunit B	2823
L2111	Type II DNA topoisomerase VI subunit B	2824
L2112	Type II DNA topoisomerase VI subunit B	2825
L2113	Type II DNA topoisomerase VI subunit B	2826
L2114	Type II DNA topoisomerase VI subunit B	2827
L2115	Type VI secretion system component	2828
L2116	Type VI secretion system component	2829
L2117	Type VI secretion system component	2830
L2118	Tyrosine-protein kinase receptor UFO	2831
L2119	Tyrosine-protein kinase receptor UFO	2832
L2120	Tyrosine-protein kinase ZAP-70	2833
L2121	Tyrosine-protein kinase ZAP-70	2834
L2122	Tyrosyl-DNA phosphodiesterase	2835
L2123	Tyrosyl-DNA phosphodiesterase	2836
L2124	Ubiquitin carboxyl-terminal hydrolase 7	2837
L2125	UDP-galactopyranose mutase	2838
L2126	UDP-galactopyranose mutase	2839
L2127	UDP-galactopyranose mutase	2840
L2128	UDP-galactopyranose mutase	2841
L2129	UDP-galactopyranose mutase	2842
L2130	UDP-glucose dehydrogenase	2843
L2131	UDP-N-acetylmuramate-L-alanine ligase	2844
L2132	UDP-N-acetylmuramate-L-alanine ligase	2845
L2133	UDP-N-acetylmuramoylalanine--D-glutamate ligase	2846
L2134	UDP-N-acetylmuramoylalanine--D-glutamate ligase	2847
L2135	UDP-N-acetylmuramoylalanine-D-glutamyl-lysine-D-alanyl-D-alanine ligase, MurF protein	2848
L2136	UDP-N-acetylmuramoylalanyl-D-glutamate--2,6-diaminopimelate ligase	2849
L2137	UDP-N-acetylmuramoylalanyl-D-glutamate--2,6-diaminopimelate ligase	2850
L2138	UDP-N-acetylmuramoylalanyl-D-glutamate--2,6-diaminopimelate ligase	2851
L2139	UDP-N-acetylmuramoylalanyl-D-glutamate--2,6-diaminopimelate ligase	2852
L2140	UDP-N-acetylmuramoylalanyl-D-glutamate--2,6-diaminopimelate ligase	2853
L2141	UDP-N-acetylmuramoylalanyl-D-glutamate--2,6-diaminopimelate ligase	2854
L2142	UDP-N-acetylmuramoylalanyl-D-glutamate--2,6-diaminopimelate ligase	2855
L2143	Uncharacterized conserved protein	2856
L2144	Uncharacterized conserved protein	2857
L2145	Uncharacterized GST-like protein yfcF	2858
L2146	Uncharacterized GST-like proteinprotein	2859
L2147	Uncharacterized GST-like proteinprotein	2860
L2148	Uncharacterized GST-like proteinprotein	2861
L2149	Uncharacterized protein	2862
L2150	Uncharacterized protein	2863
L2151	Uncharacterized protein BT_1490	2864
L2152	Uncharacterized protein ypfI	TLR
L2153	Uncharacterized protein ypfI	VHP
L2154	Uncharacterized protein ypfI	2865
L2155	Uncharacterized protein ypfI	2866
L2156	Uncharacterized protein ypfI	2867
L2157	Uncharacterized protein ypfI	2868
L2158	Uncharacterized protein ypfI	2869
L2159	Uncharacterized protein ypfI	2870
L2160	Uncharacterized protein ypfI	2871
L2161	Uncharacterized protein ypfI	2872

L2162	Uncharacterized protein ypfI	2873
L2163	Uncharacterized protein ypfI	2874
L2164	Uncharacterized protein ypfI	2875
L2165	Uncharacterized protein ypfI	2876
L2166	Uncharacterized protein ypfI	2877
L2167	Uncharacterized protein ypfI	2878
L2168	Uncharacterized protein ypfI	2879
L2169	Unknown protein	2880
L2170	Unknown protein	2881
L2171	UPF0131 protein ykqA	2882
L2172	UPF0131 protein ykqA	2883
L2173	UPF0131 protein ykqA	2884
L2174	UPF0348 protein MJ0951	2885
L2175	UPF0348 protein MJ0951	2886
L2176	UPF0348 protein MJ0951	2887
L2177	UPF0348 protein MJ0951	2888
L2178	UPF0348 protein MJ0951	2889
L2179	UPF0348 protein MJ0951	2890
L2180	UPF0348 protein MJ0951	2891
L2181	UPF0348 protein MJ0951	2892
L2182	URE2 protein	2893
L2183	Uridine diphospho-N-acetylenolpyruvylglucosaminereductase	TAK
L2184	Uridine diphospho-N-acetylenolpyruvylglucosaminereductase	2894
L2185	Uridine diphospho-N-acetylenolpyruvylglucosaminereductase	2895
L2186	Uridine diphospho-N-acetylenolpyruvylglucosaminereductase	2896
L2187	Uridine diphospho-N-acetylenolpyruvylglucosaminereductase	2897
L2188	Urokinase plasminogen activator surface receptor	2898
L2189	Urokinase plasminogen activator surface receptor	2899
L2190	Vascular cell adhesion molecule-1	2900
L2191	VCP-like ATPase	2901
L2192	VCP-like ATPase	2902
L2193	Viral CASP8 and FADD-like apoptosis regulator	2903
L2194	Vitamin K-dependent protein Z	2904
L2195	VP1 protein	2905
L2196	V-type ATP synthase alpha chain	2906
L2197	Xaa-Pro aminopeptidase	2907
L2198	Xaa-Pro aminopeptidase	2908
L2199	Xaa-Pro aminopeptidase	2909
L2200	Xaa-Pro aminopeptidase	2910
L2201	Xanthine dehydrogenase	2911
L2202	Xanthine dehydrogenase	2912
L2203	Xanthine dehydrogenase	2913
L2204	Xanthine dehydrogenase	2914
L2205	X-prolyl dipeptidyl aminopeptidase	KSY
L2206	X-prolyl dipeptidyl aminopeptidase	LDG
L2207	X-prolyl dipeptidyl aminopeptidase	LLE
L2208	X-prolyl dipeptidyl aminopeptidase	TYS
L2209	X-prolyl dipeptidyl aminopeptidase	2915
L2210	X-prolyl dipeptidyl aminopeptidase	2916
L2211	X-prolyl dipeptidyl aminopeptidase	2917
L2212	X-prolyl dipeptidyl aminopeptidase	2918
L2213	X-prolyl dipeptidyl aminopeptidase	2919
L2214	X-prolyl dipeptidyl aminopeptidase	2920
L2215	X-prolyl dipeptidyl aminopeptidase	2921
L2216	X-prolyl dipeptidyl aminopeptidase	2922
L2217	X-prolyl dipeptidyl aminopeptidase	2923
L2218	X-prolyl dipeptidyl aminopeptidase	2924
L2219	X-prolyl dipeptidyl aminopeptidase	2925

L2220	X-prolyl dipeptidyl aminopeptidase	2926
L2221	X-prolyl dipeptidyl aminopeptidase	2927
L2222	X-prolyl dipeptidyl aminopeptidase	2928
L2223	X-prolyl dipeptidyl aminopeptidase	2929
L2224	X-prolyl dipeptidyl aminopeptidase	2930
L2225	X-prolyl dipeptidyl aminopeptidase	2931
L2226	X-prolyl dipeptidyl aminopeptidase	2932
L2227	X-prolyl dipeptidyl aminopeptidase	2933
L2228	X-prolyl dipeptidyl aminopeptidase	2934
L2229	X-prolyl dipeptidyl aminopeptidase	2935
L2230	X-prolyl dipeptidyl aminopeptidase	2936
L2231	X-prolyl dipeptidyl aminopeptidase	2937
L2232	X-prolyl dipeptidyl aminopeptidase	2938
L2233	Xylosidase/arabinosidase	2939
L2234	Xylosidase/arabinosidase	2940
L2235	Xylosidase/arabinosidase	2941
L2236	Xylosidase/arabinosidase	2942
L2237	Xylosidase/arabinosidase	2943
L2238	Xylosidase/arabinosidase	2944
L2239	Xylosidase/arabinosidase	2945
L2240	YkoF	2946
L2241	Ykul protein	2947

[00147] Internal ribosomal entry site (IRES) is a nucleotide sequence (>500 nucleotides) that allows for initiation of translation in the middle of an mRNA sequence (Kim, J.H. et al., 2011. PLoS One 6(4): e18556; the contents of which are herein incorporated by reference in its entirety). Use of an IRES sequence ensures co-expression of genes before and after the IRES, though the sequence following the IRES may be transcribed and translated at lower levels than the sequence preceding the IRES sequence.

[00148] 2A peptides are small "self-cleaving" peptides (18-22 amino acids) derived from viruses such as foot-and-mouth disease virus (F2A), porcine teschovirus-1 (P2A), *Thoseaasigna* virus (T2A), or equine rhinitis A virus (E2A). The 2A designation refers specifically to a region of picornavirus polyproteins that lead to a ribosomal skip at the glycyl-prolyl bond in the C-terminus of the 2A peptide (Kim, J.H. et al., 2011. PLoS One 6(4): e18556; the contents of which are herein incorporated by reference in its entirety). This skip results in a cleavage between the 2A peptide and its immediate downstream peptide. As opposed to IRES linkers, 2A peptides generate stoichiometric expression of proteins flanking the 2A peptide and their shorter length can be advantageous in generating viral expression vectors.

[00149] Some payload regions encode linkers comprising furin cleavage sites. Furin is a calcium dependent serine endoprotease that cleaves proteins just downstream of a basic amino acid target sequence (Arg-X-(Arg/Lys)-Arg) (Thomas, G., 2002. Nature Reviews Molecular Cell Biology 3(10): 753-66; the contents of which are herein incorporated by reference in its entirety). Furin is enriched in the trans-golgi network where it is involved in processing cellular precursor

proteins. Furin also plays a role in activating a number of pathogens. This activity can be taken advantage of for expression of polypeptides of the invention.

[00150] In some embodiments, the payload region may encode one or more linkers comprising cathepsin, matrix metalloproteinases or legumain cleavage sites. Such linkers are described e.g. by Cizeau and Macdonald in International Publication No. WO2008052322, the contents of which are herein incorporated in their entirety. Cathepsins are a family of proteases with unique mechanisms to cleave specific proteins. Cathepsin B is a cysteine protease and cathepsin D is an aspartyl protease. Matrix metalloproteinases are a family of calcium-dependent and zinc-containing endopeptidases. Legumain is an enzyme catalyzing the hydrolysis of (-Asn-Xaa-) bonds of proteins and small molecule substrates.

[00151] In some embodiments, payload regions may encode linkers that are not cleaved. Such linkers may include a simple amino acid sequence, such as a glycine rich sequence. In some cases, linkers may comprise flexible peptide linkers comprising glycine and serine residues. The linker may comprise flexible peptide linkers of different lengths, e.g. nxG4S, where n=1-10 (SEQ ID NO: 4322) and the length of the encoded linker varies between 5 and 50 amino acids. In a non-limiting example, the linker may be 5xG4S (SEQ ID NO: 4321) encoded by SEQ ID NO: 903. These flexible linkers are small and without side chains so they tend not to influence secondary protein structure while providing a flexible linker between antibody segments (George, R.A., et al., 2002. Protein Engineering 15(11): 871-9; Huston, J.S. et al., 1988. PNAS 85:5879-83; and Shan, D. et al., 1999. Journal of Immunology. 162(11):6589-95; the contents of each of which are herein incorporated by reference in their entirety). Furthermore, the polarity of the serine residues improves solubility and prevents aggregation problems.

[00152] In some embodiments, payload regions of the invention may encode small and unbranched serine-rich peptide linkers, such as those described by Huston et al. in US Patent No. US5525491, the contents of which are herein incorporated in their entirety. Polypeptides encoded by the payload region of the invention, linked by serine-rich linkers, have increased solubility.

[00153] In some embodiments, payload regions of the invention may encode artificial linkers, such as those described by Whitlow and Filpula in US Patent No. US5856456 and Ladner et al. in US Patent No. US 4946778, the contents of each of which are herein incorporated by their entirety.

Viral Genome Component: Introns

[00154] In one embodiment, the payload region comprises at least one element to enhance the expression such as one or more introns or portions thereof. Non-limiting examples of introns

include, MVM (67-97 bps), F.IX truncated intron 1 (300 bps), β-globin SD/immunoglobulin heavy chain splice acceptor (250 bps), adenovirus splice donor/immunoglobin splice acceptor (500 bps), SV40 late splice donor/splice acceptor (19S/16S) (180 bps) and hybrid adenovirus splice donor/IgG splice acceptor (230 bps).

[00155] In one embodiment, the intron or intron portion may be 100-500 nucleotides in length. The intron may have a length of 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490 or 500. The intron may have a length between 80-100, 80-120, 80-140, 80-160, 80-180, 80-200, 80-250, 80-300, 80-350, 80-400, 80-450, 80-500, 200-300, 200-400, 200-500, 300-400, 300-500, or 400-500.

Payloads of the Invention

[00156] The AAV particles of the present disclosure comprise at least one payload region. As used herein, "payload" or "payload region" refers to one or more polynucleotides or polynucleotide regions encoded by or within a viral genome or an expression product of such polynucleotide or polynucleotide region, e.g., a transgene, a polynucleotide encoding a polypeptide or multi-polypeptide or a modulatory nucleic acid or regulatory nucleic acid. Payloads of the present invention typically encode polypeptides (e.g., antibodies or antibody-based compositions) or fragments or variants thereof.

[00157] The payload region may be constructed in such a way as to reflect a region similar to or mirroring the natural organization of an mRNA.

[00158] The payload region may comprise a combination of coding and non-coding nucleic acid sequences.

[00159] In some embodiments, the AAV payload region may encode a coding or non-coding RNA.

[00160] In one embodiment, the AAV particle comprises a viral genome with a payload region comprising nucleic acid sequences encoding more than one polypeptide of interest (e.g., an antibody). In such an embodiment, a viral genome encoding more than one polypeptide may be replicated and packaged into a viral particle. A target cell transduced with a viral particle comprising more than one polypeptide may express each of the polypeptides in a single cell.

[00161] In one embodiment, as shown in FIG. 1, an AAV particle comprises a viral genome with a payload region comprising a nucleic acid sequence encoding a heavy chain and a light chain of an antibody. The heavy chain and light chain are expressed and assembled to form the antibody which is secreted.

[00162] In one embodiment, the payload region may comprise the components as shown in FIG. 2. The payload region **110** is located within the viral genome **100**. At the 5` and/or the 3' end of the payload region **110** there may be at least one inverted terminal repeat (ITR) **120**. Within the payload region, there is a promoter region **130**, an intron region **140** and a coding region **150**. When the coding region **150** comprises a heavy chain region **151** and light chain region **152** of an antibody, the two chains may be separated by a linker region **155**.

[00163] In one embodiment, the coding region may comprise a heavy and light chain sequence and a linker. As shown in FIG. 3, the payload region may comprise a heavy chain and light chain sequence separated by a linker and/or a cleavage site. In one embodiment, the heavy and light chain sequence is separated by an IRES sequence (1 and 2). In one embodiment, the heavy and light chain sequence is separated by a foot and mouth virus sequence (3 and 4). In one embodiment, the heavy and light chain sequence is separated by a foot and mouth virus sequence and a furin cleavage site (5 and 6). In one embodiment, the heavy and light chain sequence is separated by a porcine teschovirus-1 virus sequence (7 and 8). In one embodiment, the heavy and light chain sequence is separated by a porcine teschovirus-1 virus and a furin cleavage site (9 and 10). In one embodiment, the heavy and light chain sequence is separated by a 5xG4S sequence (SEQ ID NO: 4321) (11).

[00164] Where the AAV particle payload region encodes a polypeptide, the polypeptide may be a peptide or protein. A protein encoded by the AAV particle payload region may comprise an antibody, an antibody related composition, a secreted protein, an intracellular protein, an extracellular protein, and/or a membrane protein. The encoded proteins may be structural or functional. In addition to the antibodies or antibody-based composition, proteins encoded by the payload region may include, in combination, certain mammalian proteins involved in immune system regulation. The AAV viral genomes encoding polypeptides described herein may be useful in the fields of human disease, viruses, infections veterinary applications and a variety of *in vivo* and *in vitro* settings.

[00165] In some embodiments, the AAV particles are useful in the field of medicine for the treatment, prophylaxis, palliation, or amelioration of neurological diseases and/or disorders.

Antibodies and Antibody-based compositions

[00166] Payload regions of the AAV particles of the invention may encode polypeptides that form one or more functional antibodies or antibody-based compositions. As used herein, the term "antibody" is referred to in the broadest sense and specifically covers various embodiments including, but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g. bispecific antibodies formed from at least two intact antibodies), and antibody

fragments (e.g., diabodies) so long as they exhibit a desired biological activity (e.g., "functional"). Antibodies are primarily amino-acid based molecules but may also comprise one or more modifications (including, but not limited to the addition of sugar moieties, fluorescent moieties, chemical tags, etc.).

[00167] As used herein, "antibody-based" or "antibody-derived" compositions are monomeric or multi-meric polypeptides which comprise at least one amino-acid region derived from a known or parental antibody sequence and at least one amino acid region derived from a non-antibody sequence, e.g., mammalian protein.

[00168] Payload regions may encode polypeptides that form or function as any antibody, including antibodies that are known in the art and/or antibodies that are commercially available. The encoded antibodies may be therapeutic, diagnostic, or for research purposes. Further, polypeptides of the invention may include fragments of such antibodies or antibodies that have been developed to comprise one or more of such fragments (e.g., variable domains or complementarity determining regions (CDRs)).

[00169] In one embodiment, the viral genome of the AAV particles may comprise nucleic acids which have been engineered to enable expression of antibodies, antibody fragments, or components of any of those described in US7041807 related to YYX epitope; US20090175884, US20110305630, US20130330275 related to misfolded proteins in cancer; US20040175775 related to PrP in eye fluid; US20030114360 related to copolymers and methods of treating prion-related diseases; WO2009121176 related to insulin-induced gene peptide compositions; US20030022243, WO2003000853 related to protein aggregation assays; WO200078344 related to prion protein peptides and uses thereof. Each of these publications are incorporated by reference in their entireties.

Antibody generation

[00170] In some embodiments, viral genomes of the AAV particles of the invention may encode antibodies or antibody-based compositions produced using methods known in the art. Such methods may include, but are not limited to immunization and display technologies (e.g., phage display, yeast display, and ribosomal display). Antibodies may be developed, for example, using any naturally occurring or synthetic antigen. As used herein, an "antigen" is an entity which induces or evokes an immune response in an organism. An immune response is characterized by the reaction of the cells, tissues and/or organs of an organism to the presence of a foreign entity. Such an immune response typically leads to the production by the organism of one or more antibodies against the foreign entity, e.g., antigen or a portion of the antigen. As

used herein, "antigens" also refer to binding partners for specific antibodies or binding agents in a display library.

[00171] In one embodiment, the sequences of the polypeptides to be encoded in the viral genomes of the invention may be derived from antibodies produced using hybridoma technology. Host animals (e.g. mice, rabbits, goats, and llamas) may be immunized by an injection with an antigenic protein to elicit lymphocytes that specifically bind to the antigen. Lymphocytes may be collected and fused with immortalized cell lines to generate hybridomas which can be cultured in a suitable culture medium to promote growth. The antibodies produced by the cultured hybridomas may be subjected to analysis to determine binding specificity of the antibodies for the target antigen. Once antibodies with desirable characteristics are identified, corresponding hybridomas may be subcloned through limiting dilution procedures and grown by standard methods. The antibodies produced by these cells may be isolated and purified using standard immunoglobulin purification procedures.

[00172] In one embodiment, the sequences of the polypeptides to be encoded in the viral genomes of the invention may be produced using heavy and light chain variable region cDNA sequences selected from hybridomas or from other sources. Sequences encoding antibody variable domains expressed by hybridomas may be determined by extracting RNA molecules from antibody-producing hybridoma cells and producing cDNA by reverse transcriptase polymerase chain reaction (PCR). PCR may be used to amplify cDNA using primers specific for heavy and light chain sequences. PCR products may then be subcloned into plasmids for sequence analysis. Antibodies may be produced by insertion of resulting variable domain sequences into expression vectors.

[00173] In one embodiment, the sequences of the polypeptides to be encoded in the viral genomes of the invention may be generated using display technologies. Display technologies used to generate polypeptides of the invention may include any of the display techniques (e.g. display library screening techniques) disclosed in International Patent Application No. WO2014074532, the contents of which are herein incorporated by reference in their entirety. In some embodiments, synthetic antibodies may be designed, selected, or optimized by screening target antigens using display technologies (e.g. phage display technologies). Phage display libraries may comprise millions to billions of phage particles, each expressing unique antibody fragments on their viral coats. Such libraries may provide richly diverse resources that may be used to select potentially hundreds of antibody fragments with diverse levels of affinity for one or more antigens of interest (McCafferty, et al., 1990. Nature. 348:552-4; Edwards, B.M. et al., 2003. JMB. 334: 103-18; Schofield, D. et al., 2007. Genome Biol. 8, R254 and Pershad, K. et al.,

2010. Protein Engineering Design and Selection. 23:279-88; the contents of each of which are herein incorporated by reference in their entirety). Often, the antibody fragments present in such libraries comprise scFv antibody fragments, comprising a fusion protein of V_H and V_L antibody domains joined by a flexible linker. In some cases, scFvs may contain the same sequence with the exception of unique sequences encoding variable loops of the CDRs. In some cases, scFvs are expressed as fusion proteins, linked to viral coat proteins (e.g. the N-terminus of the viral pIII coat protein). V_L chains may be expressed separately for assembly with V_H chains in the periplasm prior to complex incorporation into viral coats. Precipitated library members may be sequenced from the bound phage to obtain cDNA encoding desired scFvs. Antibody variable domains or CDRs from such sequences may be directly incorporated into antibody sequences for recombinant antibody production, or mutated and utilized for further optimization through in vitro affinity maturation.

[00174] In one embodiment, the sequences of the polypeptides to be encoded in the viral genomes of the invention may be produced using yeast surface display technology, wherein antibody variable domain sequences may be expressed on the cell surface of *Saccharomyces cerevisiae*. Recombinant antibodies may be developed by displaying the antibody fragment of interest as a fusion to e.g. Aga2p protein on the surface of the yeast, where the protein interacts with proteins and small molecules in a solution. scFvs with affinity toward desired receptors may be isolated from the yeast surface using magnetic separation and flow cytometry. Several cycles of yeast surface display and isolation may be done to attain scFvs with desired properties through directed evolution.

[00175] In one embodiment, the sequence of the polypeptides to be encoded in the viral genomes of the invention (e.g., antibodies) may be designed by VERSITOPE™ Antibody Generation and other methods used by BIOATLA® and described in United States Patent Publication No. US20130281303, the contents of which are herein incorporated by reference in their entirety. In brief, recombinant monoclonal antibodies are derived from B-cells of a host immuno-challenged with one or more target antigens. These methods of antibody generation do not rely on immortalized cell lines, such as hybridoma, thereby avoiding some of the associated challenges i.e., genetic instability and low production capacity, producing high affinity and high diversity recombinant monoclonal antibodies. In one embodiment, the method is a natural diversity approach. In another embodiment, the method is a high diversity approach.

[00176] In one embodiment, the sequences of the polypeptides to be encoded in the viral genomes of the invention may be generated using the BIOATLA® natural diversity approach. In the natural diversity approach of generating recombinant monoclonal antibodies described in

United States Patent Publication No. US20130281303, the original pairings of variable heavy (V_H) and variable light (V_L) domains are retained from the host, yielding recombinant monoclonal antibodies that are naturally paired. These may be advantageous due to a higher likelihood of functionality as compared to non-natural pairings of V_H and V_L. To produce the recombinant monoclonal antibodies, first a non-human host (i.e., rabbit, mouse, hamster, guinea pig, camel or goat) is immuno-challenged with an antigen of interest. In some embodiments, the host may be a previously challenged human patient. In other embodiments, the host may not have been immuno-challenged. B-cells are harvested from the host and screened by fluorescence activated cell sorting (FACS), or other method, to create a library of B-cells enriched in B-cells capable of binding the target antigen. The cDNA obtained from the mRNA of a single B-cell is then amplified to generate an immunoglobulin library of V_H and V_L domains. This library of immunoglobulins is then cloned into expression vectors capable of expressing the V_H and V_L domains, wherein the V_H and V_L domains remain naturally paired. The library of expression vectors is then used in an expression system to express the V_H and V_L domains in order to create an antibody library. Screening of the antibody library yields antibodies able to bind the target antigen, and these antibodies can be further characterized. Characterization may include one or more of the following: isoelectric point, thermal stability, sedimentation rate, folding rate, neutralization or antigen activity, antagonist or agonistic activity, expression level, specific and non-specific binding, inhibition of enzymatic activity, rigidity/flexibility, shape, charge, stability across pH, in solvents, under UV radiation, in mechanical stress conditions, or in sonic conditions, half-life, and glycosylation.

[00177] In one embodiment, the sequences of the polypeptides to be encoded in the viral genomes of the invention may be generated using the BIOATLA® high diversity approach. In the high diversity approach of generating recombinant monoclonal antibodies described in United States Patent Publication No. US20130281303, additional pairings of variable heavy (V_H) and variable light (V_L) domains are attained. To produce the recombinant monoclonal antibodies, B-cells harvested from the host are screened by fluorescence activated cell sorting (FACS), panning, or other method, to create a library of B-cells enriched in B-cells capable of binding the target antigen. The cDNA obtained from the mRNA of the pooled B-cells is then amplified to generate an immunoglobulin library of V_H and V_L domains. This library of immunoglobulins is then used in a biological display system (mammalian, yeast or bacterial cell surface display systems) to generate a population of cells displaying antibodies, fragments or derivatives comprising the V_H and V_L domains wherein, the antibodies, fragments or derivatives comprise V_H and V_L domain combinations that were not present in the B-cells in vivo.

Screening of the cell population by FACS, with the target antigen, yields a subset of cells capable of binding the target antigen and the antibodies displayed on these cells can be further characterized. In an alternate embodiment of the high diversity approach, the immunoglobulin library comprises only V_H domains obtained from the B-cells of the immuno-challenged host, while the V_L domain(s) are obtained from another source.

[00178] In one embodiment, the sequences of the polypeptides to be encoded in the viral genomes of the invention may be evolved using BIOATLA® comprehensive approaches. The methods of generating recombinant monoclonal antibodies as described in United States Patent Publication No. US20130281303, further comprises evolving the recombinant antibody by comprehensive positional evolution (CPE™), CPE™ followed by comprehensive protein synthesis (CPS™), PCR shuffling, or other method.

[00179] In one embodiment, the sequence of the polypeptides to be encoded in the viral genomes of the invention (e.g., antibodies) may be derived from any of the BIOATLA® protein evolution methods described in International Publication WO2012009026, the contents of which are herein incorporated by reference in their entirety. In this method, mutations are systematically performed throughout the polypeptide or molecule of interest, a map is created providing useful informatics to guide the subsequent evolutionary steps. Not wishing to be bound by theory, these evolutionary methods typically start with a template polypeptide and a mutant is derived therefrom, which has desirable properties or characteristics. Non-limiting examples of evolutionary techniques include polymerase chain reaction (PCR), error prone PCR, oligonucleotide-directed mutagenesis, cassette mutagenesis, shuffling, assembly PCR, sexual PCR mutagenesis, *in vivo* mutagenesis, site-specific mutagenesis, gene reassembly, gene site saturated mutagenesis, *in vitro* mutagenesis, ligase chain reaction, oligonucleotide synthesis or any combination thereof.

[00180] In one embodiment, the BIOATLA® evolution method is Comprehensive Positional Evolution (CPE™). In CPE, naturally occurring amino acid variants are generated for each of the codons of the template polypeptide, wherein 63 different codon options exist for each amino acid variant. A set of polypeptides with single amino acid mutations are generated and the mutations are then confirmed by sequencing or other method known in the art and each amino acid change screened for improved function, neutral mutations, inhibitory mutations, expression, and compatibility with the host system. An EvoMap™ is created that describes in detail the effects of each amino acid mutation on the properties and characteristics of that polypeptide. The data from the EvoMap™ may be utilized to produce polypeptides with more than one amino

acid mutation, wherein the resultant multi-site mutant polypeptides can be screened for desirable characteristics.

[00181] In one embodiment, the BIOATLA® evolution method is Synergy Evolution, wherein an EvoMap™ is used to identify amino acid positions to introduce 2-20 mutations simultaneously to produce a combinatorial effect. The resulting multi-site mutant polypeptides may be screened on one or more pre-determined characteristics to identify "upmutants" wherein the function of the mutant is improved as compared to the parent polypeptide. In one embodiment, Synergy Evolution is used to enhance binding affinity of an antibody.

[00182] In one embodiment, the BIOATLA® evolution method is Flex Evolution, wherein an EvoMap™ is used to identify fully mutable sites within a polypeptide that may then be targeted for alteration, such as introduction of glycosylation sites or chemical conjugation.

[00183] In one embodiment, the BIOATLA® evolution method is Comprehensive Positional Insertion Evolution (CPI™), wherein an amino acid is inserted after each amino acid of a template polypeptide to generate a set of lengthened polypeptides. CPI may be used to insert 1, 2, 3, 4, or 5 amino acids at each new position. The resultant lengthened polypeptides are sequenced and assayed for one or more pre-determined properties and evaluated in comparison to its template or parent molecule. In one embodiment, the binding affinity and immunogenicity of the resultant polypeptides are assayed. In one embodiment, the lengthened polypeptides are further mutated and mapped to identify polypeptides with desirable characteristics.

[00184] In one embodiment, the BIOATLA® evolution approach is Comprehensive Positional Deletion Evolution (CPD™), wherein each amino acid of the template polypeptide is individually and systematically deleted one at a time. The resultant shortened polypeptides are then sequenced and evaluated by assay for at least one pre-determined feature. In one embodiment, the shortened polypeptides are further mutated and mapped to identify polypeptides with desirable characteristics.

[00185] In one embodiment, the BIOATLA® evolution approach is Combinatorial Protein Synthesis (CPS™), wherein mutants identified in CPE, CPI, CPD, or other evolutionary techniques are combined for polypeptide synthesis. These combined mutant polypeptides are then screened for enhanced properties and characteristics. In one embodiment CPS is combined with any of the aforementioned evolutionary or polypeptide synthesis methods.

[00186] In one embodiment, the sequence of the polypeptides to be encoded in the viral genomes of the invention (e.g., antibodies) may be derived from the BIOATLA® Comprehensive Integrated Antibody Optimization (CIAO!™) described in United States Patent US8859467, the contents of which are herein incorporated by reference in their entirety. The

CIAO!™ method allows for simultaneous evolution of polypeptide performance and expression optimization, within a eukaryotic cell host (i.e., mammalian or yeast cell host). First, an antibody library is generated in a mammalian cell production host by antibody cell surface display, wherein the generated antibody library targets a particular antigen of interest. The antibody library is then screened by any method known in the art, for one or more properties or characteristics. One or more antibodies of the library, with desirable properties or characteristics are chosen for further polypeptide evolution by any of the methods known in the art, to produce a library of mutant antibodies by antibody cell surface display in a mammalian cell production host. The generated mutant antibodies are screened for one or more predetermined properties or characteristics, whereby an upmutant is selected, wherein the upmutant has enhanced or improved characteristics as compared to the parent template polypeptide.

[00187] In one embodiment, the sequences of the polypeptides to be encoded in the viral genomes of the invention may be humanized by the methods of BIOATLA® as described in United States Patent Publication US20130303399, the contents of which are herein incorporated by reference in their entirety. In this method, for generating enhanced full length humanized antibodies in mammalian cells, no back-mutations are required to retain affinity to the antigen and no CDR grafting or phage-display is necessary. The generated humanized antibody has reduced immunogenicity and equal or greater affinity for the target antigen as compared to the parent antibody. The variable regions or CDRs of the generated humanized antibody are derived from the parent or template, whereas the framework and constant regions are derived from one or more human antibodies. To start, the parent, or template antibody is selected, cloned and each CDR sequence identified and synthesized into a CDR fragment library. Double stranded DNA fragment libraries for V_H and V_L are synthesized from the CDR fragment encoding libraries, wherein at least one CDR fragment library is derived from the template antibody and framework (FW) fragment encoding libraries, wherein the FW fragment library is derived from a pool of human frameworks obtained from natively expressed and functional human antibodies. Stepwise liquid phase ligation of FW and CDR encoding fragments is then used to generate both V_H and V_L fragment libraries. The V_H and V_L fragment libraries are then cloned into expression vectors to create a humanization library, which is further transfected into cells for expression of full length humanized antibodies, and used to create a humanized antibody library. The humanized antibody library is then screened to determine expression level of the humanized antibodies, affinity or binding ability for the antigen, and additional improved or enhanced characteristics, as compared to the template or parent antibody. Non-limiting examples of characteristics that may be screened include equilibrium dissociation constant (K_D), stability,

melting temperature (T_m), pI, solubility, expression level, reduced immunogenicity, and improved effector function.

[00188] In one embodiment, the sequences of the polypeptides to be encoded in the viral genomes of the invention may be generated by the BIOATLA® method for preparing conditionally active antibodies as described in International Publications WO2016033331 and WO2016036916, the contents of which are herein incorporated by reference in their entirety. As used herein, the term "conditionally active" refers to a molecule that is active at an aberrant condition. Further, the conditionally active molecule may be virtually inactive at normal physiological conditions. Aberrant conditions may result from changes in pH, temperature, osmotic pressure, osmolality, oxidative stress, electrolyte concentration, and/or chemical or proteolytic resistance, as non-limiting examples.

[00189] The method of preparing a conditionally active antibody is described in International Publications WO2016033331 and WO2016036916 and summarized herein. Briefly, a wild-type polypeptide is selected and the DNA is evolved to create mutant DNAs. Non-limiting examples of evolutionary techniques that may be used to evolve the DNA include polymerase chain reaction (PCR), error prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis, *in vivo* mutagenesis, site-specific mutagenesis, gene reassembly, gene site saturated mutagenesis, *in vitro* mutagenesis, ligase chain reaction, oligonucleotide synthesis or any combination thereof. Once mutant DNAs are created, they are expressed in a eukaryotic cell production host (i.e., fungal, insect, mammalian, adenoviral, plant), wherein a mutant polypeptide is produced. The mutant polypeptide and the corresponding wild-type polypeptide are then subjected to assays under both normal physiological conditions and aberrant conditions in order to identify mutants that exhibit a decrease in activity in the assay at normal physiological conditions as compared to the wild-type polypeptide and/or an increase in activity in the assay under aberrant conditions, as compared to the corresponding wild-type polypeptide. The desired conditionally active mutant may then be produced in the aforementioned eukaryotic cell production host.

[00190] In one embodiment, the conditionally active antibody is a "mirac protein" as described by BIOATLA® in United States Patent No US8709755, the contents of which are herein incorporated by reference in their entirety. As used herein "mirac protein" refers to a conditionally active antibody that is virtually inactive at body temperature but active at lower temperatures.

[00191] In one embodiment, the sequence of the polypeptides to be encoded in the viral genomes of the invention (e.g., antibodies) may be derived based on any of the BIOATLA™

methods including, but not limited to, VERSITOPE™ Antibody Generation, natural diversity approaches, and high diversity approaches for generating monoclonal antibodies, methods for generation of conditionally active polypeptides, humanized antibodies, mirac proteins, multi-specific antibodies or cross-species active mutant polypeptides, Comprehensive Integrated Antibody Optimization (CIAO!™), Comprehensive Positional Evolution (CPE™), Synergy Evolution, Flex Evolution, Comprehensive Positional Insertion Evolution (CPI™), Comprehensive Positional Deletion Evolution (CPD™), Combinatorial Protein Synthesis (CPS™), or any combination thereof. These methods are described in United States Patent Nos. US8859467 and US8709755 and United States Publication Nos. US20130281303, US20130303399, US20150065690, US20150252119, US20150086562 and US20100138945, and International Publication Nos. WO2015105888, WO2012009026, WO2011109726, WO2016036916, and WO2016033331, the contents of each of which are herein incorporated by reference in their entirety.

[00192] In one embodiment, antibodies of the present invention are generated by any of the aforementioned means to target one or more of the following epitopes of the tau protein; phosphorylated tau peptides, pS396, pS396-pS404, pS404, pS396-pS404-pS422, pS422, pS199, pS199-pS202, pS202, pT181, pT231, cis-pT231, any of the following acetylated sites acK174, acK274, acK280, acK281 and/or any combination thereof

Antibody fragments and variants

[00193] In some embodiments, antibody fragments encoded by payloads of the invention comprise antigen binding regions from intact antibodies. Examples of antibody fragments may include, but are not limited to Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site. Also produced is a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-binding sites and is still capable of cross-linking antigen. Compounds and/or compositions of the present invention may comprise one or more of these fragments. For the purposes herein, an "antibody" may comprise a heavy and light variable domain as well as an Fc region.

[00194] In one embodiment, the Fc region may be a modified Fc region, as described in US Patent Publication US20150065690, wherein the Fc region may have a single amino acid substitution as compared to the corresponding sequence for the wild-type Fc region, wherein the single amino acid substitution yields an Fc region with preferred properties to those of the wild-

type Fc region. Non-limiting examples of Fc properties that may be altered by the single amino acid substitution include bind properties or response to pH conditions

[00195] As used herein, the term "native antibody" refers to an usually heterotetrameric glycoprotein of about 150,000 Daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Genes encoding antibody heavy and light chains are known and segments making up each have been well characterized and described (Matsuda, F. et al., 1998. The Journal of Experimental Medicine. 188(11); 2151-62 and Li, A. et al., 2004. Blood. 103(12: 4602-9, the content of each of which are herein incorporated by reference in their entirety). Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[00196] As used herein, the term "variable domain" refers to specific antibody domains found on both the antibody heavy and light chains that differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. Variable domains comprise hypervariable regions. As used herein, the term "hypervariable region" refers to a region within a variable domain comprising amino acid residues responsible for antigen binding. The amino acids present within the hypervariable regions determine the structure of the complementarity determining regions (CDRs) that become part of the antigen-binding site of the antibody. As used herein, the term "CDR" refers to a region of an antibody comprising a structure that is complimentary to its target antigen or epitope. Other portions of the variable domain, not interacting with the antigen, are referred to as framework (FW) regions. The antigen-binding site (also known as the antigen combining site or paratope) comprises the amino acid residues necessary to interact with a particular antigen. The exact residues making up the antigen-binding site are typically elucidated by co-crystallography with bound antigen, however computational assessments can also be used based on comparisons with other antibodies (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety). Determining residues making up CDRs may include the use of numbering schemes including, but not limited to, those taught by Kabat [Wu, T.T. et al., 1970, JEM, 132(2):211-50 and Johnson, G. et al., 2000, Nucleic Acids Res. 28(1): 214-8, the contents of each of which are

herein incorporated by reference in their entirety], Chothia [Chothia and Lesk, J. Mol. Biol. 196, 901 (1987), Chothia et al., Nature 342, 877 (1989) and Al-Lazikani, B. et al., 1997, J. Mol. Biol. 273(4):927-48, the contents of each of which are herein incorporated by reference in their entirety], Lefranc (Lefranc, M.P. et al., 2005, Immunome Res. 1:3) and Honegger (Honegger, A. and Pluckthun, A. 2001. J. Mol. Biol. 309(3):657-70, the contents of which are herein incorporated by reference in their entirety).

[00197] V_H and V_L domains have three CDRs each. V_L CDRs are referred to herein as CDR-L1, CDR-L2 and CDR-L3, in order of occurrence when moving from N- to C- terminus along the variable domain polypeptide. V_H CDRs are referred to herein as CDR-H1, CDR-H2, and CDR-H3, in order of occurrence when moving from N- to C-terminus along the variable domain polypeptide. Each of CDRs have favored canonical structures with the exception of the CDR-H3, which comprises amino acid sequences that may be highly variable in sequence and length between antibodies resulting in a variety of three-dimensional structures in antigen-binding domains (Nikoloudis, D. et al., 2014. Peer J. 2:e456; the contents of which are herein incorporated by reference in their entirety). In some cases, CDR-H3s may be analyzed among a panel of related antibodies to assess antibody diversity. Various methods of determining CDR sequences are known in the art and may be applied to known antibody sequences (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety).

[00198] As used herein, the term "Fv" refers to an antibody fragment comprising the minimum fragment on an antibody needed to form a complete antigen-binding site. These regions consist of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. Fv fragments can be generated by proteolytic cleavage, but are largely unstable. Recombinant methods are known in the art for generating stable Fv fragments, typically through insertion of a flexible linker between the light chain variable domain and the heavy chain variable domain [to form a single chain Fv (scFv)] or through the introduction of a disulfide bridge between heavy and light chain variable domains (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p46-47, the contents of which are herein incorporated by reference in their entirety).

[00199] As used herein, the term "light chain" refers to a component of an antibody from any vertebrate species assigned to one of two clearly distinct types, called kappa and lambda based on amino acid sequences of constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains, antibodies can be assigned to different classes. There are

five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

[00200] As used herein, the term "single chain Fv" or "scFv" refers to a fusion protein of V_H and V_L antibody domains, wherein these domains are linked together into a single polypeptide chain by a flexible peptide linker. In some embodiments, the Fv polypeptide linker enables the scFv to form the desired structure for antigen binding. In some embodiments, scFvs are utilized in conjunction with phage display, yeast display or other display methods where they may be expressed in association with a surface member (e.g. phage coat protein) and used in the identification of high affinity peptides for a given antigen.

[00201] As used herein, the term "bispecific antibody" refers to an antibody capable of binding two different antigens. Such antibodies typically comprise regions from at least two different antibodies. Bispecific antibodies may include any of those described in Riethmuller, G. 2012. Cancer Immunity. 12:12-18, Marvin, J.S. et al., 2005. Acta Pharmacologica Sinica. 26(6):649-58 and Schaefer, W. et al., 2011. PNAS. 108(27):11187-92, the contents of each of which are herein incorporated by reference in their entirety.

[00202] As used herein, the term "diabody" refers to a small antibody fragment with two antigen-binding sites. Diabodies comprise a heavy chain variable domain V_H connected to a light chain variable domain V_L in the same polypeptide chain. By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404097; WO 9311161; and Hollinger et al. (Hollinger, P. et al., "Diabodies": Small bivalent and bispecific antibody fragments. PNAS. 1993. 90:6444-8) the contents of each of which are incorporated herein by reference in their entirety.

[00203] The term "intrabody" refers to a form of antibody that is not secreted from a cell in which it is produced, but instead targets one or more intracellular proteins. Intrabodies may be used to affect a multitude of cellular processes including, but not limited to intracellular trafficking, transcription, translation, metabolic processes, proliferative signaling, and cell division. In some embodiments, methods of the present invention may include intrabody-based therapies. In some such embodiments, variable domain sequences and/or CDR sequences disclosed herein may be incorporated into one or more constructs for intrabody-based therapy.

[00204] As used herein, the term "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous cells (or clones), i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variants that may arise during production of the monoclonal antibodies, such variants generally being

present in minor amounts. In contrast to polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen

[00205] The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. The monoclonal antibodies herein include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies.

[00206] As used herein, the term "humanized antibody" refers to a chimeric antibody comprising a minimal portion from one or more non-human (e.g., murine) antibody source(s) with the remainder derived from one or more human immunoglobulin sources. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from the hypervariable region from an antibody of the recipient are replaced by residues from the hypervariable region from an antibody of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and/or capacity.

[00207] In some embodiments, viral genomes of the present invention may encode antibody mimetics. As used herein, the term "antibody mimetic" refers to any molecule which mimics the function or effect of an antibody and which binds specifically and with high affinity to their molecular targets. In some embodiments, antibody mimetics may be monobodies, designed to incorporate the fibronectin type III domain (Fn3) as a protein scaffold (US6673901; US6348584). In some embodiments, antibody mimetics may be those known in the art including, but are not limited to affibody molecules, affilins, affitins, anticalins, avimers, Centyrins, DARPINS™, fynomers, Kunitz domains, and domain peptides. In other embodiments, antibody mimetics may include one or more non-peptide regions.

[00208] As used herein, the term "antibody variant" refers to a modified antibody (in relation to a native or starting antibody) or a biomolecule resembling a native or starting antibody in structure and/or function (e.g., an antibody mimetic). Antibody variants may be altered in their amino acid sequence, composition, or structure as compared to a native antibody. Antibody variants may include, but are not limited to, antibodies with altered isotypes (e.g., IgA, IgD, IgE,

IgG_1, IgG_2, IgG_3, IgG_4, or IgM), humanized variants, optimized variants, multispecific antibody variants (e.g., bispecific variants), and antibody fragments.

[00209] The preparation of antibodies, whether monoclonal or polyclonal, is known in the art. Techniques for the production of antibodies are well known in the art and described, e.g. in Harlow and Lane "Antibodies, A Laboratory Manual", Cold Spring Harbor Laboratory Press, 1988; Harlow and Lane "Using Antibodies: A Laboratory Manual" Cold Spring Harbor Laboratory Press, 1999 and "Therapeutic Antibody Engineering: Current and Future Advances Driving the Strongest Growth Area in the Pharmaceutical Industry" Woodhead Publishing, 2012.

Multispecific antibodies

[00210] In some embodiments, payloads of the invention may encode antibodies that bind more than one epitope. As used herein, the terms "multibody" or "multispecific antibody" refer to an antibody wherein two or more variable regions bind to different epitopes. The epitopes may be on the same or different targets. In certain embodiments, a multi-specific antibody is a "bispecific antibody," which recognizes two different epitopes on the same or different antigens.

[00211] In one embodiment, multi-specific antibodies may be prepared by the methods used by BIOATLA® and described in International Patent publication WO201109726, the contents of which are herein incorporated by reference in their entirety. First a library of homologous, naturally occurring antibodies is generated by any method known in the art (i.e., mammalian cell surface display), then screened by FACSAria or another screening method, for multi-specific antibodies that specifically bind to two or more target antigens. In one embodiment, the identified multi-specific antibodies are further evolved by any method known in the art, to produce a set of modified multi-specific antibodies. These modified multi-specific antibodies are screened for binding to the target antigens. In one embodiment, the multi-specific antibody may be further optimized by screening the evolved modified multi-specific antibodies for optimized or desired characteristics.

[00212] In one embodiment, multi-specific antibodies may be prepared by the methods used by BIOATLA® and described in Unites States Publication No. US20150252119, the contents of which are herein incorporated by reference in their entirety. In one approach, the variable domains of two parent antibodies, wherein the parent antibodies are monoclonal antibodies are evolved using any method known in the art in a manner that allows a single light chain to functionally complement heavy chains of two different parent antibodies. Another approach requires evolving the heavy chain of a single parent antibody to recognize a second target antigen. A third approach involves evolving the light chain of a parent antibody so as to recognize a second target antigen. Methods for polypeptide evolution are described in

International Publication WO2012009026, the contents of which are herein incorporated by reference in their entirety, and include as non-limiting examples, Comprehensive Positional Evolution (CPE), Combinatorial Protein Synthesis (CPS), Comprehensive Positional Insertion (CPI), Comprehensive Positional Deletion (CPD), or any combination thereof. The Fc region of the multi-specific antibodies described in United States Publication No. US20150252119 may be created using a knob-in-hole approach, or any other method that allows the Fc domain to form heterodimers. The resultant multi-specific antibodies may be further evolved for improved characteristics or properties such as binding affinity for the target antigen.

Bispecific antibodies

[00213] In some embodiments, payloads of the invention may encode bispecific antibodies. Bispecific antibodies are capable of binding two different antigens. Such antibodies typically comprise antigen-binding regions from at least two different antibodies. For example, a bispecific monoclonal antibody (BsMAb, BsAb) is an artificial protein composed of fragments of two different monoclonal antibodies, thus allowing the BsAb to bind to two different types of antigen.

[00214] In some cases, payloads encode bispecific antibodies comprising antigen-binding regions from two different anti-tau antibodies. For example, such bispecific antibodies may comprise binding regions from two different antibodies selected from Table 3.

[00215] Bispecific antibody frameworks may include any of those described in Riethmuller, G., 2012. *Cancer Immunity*. 12:12-18; Marvin, J.S. *et al.*, 2005. *Acta Pharmacologica Sinica*. 26(6):649-58; and Schaefer, W. *et al.*, 2011. *PNAS*. 108(27):11187-92, the contents of each of which are herein incorporated by reference in their entirety.

[00216] New generations of BsMAb, called "trifunctional bispecific" antibodies, have been developed. These consist of two heavy and two light chains, one each from two different antibodies, where the two Fab regions (the arms) are directed against two antigens, and the Fc region (the foot) comprises the two heavy chains and forms the third binding site.

[00217] Of the two paratopes that form the tops of the variable domains of a bispecific antibody, one can be directed against a target antigen and the other against a T-lymphocyte antigen like CD3. In the case of trifunctional antibodies, the Fc region may additionally bind to a cell that expresses Fc receptors, like a macrophage, a natural killer (NK) cell or a dendritic cell. In sum, the targeted cell is connected to one or two cells of the immune system, which subsequently destroy it.

[00218] Other types of bispecific antibodies have been designed to overcome certain problems, such as short half-life, immunogenicity and side-effects caused by cytokine liberation. They

include chemically linked Fabs, consisting only of the Fab regions, and various types of bivalent and trivalent single-chain variable fragments (scFvs), fusion proteins mimicking the variable domains of two antibodies. The furthest developed of these newer formats are the bi-specific T-cell engagers (BiTEs) and mAb2's, antibodies engineered to contain an Fcab antigen-binding fragment instead of the Fc constant region.

[00219] Using molecular genetics, two scFvs can be engineered in tandem into a single polypeptide, separated by a linker domain, called a "tandem scFv" (tascFv). TascFvs have been found to be poorly soluble and require refolding when produced in bacteria, or they may be manufactured in mammalian cell culture systems, which avoids refolding requirements but may result in poor yields. Construction of a tascFv with genes for two different scFvs yields a "bispecific single-chain variable fragments" (bis-scFvs). Only two tascFvs have been developed clinically by commercial firms; both are bispecific agents in active early phase development by Micromet for oncologic indications, and are described as "Bispecific T-cell Engagers (BiTE)." Blinatumomab is an anti-CD19/anti-CD3 bispecific tascFv that potentiates T-cell responses to B-cell non-Hodgkin lymphoma in Phase 2. MT110 is an anti-EP-CAM/anti-CD3 bispecific tascFv that potentiates T-cell responses to solid tumors in Phase 1. Bispecific, tetravalent "TandAbs" are also being researched by Affimed (Nelson, A. L., *MAbs*.2010. Jan-Feb; 2(1):77–83).

[00220] In some embodiments, payloads may encode antibodies comprising a single antigen-binding domain. These molecules are extremely small, with molecular weights approximately one-tenth of those observed for full-sized mAbs. Further antibodies may include "nanobodies" derived from the antigen-binding variable heavy chain regions (Vnns) of heavy chain antibodies found in camels and llamas, which lack light chains (Nelson, A. L., *MAbs*.2010. Jan-Feb; 2(1):77–83).

[00221] Disclosed and claimed in PCT Publication WO2014144573 to Memorial Sloan-Kettering Cancer Center are multimerization technologies for making dimeric multispecific binding agents (*e.g.*, fusion proteins comprising antibody components) with improved properties over multispecific binding agents without the capability of dimerization.

[00222] In some cases, payloads of the invention may encode tetravalent bispecific antibodies (TetBiAbs as disclosed and claimed in PCT Publication WO2014144357). TetBiAbs feature a second pair of Fab fragments with a second antigen specificity attached to the C-terminus of an antibody, thus providing a molecule that is bivalent for each of the two antigen specificities. The tetravalent antibody is produced by genetic engineering methods, by linking an antibody heavy chain covalently to a Fab light chain, which associates with its cognate, co-expressed Fab heavy chain.

[00223] In some aspects, payloads of the invention may encode biosynthetic antibodies as described in U.S. Patent No. 5,091,513, the contents of which are herein incorporated by reference in their entirety. Such antibody may include one or more sequences of amino acids constituting a region which behaves as a biosynthetic antibody binding site (BABS). The sites comprise 1) non-covalently associated or disulfide bonded synthetic V_H and V_L dimers, 2) V_H-V_L or V_L-V_H single chains wherein the V_H and V_L are attached by a polypeptide linker, or 3) individuals V_H or V_L domains. The binding domains comprise linked CDR and FR regions, which may be derived from separate immunoglobulins. The biosynthetic antibodies may also include other polypeptide sequences which function, *e.g.*, as an enzyme, toxin, binding site, or site of attachment to an immobilization media or radioactive atom. Methods are disclosed for producing the biosynthetic antibodies, for designing BABS having any specificity that can be elicited by in vivo generation of antibody, and for producing analogs thereof.

[00224] In some embodiments, payloads may encode antibodies with antibody acceptor frameworks taught in U.S. Patent No. 8,399,625. Such antibody acceptor frameworks may be particularly well suited accepting CDRs from an antibody of interest. In some cases, CDRs from anti-tau antibodies known in the art or developed according to the methods presented herein may be used.

Miniaturized Antibody

[00225] In one embodiment, the antibody encoded by the payloads of the invention may be a "miniaturized" antibody. Among the best examples of mAb miniaturization are the small modular immunopharmaceuticals (SMIPs) from Trubion Pharmaceuticals. These molecules, which can be monovalent or bivalent, are recombinant single-chain molecules containing one V_L, one V_H antigen-binding domain, and one or two constant "effector" domains, all connected by linker domains. Presumably, such a molecule might offer the advantages of increased tissue or tumor penetration claimed by fragments while retaining the immune effector functions conferred by constant domains. At least three "miniaturized" SMIPs have entered clinical development. TRU-015, an anti-CD20 SMIP developed in collaboration with Wyeth, is the most advanced project, having progressed to Phase 2 for rheumatoid arthritis (RA). Earlier attempts in systemic lupus erythrematosus (SLE) and B cell lymphomas were ultimately discontinued. Trubion and Facet Biotechnology are collaborating in the development of TRU-016, an anti-CD37 SMIP, for the treatment of CLL and other lymphoid neoplasias, a project that has reached Phase 2. Wyeth has licensed the anti-CD20 SMIP SBI-087 for the treatment of autoimmune diseases, including RA, SLE, and possibly multiple sclerosis, although these projects remain in the earliest stages of clinical testing. (Nelson, A. L., *MAbs*.2010. Jan-Feb; 2(1):77–83).

Diabodies

[00226] In some embodiments, payloads of the invention may encode diabodies. Diabodies are functional bispecific single-chain antibodies (bscAb). These bivalent antigen-binding molecules are composed of non-covalent dimers of scFvs, and can be produced in mammalian cells using recombinant methods. (*See, e.g.*, Mack *et al*, *Proc. Natl. Acad. Sci.*, 92: 7021-7025, 1995). Few diabodies have entered clinical development. An iodine-123-labeled diabody version of the anti-CEA chimeric antibody cT84.66 has been evaluated for pre-surgical immunoscintigraphic detection of colorectal cancer in a study sponsored by the Beckman Research Institute of the City of Hope (Clinicaltrials.gov NCT00647153) (Nelson, A. L., *MAbs.*, 2010. Jan-Feb; 2(1):77–83).

Unibody

[00227] In some embodiments, payloads may encode a "unibody," in which the hinge region has been removed from IgG4 molecules. While IgG4 molecules are unstable and can exchange light-heavy chain heterodimers with one another, deletion of the hinge region prevents heavy chain-heavy chain pairing entirely, leaving highly specific monovalent light/heavy heterodimers, while retaining the Fc region to ensure stability and half-life in vivo. This configuration may minimize the risk of immune activation or oncogenic growth, as IgG4 interacts poorly with FcRs and monovalent unibodies fail to promote intracellular signaling complex formation. These contentions are, however, largely supported by laboratory, rather than clinical, evidence. Other antibodies may be "miniaturized" antibodies, which are compacted 100 kDa antibodies (see, e.g., Nelson, A. L., *MAbs.*, 2010. Jan-Feb; 2(1):77–83).

Intrabodies

[00228] In some embodiments, payloads of the invention may encode intrabodies. Intrabodies are a form of antibody that is not secreted from a cell in which it is produced, but instead targets one or more intracellular proteins. Intrabodies are expressed and function intracellularly, and may be used to affect a multitude of cellular processes including, but not limited to intracellular trafficking, transcription, translation, metabolic processes, proliferative signaling and cell division. In some embodiments, methods described herein include intrabody-based therapies. In some such embodiments, variable domain sequences and/or CDR sequences disclosed herein are incorporated into one or more constructs for intrabody-based therapy. For example, intrabodies may target one or more glycated intracellular proteins or may modulate the interaction between one or more glycated intracellular proteins and an alternative protein.

[00229] More than two decades ago, intracellular antibodies against intracellular targets were first described (Biocca, Neuberger and Cattaneo *EMBO J.* 9: 101-108, 1990). The intracellular expression of intrabodies in different compartments of mammalian cells allows blocking or

modulation of the function of endogenous molecules (Biocca, *et al.*, *EMBO J.* 9: 101-108, 1990; Colby et al., Proc. Natl. Acad. Sci. U.S.A. 101: 17616-21, 2004). Intrabodies can alter protein folding, protein-protein, protein-DNA, protein-RNA interactions and protein modification. They can induce a phenotypic knockout and work as neutralizing agents by direct binding to the target antigen, by diverting its intracellular trafficking or by inhibiting its association with binding partners. They have been largely employed as research tools and are emerging as therapeutic molecules for the treatment of human diseases such as viral pathologies, cancer and misfolding diseases. The fast-growing bio-market of recombinant antibodies provides intrabodies with enhanced binding specificity, stability, and solubility, together with lower immunogenicity, for their use in therapy (Biocca, abstract in Antibody Expression and Production Cell Engineering Volume 7, 2011, pp. 179-195).

[00230] In some embodiments, intrabodies have advantages over interfering RNA (iRNA); for example, iRNA has been shown to exert multiple non-specific effects, whereas intrabodies have been shown to have high specificity and affinity to target antigens. Furthermore, as proteins, intrabodies possess a much longer active half-life than iRNA. Thus, when the active half-life of the intracellular target molecule is long, gene silencing through iRNA may be slow to yield an effect, whereas the effects of intrabody expression can be almost instantaneous. Lastly, it is possible to design intrabodies to block certain binding interactions of a particular target molecule, while sparing others.

[00231] Intrabodies are often single chain variable fragments (scFvs) expressed from a recombinant nucleic acid molecule and engineered to be retained intracellularly (*e.g.*, retained in the cytoplasm, endoplasmic reticulum, or periplasm). Intrabodies may be used, for example, to ablate the function of a protein to which the intrabody binds. The expression of intrabodies may also be regulated through the use of inducible promoters in the nucleic acid expression vector comprising the intrabody. Intrabodies may be produced for use in the viral genomes of the invention using methods known in the art, such as those disclosed and reviewed in: (Marasco *et al.*, 1993 *Proc. Natl. Acad. Sci. USA*, 90: 7889-7893; Chen *et al.*, 1994, *Hum. Gene Ther.* 5:595-601; Chen *et al.*, 1994, *Proc. Natl. Acad. Sci. USA*, 91: 5932-5936; Maciejewski *et al.*, 1995, *Nature Med.*, 1: 667-673; Marasco, 1995, *Immunotech*, 1: 1-19; Mhashilkar, *et al.*, 1995, *EMBO J.* 14: 1542-51; Chen *et al.*, 1996, *Hum. Gene Therap.*, 7: 1515-1525; Marasco, *Gene Ther.* 4:11-15, 1997; Rondon and Marasco, 1997, *Annu. Rev. Microbiol.* 51:257-283; Cohen, *et al.*, 1998, *Oncogene* 17:2445-56; Proba *et al.*, 1998, *J. Mol. Biol.* 275:245-253; Cohen *et al.*, 1998, *Oncogene* 17:2445-2456; Hassanzadeh, *et al.*, 1998, *FEBS Lett.* 437:81-6; Richardson *et al.*, 1998, *Gene Ther.* 5:635-44; Ohage and Steipe, 1999, *J. Mol. Biol.* 291:1119-1128; Ohage *et al.*,

1999, *J. Mol. Biol.* 291:1129-1134; Wirtz and Steipe, 1999, *Protein Sci.* 8:2245-2250; Zhu *et al.*, 1999, *J. Immunol. Methods* 231:207-222; Arafat *et al.*, 2000, *Cancer Gene Ther.* 7:1250-6; der Maur *et al.*, 2002, *J. Biol. Chem.* 277:45075-85; Mhashilkar *et al.*, 2002, *Gene Ther.* 9:307-19; and Wheeler *et al.*, 2003, *FASEB J.* 17: 1733-5; and references cited therein). In particular, a CCR5 intrabody has been produced by Steinberger *et al.*, 2000, *Proc. Natl. Acad. Sci. USA* 97:805-810). *See* generally Marasco, WA, 1998, "Intrabodies: Basic Research and Clinical Gene Therapy Applications" Springer: New York; and for a review of scFvs, *see* Pluckthun in "The Pharmacology of Monoclonal Antibodies," 1994, vol. 113, Rosenburg and Moore *eds.* Springer-Verlag, New York, pp. 269-315.

[00232] Sequences from donor antibodies may be used to develop intrabodies. Intrabodies are often recombinantly expressed as single domain fragments such as isolated V_H and V_L domains or as a single chain variable fragment (scFv) antibody within the cell. For example, intrabodies are often expressed as a single polypeptide to form a single chain antibody comprising the variable domains of the heavy and light chains joined by a flexible linker polypeptide. Intrabodies typically lack disulfide bonds and are capable of modulating the expression or activity of target genes through their specific binding activity. Single chain antibodies can also be expressed as a single chain variable region fragment joined to the light chain constant region.

[00233] As is known in the art, an intrabody can be engineered into recombinant polynucleotide vectors to encode sub-cellular trafficking signals at its N or C terminus to allow expression at high concentrations in the sub-cellular compartments where a target protein is located. For example, intrabodies targeted to the endoplasmic reticulum (ER) are engineered to incorporate a leader peptide and, optionally, a C-terminal ER retention signal, such as the KDEL amino acid motif (SEQ ID NO: 4323). Intrabodies intended to exert activity in the nucleus are engineered to include a nuclear localization signal. Lipid moieties are joined to intrabodies in order to tether the intrabody to the cytosolic side of the plasma membrane. Intrabodies can also be targeted to exert function in the cytosol. For example, cytosolic intrabodies are used to sequester factors within the cytosol, thereby preventing them from being transported to their natural cellular destination.

[00234] There are certain technical challenges with intrabody expression. In particular, protein conformational folding and structural stability of the newly-synthesized intrabody within the cell is affected by reducing conditions of the intracellular environment.

[00235] Intrabodies of the invention may be promising therapeutic agents for the treatment of misfolding diseases, including Tauopathies, prion diseases, Alzheimer's, Parkinson's, and Huntington's, because of their virtually infinite ability to specifically recognize the different

conformations of a protein, including pathological isoforms, and because they can be targeted to the potential sites of aggregation (both intra- and extracellular sites). These molecules can work as neutralizing agents against amyloidogenic proteins by preventing their aggregation, and/or as molecular shunters of intracellular traffic by rerouting the protein from its potential aggregation site (Cardinale, and Biocca, *Curr. Mol. Med.* 2008, 8:2-11).

Maxibodies

[00236] In one embodiment, the payloads of the invention encode a maxibody (bivalent scFV fused to the amino terminus of the Fc (CH2-CH3 domains) of IgG.

Chimeric antigen receptors

[00237] In some embodiments, the polypeptides encoded by the viral genomes of the invention (e.g., antibodies) may be used to generate chimeric antigen receptors (CARs) as described by BIOATLA® in International Publications WO2016033331 and WO2016036916, the contents of which are herein incorporated by reference in their entirety. As used herein, a "chimeric antigen receptor (CAR)" refers to an artificial chimeric protein comprising at least one antigen specific targeting region (ASTR), wherein the antigen specific targeting region comprises a full-length antibody or a fragment thereof that specifically binds to a target antigen. The ASTR may comprise any of the following; a full length heavy or light chain, an Fab fragment, a single chain Fv fragment, a divalent single chain antibody, or a diabody. As a non-limiting example the ASTR of a CAR may be any of the antibodies listed in Table 3, antibody-based compositions or fragments thereof. Any molecule that is capable of binding a target antigen with high affinity can be used in the ASTR of a CAR. In one embodiment, the CAR may have more than one ASTR. These ASTRs may target two or more antigens or two or more epitopes of the same antigen. In one embodiment, the CAR is conditionally active. In one embodiment, the CAR is used to produce a genetically engineered cytotoxic cell carrying the CAR and capable of targeting the antigen bound by the ASTR.

[00238] Chimeric antigen receptors (CARs) are particularly useful in the treatment of cancers, though also therapeutically effective in treatment of a wide variety of other diseases and disorders. Non-limiting examples of disease categories that may be treated with CARs or CAR-based therapeutics include autoimmune disorders, B-cell mediated diseases, inflammatory diseases, neuronal disorders, cardiovascular disease and circulatory disorders, or infectious diseases. Not wishing to be bound by theory, CARs traditionally work by targeting antigens presented on the surface of or on the inside of cells to be destroyed e.g., cancer tumor cells, by the cytotoxic cell of the CAR.

Senescent Cell Surface Protein Antibodies

[00239] In some embodiments, the AAV particles may comprise nucleic acids which have been engineered to express of antibodies that selectively bind to surface marker proteins of senescent cells. For example, the antibodies may selectively bind to proteins that are in misfolded conformation. The binding antibodies may reduce the number of senescent cells and be used to treat age-related conditions, such as, but not limited to, Alzheimer's disease, cardiovascular disease, emphysema, sarcopenia, and tumorigenesis as well as conditions more cosmetic in nature such as signs of skin aging including wrinkling, sagging, discoloration, age-related tissue dysfunction, tumor formation, and other age-related conditions.

[00240] In one embodiment, the expressed antibodies binding to epitopes of senescent cell surface proteins may be, but are not limited to, such as prion epitopes presented by SEQ ID NO: 1-14 of International Publication No. WO2014186878; CD44 epitopes presented by SEQ ID NO: 47-51 of International Publication No. WO2014186878; TNFR epitopes presented by SEQ ID NO: 52-56 of International Publication No. WO2014186878; NOTCH1 epitope presented by SEQ ID NO: 57-61 of International Publication No. WO2014186878; FasR epitopes presented by SEQ ID NO: 62-66 of International Publication No. WO2014186878; epidermal growth factor epitopes presented by SEQ ID NO: 67-81 of International Publication No. WO2014186878; CD38 epitopes presented by SEQ ID NO: 82-86 of International Publication No. WO2014186878, the contents of each of which are herein incorporated by reference in their entirety.

[00241] In one embodiment, the expressed antibodies may comprise peptides binding to senescent cell surface prion proteins, such as, but not limited to, those presented by SEQ ID NO: 15-36 of International Publication No. WO2014186878, the contents of which are herein incorporated by reference in their entirety.

[00242] In one embodiment, the expressed antibody may be AMF-3a-118 or AMF 3d-19 (SEQ ID NO: 89-92 and 103-106 of International publication WO2014186878, respectively, the contents of which are herein incorporated by reference in their entirety) targeting senescent cell surface protein FasR. In one embodiment, the expressed antibody may be Ab c-120 (SEQ ID NO: 37-40 of International publication WO2014186878, the contents of which are herein incorporated by reference in their entirety) targeting senescent cell surface protein PrP.

Payload antibodies of the invention

[00243] In one embodiment, the payload region of the AAV particle comprises one or more nucleic acid sequences encoding one or more of the payload antibody polypeptides listed in Table 3.

[00244] In one embodiment, the payload region of the AAV particle comprises one or more nucleic acid sequences listed in Table 3 or Table 4.

[00245] In some embodiments, the payload region of the AAV particle comprises a nucleic acid sequence encoding a payload antibody with at least 50% identity to one or more payload antibody polypeptides listed in Tables 3 or 4. The encoded antibody polypeptide may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more of the payload antibody polypeptides listed in Tables 3 or 4.

[00246] In one embodiment, the full sequence of the encoded antibody polypeptide may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more of the payload antibody polypeptides listed in Tables 3 or 4.

[00247] In one embodiment, the variable region sequence(s) of the encoded antibody polypeptide may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more of the payload antibody polypeptides listed in Tables 3 or 4.

[00248] In one embodiment, the heavy chain of the encoded antibody polypeptide may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more of the payload heavy chain antibody polypeptides listed in Tables 3 or 4.

[00249] In one embodiment, the light chain of the encoded antibody polypeptide may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more of the payload light chain antibody polypeptides listed in Tables 3 or 4.

[00250] In one embodiment, the CDR region of the encoded antibody polypeptide may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the CDRs of one or more of the payload antibody polypeptides listed in Tables 3 or 4.

[00251] In one embodiment, the payload antibody has 90% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00252] In one embodiment, the payload antibody has 91% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00253] In one embodiment, the payload antibody has 92% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00254] In one embodiment, the payload antibody has 93% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00255] In one embodiment, the payload antibody has 94% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00256] In one embodiment, the payload antibody has 95% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00257] In one embodiment, the payload antibody has 96% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00258] In one embodiment, the payload antibody has 97% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00259] In one embodiment, the payload antibody has 98% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00260] In one embodiment, the payload antibody has 99% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00261] In one embodiment, the payload antibody has 100% identity to one or more of the antibody polypeptides listed in Tables 3 or 4.

[00262] In some embodiments, the payload region of the AAV particle comprises a nucleic acid sequence with at least 50% identity to one or more nucleic acid sequences listed in Tables 3 or 4. The payload nucleic acid sequence may have 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%,

89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to one or more nucleic acid sequences listed in Tables 3 or 4.

[00263] In one embodiment, the payload nucleic acid sequence has 90% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

[00264] In one embodiment, the payload nucleic acid sequence has 91% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

[00265] In one embodiment, the payload nucleic acid sequence has 92% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

[00266] In one embodiment, the payload nucleic acid sequence has 93% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

[00267] In one embodiment, the payload nucleic acid sequence has 94% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

[00268] In one embodiment, the payload nucleic acid sequence has 95% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

[00269] In one embodiment, the payload nucleic acid sequence has 96% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

[00270] In one embodiment, the payload nucleic acid sequence has 97% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

[00271] In one embodiment, the payload nucleic acid sequence has 98% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

[00272] In one embodiment, the payload nucleic acid sequence has 99% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

[00273] In one embodiment, the payload nucleic acid sequence has 100% identity to one or more of the nucleic acid sequences listed in Tables 3 or 4.

Table 3. Tau Associated Disease Antibodies

Antibody No.	Target	Description	Antibody Name	Reference	SEQ ID NO
TAU1	tau	Heavy chain	MC-1		2948
TAU2	tau	Heavy chain	PHF-1		2949
TAU3	tau	Heavy chain	IPN002		2950
TAU4	amyloids	Heavy chain	#118	WO2010012004 SEQ ID NO: 11	2951
TAU5	amyloids	Heavy chain	#121	WO2010012004 SEQ ID NO: 13	2952
TAU6	amyloids	Heavy chain	#204	WO2010012004 SEQ ID NO: 17	2953
TAU7	amyloids	Heavy chain	#205	WO2010012004 SEQ ID NO: 19	2954
TAU8	NOGO	Heavy chain	H6L13 FL	US20140147435 SEQ ID NO: 27	2955
TAU9	NOGO	Heavy chain	H16L16 FL, H16L18 FL	US20140147435 SEQ ID NO: 31	2956

TAU10	NOGO	Heavy chain	H18L16 FL	US20140147435 SEQ ID NO: 33	2957
TAU11	NOGO	Heavy chain	H19L13 FL, H19L16 FL, H19L18 FL	US20140147435 SEQ ID NO: 92	2958
TAU12	NOGO	Heavy chain	H20L13 FL, H20L16 FL, H20L18 FL	US20140147435 SEQ ID NO: 93	2959
TAU13	NOGO	Heavy chain	H21L13 FL, H21L16 FL, H21L18 FL	US20140147435 SEQ ID NO: 94	2960
TAU14	NOGO	Heavy chain	H25L13 FL, H25L16 FL, H25L18 FL	US20140147435 SEQ ID NO: 98	2961
TAU15	Nogo receptor-1	Heavy chain	5B10	US20090215691 SEQ ID NO: 16	2962
TAU16	Nogo receptor-1	Heavy chain	5B10	US20090215691 SEQ ID NO: 18	2963
TAU17	PrP	Heavy chain	Ab c-120	WO2014186878 SEQ ID NO: 38	2964
TAU18	PrPC and/or PrPSc	Heavy chain		US20150166668 SEQ ID NO: 10	2965
TAU19	PrPC and/or PrPSc	Heavy chain		US8852587 SEQ ID NO: 4	2966
TAU20	tau	Heavy chain	VH antibody	US20150252102 SEQ ID NO: 93	2967
TAU21	tau	Heavy chain	hACI-36-3A8 Ab1	WO2013151762 SEQ ID NO: 24	2968
TAU22	tau	Heavy chain	hACI-36-3B8 Ab1	WO2013151762 SEQ ID NO: 25	2969
TAU23	tau	Heavy chain	hACI-36-3A8 Ab1.v2	WO2013151762 SEQ ID NO: 26	2970
TAU24	tau	Heavy chain	hACI-36-3A8 Ab1.v3	WO2013151762 SEQ ID NO: 27	2971
TAU25	tau	Heavy chain	hACI-36-3A8 Ab1.v4	WO2013151762 SEQ ID NO: 28	2972
TAU26	tau	Heavy chain	hACI-36-3B8 Ab1.v2	WO2013151762 SEQ ID NO: 29	2973
TAU27	tau	Heavy chain	hACI-36-3B8 Ab1.v3	WO2013151762 SEQ ID NO: 30	2974
TAU28	tau	Heavy chain	hACI-36-3B8 Ab1.v4	WO2013151762 SEQ ID NO: 31	2975
TAU29	tau	Heavy chain	IPN001	US8980271 SEQ ID NO: 14	2976
TAU30	tau	Heavy chain	IPN002	US8980271 SEQ ID NO: 16	2977
TAU31	tau	Heavy chain	ACI-36-3A8-Ab1 and hACI-36-2B6-Ab1	US20150175682 SEQ ID NO: 16	2978
TAU32	tau	Heavy chain	hACI-36-3A8-Ab1 and hACI-36-2B6-Ab1	US20150175682 SEQ ID NO: 17	2979
TAU33	tau	Heavy chain	hACI-36-2B6-Ab1 (IgG4)	US20150175682 SEQ ID NO: 25	2980
TAU34	tau	Heavy chain	hACI-36-3A8-Ab1.v2 (IgG4)	US20150175682 SEQ ID NO: 26	2981
TAU35	tau	Heavy chain	hACI-36-3A8-Ab1.v3 (IgG1)	US20150175682 SEQ ID NO: 27	2982
TAU36	tau	Heavy chain	hACI-36-3A8-Ab1.v4 (IgG1 N297G)	US20150175682 SEQ ID NO: 28	2983
TAU37	tau	Heavy chain	hACI-36-2B6-Ab1.v2 (IgG4)	US20150175682 SEQ ID NO: 29	2984

TAU38	tau	Heavy chain	hACI-36-2B6-Ab1.v3 (IgG1)	US20150175682 SEQ ID NO: 30	2985
TAU39	tau	Heavy chain	hACI-36-2B6-Ab1.v4 (IgG1 N297G)	US20150175682 SEQ ID NO: 31	2986
TAU40	trk-C	Heavy chain	2250	US7615383 SEQ ID NO: 42	2987
TAU41	trk-C	Heavy chain	2253	US7615383 SEQ ID NO: 43	2988
TAU42	trk-C	Heavy chain	2256	US7615383 SEQ ID NO: 44	2989
TAU43	trk-C	Heavy chain	6.1.2	US7615383 SEQ ID NO: 45	2990
TAU44	trk-C	Heavy chain	6.4.1	US7615383 SEQ ID NO: 46	2991
TAU45	trk-C	Heavy chain	2345	US7615383 SEQ ID NO: 47	2992
TAU46	trk-C	Heavy chain	2349	US7615383 SEQ ID NO: 48	2993
TAU47	tau	Heavy chain constant region	hACI-36-3A8-Ab1 and hACI-36-2B6-Ab1	US20150175682 SEQ ID NO: 14	2994
TAU48	many	Heavy chain fusion protein		US8053569 SEQ ID NO: 25	2995
TAU49	many	Heavy chain fusion protein		US8053569 SEQ ID NO: 28	2996
TAU50	many	Heavy chain fusion protein		US8053569 SEQ ID NO: 34	2997
TAU51	many - growth factors (to increase transport across BBB)	Heavy chain fusion protein		US8053569 SEQ ID NO: 24	2998
TAU52	NOGO	Heavy chain humanized construct H1	2A10 construct	WO2007003421 SEQ ID NO: 79	2999
TAU53	NOGO	Heavy chain humanized construct H14	2A10 construct	WO2007003421 SEQ ID NO: 29	3000
TAU54	NOGO	Heavy chain humanized construct H15	2A10 construct	WO2007003421 SEQ ID NO: 30	3001
TAU55	NOGO	Heavy chain humanized construct H16	2A10 construct	WO2007003421 SEQ ID NO: 31	3002
TAU56	NOGO	Heavy chain humanized construct H17	2A10 construct	WO2007003421 SEQ ID NO: 32	3003
TAU57	NOGO	Heavy chain humanized construct H18	2A10 construct	WO2007003421 SEQ ID NO: 33	3004
TAU58	NOGO	Heavy chain humanized construct H19	2A10 construct	WO2007003421 SEQ ID NO: 92	3005
TAU59	NOGO	Heavy chain humanized construct H20	2A10 construct	WO2007003421 SEQ ID NO: 93	3006
TAU60	NOGO	Heavy chain humanized construct H21	2A10 construct	WO2007003421 SEQ ID NO: 94	3007
TAU61	NOGO	Heavy chain humanized construct H22	2A10 construct	WO2007003421 SEQ ID NO: 95	3008

TAU62	NOGO	Heavy chain humanized construct H23	2A10 construct	WO2007003421 SEQ ID NO: 96	3009
TAU63	NOGO	Heavy chain humanized construct H24	2A10 construct	WO2007003421 SEQ ID NO: 97	3010
TAU64	NOGO	Heavy chain humanized construct H25	2A10 construct	WO2007003421 SEQ ID NO: 98	3011
TAU65	NOGO	Heavy chain humanized construct H5	2A10 construct	WO2007003421 SEQ ID NO: 26	3012
TAU66	NOGO	Heavy chain humanized construct H6	2A10 construct	WO2007003421 SEQ ID NO: 27	3013
TAU67	NOGO	Heavy chain humanized construct H700	2A10 construct	WO2007003421 SEQ ID NO: 28	3014
TAU68	RTN4 (NOGO)	Heavy chain IgG4, immunomodulator	Atinumab	US8163285 SEQ ID NO: 24	3015
TAU69	tau	Heavy chain mature	ch4E4	US20150252102 SEQ ID NO: 20	3016
TAU70	tau	Heavy chain mature	ch4E4(N30Q)	US20150252102 SEQ ID NO: 22	3017
TAU71	NOGO	Heavy chain variable humanized construct H1	2A10 construct	WO2007003421 SEQ ID NO: 77	3018
TAU72	NOGO	Heavy chain variable humanized construct H14	2A10 construct	WO2007003421 SEQ ID NO: 14	3019
TAU73	NOGO	Heavy chain variable humanized construct H15	2A10 construct	WO2007003421 SEQ ID NO: 15	3020
TAU74	NOGO	Heavy chain variable humanized construct H16	2A10 construct	WO2007003421 SEQ ID NO: 16	3021
TAU75	NOGO	Heavy chain variable humanized construct H17	2A10 construct	WO2007003421 SEQ ID NO: 17	3022
TAU76	NOGO	Heavy chain variable humanized construct H18	2A10 construct	WO2007003421 SEQ ID NO: 18	3023
TAU77	NOGO	Heavy chain variable humanized construct H19	2A10 construct	WO2007003421 SEQ ID NO: 85	3024
TAU78	NOGO	Heavy chain variable humanized construct H20	2A10 construct	WO2007003421 SEQ ID NO: 86	3025

TAU79	NOGO	Heavy chain variable humanized construct H21	2A10 construct	WO2007003421 SEQ ID NO: 87	3026
TAU80	NOGO	Heavy chain variable humanized construct H22	2A10 construct	WO2007003421 SEQ ID NO: 88	3027
TAU81	NOGO	Heavy chain variable humanized construct H23	2A10 construct	WO2007003421 SEQ ID NO: 89	3028
TAU82	NOGO	Heavy chain variable humanized construct H24	2A10 construct	WO2007003421 SEQ ID NO: 90	3029
TAU83	NOGO	Heavy chain variable humanized construct H25	2A10 construct	WO2007003421 SEQ ID NO: 91	3030
TAU84	NOGO	Heavy chain variable humanized construct H5	2A10 construct	WO2007003421 SEQ ID NO: 11	3031
TAU85	NOGO	Heavy chain variable humanized construct H6	2A10 construct	WO2007003421 SEQ ID NO: 12	3032
TAU86	NOGO	Heavy chain variable humanized construct H700	2A10 construct	WO2007003421 SEQ ID NO: 13	3033
TAU87	amyloid oligomers	Heavy chain variable region	F11G3	US9125846 SEQ ID NO: 11	3034
TAU88	LPG(lysophosphatidylglucoside)	Heavy chain variable region	#7	US8591902 SEQ ID NO: 18	3035
TAU89	LPG(lysophosphatidylglucoside)	Heavy chain variable region	#15	US8591902 SEQ ID NO: 8	3036
TAU90	MAG	Heavy chain variable region		US8071731 SEQ ID NO: 13	3037
TAU91	MAG	Heavy chain variable region		US8071731 SEQ ID NO: 14	3038
TAU92	MAG	Heavy chain variable region		US8071731 SEQ ID NO: 15	3039
TAU93	MAI (myelin associated inhibitor)	Heavy chain variable region		WO2013158748 SEQ ID NO: 1	3040
TAU94	MAI (myelin associated inhibitor)	Heavy chain variable region		WO2013158748 SEQ ID NO: 17	3041
TAU95	NMDA	Heavy chain variable region		EP2805972 SEQ ID NO: 43	3042

TAU96	NOGO	Heavy chain variable region	H5L13, H5L16, H5L18, H5L14, H5L15, H5L17, H5L6, H5L11	US20140147435 SEQ ID NO: 11	3043
TAU97	NOGO	Heavy chain variable region	H6L13, H6L16, H6L18, H6L14, H6L15, H6L17, H6L6	US20140147435 SEQ ID NO: 12	3044
TAU98	NOGO	Heavy chain variable region	H700L13, H700L16, H700L18, H700L14, H700L15, H700L17, H700L6, H700L11	US20140147435 SEQ ID NO: 13	3045
TAU99	NOGO	Heavy chain variable region	H14L13, H14L16, H14L18, H14L14, H14L15, H14L17, H14L6, H14L11	US20140147435 SEQ ID NO: 14	3046
TAU100	NOGO	Heavy chain variable region	H15L13, H15L16, H15L18, H15L14, H15L15, H15L17, H15L6, H15L11	US20140147435 SEQ ID NO: 15	3047
TAU101	NOGO	Heavy chain variable region	H16L13, H16L16, H16L18, H16L14, H16L15, H16L17, H16L6, H16L11	US20140147435 SEQ ID NO: 16	3048
TAU102	NOGO	Heavy chain variable region	H17L13, H17L16, H17L18, H17L14, H17L15, H17L17, H17L6, H17L11	US20140147435 SEQ ID NO: 17	3049
TAU103	NOGO	Heavy chain variable region	H18L13, H18L16, H18L18, H18L14, H18L15, H18L17, H18L6, H18L11	US20140147435 SEQ ID NO: 18	3050
TAU104	NOGO	Heavy chain variable region	H1L13, H1L16, H1L18, H1L14, H1L15, H1L17, H1L6	US20140147435 SEQ ID NO: 77	3051
TAU105	NOGO	Heavy chain variable region	H19L13, H19L16, H19L18, H19L14, H19L15,	US20140147435 SEQ ID NO: 85	3052

			H19L17, H19L6, H19L11		
TAU106	NOGO	Heavy chain variable region	H20L13, H20L16, H20L18, H20L14, H20L15, H20L17, H20L6, H20L11	US20140147435 SEQ ID NO: 86	3053
TAU107	NOGO	Heavy chain variable region	H21L13, H21L16, H21L18, H21L14, H21L15, H21L17, H21L6, H21L11	US20140147435 SEQ ID NO: 87	3054
TAU108	NOGO	Heavy chain variable region	H22L13, H22L16, H22L18, H22L14, H22L15, H22L17, H22L6, H22L11	US20140147435 SEQ ID NO: 88	3055
TAU109	NOGO	Heavy chain variable region	H23L13, H23L16, H23L18, H23L14, H23L15, H23L17, H23L6, H23L11	US20140147435 SEQ ID NO: 89	3056
TAU110	NOGO	Heavy chain variable region	H24L13, H24L16, H24L18, H24L14, H24L15, H24L17, H24L6, H24L11	US20140147435 SEQ ID NO: 90	3057
TAU111	NOGO	Heavy chain variable region	H25L13, H25L16, H25L18, H25L14, H25L15, H25L17, H25L6, H25L11	US20140147435 SEQ ID NO: 91	3058
TAU112	NOGO	Heavy chain variable region	2A10	US7988964 SEQ ID NO: 37	3059
TAU113	NOGO	Heavy chain variable region	2C4	US7988964 SEQ ID NO: 38	3060
TAU114	NOGO	Heavy chain variable region	15C3	US7988964 SEQ ID NO: 39	3061
TAU115	Nogo-66	Heavy chain variable region	Antibody clone 50	US20140065155 SEQ ID NO: 3	3062
TAU116	Nogo-66	Heavy chain variable region	Antibody clone 51	US20140065155 SEQ ID NO: 5	3063

TAU117	NogoA/NiG	Heavy chain variable region	6A3-Ig4	WO2009056509 SEQ ID NO: 24	3064
TAU118	NogoA/NiG	Heavy chain variable region	6A3-IgG1	WO2009056509 SEQ ID NO: 4	3065
TAU119	PrP	Heavy chain variable region	1CSM18VH	US20140294844 SEQ ID NO: 4	3066
TAU120	PrP	Heavy chain variable region	Ab c-120	WO2014186878 SEQ ID NO: 40	3067
TAU121	PrPC and/or PrPSc	Heavy chain variable region		US20150166668 SEQ ID NO: 8	3068
TAU122	RGM A	Heavy chain variable region	5F9.1-GL	US20150183871 SEQ ID NO: 35	3069
TAU123	RGM A	Heavy chain variable region	5F9.2-GL	US20150183871 SEQ ID NO: 36	3070
TAU124	RGM A	Heavy chain variable region	5F9.3-GL	US20150183871 SEQ ID NO: 37	3071
TAU125	RGM A	Heavy chain variable region	5F9.4-GL	US20150183871 SEQ ID NO: 38	3072
TAU126	RGM A	Heavy chain variable region	5F9.5-GL	US20150183871 SEQ ID NO: 39	3073
TAU127	RGM A	Heavy chain variable region	5F9.6-GL	US20150183871 SEQ ID NO: 40	3074
TAU128	RGM A	Heavy chain variable region	5F9.7-GL	US20150183871 SEQ ID NO: 41	3075
TAU129	RGM A	Heavy chain variable region	5F9.8-GL	US20150183871 SEQ ID NO: 42	3076
TAU130	RGM A	Heavy chain variable region	5F9.9-GL	US20150183871 SEQ ID NO: 43	3077
TAU131	RGM A	Heavy chain variable region	h5F9.1, h5F9.1, h5F9.1, h5F9.1, h5F9.1, h5F9.2, h5F9.3	US20150183871 SEQ ID NO: 47	3078
TAU132	RGM A	Heavy chain variable region	h5F9.3, h5F9.9, h5F9.25	US20150183871 SEQ ID NO: 53	3079
TAU133	RGM A	Heavy chain variable region	h5F9.4, h5F9.10, h5F9.26	US20150183871 SEQ ID NO: 54	3080
TAU134	RGMa	Heavy chain variable region	AE12-1	US20140023659 SEQ ID NO: 1	3081
TAU135	RGMa	Heavy chain variable region	AE12-20	US20140023659 SEQ ID NO: 107	3082

TAU136	RGMa	Heavy chain variable region	AE12-21	US20140023659 SEQ ID NO: 115	3083
TAU137	RGMa	Heavy chain variable region	AE12-23	US20140023659 SEQ ID NO: 123	3084
TAU138	RGMa	Heavy chain variable region	AE12-24	US20140023659 SEQ ID NO: 131	3085
TAU139	RGMa	Heavy chain variable region	AE12-3	US20140023659 SEQ ID NO: 17	3086
TAU140	RGMa	Heavy chain variable region	AE12-4	US20140023659 SEQ ID NO: 25	3087
TAU141	RGMa	Heavy chain variable region	AE12-5	US20140023659 SEQ ID NO: 33	3088
TAU142	RGMa	Heavy chain variable region	AE12-6	US20140023659 SEQ ID NO: 41	3089
TAU143	RGMa	Heavy chain variable region	AE12-7	US20140023659 SEQ ID NO: 49	3090
TAU144	RGMa	Heavy chain variable region	AE12-8	US20140023659 SEQ ID NO: 57	3091
TAU145	RGMa	Heavy chain variable region	AE12-2	US20140023659 SEQ ID NO: 9	3092
TAU146	RGMa	Heavy chain variable region	AE12-13	US20140023659 SEQ ID NO: 91	3093
TAU147	RGMa	Heavy chain variable region	AE12-15	US20140023659 SEQ ID NO: 99	3094
TAU148	tau	Heavy chain variable region		WO2014100600 SEQ ID NO: 45	3095
TAU149	tau	Heavy chain variable region	NI-105.24B2	US20150252102 SEQ ID NO: 13	3096
TAU150	tau	Heavy chain variable region	NI-105.4A3	US20150252102 SEQ ID NO: 17	3097
TAU151	tau	Heavy chain variable region	NI-105.4E4	US20150252102 SEQ ID NO: 9	3098
TAU152	tau	Heavy chain variable region		WO2013041962 SEQ ID NO: 138	3099
TAU153	tau	Heavy chain variable region		WO2013041962 SEQ ID NO: 139	3100
TAU154	tau	Heavy chain variable region		WO2013041962 SEQ ID NO: 140	3101

TAU155	tau	Heavy chain variable region		WO2013041962 SEQ ID NO: 145	3102
TAU156	tau	Heavy chain variable region		WO2013041962 SEQ ID NO: 147	3103
TAU157	tau	Heavy chain variable region		WO2013041962 SEQ ID NO: 148	3104
TAU158	tau	Heavy chain variable region		WO2014100600 SEQ ID NO: 220	3105
TAU159	tau	Heavy chain variable region	NI-105.17C1	WO2014100600 SEQ ID NO: 44	3106
TAU160	tau	Heavy chain variable region		WO2014100600 SEQ ID NO: 47	3107
TAU161	tau	Heavy chain variable region	NI-105.6C5	WO2014100600 SEQ ID NO: 48	3108
TAU162	tau	Heavy chain variable region	NI-105.29G10	WO2014100600 SEQ ID NO: 50	3109
TAU163	tau	Heavy chain variable region	NI-105.6L9	WO2014100600 SEQ ID NO: 52	3110
TAU164	tau	Heavy chain variable region	NI-105.40E8	WO2014100600 SEQ ID NO: 54	3111
TAU165	tau	Heavy chain variable region	NI-105.48E5	WO2014100600 SEQ ID NO: 56	3112
TAU166	tau	Heavy chain variable region	NI-105.6E3	WO2014100600 SEQ ID NO: 58	3113
TAU167	tau	Heavy chain variable region	NI-105.22E1	WO2014100600 SEQ ID NO: 60	3114
TAU168	tau	Heavy chain variable region	NI-105.26B12	WO2014100600 SEQ ID NO: 62	3115
TAU169	tau	Heavy chain variable region	NI-105.12E12	WO2014100600 SEQ ID NO: 65	3116
TAU170	tau	Heavy chain variable region	NI-105.60E7	WO2014100600 SEQ ID NO: 67	3117
TAU171	tau	Heavy chain variable region	NI-105.14E2	WO2014100600 SEQ ID NO: 69	3118
TAU172	tau	Heavy chain variable region	NI-105.39E2	WO2014100600 SEQ ID NO: 71	3119
TAU173	tau	Heavy chain variable region	NI-105.19C6	WO2014100600 SEQ ID NO: 73	3120

TAU174	tau	Heavy chain variable region		WO2014100600 SEQ ID NO: 75	3121
TAU175	tau	Heavy chain variable region	NI-105.9C4	WO2014100600 SEQ ID NO: 76	3122
TAU176	tau	Heavy chain variable region		US9304138 SEQ ID NO: 1	3123
TAU177	tau	Heavy chain variable region		US9304138 SEQ ID NO: 2	3124
TAU178	tau	Heavy chain variable region		US9304138 SEQ ID NO: 3	3125
TAU179	tau	Heavy chain variable region		US9304138 SEQ ID NO: 4	3126
TAU180	tau	Heavy chain variable region		US9304138 SEQ ID NO: 5	3127
TAU181	tau	Heavy chain variable region		US9304138 SEQ ID NO: 68	3128
TAU182	tau	Heavy chain variable region		US9304138 SEQ ID NO: 76	3129
TAU183	tau	Heavy chain variable region		US9304138 SEQ ID NO: 88	3130
TAU184	tau	Heavy chain variable region		US9304138 SEQ ID NO: 96	3131
TAU185	tau	Heavy chain variable region		US9304138 SEQ ID NO: 104	3132
TAU186	tau	Heavy chain variable region	hACI-36-3A8-Ab1 and hACI-36-2B6-Ab1	US20150175682 SEQ ID NO: 7	3133
TAU187	tau	Heavy chain variable region	hACI-36-3A8-Ab1.v2.	US20150175682 SEQ ID NO: 20	3134
TAU188	tau	Heavy chain variable region	hACI-36-2B6-Ab1.v2	US20150175682 SEQ ID NO: 21	3135
TAU189	tau	Heavy chain variable region	ADx210	US20140161875 SEQ ID NO: 15	3136
TAU190	tau	Heavy chain variable region	ADx210 subpart	US20140161875 SEQ ID NO: 17	3137
TAU191	tau	Heavy chain variable region	ADx215	US20140161875 SEQ ID NO: 25	3138
TAU192	tau	Heavy chain variable region	IPN002 variant 1	US8926974 SEQ ID NO: 36	3139

TAU193	tau	Heavy chain variable region	IPN002 variant 2	US8926974 SEQ ID NO: 37	3140
TAU194	tau	Heavy chain variable region	IPN002 variant 3	US8926974 SEQ ID NO: 38	3141
TAU195	tau	Heavy chain variable region	IPN002 variant 4	US8926974 SEQ ID NO: 39	3142
TAU196	tau	Heavy chain variable region	PT1	US20150307600 SEQ ID NO: 35	3143
TAU197	tau	Heavy chain variable region	PT3	US20150307600 SEQ ID NO: 37	3144
TAU198	tau antigen	Heavy chain variable region	ADx202	WO2015004163 SEQ ID NO: 14	3145
TAU199	tau pS422	Heavy chain variable region	antibody Mab2.10.3	US20110059093 SEQ ID NO: 2	3146
TAU200	tau pS422	Heavy chain variable region	Mab 005	US20110059093 SEQ ID NO: 22	3147
TAU201	tau pS422	Heavy chain variable region	Mab 019	US20110059093 SEQ ID NO: 30	3148
TAU202	tau pS422	Heavy chain variable region	Mab 020	US20110059093 SEQ ID NO: 38	3149
TAU203	tau pS422	Heavy chain variable region	Mab 085	US20110059093 SEQ ID NO: 46	3150
TAU204	tau pS422	Heavy chain variable region	Mab 086	US20110059093 SEQ ID NO: 54	3151
TAU205	tau pS422	Heavy chain variable region	Mab 097	US20110059093 SEQ ID NO: 62	3152
TAU206	tau	Light chain	MC-1		3153
TAU207	tau	Light chain	PHF-1		3154
TAU208	tau	Light chain	IPN002		3155
TAU209	amyloids	Light chain	#118	WO2010012004 SEQ ID NO: 12	3156
TAU210	amyloids	Light chain	#121	WO2010012004 SEQ ID NO: 14	3157
TAU211	amyloids	Light chain	#201	WO2010012004 SEQ ID NO: 15	3158
TAU212	amyloids	Light chain	#204	WO2010012004 SEQ ID NO: 16	3159
TAU213	amyloids	Light chain	#205	WO2010012004 SEQ ID NO: 18	3160
TAU214	NOGO	Light chain	H6L13 FL, H19L13 FL, H20L13 FL, H21L13 FL, H25L13 FL	US20140147435 SEQ ID NO: 35	3161
TAU215	NOGO	Light chain	H16L16 FL, H19L16 FL, H20L16 FL, H21L16 FL,	US20140147435 SEQ ID NO: 38	3162

			H25L16 FL, H18L16 FL		
TAU216	NOGO	Light chain	H16L18 FL, H19L18 FL, H20L18 FL, H21L18 FL, H25L18 FL	US20140147435 SEQ ID NO: 40	3163
TAU217	Nogo receptor-1	Light chain	7.00E+11	US20090215691 SEQ ID NO: 15	3164
TAU218	Nogo receptor-1	Light chain	7.00E+11	US20090215691 SEQ ID NO: 17	3165
TAU219	PrP	Light chain	Ab c-120	WO2014186878 SEQ ID NO: 37	3166
TAU220	PrPC and/or PrPSc	Light chain		US20150166668 SEQ ID NO: 9	3167
TAU221	PrPC and/or PrPSc	Light chain		US8852587 SEQ ID NO: 5	3168
TAU222	tau	Light chain	hACI-36-3A8 Ab1, hACI-36-3A8 Ab1.v2, hACI-36-3A8 Ab1.v3, hACI-36-3A8 Ab1.v4	WO2013151762 SEQ ID NO: 22	3169
TAU223	tau	Light chain	hACI-36-3B8 Ab1, hACI-36-3B8 Ab1.v2, hACI-36-3B8 Ab1.v3, hACI-36-3B8 Ab1.v4	WO2013151762 SEQ ID NO: 23	3170
TAU224	tau	Light chain	IPN001	US8980271 SEQ ID NO: 13	3171
TAU225	tau	Light chain	IPN002	US8980271 SEQ ID NO: 15	3172
TAU226	tau	Light chain	hACI-36-3A8-Ab1 and hACI-36-2B6-Ab1	US20150175682 SEQ ID NO: 18	3173
TAU227	tau	Light chain	hACI-36-3A8-Ab1 (IgG4), hACI-36-3A8-Ab1.v2 (IgG4), hACI-36-3A8-Ab1.v3 (IgG1), and hACI-36-3A8-Ab1.v4 (IgG1 N297G)	US20150175682 SEQ ID NO: 22	3174
TAU228	tau	Light chain	hACI-36-2B6-Ab1 (IgG4), hACI-36-2B6-Ab1.v2 (IgG4), hACI-36-2B6-Ab1.v3 (IgG1), and hACI-36-2B6-Ab1.v4 (IgG1 N297G)	US20150175682 SEQ ID NO: 23	3175
TAU229	tau	Light chain	hACI-36-3A8-Ab1 (IgG4)	US20150175682 SEQ ID NO: 24	3176
TAU230	trk-C	Light chain	2250	US7615383 SEQ ID NO: 49	3177
TAU231	trk-C	Light chain	2253	US7615383 SEQ ID NO: 50	3178
TAU232	trk-C	Light chain	2256	US7615383 SEQ ID NO: 51	3179
TAU233	trk-C	Light chain	6.1.2	US7615383 SEQ ID NO: 52	3180

TAU234	trk-C	Light chain	6.4.1	US7615383 SEQ ID NO: 53	3181
TAU235	trk-C	Light chain	2345	US7615383 SEQ ID NO: 54	3182
TAU236	trk-C	Light chain	2349	US7615383 SEQ ID NO: 55	3183
TAU237	many	Light chain fusion protein		US8053569 SEQ ID NO: 31	3184
TAU238	many	Light chain fusion protein		US8053569 SEQ ID NO: 36	3185
TAU239	NOGO	Light chain humanized construct L11	2A10 construct	WO2007003421 SEQ ID NO: 80	3186
TAU240	NOGO	Light chain humanized construct L13	2A10 construct	WO2007003421 SEQ ID NO: 35	3187
TAU241	NOGO	Light chain humanized construct L14	2A10 construct	WO2007003421 SEQ ID NO: 36	3188
TAU242	NOGO	Light chain humanized construct L15	2A10 construct	WO2007003421 SEQ ID NO: 37	3189
TAU243	NOGO	Light chain humanized construct L16	2A10 construct	WO2007003421 SEQ ID NO: 38	3190
TAU244	NOGO	Light chain humanized construct L17	2A10 construct	WO2007003421 SEQ ID NO: 39	3191
TAU245	NOGO	Light chain humanized construct L18	2A10 construct	WO2007003421 SEQ ID NO: 40	3192
TAU246	NOGO	Light chain humanized construct L6	2A10 construct	WO2007003421 SEQ ID NO: 34	3193
TAU247	RTN4	Light chain IgG4, immunomodulator	Atinumab	US8163285 SEQ ID NO: 25	3194
TAU248	tau	Light chain mature	ch4E4	US20150252102 SEQ ID NO: 21	3195
TAU249	NOGO	Light chain variable humanized construct L11	2A10 construct	WO2007003421 SEQ ID NO: 78	3196
TAU250	NOGO	Light chain variable humanized construct L13	2A10 construct	WO2007003421 SEQ ID NO: 20	3197
TAU251	NOGO	Light chain variable humanized construct L14	2A10 construct	WO2007003421 SEQ ID NO: 21	3198
TAU252	NOGO	Light chain variable humanized construct L15	2A10 construct	WO2007003421 SEQ ID NO: 22	3199
TAU253	NOGO	Light chain variable humanized construct L16	2A10 construct	WO2007003421 SEQ ID NO: 23	3200

TAU254	NOGO	Light chain variable humanized construct L17	2A10 construct	WO2007003421 SEQ ID NO: 24	3201
TAU255	NOGO	Light chain variable humanized construct L18	2A10 construct	WO2007003421 SEQ ID NO: 25	3202
TAU256	NOGO	Light chain variable humanized construct L6	2A10 construct	WO2007003421 SEQ ID NO: 19	3203
TAU257	amyloid oligomers	Light chain variable region	F11G3	US9125846 SEQ ID NO: 12	3204
TAU258	LPG(lysophosphatidylglucoside)	Light chain variable region	#7	US8591902 SEQ ID NO: 17	3205
TAU259	LPG(lysophosphatidylglucoside)	Light chain variable region	#15	US8591902 SEQ ID NO: 7	3206
TAU260	MAG	Light chain variable region		US8071731 SEQ ID NO: 16	3207
TAU261	MAG	Light chain variable region		US8071731 SEQ ID NO: 17	3208
TAU262	MAG	Light chain variable region		US8071731 SEQ ID NO: 18	3209
TAU263	MAG	Light chain variable region		US8071731 SEQ ID NO: 19	3210
TAU264	MAI (myelin associated inhibitor)	Light chain variable region		WO2013158748 SEQ ID NO: 11	3211
TAU265	MAI (myelin associated inhibitor)	Light chain variable region		WO2013158748 SEQ ID NO: 27	3212
TAU266	NMDA	Light chain variable region		EP2805972 SEQ ID NO: 44	3213
TAU267	NOGO	Light chain variable region	H1L6, H5L6, H6L6, H14L6, H15L6, H16L6, H17L6, H18L6, H19L6, H20L6, H21L6, H22L6, H23L6, H24L6, H25L6, H700L6	US20140147435 SEQ ID NO: 19	3214
TAU268	NOGO	Light chain variable region	H1L13, H5L13, H6L13, H14L13, H15L13, H16L13, H17L13, H18L13, H19L13, H20L13, H21L13, H22L13,	US20140147435 SEQ ID NO: 20	3215

			H23L13, H24L13, H25L13, H700L13		
TAU269	NOGO	Light chain variable region	H1L14, H5L14, H6L14, H14L14, H15L14, H16L14, H17L14, H18L14, H19L14, H20L14, H21L14, H22L14, H23L14, H24L14, H25L14, H700L14	US20140147435 SEQ ID NO: 21	3216
TAU270	NOGO	Light chain variable region	H1L15, H5L15, H6L15, H14L15, H15L15, H16L15, H17L15, H18L15, H19L15, H20L15, H21L15, H22L15, H23L15, H24L15, H25L15, H700L15	US20140147435 SEQ ID NO: 22	3217
TAU271	NOGO	Light chain variable region	H1L16, H5L16, H6L16, H14L16, H15L16, H16L16, H17L16, H18L16, H19L16, H20L16, H21L16, H22L16, H23L16, H24L16, H25L16, H700L16	US20140147435 SEQ ID NO: 23	3218
TAU272	NOGO	Light chain variable region	H1L17, H5L17, H6L17, H14L17, H15L17, H16L17, H17L17, H18L17, H19L17, H20L17, H21L17, H22L17, H23L17, H24L17, H25L17, H700L17	US20140147435 SEQ ID NO: 24	3219

TAU273	NOGO	Light chain variable region	H1L18, H5L18, H6L18, H14L18, H15L18, H16L18, H17L18, H18L18, H19L18, H20L18, H21L18, H22L18, H23L18, H24L18, H25L18, H700L18	US20140147435 SEQ ID NO: 25	3220
TAU274	NOGO	Light chain variable region	H5L11, H6L11, H14L11, H15L11, H16L11, H17L11, H18L11, H19L11, H20L11, H21L11, H22L11, H23L11, H24L11, H25L11, H700L11	US20140147435 SEQ ID NO: 78	3221
TAU275	NOGO	Light chain variable region	2A10	US7988964 SEQ ID NO: 40	3222
TAU276	NOGO	Light chain variable region	2C4	US7988964 SEQ ID NO: 41	3223
TAU277	Nogo-66	Light chain variable region	Antibody clone 50	US20140065155 SEQ ID NO: 4	3224
TAU278	Nogo-66	Light chain variable region	Antibody clone 51	US20140065155 SEQ ID NO: 6	3225
TAU279	NogoA/NiG	Light chain variable region	6A3-Ig4	WO2009056509 SEQ ID NO: 25	3226
TAU280	NogoA/NiG	Light chain variable region	6A3-IgG1	WO2009056509 SEQ ID NO: 5	3227
TAU281	PrP	Light chain variable region	Ab c-120	WO2014186878 SEQ ID NO: 39	3228
TAU282	PrPC and/or PrPSc	Light chain variable region		US20150166668 SEQ ID NO: 7	3229
TAU283	RGM A	Light chain variable region	5F9.1-GL, 5F9.1-GL, 5F9.1-GL, 5F9.1-GL, 5F9.1-GL, 5F9.1-GL, 5F9.1-GL, 5F9.1-GL,	US20150183871 SEQ ID NO: 44	3230

			5F9.1-GL, 5F9.1-GL, h5F9.4, h5F9.11, h5F9.12		
TAU284	RGM A	Light chain variable region	5F9.2-GL, 5F9.2-GL, 5F9.2-GL, 5F9.2-GL, 5F9.2-GL, 5F9.2-GL, 5F9.2-GL, 5F9.2-GL, 5F9.2-GL, h5F9.5, h5F9.19, h5F9.20	US20150183871 SEQ ID NO: 45	3231
TAU285	RGM A	Light chain variable region	5F9.3-GL, 5F9.3-GL, 5F9.3-GL, 5F9.3-GL, 5F9.3-GL, 5F9.3-GL, 5F9.3-GL, 5F9.3-GL, 5F9.3-GL, h5F9.6, h5F9.21, h5F9.22	US20150183871 SEQ ID NO: 46	3232
TAU286	RGM A	Light chain variable region	h5F9.5, h5F9.6, h5F9.7, h5F9.8, h5F9.9, h5F9.10	US20150183871 SEQ ID NO: 48	3233
TAU287	RGM A	Light chain variable region	h5F9.11, h5F9.19, h5F9.21	US20150183871 SEQ ID NO: 49	3234
TAU288	RGM A	Light chain variable region	h5F9.12, h5F9.20, h5F9.22, h5F9.23, h5F9.25, h5F9.25, h5F9.26	US20150183871 SEQ ID NO: 50	3235
TAU289	RGM A	Light chain variable region	h5F9.1, h5F9.7, h5F9.23	US20150183871 SEQ ID NO: 51	3236
TAU290	RGM A	Light chain variable region	h5F9.2, h5F9.8, h5F9.25	US20150183871 SEQ ID NO: 52	3237
TAU291	RGMa	Light chain variable region	AE12-15	US20140023659 SEQ ID NO: 103	3238
TAU292	RGMa	Light chain variable region	AE12-20	US20140023659 SEQ ID NO: 111	3239
TAU293	RGMa	Light chain variable region	AE12-21	US20140023659 SEQ ID NO: 119	3240
TAU294	RGMa	Light chain variable region	AE12-23	US20140023659 SEQ ID NO: 127	3241

TAU295	RGMa	Light chain variable region	AE12-2	US20140023659 SEQ ID NO: 13	3242
TAU296	RGMa	Light chain variable region	AE12-24	US20140023659 SEQ ID NO: 135	3243
TAU297	RGMa	Light chain variable region	AE12-3	US20140023659 SEQ ID NO: 21	3244
TAU298	RGMa	Light chain variable region	AE12-4	US20140023659 SEQ ID NO: 29	3245
TAU299	RGMa	Light chain variable region	AE12-5	US20140023659 SEQ ID NO: 37	3246
TAU300	RGMa	Light chain variable region	AE12-6	US20140023659 SEQ ID NO: 45	3247
TAU301	RGMa	Light chain variable region	AE12-1	US20140023659 SEQ ID NO: 5	3248
TAU302	RGMa	Light chain variable region	AE12-7	US20140023659 SEQ ID NO: 53	3249
TAU303	RGMa	Light chain variable region	AE12-8	US20140023659 SEQ ID NO: 61	3250
TAU304	RGMa	Light chain variable region	AE12-13	US20140023659 SEQ ID NO: 95	3251
TAU305	tau	Light chain variable region	NI-105.4E4	US20150252102 SEQ ID NO: 11	3252
TAU306	tau	Light chain variable region	NI-105.24B2	US20150252102 SEQ ID NO: 15	3253
TAU307	tau	Light chain variable region	NI-105.4A3	US20150252102 SEQ ID NO: 19	3254
TAU308	tau	Light chain variable region		WO2013041962 SEQ ID NO: 141	3255
TAU309	tau	Light chain variable region		WO2013041962 SEQ ID NO: 142	3256
TAU310	tau	Light chain variable region		WO2013041962 SEQ ID NO: 143	3257
TAU311	tau	Light chain variable region		WO2013041962 SEQ ID NO: 150	3258
TAU312	tau	Light chain variable region		WO2013041962 SEQ ID NO: 152	3259
TAU313	tau	Light chain variable region		WO2013041962 SEQ ID NO: 153	3260

TAU314	tau	Light chain variable region		WO2014100600 SEQ ID NO: 221	3261
TAU315	tau	Light chain variable region		WO2014100600 SEQ ID NO: 222	3262
TAU316	tau	Light chain variable region	NI-105.17C1	WO2014100600 SEQ ID NO: 46	3263
TAU317	tau	Light chain variable region	NI-105.6C5	WO2014100600 SEQ ID NO: 49	3264
TAU318	tau	Light chain variable region	NI-105.29G10	WO2014100600 SEQ ID NO: 51	3265
TAU319	tau	Light chain variable region	NI-105.6L9	WO2014100600 SEQ ID NO: 53	3266
TAU320	tau	Light chain variable region	NI-105.40E8	WO2014100600 SEQ ID NO: 55	3267
TAU321	tau	Light chain variable region	NI-105.48E5	WO2014100600 SEQ ID NO: 57	3268
TAU322	tau	Light chain variable region	NI-105.6E3	WO2014100600 SEQ ID NO: 59	3269
TAU323	tau	Light chain variable region	NI-105.22E1	WO2014100600 SEQ ID NO: 61	3270
TAU324	tau	Light chain variable region		WO2014100600 SEQ ID NO: 63	3271
TAU325	tau	Light chain variable region	NI-105.26B12	WO2014100600 SEQ ID NO: 64	3272
TAU326	tau	Light chain variable region	NI-105.12E12	WO2014100600 SEQ ID NO: 66	3273
TAU327	tau	Light chain variable region	NI-105.60E7	WO2014100600 SEQ ID NO: 68	3274
TAU328	tau	Light chain variable region	NI-105.14E2	WO2014100600 SEQ ID NO: 70	3275
TAU329	tau	Light chain variable region	NI-105.39E2	WO2014100600 SEQ ID NO: 72	3276
TAU330	tau	Light chain variable region	NI-105.19C6	WO2014100600 SEQ ID NO: 74	3277
TAU331	tau	Light chain variable region		WO2014100600 SEQ ID NO: 77	3278
TAU332	tau	Light chain variable region	NI-105.9C4	WO2014100600 SEQ ID NO: 78	3279

TAU333	tau	Light chain variable region	IPN002 variant 1	US8926974 SEQ ID NO: 40	3280
TAU334	tau	Light chain variable region	IPN002 variant 2	US8926974 SEQ ID NO: 41	3281
TAU335	tau	Light chain variable region	IPN002 variant 3	US8926974 SEQ ID NO: 42	3282
TAU336	tau	Light chain variable region	IPN002 variant 4	US8926974 SEQ ID NO: 43	3283
TAU337	tau	Light chain variable region	PT1	US20150307600 SEQ ID NO: 36	3284
TAU338	tau	Light chain variable region	PT3	US20150307600 SEQ ID NO: 38	3285
TAU339	tau	Light chain variable region		US9304138 SEQ ID NO: 6	3286
TAU340	tau	Light chain variable region		US9304138 SEQ ID NO: 7	3287
TAU341	tau	Light chain variable region		US9304138 SEQ ID NO: 8	3288
TAU342	tau	Light chain variable region		US9304138 SEQ ID NO: 9	3289
TAU343	tau	Light chain variable region		US9304138 SEQ ID NO: 10	3290
TAU344	tau	Light chain variable region		US9304138 SEQ ID NO: 11	3291
TAU345	tau	Light chain variable region		US9304138 SEQ ID NO: 69	3292
TAU346	tau	Light chain variable region		US9304138 SEQ ID NO: 77	3293
TAU347	tau	Light chain variable region		US9304138 SEQ ID NO: 92	3294
TAU348	tau	Light chain variable region		US9304138 SEQ ID NO: 97	3295
TAU349	tau	Light chain variable region		US9304138 SEQ ID NO: 105	3296
TAU350	tau	Light chain variable region		US9304138 SEQ ID NO: 116	3297
TAU351	tau	Light chain variable region		US9304138 SEQ ID NO: 118	3298

TAU352	tau	Light chain variable region	hACI-36-3A8-Ab1	US20150175682 SEQ ID NO: 8	3299
TAU353	tau	Light chain variable region	hACI-36-2B6-Ab1	US20150175682 SEQ ID NO: 9	3300
TAU354	tau	Light chain variable region	ADx210	US20140161875 SEQ ID NO: 16	3301
TAU355	tau	Light chain variable region	ADx210 isoform	US20140161875 SEQ ID NO: 18	3302
TAU356	tau	Light chain variable region	ADx215	US20140161875 SEQ ID NO: 26	3303
TAU357	tau antigen	Light chain variable region	ADx202	WO2015004163 SEQ ID NO: 9	3304
TAU358	tau pS422	Light chain variable region	antibody Mab2.10.3	US20110059093 SEQ ID NO: 1	3305
TAU359	tau pS422	Light chain variable region	Mab 005	US20110059093 SEQ ID NO: 26	3306
TAU360	tau pS422	Light chain variable region	Mab 019	US20110059093 SEQ ID NO: 34	3307
TAU361	tau pS422	Light chain variable region	Mab 020	US20110059093 SEQ ID NO: 42	3308
TAU362	tau pS422	Light chain variable region	Mab 085	US20110059093 SEQ ID NO: 50	3309
TAU363	tau pS422	Light chain variable region	Mab 086	US20110059093 SEQ ID NO: 58	3310
TAU364	tau pS422	Light chain variable region	Mab 097	US20110059093 SEQ ID NO: 66	3311
TAU365	PrPC and/or PrPSc	scFv		US8852587 SEQ ID NO: 6	3312
TAU366	amyloid proteins		M13 g3p	US20150376239 SEQ ID NO: 1	3313
TAU367	amyloid proteins		Construct 5	US20150376239 SEQ ID NO: 11	3314
TAU368	amyloid proteins		Construct 6	US20150376239 SEQ ID NO: 13	3315
TAU369	amyloid proteins		fd N2	US20150376239 SEQ ID NO: 14	3316
TAU370	amyloid proteins		f1 N2	US20150376239 SEQ ID NO: 15	3317
TAU371	amyloid proteins		M13 N2	US20150376239 SEQ ID NO: 16	3318
TAU372	amyloid proteins		Ike N2	US20150376239 SEQ ID NO: 17	3319
TAU373	amyloid proteins		12-2 N2	US20150376239 SEQ ID NO: 18	3320
TAU374	amyloid proteins		If1 N2	US20150376239 SEQ ID NO: 19	3321

TAU375	amyloid proteins		fd g3p	US20150376239 SEQ ID NO: 2	3322
TAU376	amyloid proteins		Construct 3	US20150376239 SEQ ID NO: 20	3323
TAU377	amyloid proteins		Construct 3m g3p portion	US20150376239 SEQ ID NO: 24	3324
TAU378	amyloid proteins		If1 g3p	US20150376239 SEQ ID NO: 29	3325
TAU379	amyloid proteins		f1 g3p	US20150376239 SEQ ID NO: 3	3326
TAU380	amyloid proteins		fd g3p	US20150376239 SEQ ID NO: 30	3327
TAU381	amyloid proteins		Construct 8, rs-g3p (If1-N1N2)-hIgG1-Fc	US20150376239 SEQ ID NO: 31	3328
TAU382	amyloid proteins		consensus sequence of M13 g3p, fd g3p, f1 g3p	US20150376239 SEQ ID NO: 4	3329
TAU383	amyloid proteins		I2-2 g3p	US20150376239 SEQ ID NO: 5	3330
TAU384	amyloid proteins		Ike g3p	US20150376239 SEQ ID NO: 6	3331
TAU385	amyloid proteins		consensus sequence of I2-2 g3p, Ike g3p	US20150376239 SEQ ID NO: 7	3332
TAU386	amyloid proteins		If1 g3p	US20150376239 SEQ ID NO: 8	3333
TAU387	amyloid proteins		Construct 4	US20150376239 SEQ ID NO: 9	3334
TAU388	PrP		ICSM181c	US20140294844 SEQ ID NO: 6	3335
TAU389	PrPC and/or PrPSc			US8852587 SEQ ID NO: 3	3336
TAU390	tau			US20140302046 SEQ ID NO: 103	3337
TAU391	B-amyloid	Heavy chain variable region antibody	1B 1-40	US20100323905 SEQ ID NO: 92	3338
TAU392	B-amyloid	Heavy chain variable region antibody	3A 1-42	US20100323905 SEQ ID NO: 94	3339
TAU393	B-amyloid	Heavy chain variable region antibody	FC5	US20100323905 SEQ ID NO: 96	3340
TAU394	Tau	Chain A, Structure Of Tau Peptide In Complex With Tau5 Antibody Fab Fragment		Cehlar, O. et al., "Structure Of Tau Peptide In Complex With Tau5 Antib Fragment", unpublished, 4TQE_A	3341
TAU395	Tau	Chain A and B, Structure Of The Anti-ptau Fab (pt231/ps235_1) In		Shih, H.H., et al., An ultra-specific avian antibody to phosphorylated tau protein reveals a unique mechanism for phosphoepitope recognition", J. Biol. Chem. 287 (53), 44425-44434 (2012),	3342

		Complex With Phosphoepitope Pt231/ps235		Accession number 4GLR_A and 4GLR_B	
TAU396	Tau	Chain P, Anti-tau At8 Fab With Doubly Phosphorylated Tau Peptide	At8 Fab	Malia, T.J. et al, "Epitope mapping and structural basis for the recognition of phosphorylated tau by the anti-tau antibody AT8", Proteins 84 (4), 427-434 (2016), Accession number 5E2V_P	3343
TAU397	Tau	Chain P, Anti-tau At8 Fab With Triply Phosphorylated Tau Peptide	At8 Fab	Malia, T.J. et al, "Epitope mapping and structural basis for the recognition of phosphorylated tau by the anti-tau antibody AT8", Proteins 84 (4), 427-434 (2016), Accession number 5E2W_P	3344
TAU398	Tau	Chain P, X-ray Structure Of The Fab Fragment Of The Anti Tau Antibody Rb86 In Complex With The Phosphorylated Tau Peptide (416-430)	Rb86	Bujotzek, A. et al, "VH-VL orientation prediction for antibody humanization candidate selection: A case study", MAbs 8 (2), 288-305 (2016), Accession number 5DMG_P, 5DMG_X, 5DMG_Z	3345
TAU399	Tau	Heavy chain	cDC8E8 VH	WO2016079597 SEQ ID NO: 9; US20150050215 SEQ ID NO: 138	3346
TAU400	Tau	Heavy chain	RHA - IgG1	WO2016079597 SEQ ID NO: 28	3347
TAU401	Tau	Heavy chain	RHB - IgG1	WO2016079597 SEQ ID NO: 29	3348
TAU402	Tau	Heavy chain	RHC - IgG1	WO2016079597 SEQ ID NO: 30	3349
TAU403	Tau	Heavy chain	RHD - IgG1	WO2016079597 SEQ ID NO: 31	3350
TAU404	Tau	Heavy chain	RHE - IgG1	WO2016079597 SEQ ID NO: 32	3351
TAU405	Tau	Heavy chain	RHF - IgG1	WO2016079597 SEQ ID NO: 33	3352
TAU406	Tau	Heavy chain	RHG - IgG1	WO2016079597 SEQ ID NO: 34	3353
TAU407	Tau	Heavy chain	RHH - IgG1	WO2016079597 SEQ ID NO: 35	3354
TAU408	Tau	Heavy chain	RHI - IgG1	WO2016079597 SEQ ID NO: 36	3355
TAU409	Tau	Heavy chain	RHJ - IgG1	WO2016079597 SEQ ID NO: 37	3356
TAU410	Tau	Heavy chain	RHK - IgG1	WO2016079597 SEQ ID NO: 38	3357
TAU411	Tau	Heavy chain	RHL - IgG1	WO2016079597 SEQ ID NO: 39	3358
TAU412	Tau	Heavy chain	RHM - IgG1	WO2016079597 SEQ ID NO: 40	3359
TAU413	Tau	Heavy chain	cDC8E8 - IgG1	WO2016079597 SEQ ID NO: 41	3360
TAU414	Tau	Heavy chain	mouse DC8E8 - IgG1	WO2016079597 SEQ ID NO: 42	3361
TAU415	Tau	Heavy chain	RHA - IgG4	WO2016079597 SEQ ID NO: 43	3362
TAU416	Tau	Heavy chain	RHB - IgG4	WO2016079597 SEQ ID NO: 44	3363
TAU417	Tau	Heavy chain	RHC - IgG4	WO2016079597 SEQ ID NO: 45	3364
TAU418	Tau	Heavy chain	RHD - IgG4	WO2016079597 SEQ ID NO: 46	3365

TAU419	Tau	Heavy chain	RHE - IgG4	WO2016079597 SEQ ID NO: 47	3366
TAU420	Tau	Heavy chain	RHF - IgG4	WO2016079597 SEQ ID NO: 48	3367
TAU421	Tau	Heavy chain	RHG - IgG4	WO2016079597 SEQ ID NO: 49	3368
TAU422	Tau	Heavy chain	RHH - IgG4	WO2016079597 SEQ ID NO: 50	3369
TAU423	Tau	Heavy chain	RHI - IgG4	WO2016079597 SEQ ID NO: 51	3370
TAU424	Tau	Heavy chain	RHJ - IgG4	WO2016079597 SEQ ID NO: 52	3371
TAU425	Tau	Heavy chain	RHK - IgG4	WO2016079597 SEQ ID NO: 53	3372
TAU426	Tau	Heavy chain	RHL - IgG4	WO2016079597 SEQ ID NO: 54	3373
TAU427	Tau	Heavy chain	RHM - IgG4	WO2016079597 SEQ ID NO: 55	3374
TAU428	Tau	Heavy chain	cDC8E8 - IgG4	WO2016079597 SEQ ID NO: 56	3375
TAU429	Tau	Heavy chain	DC8E8	WO2016079597 SEQ ID NO: 90	3376
TAU430	Tau	Heavy chain	cDC8E8	WO2016079597 SEQ ID NO: 92	3377
TAU431	Tau	Heavy chain	OptiDC8E8	WO2016079597 SEQ ID NO: 94	3378
TAU432	Tau	Heavy chain	RHA	WO2016079597 SEQ ID NO: 96	3379
TAU433	Tau	Heavy chain	RHB	WO2016079597 SEQ ID NO: 97	3380
TAU434	Tau	Heavy chain	RHC	WO2016079597 SEQ ID NO: 98	3381
TAU435	Tau	Heavy chain	RHD	WO2016079597 SEQ ID NO: 99	3382
TAU436	Tau	Heavy chain	RHE	WO2016079597 SEQ ID NO: 100	3383
TAU437	Tau	Heavy chain	RHF	WO2016079597 SEQ ID NO: 101	3384
TAU438	Tau	Heavy chain	RHG	WO2016079597 SEQ ID NO: 102	3385
TAU439	Tau	Heavy chain	RHH	WO2016079597 SEQ ID NO: 103	3386
TAU440	Tau	Heavy chain	RHI	WO2016079597 SEQ ID NO: 104	3387
TAU441	Tau	Heavy chain	RHJ	WO2016079597 SEQ ID NO: 105	3388
TAU442	Tau	Heavy chain	RHK	WO2016079597 SEQ ID NO: 106	3389
TAU443	Tau	Heavy chain	RHL	WO2016079597 SEQ ID NO: 107	3390
TAU444	Tau	Heavy chain	RHM	WO2016079597 SEQ ID NO: 108	3391
TAU445	Tau	Heavy chain	RHA - IgG1	WO2016079597 SEQ ID NO: 111	3392
TAU446	Tau	Heavy chain	RHB - IgG1	WO2016079597 SEQ ID NO: 112	3393
TAU447	Tau	Heavy chain	RHC - IgG1	WO2016079597 SEQ ID NO: 113	3394
TAU448	Tau	Heavy chain	RHD - IgG1	WO2016079597 SEQ ID NO: 114	3395
TAU449	Tau	Heavy chain	RHE - IgG1	WO2016079597 SEQ ID NO: 115	3396
TAU450	Tau	Heavy chain	RHF - IgG1	WO2016079597 SEQ ID NO: 116	3397
TAU451	Tau	Heavy chain	RHG - IgG1	WO2016079597 SEQ ID NO: 117	3398
TAU452	Tau	Heavy chain	RHH - IgG1	WO2016079597 SEQ ID NO: 118	3399
TAU453	Tau	Heavy chain	RHI - IgG1	WO2016079597 SEQ ID NO: 119	3400
TAU454	Tau	Heavy chain	RHJ - IgG1	WO2016079597 SEQ ID NO: 120	3401
TAU455	Tau	Heavy chain	RHK - IgG1	WO2016079597 SEQ ID NO: 121	3402
TAU456	Tau	Heavy chain	RHL - IgG1	WO2016079597 SEQ ID NO: 122	3403
TAU457	Tau	Heavy chain	RHM - IgG1	WO2016079597 SEQ ID NO: 123	3404
TAU458	Tau	Heavy chain	cDC8E8 - IgG1	WO2016079597 SEQ ID NO: 124	3405
TAU459	Tau	Heavy chain	mouse DC8E8 - IgG1	WO2016079597 SEQ ID NO: 125	3406
TAU460	Tau	Heavy chain	codon opt mouse DC8E8	WO2016079597 SEQ ID NO: 126	3407
TAU461	Tau	Heavy chain	RHA - IgG4	WO2016079597 SEQ ID NO: 127	3408

TAU462	Tau	Heavy chain	RHB - IgG4	WO2016079597 SEQ ID NO: 128	3409
TAU463	Tau	Heavy chain	RHC - IgG4	WO2016079597 SEQ ID NO: 129	3410
TAU464	Tau	Heavy chain	RHD - IgG4	WO2016079597 SEQ ID NO: 130	3411
TAU465	Tau	Heavy chain	RHE - IgG4	WO2016079597 SEQ ID NO: 131	3412
TAU466	Tau	Heavy chain	RHF - IgG4	WO2016079597 SEQ ID NO: 132	3413
TAU467	Tau	Heavy chain	RHG - IgG4	WO2016079597 SEQ ID NO: 133	3414
TAU468	Tau	Heavy chain	RHH - IgG4	WO2016079597 SEQ ID NO: 134	3415
TAU469	Tau	Heavy chain	RHI - IgG4	WO2016079597 SEQ ID NO: 135	3416
TAU470	Tau	Heavy chain	RHJ - IgG4	WO2016079597 SEQ ID NO: 136	3417
TAU471	Tau	Heavy chain	RHK - IgG4	WO2016079597 SEQ ID NO: 137	3418
TAU472	Tau	Heavy chain	RHL - IgG4	WO2016079597 SEQ ID NO: 138	3419
TAU473	Tau	Heavy chain	RHM - IgG4	WO2016079597 SEQ ID NO: 139	3420
TAU474	Tau	Heavy chain	cDC8E8 - IgG4	WO2016079597 SEQ ID NO: 140	3421
TAU475	Tau	Heavy chain		US8697076 SEQ ID NO: 12	3422
TAU476	Tau	Heavy chain	5202.4	US20160024193 SEQ ID NO: 63	3423
TAU477	Tau	Heavy chain		US20160031977 SEQ ID NO: 22	3424
TAU478	Tau	Heavy chain		US20160031977 SEQ ID NO: 24	3425
TAU479	Tau	Heavy chain		US20160031977 SEQ ID NO: 26	3426
TAU480	Tau	heavy chain	ch4A3-mIgG1-Agly	US20150344553 SEQ ID NO: 213	3427
TAU481	Tau	heavy chain	ch4E4(N30Q)-mIgG1-Agly	US20150344553 SEQ ID NO: 214	3428
TAU482	Tau	heavy chain	ch6C5-mIgG1-Agly	US20150344553 SEQ ID NO: 215	3429
TAU483	Tau	heavy chain	ch17C1-mIgG1-Agly	US20150344553 SEQ ID NO: 216	3430
TAU484	Tau	Heavy chain	human NI-105.40E8(R104W)-hIgG1	US20150344553 SEQ ID NO: 218	3431
TAU485	Tau	Heavy chain	NI-105.4E4(N30Q)	US20150344553 SEQ ID NO: 43; US8940272 SEQ ID NO: 93	3432
TAU486	Tau	Heavy chain		US20150050215 SEQ ID NO: 140	3433
TAU487	Tau	Heavy chain		US20150050215 SEQ ID NO: 142	3434
TAU488	Tau	Heavy chain	pT231/pS235	WO2014016737 SEQ ID NO: 70	3435
TAU489	Tau	heavy chain (mouse IgG2a)	ch40E8(R104W)	US20150344553 SEQ ID NO: 208	3436
TAU490	Tau	heavy chain (mouse IgG2a)	ch17C1	US20150344553 SEQ ID NO: 203	3437
TAU491	Tau	heavy chain (mouse IgG2a)	ch6C5	US20150344553 SEQ ID NO: 205	3438
TAU492	Tau	heavy chain (mouse IgG2a)	ch40E8	US20150344553 SEQ ID NO: 207	3439
TAU493	Tau	heavy chain (mouse IgG2a)	ch6E3	US20150344553 SEQ ID NO: 210	3440
TAU494	Tau	heavy chain constant region		WO2016079597 SEQ ID NO: 172	3441

TAU495	Tau	heavy chain constant region		WO2016079597 SEQ ID NO: 173	3442
TAU496	Tau	Heavy chain constant region, IgGI		WO2015197823 SEQ ID NO: 83	3443
TAU497	Tau	Heavy chain mature (mouse IgG2a)	ch4E4(N30Q)	US8940272 SEQ ID NO: 22	3444
TAU498	Tau	Heavy chain mature (mouse IgG2a)	ch4E4	US8940272 SEQ ID NO: 20	3445
TAU499	Tau	Heavy chain mature (mouse IgG2a)	ch4E4	US20150344553 SEQ ID NO: 20	3446
TAU500	Tau	Heavy chain mature (monse IgG2a)	ch4E4(N30Q)	US20150344553 SEQ ID NO: 22	3447
TAU501	Tau	Heavy chain variable	NI-105.4A3-VH	US20150344553 SEQ ID NO: 17; US8940272 SEQ ID NO: 17	3448
TAU502	Tau	Heavy chain variable	NI-105.24B2-VH	US20150344553 SEQ ID NO: 13; US8940272 SEQ ID NO: 13	3449
TAU503	Tau	Heavy chain variable	NI-105.4E4-VH	US20150344553 SEQ ID NO: 9; US8940272 SEQ ID NO: 9	3450
TAU504	Tau	Heavy chain variable		US20150307600 SEQ ID NO: 35	3451
TAU505	Tau	Heavy chain variable		US20150307600 SEQ ID NO: 37	3452
TAU506	Tau	Heavy chain variable region	RHA	WO2016079597 SEQ ID NO: 13	3453
TAU507	Tau	Heavy chain variable region	RHB	WO2016079597 SEQ ID NO: 14	3454
TAU508	Tau	Heavy chain variable region	RHC	WO2016079597 SEQ ID NO: 15	3455
TAU509	Tau	Heavy chain variable region	RHD	WO2016079597 SEQ ID NO: 16	3456
TAU510	Tau	Heavy chain variable region	RHE	WO2016079597 SEQ ID NO: 17	3457
TAU511	Tau	Heavy chain variable region	RHF	WO2016079597 SEQ ID NO: 18	3458
TAU512	Tau	Heavy chain variable region	RHG	WO2016079597 SEQ ID NO: 19	3459
TAU513	Tau	Heavy chain variable region	RHH	WO2016079597 SEQ ID NO: 20	3460
TAU514	Tau	Heavy chain variable region	RHI	WO2016079597 SEQ ID NO: 21	3461

TAU515	Tau	Heavy chain variable region	RHJ	WO2016079597 SEQ ID NO: 22	3462
TAU516	Tau	Heavy chain variable region	RHK	WO2016079597 SEQ ID NO: 23	3463
TAU517	Tau	Heavy chain variable region	RHL	WO2016079597 SEQ ID NO: 24	3464
TAU518	Tau	Heavy chain variable region	RHM	WO2016079597 SEQ ID NO: 25	3465
TAU519	Tau	Heavy chain variable region		US8697076 SEQ ID NO: 7	3466
TAU520	Tau	Heavy chain variable region		US20160024193 SEQ ID NO: 58 and 62	3467
TAU521	Tau	Heavy chain variable region	16B5	US20160031976 SEQ ID NO: 10	3468
TAU522	Tau	Heavy chain variable region	NI-105.17C1	US20150344553 SEQ ID NO: 45	3469
TAU523	Tau	Heavy chain variable region	NI-105.6C5	US20150344553 SEQ ID NO: 48	3470
TAU524	Tau	Heavy chain variable region	M-105.29G10	US20150344553 SEQ ID NO: 50	3471
TAU525	Tau	Heavy chain variable region	NI-105.6L9	US20150344553 SEQ ID NO: 52	3472
TAU526	Tau	Heavy chain variable region	NI-105.40E8	US20150344553 SEQ ID NO: 54	3473
TAU527	Tau	Heavy chain variable region	NI-105.40E8 R104W	US20150344553 SEQ ID NO: 220	3474
TAU528	Tau	Heavy chain variable region	NI-105.48E5	US20150344553 SEQ ID NO: 56	3475
TAU529	Tau	Heavy chain variable region	NI-105.6E3	US20150344553 SEQ ID NO: 58	3476
TAU530	Tau	Heavy chain variable region	NI-105.22E1	US20150344553 SEQ ID NO: 60	3477
TAU531	Tau	Heavy chain variable region	NI-105.26B12	US20150344553 SEQ ID NO: 62	3478
TAU532	Tau	Heavy chain variable region	NI-105.12E12	US20150344553 SEQ ID NO: 65	3479
TAU533	Tau	Heavy chain variable region	NI-105.60E7	US20150344553 SEQ ID NO: 67	3480

TAU534	Tau	Heavy chain variable region	NI-105.14E2	US20150344553 SEQ ID NO: 69	3481
TAU535	Tau	Heavy chain variable region	NI-105.39E2	US20150344553 SEQ ID NO: 71	3482
TAU536	Tau	Heavy chain variable region	NI-105.19C6	US20150344553 SEQ ID NO: 73	3483
TAU537	Tau	Heavy chain variable region	NI-105.9C4	US20150344553 SEQ ID NO: 76	3484
TAU538	Tau	Heavy chain variable region	19.3	US20150320860 SEQ ID NO: 7	3485
TAU539	Tau	Heavy chain variable region	3-66	US20150320860 SEQ ID NO: 8	3486
TAU540	Tau	Heavy chain variable region		US20150253341 SEQ ID NO: 37	3487
TAU541	Tau	Heavy chain variable region	NI-101.10	US20150147343 SEQ ID NO: 4	3488
TAU542	Tau	Heavy chain variable region	NI-101.11	US20150147343 SEQ ID NO: 6	3489
TAU543	Tau	Heavy chain variable region	NI-101.12	US20150147343 SEQ ID NO: 10	3490
TAU544	Tau	Heavy chain variable region	NI-101.13; NI-101.13A; NI-101.13B	US20150147343 SEQ ID NO: 14, 42, 43	3491
TAU545	Tau	Heavy chain variable region	NI-101.12F6A	US20150147343 SEQ ID NO: 39	3492
TAU546	Tau	Heavy chain variable region	Ta1501	US20150183854 SEQ ID NO: 18	3493
TAU547	Tau	Heavy chain variable region	Ta1502	US20150183854 SEQ ID NO: 19	3494
TAU548	Tau	Heavy chain variable region	Ta1505	US20150183854 SEQ ID NO: 20	3495
TAU549	Tau	Heavy chain variable region	Ta1506	US20150183854 SEQ ID NO: 21	3496
TAU550	Tau	Heavy chain variable region	Ta1507	US20150183854 SEQ ID NO: 22	3497
TAU551	Tau	Heavy chain variable region	Ta1508	US20150183854 SEQ ID NO: 23	3498
TAU552	Tau	Heavy chain variable region	Ta1509	US20150183854 SEQ ID NO: 24	3499

TAU553	Tau	Heavy chain variable region		US20150050215 SEQ ID NO: 145	3500
TAU554	Tau	Heavy chain variable region		US20150050215 SEQ ID NO: 147	3501
TAU555	Tau	Heavy chain variable region		US20150050215 SEQ ID NO: 148	3502
TAU556	Tau	Heavy chain variable region		US8980270 SEQ ID NO: 14	3503
TAU557	Tau	Heavy chain variable region		US8980270 SEQ ID NO: 16	3504
TAU558	Tau	Heavy chain variable region		US20150183855 SEQ ID NO: 15; WO2016126993 SEQ ID NO: 15	3505
TAU559	Tau	Heavy chain variable region	CBTAU-7.1	WO2015197823 SEQ ID NO: 87	3506
TAU560	Tau	Heavy chain variable region	CBTAU-8.1	WO2015197823 SEQ ID NO: 91	3507
TAU561	Tau	Heavy chain variable region	CBTAU- 16.1	WO2015197823 SEQ ID NO: 95	3508
TAU562	Tau	Heavy chain variable region	CBTAU- 18.1	WO2015197823 SEQ ID NO: 99	3509
TAU563	Tau	Heavy chain variable region	CBTAU-20.1	WO2015197823 SEQ ID NO: 103	3510
TAU564	Tau	Heavy chain variable region	CBTAU-22.1	WO2015197823 SEQ ID NO: 107	3511
TAU565	Tau	Heavy chain variable region	CBTAU-24.1	WO2015197823 SEQ ID NO: 111	3512
TAU566	Tau	Heavy chain variable region	CBTAU-27.1	WO2015197823 SEQ ID NO: 115	3513
TAU567	Tau	Heavy chain variable region	CBTAU 28.1	WO2015197823 SEQ ID NO: 119	3514
TAU568	Tau	Heavy chain variable region	CBTAU -41.1	WO2015197823 SEQ ID NO: 123	3515
TAU569	Tau	Heavy chain variable region	CBTAU -41.2	WO2015197823 SEQ ID NO: 127	3516
TAU570	Tau	Heavy chain variable region	CBTAU -42.1	WO2015197823 SEQ ID NO: 131	3517
TAU571	Tau	Heavy chain variable region	CBTAU 43.1	WO2015197823 SEQ ID NO: 135	3518

TAU572	Tau	Heavy chain variable region	CBTAU 44.1	WO2015197823 SEQ ID NO: 139	3519
TAU573	Tau	Heavy chain variable region	CBTAU 45.1	WO2015197823 SEQ ID NO: 143	3520
TAU574	Tau	Heavy chain variable region	CBTAU 46.1	WO2015197823 SEQ ID NO: 147	3521
TAU575	Tau	Heavy chain variable region	CBTAU 47.1	WO2015197823 SEQ ID NO: 151	3522
TAU576	Tau	Heavy chain variable region	CBTAU 47.2	WO2015197823 SEQ ID NO: 155	3523
TAU577	Tau	Heavy chain variable region	CBTAU 49.1	WO2015197823 SEQ ID NO: 159	3524
TAU578	Tau	Heavy chain variable region	Native 7.1	WO2015197823 SEQ ID NO: 257	3525
TAU579	Tau	Heavy chain variable region	Native 8.1	WO2015197823 SEQ ID NO: 261	3526
TAU580	Tau	Heavy chain variable region	Native 16.1	WO2015197823 SEQ ID NO: 265	3527
TAU581	Tau	Heavy chain variable region	Native 18.1	WO2015197823 SEQ ID NO: 269	3528
TAU582	Tau	Heavy chain variable region	Native 20.1	WO2015197823 SEQ ID NO: 272	3529
TAU583	Tau	Heavy chain variable region	Native 22.1	WO2015197823 SEQ ID NO: 275	3530
TAU584	Tau	Heavy chain variable region	Native 24.1	WO2015197823 SEQ ID NO: 279	3531
TAU585	Tau	Heavy chain variable region	Native 27.1	WO2015197823 SEQ ID NO: 282	3532
TAU586	Tau	Heavy chain variable region	Native 28.1	WO2015197823 SEQ ID NO: 284	3533
TAU587	Tau	Heavy chain variable region	Native 41.1; Native 41.2	WO2015197823 SEQ ID NO: 287, 289	3534
TAU588	Tau	Heavy chain variable region	Native 42.1	WO2015197823 SEQ ID NO: 292	3535
TAU589	Tau	Heavy chain variable region	Native 43.1	WO2015197823 SEQ ID NO: 295	3536
TAU590	Tau	Heavy chain variable region	Native 44.1	WO2015197823 SEQ ID NO: 298	3537

TAU591	Tau	Heavy chain variable region	Native 45.1	WO2015197823 SEQ ID NO: 302	3538
TAU592	Tau	Heavy chain variable region	Native 46.1	WO2015197823 SEQ ID NO: 306	3539
TAU593	Tau	Heavy chain variable region	Native 47.1	WO2015197823 SEQ ID NO: 309	3540
TAU594	Tau	Heavy chain variable region	Native 47.2	WO2015197823 SEQ ID NO: 311	3541
TAU595	Tau	Heavy chain variable region	Native 49.1	WO2015197823 SEQ ID NO: 313	3542
TAU596	Tau	Heavy chain variable region	6B2G12; scFv235	WO2016007414 SEQ ID NO: 9 and 11	3543
TAU597	Tau	Heavy chain variable region		WO2015120364 SEQ ID NO: 30	3544
TAU598	Tau	Heavy chain variable region		WO2015120364 SEQ ID NO: 42	3545
TAU599	Tau	Heavy chain variable region	pT231/pS235_1; pT231/pS235_2	WO2014016737 SEQ ID NO: 15 and 17	3546
TAU600	Tau	Heavy chain variable region	pT212/pS214_1	WO2014016737 SEQ ID NO: 19	3547
TAU601	Tau	Heavy chain variable region	pT212/pS214_2	WO2014016737 SEQ ID NO: 21	3548
TAU602	Tau	Heavy chain variable region	pS396/pS404_1	WO2014016737 SEQ ID NO: 23	3549
TAU603	Tau	Heavy chain variable region	pS396/pS404_2	WO2014016737 SEQ ID NO: 25	3550
TAU604	Tau	Heavy chain variable region	2H9	WO2014096321 SEQ ID NO: 11	3551
TAU605	Tau	Heavy chain variable region		WO2015122922 SEQ ID NO: 16 and 24	3552
TAU606	Tau	Heavy chain variable region		WO2015122922 SEQ ID NO: 32	3553
TAU607	Tau	Heavy chain variable region		WO2015122922 SEQ ID NO: 40	3554
TAU608	Tau	Heavy chain variable region		WO2015122922 SEQ ID NO: 48	3555
TAU609	Tau	Heavy chain variable region		WO2015122922 SEQ ID NO: 56	3556

TAU610	Tau	Heavy chain variable region		WO2015122922 SEQ ID NO: 64	3557
TAU611	Tau	Heavy chain variable region		WO2015122922 SEQ ID NO: 72	3558
TAU612	Tau	Heavy chain variable region fused with a human IgG2 heavy chain constant region		US20150320860 SEQ ID NO: 34	3559
TAU613	Tau	Heavy chain variable region, before germlining	NI-105.17C1	US20150344553 SEQ ID NO: 44	3560
TAU614	Tau	Heavy chain variable region, before germlining	NI-105.6C5	US20150344553 SEQ ID NO: 47	3561
TAU615	Tau	Heavy chain variable region, before germlining	NI-105.26B12	US20150344553 SEQ ID NO: 63	3562
TAU616	Tau	Heavy chain variable region, before germlining	NI-105.9C4	US20150344553 SEQ ID NO: 75	3563
TAU617	Tau	Heavy chain variable region, humanized	variant 1-VH32	US20150175685 SEQ ID NO: 19; WO2015197735 SEQ ID NO: 19	3564
TAU618	Tau	Heavy chain variable region, humanized	variant 2-VH20	US20150175685 SEQ ID NO: 20; WO2015197735 SEQ ID NO: 20	3565
TAU619	Tau	Heavy chain variable region, humanized	IPN002 VH variant 1	US8980270 SEQ ID NO: 36	3566
TAU620	Tau	Heavy chain variable region, humanized	IPN002 VH variant 2	US8980270 SEQ ID NO: 37	3567
TAU621	Tau	Heavy chain variable region, humanized	IPN002 VH variant 3	US8980270 SEQ ID NO: 38	3568
TAU622	Tau	Heavy chain variable region, humanized	IPN002 VH variant 4	US8980270 SEQ ID NO: 39	3569
TAU623	Tau	Heavy chain, human Ig	BACO2002.1	US20160031976 SEQ ID NO: 14	3570
TAU624	Tau	Heavy chain, human IgG1 constant region		US20160031976 SEQ ID NO: 29	3571

TAU625	Tau	Heavy chain, IgG1	TAM_1, TAM_2, TAM_3, TAM_4, TAM_5, TAM_6, TAM_7, TAM_8, TAM_9, TAM_10, TAM_11, TAM_12, TAM_13, TAM_14, TAM_15, TAM_16, TAM_17, TAM_18, TAM_19, TAM_20, TAM_21, TAM_22, TAM_23	US20160024193 SEQ ID NO: 87	3572
TAU626	Tau	Heavy chain, IgG1 N297G	TAM_1, TAM_2, TAM_3, TAM_4, TAM_5, TAM_6, TAM_7, TAM_8, TAM_9, TAM_10, TAM_11, TAM_12, TAM_13, TAM_14, TAM_15, TAM_16, TAM_17, TAM_18, TAM_19, TAM_20, TAM_21, TAM_22, TAM_23	US20160024193 SEQ ID NO: 88	3573
TAU627	Tau	Heavy chain, IgG4 isotypes	TAM_1, TAM_2, TAM_3, TAM_4, TAM_5, TAM_6, TAM_7, TAM_8, TAM_9, TAM_10, TAM_11, TAM_12, TAM_13, TAM_14,	US20160024193 SEQ ID NO: 86	3574

			TAM_15, TAM_16, TAM_17, TAM_18, TAM_19, TAM_20, TAM_21, TAM_22, TAM_23		
TAU628	Tau	Heavy chain, mature		US20160031976 SEQ ID NO: 15	3575
TAU629	Tau	heavy-chain antibody; camelid	Tau-A2-SH	WO2015114538 SEQ ID NO: 14	3576
TAU630	Tau	heavy-chain antibody; Camelid	TauA2var-SH	WO2015114538 SEQ ID NO: 17	3577
TAU631	Tau	heavy-chain antibody; Camelid	Tau-A2 variant	WO2015114538 SEQ ID NO: 15	3578
TAU632	Tau	heavy-chain antibody; Camelid	Tau-A2 variant	WO2015114538 SEQ ID NO: 16	3579
TAU633	Tau	Light chain	cDC8E8 VK	US20150050215 SEQ ID NO: 141; WO2016079597 SEQ ID NO: 10	3580
TAU634	Tau	Light chain	RKA	WO2016079597 SEQ ID NO: 57	3581
TAU635	Tau	Light chain	cDC8E8	WO2016079597 SEQ ID NO: 59	3582
TAU636	Tau	Light chain	OptiDC8E8	WO2016079597 SEQ ID NO: 95	3583
TAU637	Tau	Light chain	RKA	WO2016079597 SEQ ID NO: 109	3584
TAU638	Tau	Light chain	RKB	WO2016079597 SEQ ID NO: 110	3585
TAU639	Tau	Light chain	RKA	WO2016079597 SEQ ID NO: 141	3586
TAU640	Tau	Light chain	RKB	WO2016079597 SEQ ID NO: 142	3587
TAU641	Tau	Light chain	cDC8E8	WO2016079597 SEQ ID NO: 143	3588
TAU642	Tau	Light chain		US8697076 SEQ ID NO: 14	3589
TAU643	Tau	Light chain	5202.4	US20160024193 SEQ ID NO: 61	3590
TAU644	Tau	Light chain	TAM_1	US20160024193 SEQ ID NO: 64	3591
TAU645	Tau	Light chain	TAM_2	US20160024193 SEQ ID NO: 65	3592
TAU646	Tau	Light chain	TAM_3	US20160024193 SEQ ID NO: 66	3593
TAU647	Tau	Light chain	TAM_4	US20160024193 SEQ ID NO: 67	3594
TAU648	Tau	Light chain	TAM_5	US20160024193 SEQ ID NO: 68	3595
TAU649	Tau	Light chain	TAM_6	US20160024193 SEQ ID NO: 69	3596
TAU650	Tau	Light chain	TAM_7	US20160024193 SEQ ID NO: 70	3597
TAU651	Tau	Light chain	TAM_8	US20160024193 SEQ ID NO: 71	3598
TAU652	Tau	Light chain	TAM_9	US20160024193 SEQ ID NO: 72	3599
TAU653	Tau	Light chain	TAM_10	US20160024193 SEQ ID NO: 73	3600
TAU654	Tau	Light chain	TAM_11	US20160024193 SEQ ID NO: 74	3601
TAU655	Tau	Light chain	TAM_12	US20160024193 SEQ ID NO: 75	3602
TAU656	Tau	Light chain	TAM_13	US20160024193 SEQ ID NO: 76	3603
TAU657	Tau	Light chain	TAM_14	US20160024193 SEQ ID NO: 77	3604
TAU658	Tau	Light chain	TAM_15	US20160024193 SEQ ID NO: 78	3605
TAU659	Tau	Light chain	TAM_16	US20160024193 SEQ ID NO: 79	3606

TAU660	Tau	Light chain	TAM_17	US20160024193 SEQ ID NO: 80	3607
TAU661	Tau	Light chain	TAM_18	US20160024193 SEQ ID NO: 81	3608
TAU662	Tau	Light chain	TAM_19	US20160024193 SEQ ID NO: 82	3609
TAU663	Tau	Light chain	TAM_20; TAM_22	US20160024193 SEQ ID NO: 83 and 85	3610
TAU664	Tau	Light chain	TAM_21	US20160024193 SEQ ID NO: 84	3611
TAU665	Tau	Light chain		US20160031977 SEQ ID NO: 23	3612
TAU666	Tau	Light chain		US20160031977 SEQ ID NO: 25	3613
TAU667	Tau	Light chain		US20160031977 SEQ ID NO: 27	3614
TAU668	Tau	Light chain		US20160031977 SEQ ID NO: 28	3615
TAU669	Tau	Light chain		US20150050215 SEQ ID NO: 139	3616
TAU670	Tau	Light chain		US20150050215 SEQ ID NO: 143	3617
TAU671	Tau	Light Chain	pT231/pS235	WO2014016737 SEQ ID NO: 71	3618
TAU672	Tau	Light chain	RKB	WO2016079597 SEQ ID NO: 58	3619
TAU673	Tau	Light chain	cDC8E8	WO2016079597 SEQ ID NO: 93	3620
TAU674	Tau	light chain (lambda)	ch40E8	US20150344553 SEQ ID NO: 209	3621
TAU675	Tau	light chain (mouse kappa)	ch6E3	US20150344553 SEQ ID NO: 211	3622
TAU676	Tau	light chain (mouse lambda)	ch17C1	US20150344553 SEQ ID NO: 204	3623
TAU677	Tau	light chain (mouse lambda)	ch6C5	US20150344553 SEQ ID NO: 206	3624
TAU678	Tau	light chain (mouse lambda)	ch17C1(N31Q)	US20150344553 SEQ ID NO: 212	3625
TAU679	Tau	light chain constant region		WO2016079597 SEQ ID NO: 170; WO2015197823 SEQ ID NO: 84; US20150320860 SEQ ID NO: 36; WO2015197735 SEQ ID NO: 59; US9290567 SEQ ID NO: 11	3626
TAU680	Tau	light chain constant region		WO2016079597 SEQ ID NO: 171; US20160031976 SEQ ID NO: 32	3627
TAU681	Tau	Light chain lambda	human NI-105.40E8 light chain	US20150344553 SEQ ID NO: 219	3628
TAU682	Tau	Light chain lambda mouse	ch17C1(N31Q, I48V)	US20150344553 SEQ ID NO: 217	3629
TAU683	Tau	Light chain mature (mouse lambda)	ch4E4	US20150344553 SEQ ID NO: 21; US8940272 SEQ ID NO: 21	3630
TAU684	Tau	Light chain variable	NI-105.4A3-VL	US20150344553 SEQ ID NO: 19; US8940272 SEQ ID NO: 19	3631
TAU685	Tau	Light chain variable		US20150344553 SEQ ID NO: 15	3632
TAU686	Tau	Light chain variable	NI-105.4E4-VL; NI-105.24B2-VL	US20150344553 SEQ ID NO: 11, 15	3633
TAU687	Tau	Light chain variable		US20150307600 SEQ ID NO: 36	3634

TAU688	Tau	Light chain variable		US20150307600 SEQ ID NO: 38	3635
TAU689	Tau	Light chain variable region	RKA	WO2016079597 SEQ ID NO: 26	3636
TAU690	Tau	Light chain variable region	RKB	WO2016079597 SEQ ID NO: 27	3637
TAU691	Tau	Light chain variable region	DC8E8	WO2016079597 SEQ ID NO: 91	3638
TAU692	Tau	Light chain variable region		US8940272 SEQ ID NO: 15	3639
TAU693	Tau	Light chain variable region		US8697076 SEQ ID NO: 8	3640
TAU694	Tau	Light chain variable region		US20160024193 SEQ ID NO: 36	3641
TAU695	Tau	Light chain variable region		US20160024193 SEQ ID NO: 37	3642
TAU696	Tau	Light chain variable region		US20160024193 SEQ ID NO: 38	3643
TAU697	Tau	Light chain variable region		US20160024193 SEQ ID NO: 39	3644
TAU698	Tau	Light chain variable region		US20160024193 SEQ ID NO: 40	3645
TAU699	Tau	Light chain variable region		US20160024193 SEQ ID NO: 41	3646
TAU700	Tau	Light chain variable region		US20160024193 SEQ ID NO: 42	3647
TAU701	Tau	Light chain variable region		US20160024193 SEQ ID NO: 43	3648
TAU702	Tau	Light chain variable region		US20160024193 SEQ ID NO: 44	3649
TAU703	Tau	Light chain variable region		US20160024193 SEQ ID NO: 45	3650
TAU704	Tau	Light chain variable region		US20160024193 SEQ ID NO: 46	3651
TAU705	Tau	Light chain variable region		US20160024193 SEQ ID NO: 47	3652
TAU706	Tau	Light chain variable region		US20160024193 SEQ ID NO: 48	3653
TAU707	Tau	Light chain variable region		US20160024193 SEQ ID NO: 49	3654

TAU708	Tau	Light chain variable region		US20160024193 SEQ ID NO: 50	3655
TAU709	Tau	Light chain variable region		US20160024193 SEQ ID NO: 51	3656
TAU710	Tau	Light chain variable region		US20160024193 SEQ ID NO: 52	3657
TAU711	Tau	Light chain variable region		US20160024193 SEQ ID NO: 53	3658
TAU712	Tau	Light chain variable region		US20160024193 SEQ ID NO: 54	3659
TAU713	Tau	Light chain variable region		US20160024193 SEQ ID NO: 55 and 57	3660
TAU714	Tau	Light chain variable region		US20160024193 SEQ ID NO: 56	3661
TAU715	Tau	Light chain variable region	5202.4	US20160024193 SEQ ID NO: 60	3662
TAU716	Tau	Light chain variable region	NI-105.17C1	US20150344553 SEQ ID NO: 46	3663
TAU717	Tau	Light chain variable region	NI-105.17C1 N31Q	US20150344553 SEQ ID NO: 221	3664
TAU718	Tau	Light chain variable region	NI-105.17C1 N31Q, I48V	US20150344553 SEQ ID NO: 222	3665
TAU719	Tau	Light chain variable region	NI-105.6C5	US20150344553 SEQ ID NO: 49	3666
TAU720	Tau	Light chain variable region	M-105.29G10	US20150344553 SEQ ID NO: 51	3667
TAU721	Tau	Light chain variable region	NI-105.6L9	US20150344553 SEQ ID NO: 53	3668
TAU722	Tau	Light chain variable region	NI-105.40E8	US20150344553 SEQ ID NO: 55	3669
TAU723	Tau	Light chain variable region	NI-105.48E5	US20150344553 SEQ ID NO: 57	3670
TAU724	Tau	Light chain variable region	NI-105.6E3	US20150344553 SEQ ID NO: 59	3671
TAU725	Tau	Light chain variable region	NI-105.22E1	US20150344553 SEQ ID NO: 61	3672
TAU726	Tau	Light chain variable region	NI-105.26B13	US20150344553 SEQ ID NO: 64	3673

TAU727	Tau	Light chain variable region	NI-105.12E12	US20150344553 SEQ ID NO: 66	3674
TAU728	Tau	Light chain variable region	NI-105.60E7	US20150344553 SEQ ID NO: 68	3675
TAU729	Tau	Light chain variable region	NI-105.14E2	US20150344553 SEQ ID NO: 70	3676
TAU730	Tau	Light chain variable region	NI-105.39E2	US20150344553 SEQ ID NO: 72	3677
TAU731	Tau	Light chain variable region	NI-105.19C6	US20150344553 SEQ ID NO: 74	3678
TAU732	Tau	Light chain variable region	NI-105.9C4	US20150344553 SEQ ID NO: 78	3679
TAU733	Tau	Light chain variable region	19.3	US20150320860 SEQ ID NO: 9	3680
TAU734	Tau	Light chain variable region	3-66	US20150320860 SEQ ID NO: 10	3681
TAU735	Tau	Light chain variable region	h3B3	US20150320860 SEQ ID NO: 25	3682
TAU736	Tau	Light chain variable region	19.3	US20150320860 SEQ ID NO: 26	3683
TAU737	Tau	Light chain variable region	17.1	US20150320860 SEQ ID NO: 27	3684
TAU738	Tau	Light chain variable region	14.2	US20150320860 SEQ ID NO: 28	3685
TAU739	Tau	Light chain variable region	13.1	US20150320860 SEQ ID NO: 29	3686
TAU740	Tau	Light chain variable region	7.2	US20150320860 SEQ ID NO: 30	3687
TAU741	Tau	Light chain variable region	9.2	US20150320860 SEQ ID NO: 31	3688
TAU742	Tau	Light chain variable region	11.4	US20150320860 SEQ ID NO: 32	3689
TAU743	Tau	Light chain variable region		US20150253341 SEQ ID NO: 39	3690
TAU744	Tau	Light chain variable region	NI-101.10; NI-101.11	US20150147343 SEQ ID NO: 8	3691
TAU745	Tau	Light chain variable region	NI-101.12	US20150147343 SEQ ID NO: 12	3692

TAU746	Tau	Light chain variable region	NI-101.13	US20150147343 SEQ ID NO: 16	3693
TAU747	Tau	Light chain variable region	NI-101.12F6A	US20150147343 SEQ ID NO: 41	3694
TAU748	Tau	Light chain variable region	NI-101.13A	US20150147343 SEQ ID NO: 44	3695
TAU749	Tau	Light chain variable region	NI-101.13B	US20150147343 SEQ ID NO: 45	3696
TAU750	Tau	Light chain variable region	Ta1501	US20150183854 SEQ ID NO: 25	3697
TAU751	Tau	Light chain variable region	Ta1502; Ta1505	US20150183854 SEQ ID NO: 26	3698
TAU752	Tau	Light chain variable region	Ta1506	US20150183854 SEQ ID NO: 27	3699
TAU753	Tau	Light chain variable region	Ta1507	US20150183854 SEQ ID NO: 28	3700
TAU754	Tau	Light chain variable region	Ta1508	US20150183854 SEQ ID NO: 29	3701
TAU755	Tau	Light chain variable region	Ta1509	US20150183854 SEQ ID NO: 30	3702
TAU756	Tau	Light chain variable region		US20150050215 SEQ ID NO: 150	3703
TAU757	Tau	Light chain variable region		US20150050215 SEQ ID NO: 152	3704
TAU758	Tau	Light chain variable region		US20150050215 SEQ ID NO: 153	3705
TAU759	Tau	Light chain variable region		US8980270 SEQ ID NO: 13	3706
TAU760	Tau	Light chain variable region		US8980270 SEQ ID NO: 15	3707
TAU761	Tau	Light chain variable region	CBTAU-7.1	WO2015197823 SEQ ID NO: 88	3708
TAU762	Tau	Light chain variable region	CBTAU-8.1	WO2015197823 SEQ ID NO: 92	3709
TAU763	Tau	Light chain variable region	CBTAU- 16.1	WO2015197823 SEQ ID NO: 96	3710
TAU764	Tau	Light chain variable region	CBTAU- 18.1	WO2015197823 SEQ ID NO: 100	3711

TAU765	Tau	Light chain variable region	CBTAU-20.1	WO2015197823 SEQ ID NO: 104	3712
TAU766	Tau	Light chain variable region	CBTAU-22.1	WO2015197823 SEQ ID NO: 108	3713
TAU767	Tau	Light chain variable region	CBTAU-24.1	WO2015197823 SEQ ID NO: 112	3714
TAU768	Tau	Light chain variable region	CBTAU-27.1	WO2015197823 SEQ ID NO: 116	3715
TAU769	Tau	Light chain variable region	CBTAU 28.1	WO2015197823 SEQ ID NO: 120	3716
TAU770	Tau	Light chain variable region	CBTAU -41.1	WO2015197823 SEQ ID NO: 124	3717
TAU771	Tau	Light chain variable region	CBTAU -41.2	WO2015197823 SEQ ID NO: 128	3718
TAU772	Tau	Light chain variable region	CBTAU -42.1	WO2015197823 SEQ ID NO: 132	3719
TAU773	Tau	Light chain variable region	CBTAU 43.1	WO2015197823 SEQ ID NO: 136	3720
TAU774	Tau	Light chain variable region	CBTAU 44.1	WO2015197823 SEQ ID NO: 140	3721
TAU775	Tau	Light chain variable region	CBTAU 45.1	WO2015197823 SEQ ID NO: 144	3722
TAU776	Tau	Light chain variable region	CBTAU 46.1	WO2015197823 SEQ ID NO: 148	3723
TAU777	Tau	Light chain variable region	CBTAU 47.1	WO2015197823 SEQ ID NO: 152	3724
TAU778	Tau	Light chain variable region	CBTAU 47.2	WO2015197823 SEQ ID NO: 156	3725
TAU779	Tau	Light chain variable region	CBTAU 49.1	WO2015197823 SEQ ID NO: 160	3726
TAU780	Tau	Light chain variable region	Native 7.1	WO2015197823 SEQ ID NO: 259	3727
TAU781	Tau	Light chain variable region	Native 8.1	WO2015197823 SEQ ID NO: 263	3728
TAU782	Tau	Light chain variable region	Native 16.1	WO2015197823 SEQ ID NO: 267	3729
TAU783	Tau	Light chain variable region	Native 18.1	WO2015197823 SEQ ID NO: 270	3730

TAU784	Tau	Light chain variable region	Native 20.1	WO2015197823 SEQ ID NO: 273	3731
TAU785	Tau	Light chain variable region	Native 22.1	WO2015197823 SEQ ID NO: 277	3732
TAU786	Tau	Light chain variable region	Native 24.1	WO2015197823 SEQ ID NO: 280	3733
TAU787	Tau	Light chain variable region	Native 27.1	WO2015197823 SEQ ID NO: 283	3734
TAU788	Tau	Light chain variable region	Native 28.1	WO2015197823 SEQ ID NO: 285	3735
TAU789	Tau	Light chain variable region	Native 41.1	WO2015197823 SEQ ID NO: 288	3736
TAU790	Tau	Light chain variable region	Native 41.2; Native 42.1	WO2015197823 SEQ ID NO: 290; WO2015197823 SEQ ID NO: 293	3737
TAU791	Tau	Light chain variable region	Native 43.1	WO2015197823 SEQ ID NO: 296	3738
TAU792	Tau	Light chain variable region	Native 44.1	WO2015197823 SEQ ID NO: 300	3739
TAU793	Tau	Light chain variable region	Native 45.1	WO2015197823 SEQ ID NO: 304	3740
TAU794	Tau	Light chain variable region	Native 46.1	WO2015197823 SEQ ID NO: 307	3741
TAU795	Tau	Light chain variable region	Native 47.1	WO2015197823 SEQ ID NO: 310	3742
TAU796	Tau	Light chain variable region	Native 47.2	WO2015197823 SEQ ID NO: 312	3743
TAU797	Tau	Light chain variable region	Native 49.1	WO2015197823 SEQ ID NO: 314	3744
TAU798	Tau	Light chain variable region	6B2G12	WO2016007414 SEQ ID NO: 8	3745
TAU799	Tau	Light chain variable region	scFv235	WO2016007414 SEQ ID NO: 10	3746
TAU800	Tau	Light chain variable region		WO2015120364 SEQ ID NO: 24	3747
TAU801	Tau	Light chain variable region		WO2015120364 SEQ ID NO: 36	3748
TAU802	Tau	Light chain variable region	pT231/pS235_1	WO2014016737 SEQ ID NO: 14	3749

TAU803	Tau	Light chain variable region	pT231/pS235_2	WO2014016737 SEQ ID NO: 16	3750
TAU804	Tau	Light chain variable region	pT212/pS214_1	WO2014016737 SEQ ID NO: 18	3751
TAU805	Tau	Light chain variable region	pT212/pS214_2	WO2014016737 SEQ ID NO: 20	3752
TAU806	Tau	Light chain variable region	pS396/pS404_1	WO2014016737 SEQ ID NO: 22	3753
TAU807	Tau	Light chain variable region	pS396/pS404_2	WO2014016737 SEQ ID NO: 24	3754
TAU808	Tau	Light chain variable region	2H9	WO2014096321 SEQ ID NO: 15	3755
TAU809	Tau	Light chain variable region		WO2015122922 SEQ ID NO: 15 and 23	3756
TAU810	Tau	Light chain variable region		WO2015122922 SEQ ID NO: 31 and 39	3757
TAU811	Tau	Light chain variable region		WO2015122922 SEQ ID NO: 47	3758
TAU812	Tau	Light chain variable region		WO2015122922 SEQ ID NO: 55	3759
TAU813	Tau	Light chain variable region		WO2015122922 SEQ ID NO: 63	3760
TAU814	Tau	Light chain variable region		WO2015122922 SEQ ID NO: 71	3761
TAU815	Tau	light chain variable region kappa	16B5	US20160031976 SEQ ID NO: 16	3762
TAU816	Tau	light chain variable region kappa		US20160031976 SEQ ID NO: 20	3763
TAU817	Tau	Light chain variable region, before germlining	NI-105.9C4	US20150344553 SEQ ID NO: 77	3764
TAU818	Tau	Light chain variable region, humanized	variant 1-VL21	US20150175685 SEQ ID NO: 16; WO2015197735 SEQ ID NO: 16	3765
TAU819	Tau	Light chain variable region, humanized	variant 2-VL22	US20150175685 SEQ ID NO: 17; WO2015197735 SEQ ID NO: 17	3766
TAU820	Tau	Light chain variable region, humanized	variant 4-VL01	US20150175685 SEQ ID NO: 32	3767
TAU821	Tau	Light chain variable	variant 5-VL09	US20150175685 SEQ ID NO: 33	3768

		region, humanized			
TAU822	Tau	Light chain variable region, humanized	variant 6-VL12	US20150175685 SEQ ID NO: 34	3769
TAU823	Tau	Light chain variable region, humanized	variant 7-VL15	US20150175685 SEQ ID NO: 35	3770
TAU824	Tau	Light chain variable region, humanized	variant 8-VL16	US20150175685 SEQ ID NO: 36	3771
TAU825	Tau	Light chain variable region, humanized	variant 9-VL17	US20150175685 SEQ ID NO: 37	3772
TAU826	Tau	Light chain variable region, humanized	variant 10-VL19	US20150175685 SEQ ID NO: 38	3773
TAU827	Tau	Light chain variable region, humanized	variant 11-VL28	US20150175685 SEQ ID NO: 39	3774
TAU828	Tau (pS422)	Light chain variable region, humanized	variant 12-VL33	US20150175685 SEQ ID NO: 40	3775
TAU829	Tau	Light chain variable region, humanized	variant 13-VL35	US20150175685 SEQ ID NO: 41	3776
TAU830	Tau	Light chain variable region, humanized	variant 14-VL39	US20150175685 SEQ ID NO: 42	3777
TAU831	Tau	Light chain variable region, humanized	variant 15-VL40	US20150175685 SEQ ID NO: 43	3778
TAU832	Tau	Light chain variable region, humanized	variant 16-VL41	US20150175685 SEQ ID NO: 44	3779
TAU833	Tau	Light chain variable region, humanized	variant 17-VL42	US20150175685 SEQ ID NO: 45	3780
TAU834	Tau	Light chain variable region, humanized	variant 4-VH01	US20150175685 SEQ ID NO: 46	3781
TAU835	Tau	Light chain variable region, humanized	variant 5-VH02	US20150175685 SEQ ID NO: 47	3782
TAU836	Tau	Light chain variable	variant 6-VH03	US20150175685 SEQ ID NO: 48	3783

		region, humanized			
TAU837	Tau	Light chain variable region, humanized	variant 7-VH04	US20150175685 SEQ ID NO: 49	3784
TAU838	Tau	Light chain variable region, humanized	variant 8-VH14	US20150175685 SEQ ID NO: 50	3785
TAU839	Tau	Light chain variable region, humanized	variant 9-VH15	US20150175685 SEQ ID NO: 51	3786
TAU840	Tau	Light chain variable region, humanized	variant 10-VH18	US20150175685 SEQ ID NO: 52	3787
TAU841	Tau	Light chain variable region, humanized	variant 11-VH19	US20150175685 SEQ ID NO: 53	3788
TAU842	Tau	Light chain variable region, humanized	variant 12-VH22	US20150175685 SEQ ID NO: 54	3789
TAU843	Tau	Light chain variable region, humanized	variant 13-VH23	US20150175685 SEQ ID NO: 55	3790
TAU844	Tau	Light chain variable region, humanized	variant 14-VH24	US20150175685 SEQ ID NO: 56	3791
TAU845	Tau	Light chain variable region, humanized	variant 15-VH31	US20150175685 SEQ ID NO: 57	3792
TAU846	Tau	Light chain variable region, humanized	IPN002 Vk variant 1	US8980270 SEQ ID NO: 40	3793
TAU847	Tau	Light chain variable region, humanized	IPN002 Vk variant 2	US8980270 SEQ ID NO: 41	3794
TAU848	Tau	Light chain variable region, humanized	IPN002 Vk variant 3	US8980270 SEQ ID NO: 42	3795
TAU849	Tau	Light chain variable region, humanized	IPN002 Vk variant 4	US8980270 SEQ ID NO: 43	3796
TAU850	Tau	Light chain variable region, mature		US20160031976 SEQ ID NO: 21	3797
TAU851	Tau	Light chain variable		US20160031976 SEQ ID NO: 22	3798

		region, mature			
TAU852	Tau	Light chain variable region, mature		US20160031976 SEQ ID NO: 23	3799
TAU853	Tau	ScFv	scFv235	WO2016007414 SEQ ID NO: 18	3800
TAU854	Tau	scFv235 Fusion Protein		WO2016007414 SEQ ID NO: 22	3801
TAU855	Tau	scFv235 Fusion Protein		WO2016007414 SEQ ID NO: 23	3802
TAU856	Tau	scFv235 Fusion Protein		WO2016007414 SEQ ID NO: 24	3803
TAU857	Tau	scFv235 Fusion Protein		WO2016007414 SEQ ID NO: 25	3804
TAU858	Tau	scFv235 Fusion Protein		WO2016007414 SEQ ID NO: 26	3805
TAU859	Tau		Y15982 Igkv8-21*01	WO2016079597 SEQ ID NO: 60	3806
TAU860	Tau		L17135 Igkv8-28*02	WO2016079597 SEQ ID NO: 61	3807
TAU861	Tau		Y15980 IGKV8-19*01	WO2016079597 SEQ ID NO: 62	3808
TAU862	Tau		AJ235948 IGKV8-30*01	WO2016079597 SEQ ID NO: 63	3809
TAU863	Tau		AJ235947 IGKV8-28*01	WO2016079597 SEQ ID NO: 64	3810
TAU864	Tau		X72449	WO2016079597 SEQ ID NO: 65	3811
TAU865	Tau		AC160990 Musmus IGHV1-81*01	WO2016079597 SEQ ID NO: 66	3812
TAU866	Tau		AC160473 Musmus IGHV1-83*01	WO2016079597 SEQ ID NO: 67	3813
TAU867	Tau		AC160990 Musmus IGHV1-83*01	WO2016079597 SEQ ID NO: 68	3814
TAU868	Tau		AC160473 Musmus IGHV1-75*01	WO2016079597 SEQ ID NO: 69	3815
TAU869	Tau		X02064 Musmus IGHV1-54*02	WO2016079597 SEQ ID NO: 70	3816
TAU870	Tau		M65092	WO2016079597 SEQ ID NO: 71	3817
TAU871	Tau			US20150320860 SEQ ID NO: 56	3818
TAU872	Tau			US20150320860 SEQ ID NO: 57	3819
TAU873	Tau			US20150320860 SEQ ID NO: 58	3820
TAU874	Tau			US20150320860 SEQ ID NO: 59	3821
TAU875	Tau	Light chain variable region		US20150183855 SEQ ID NO: 14; WO2016126993 SEQ ID NO: 14	3822

TAU876	Tau (O-GlcNAc)	Heavy chain variable region		WO2014159244 SEQ ID NO: 1	3823
TAU877	Tau (O-GlcNAc)	Light chain variable region		WO2014159244 SEQ ID NO: 2	3824
TAU878	Tau (pS422)	Heavy chain constant region		WO2015197735 SEQ ID NO: 58	3825
TAU879	Tau (pS422)	Heavy chain HC anti-TfR2 antibody conjugated to scFv anti-biotin antibody fragment		WO2015197735 SEQ ID NO: 139	3826
TAU880	Tau (pS422)	Heavy chain HC anti-TfR2 antibody conjugated to scFv anti-digoxigenin antibody fragment		WO2015197735 SEQ ID NO: 138	3827
TAU881	Tau (pS422)	Heavy chain HC anti-TfR1 antibody conjugated to scFv anti-digoxigenin antibody fragment		WO2015197735 SEQ ID NO: 135	3828
TAU882	Tau (pS422)	Heavy chain variable region	VH00	WO2015197735 SEQ ID NO: 11; US9290567 SEQ ID NO: 54	3829
TAU883	Tau (pS422)	Heavy chain variable region		WO2015197735 SEQ ID NO: 68	3830
TAU884	Tau (pS422)	Heavy chain variable region		WO2015197735 SEQ ID NO: 76	3831
TAU885	Tau (pS422)	Heavy chain variable region		WO2015197735 SEQ ID NO: 84	3832
TAU886	Tau (pS422)	Heavy chain variable region		WO2015197735 SEQ ID NO: 92	3833
TAU887	Tau (pS422)	Heavy chain variable region		WO2015197735 SEQ ID NO: 100	3834
TAU888	Tau (pS422)	Heavy chain variable region		WO2015197735 SEQ ID NO: 108	3835
TAU889	Tau (pS422)	Heavy chain variable region		WO2015197735 SEQ ID NO: 116	3836
TAU890	Tau (pS422)	Heavy chain variable region		WO2015197735 SEQ ID NO: 129	3837

TAU891	Tau (pS422)	Heavy chain variable region		WO2015197735 SEQ ID NO: 131	3838
TAU892	Tau (pS422)	Heavy chain variable region of the anti-HeliCar motif		WO2015197735 SEQ ID NO: 148	3839
TAU893	Tau (pS422)	Heavy chainHC anti-TfR1 antibody conjugated to scFv anti-biotin antibody fragment		WO2015197735 SEQ ID NO: 136	3840
TAU894	Tau (pS422)	Helicar motif amino acid sequence cystein variant 1 fused to pseudomonas exotoxin LR8M with a GGG-peptidic linker and the C-terminal K deleted		WO2015197735 SEQ ID NO: 152	3841
TAU895	Tau (pS422)	human Ig-lambda constant region		WO2015197735 SEQ ID NO: 60	3842
TAU896	Tau (pS422)	Light chain LC anti-TfR2 antibody		WO2015197735 SEQ ID NO: 137	3843
TAU897	Tau (pS422)	Light chain LC anti-TfR1 antibody	LC anti-TfR1 antibody	WO2015197735 SEQ ID NO: 134	3844
TAU898	Tau (pS422)	Light chain variable region	VL00	WO2015197735 SEQ ID NO: 7	3845
TAU899	Tau (pS422)	Light chain variable region		WO2015197735 SEQ ID NO: 72	3846
TAU900	Tau (pS422)	Light chain variable region		WO2015197735 SEQ ID NO: 80	3847
TAU901	Tau (pS422)	Light chain variable region		WO2015197735 SEQ ID NO: 88	3848
TAU902	Tau (pS422)	Light chain variable region		WO2015197735 SEQ ID NO: 96	3849
TAU903	Tau (pS422)	Light chain variable region		WO2015197735 SEQ ID NO: 104	3850

TAU904	Tau (pS422)	Light chain variable region		WO2015197735 SEQ ID NO: 112	3851
TAU905	Tau (pS422)	Light chain variable region		WO2015197735 SEQ ID NO: 120	3852
TAU906	Tau (pS422)	Light chain variable region		WO2015197735 SEQ ID NO: 130	3853
TAU907	Tau (pS422)	Light chain variable region		WO2015197735 SEQ ID NO: 132	3854
TAU908	Tau (pS422)	Light chain variable region N51C variant of the anti-HeliCar motif		WO2015197735 SEQ ID NO: 151	3855
TAU909	Tau (pS422)	Light chain variable region N55C variant of the anti-HeliCar motif		WO2015197735 SEQ ID NO: 150	3856
TAU910	Tau (pS422)	Light chain variable region of the anti-HeliCar motif		WO2015197735 SEQ ID NO: 149	3857
TAU911	Tau pS422	Heavy chain constant region		US9290567 SEQ ID NO:13	3858
TAU912	Tau pS422	Heavy chain constant region		US9290567 SEQ ID NO:14	3859
TAU913	Tau pS422	Heavy chain constant region		US9290567 SEQ ID NO: 15	3860
TAU914	Tau pS422	Heavy chain constant region		US9290567 SEQ ID NO: 16	3861
TAU915	Tau pS422	Heavy chain variable region	Mab2.10.3	US9290567 SEQ ID NO: 2	3862
TAU916	Tau pS422	Heavy chain variable region	Mab 005	US9290567 SEQ ID NO: 22	3863
TAU917	Tau pS422	Heavy chain variable region	Mab 019	US9290567 SEQ ID NO: 30	3864
TAU918	Tau pS422	Heavy chain variable region	Mab 020	US9290567 SEQ ID NO: 38	3865
TAU919	Tau pS422	Heavy chain variable region	Mab 085	US9290567 SEQ ID NO: 46	3866
TAU920	Tau pS422	Heavy chain variable region	Mab 097	US9290567 SEQ ID NO: 62	3867

TAU921	Tau pS422	Light chain variable region	Mab2.10.3	US9290567 SEQ ID NO: 1	3868
TAU922	Tau pS422	Light chain variable region	Mab 005	US9290567 SEQ ID NO: 26	3869
TAU923	Tau pS422	Light chain variable region	Mab 019	US9290567 SEQ ID NO: 34	3870
TAU924	Tau pS422	Light chain variable region	Mab 020	US9290567 SEQ ID NO: 42	3871
TAU925	Tau pS422	Light chain variable region	Mab 085	US9290567 SEQ ID NO: 50	3872
TAU926	Tau pS422	Light chain variable region	Mab 086	US9290567 SEQ ID NO: 58	3873
TAU927	Tau pS422	Light chain variable region	Mab 097	US9290567 SEQ ID NO: 66	3874
TAU928	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	3.F5	US20100323905 SEQ ID NO: 13 and 119	3875
TAU929	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	3.A9	US20100323905 SEQ ID NO: 14 and 120	3876
TAU930	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	3.00E+09	US20100323905 SEQ ID NO: 15, 110	3877
TAU931	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	#08	US20100323905 SEQ ID NO: 16 and 111	3878
TAU932	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH29	US20100323905 SEQ ID NO: 18, 118	3879
TAU933	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH07	US20100323905 SEQ ID NO: 97, 98	3880
TAU934	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH15	US20100323905 SEQ ID NO: 99-101	3881
TAU935	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH01	US20100323905 SEQ ID NO: 102	3882
TAU936	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH04	US20100323905 SEQ ID NO: 103	3883
TAU937	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable	VHH19	US20100323905 SEQ ID NO: 104	3884

		region antibody			
TAU938	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH21	US20100323905 SEQ ID NO: 105	3885
TAU939	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH05	US20100323905 SEQ ID NO: 106	3886
TAU940	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH23	US20100323905 SEQ ID NO: 107	3887
TAU941	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH34	US20100323905 SEQ ID NO: 108	3888
TAU942	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH26	US20100323905 SEQ ID NO: 109	3889
TAU943	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH18	US20100323905 SEQ ID NO: 17 and 112	3890
TAU944	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH09	US20100323905 SEQ ID NO: 113	3891
TAU945	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH20	US20100323905 SEQ ID NO: 114	3892
TAU946	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH32	US20100323905 SEQ ID NO: 115	3893
TAU947	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH30	US20100323905 SEQ ID NO: 116	3894
TAU948	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH28	US20100323905 SEQ ID NO: 117	3895
TAU949	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH14	US20100323905 SEQ ID NO: 121	3896
TAU950	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody	VHH12	US20100323905 SEQ ID NO: 122	3897
TAU951	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, amyloid 42 VHH	1B	US20100323905 SEQ ID NO: 52	3898

TAU952	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, amyloid 42 VHH	1D	US20100323905 SEQ ID NO: 53	3899
TAU953	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, amyloid 42 VHH	2A	US20100323905 SEQ ID NO: 54	3900
TAU954	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, amyloid 42 VHH	2B	US20100323905 SEQ ID NO: 55	3901
TAU955	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, amyloid 42 VHH	2F	US20100323905 SEQ ID NO: 56	3902
TAU956	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, amyloid 42 VHH	3A	US20100323905 SEQ ID NO: 57	3903
TAU957	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, amyloid 42 VHH	3H	US20100323905 SEQ ID NO: 58	3904
TAU958	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, amyloid 42 VHH	4C	US20100323905 SEQ ID NO: 59	3905
TAU959	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, amyloid 42 VHH	8F	US20100323905 SEQ ID NO: 60	3906
TAU960	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, amyloid 42 VHH	11D	US20100323905 SEQ ID NO: 61	3907
TAU961	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	EME7E	US20100323905 SEQ ID NO: 62	3908

TAU962	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	EME1C	US20100323905 SEQ ID NO: 63	3909
TAU963	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH01	US20100323905 SEQ ID NO: 64	3910
TAU964	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH03 / VHH23	US20100323905 SEQ ID NO: 65	3911
TAU965	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	EME3H	US20100323905 SEQ ID NO: 66	3912
TAU966	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH09	US20100323905 SEQ ID NO: 67	3913
TAU967	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH12	US20100323905 SEQ ID NO: 68	3914
TAU968	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH05	US20100323905 SEQ ID NO: 69	3915
TAU969	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH11	US20100323905 SEQ ID NO: 70	3916
TAU970	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	EME8A	US20100323905 SEQ ID NO: 71	3917
TAU971	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH02	US20100323905 SEQ ID NO: 72	3918

TAU972	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH15	US20100323905 SEQ ID NO: 73	3919
TAU973	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH10	US20100323905 SEQ ID NO: 74	3920
TAU974	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	EME4B	US20100323905 SEQ ID NO: 75	3921
TAU975	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH13	US20100323905 SEQ ID NO: 76	3922
TAU976	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	EME7F	US20100323905 SEQ ID NO: 77	3923
TAU977	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH14	US20100323905 SEQ ID NO: 78	3924
TAU978	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	EME2G	US20100323905 SEQ ID NO: 79	3925
TAU979	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	EME8D	US20100323905 SEQ ID NO: 80	3926
TAU980	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH04	US20100323905 SEQ ID NO: 81	3927
TAU981	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH07 / VHH08	US20100323905 SEQ ID NO: 82	3928

TAU982	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH16	US20100323905 SEQ ID NO: 83	3929
TAU983	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	3.6B	US20100323905 SEQ ID NO: 84	3930
TAU984	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	3.8B	US20100323905 SEQ ID NO: 85	3931
TAU985	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH24	US20100323905 SEQ ID NO: 86	3932
TAU986	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	VHH21	US20100323905 SEQ ID NO: 87	3933
TAU987	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH for emerin	3.8E	US20100323905 SEQ ID NO: 88	3934
TAU988	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH which can translocate via blood brain barrier		US20100323905 SEQ ID NO: 89	3935
TAU989	Tau/Amyloid beta/Alpha synuclein	Heavy chain variable region antibody, VHH which can translocate via blood brain barrier		US20100323905 SEQ ID NO: 90	3936
TAU990	Tau/Aβ peptides			US20110002945 SEQ ID NO: 2	3937
TAU991	Tau/Aβ peptides			US20110002945 SEQ ID NO: 3	3938
TAU992	Tau	CDR		WO2016137811 SEQ ID NO: 3	3939

TAU993	Tau	CDR		WO2016137811 SEQ ID NO: 4	3940
TAU994	Tau	CDR		WO2016137811 SEQ ID NO: 5	3941
TAU995	Tau	CDR		WO2016137811 SEQ ID NO: 6	3942
TAU996	Tau	CDR		WO2016137811 SEQ ID NO: 7	3943
TAU997	Tau	CDR		WO2016137811 SEQ ID NO: 8	3944
TAU998	Tau	CDR		WO2015122922 SEQ ID NO: 41	3945
TAU999	Tau	CDR		WO2015122922 SEQ ID NO: 49 and 57	3946
TAU1000	Tau	CDR		WO2016126993 SEQ ID NO: 16	3947
TAU1001	Tau	CDR		WO2016126993 SEQ ID NO: 17	3948
TAU1002	Tau	CDR		WO2016126993 SEQ ID NO: 18	3949
TAU1003	Tau	CDR		WO2016126993 SEQ ID NO: 19	3950
TAU1004	Tau	CDR		WO2016126993 SEQ ID NO: 20	3951
TAU1005	Tau	CDR		WO2016126993 SEQ ID NO: 21	3952
TAU1006	Tau	dimeric antibody	DH-Tau15	WO2016055941 SEQ ID NO: 20	3953
TAU1007	Tau	Fc	Fc-Tau15	WO2016055941 SEQ ID NO: 23	3954
TAU1008	Tau	full antibody	MC-1 Furin 2A	WO2015035190 SEQ ID NO: 2	3955
TAU1009	Tau	full antibody	MC-1 Furin 2A	WO2015035190 SEQ ID NO: 4	3956
TAU1010	Tau	full antibody	MC-1 optimized seq	WO2015035190 SEQ ID NO: 6	3957
TAU1011	Tau	full antibody	PHF-1 Furin 2A	WO2015035190 SEQ ID NO: 1	3958
TAU1012	Tau	full antibody	PHF-1 Furin 2A	WO2015035190 SEQ ID NO: 3	3959
TAU1013	Tau	full antibody	PHF-1 optimized seq	WO2015035190 SEQ ID NO: 5	3960
TAU1014	Tau	Heavy chain	1 A6	WO2016137950 SEQ ID NO: 46	3961
TAU1015	Tau	heavy chain	113F5-F7	WO2016196726 SEQ ID NO: 90	3962
TAU1016	Tau	heavy chain	11E10-B8	WO2016196726 SEQ ID NO: 30	3963
TAU1017	Tau	heavy chain	123E9-A1	WO2016196726 SEQ ID NO: 140	3964
TAU1018	Tau	heavy chain	125B11-H3	WO2016196726 SEQ ID NO: 80	3965
TAU1019	Tau	heavy chain	126F11-G11	WO2016196726 SEQ ID NO: 180	3966
TAU1020	Tau	heavy chain	12A10-E8	WO2016196726 SEQ ID NO: 250	3967
TAU1021	Tau	heavy chain	14F5-D9	WO2016196726 SEQ ID NO: 210	3968
TAU1022	Tau	heavy chain	15C6-A7	WO2016196726 SEQ ID NO: 150	3969
TAU1023	Tau	Heavy chain	17H3.2	WO2016112078 SEQ ID NO: 20	3970
TAU1024	Tau	heavy chain	19F8-B1	WO2016196726 SEQ ID NO: 160	3971
TAU1025	Tau	heavy chain	19H6-F7	WO2016196726 SEQ ID NO: 60	3972
TAU1026	Tau	heavy chain	22G7-C9	WO2016196726 SEQ ID NO: 230	3973
TAU1027	Tau	heavy chain	24A11-D5	WO2016196726 SEQ ID NO: 170	3974
TAU1028	Tau	heavy chain	26C1-B11 and 26C1-C8	WO2016196726 SEQ ID NO: 100 and 110	3975
TAU1029	Tau	Heavy chain	29H2.10	WO2016112078 SEQ ID NO: 22	3976
TAU1030	Tau	Heavy chain	29H2.10N31S (Mutant)	WO2016112078 SEQ ID NO: 23	3977
TAU1031	Tau	heavy chain	30G1-B2	WO2016196726 SEQ ID NO: 120	3978
TAU1032	Tau	heavy chain	37D3-H9 and 37D3-H9b	WO2016196726 SEQ ID NO: 10 and 20	3979
TAU1033	Tau	heavy chain	3A4-H4	WO2016196726 SEQ ID NO: 50	3980

TAU1034	Tau	Heavy chain	4G11	WO2016137950 SEQ ID NO: 42	3981
TAU1035	Tau	heavy chain	52F6-F11	WO2016196726 SEQ ID NO: 270	3982
TAU1036	Tau	heavy chain	54C1-H11 and 61E7-C4	WO2016196726 SEQ ID NO: 40	3983
TAU1037	Tau	heavy chain	55E7-F11	WO2016196726 SEQ ID NO: 260	3984
TAU1038	Tau	heavy chain	66F5-A1	WO2016196726 SEQ ID NO: 130	3985
TAU1039	Tau	heavy chain	73H6-B8	WO2016196726 SEQ ID NO: 220	3986
TAU1040	Tau	heavy chain	7A11-C12	WO2016196726 SEQ ID NO: 240	3987
TAU1041	Tau	heavy chain	89F4-A1	WO2016196726 SEQ ID NO: 190	3988
TAU1042	Tau	heavy chain	93A8-D2	WO2016196726 SEQ ID NO: 200	3989
TAU1043	Tau	heavy chain	94B2-C1	WO2016196726 SEQ ID NO: 70	3990
TAU1044	Tau ps409	heavy chain	hACI-36-3A8-Ab1	US20150175682 SEQ ID NO: 11	3991
TAU1045	Tau	heavy chain	hu125B11.v17 and hu125B11-H3.HC3	WO2016196726 SEQ ID NO: 310 and 448	3992
TAU1046	Tau	heavy chain	hu125B11.v17	WO2016196726 SEQ ID NO: 311	3993
TAU1047	Tau	heavy chain	hu125B11.v26	WO2016196726 SEQ ID NO: 320	3994
TAU1048	Tau	heavy chain	hu125B11.v26	WO2016196726 SEQ ID NO: 321	3995
TAU1049	Tau	heavy chain	hu125B11.v28	WO2016196726 SEQ ID NO: 330	3996
TAU1050	Tau	heavy chain	hu125B11.v28	WO2016196726 SEQ ID NO: 331	3997
TAU1051	Tau	heavy chain	hu125B11-H3.HC1	WO2016196726 SEQ ID NO: 446	3998
TAU1052	Tau	heavy chain	hu125B11-H3.HC2	WO2016196726 SEQ ID NO: 447	3999
TAU1053	Tau	heavy chain	hu125B11-H3.HC4	WO2016196726 SEQ ID NO: 449	4000
TAU1054	Tau	heavy chain	hu125B11-H3.HC5	WO2016196726 SEQ ID NO: 450	4001
TAU1055	Tau	heavy chain	hu125B11-H3.HC6	WO2016196726 SEQ ID NO: 451	4002
TAU1056	Tau	heavy chain	Hu37D3.v39	WO2016196726 SEQ ID NO: 560, 570, 580	4003
TAU1057	Tau	heavy chain	Hu37D3-H9.v1	WO2016196726 SEQ ID NO: 280	4004
TAU1058	Tau	heavy chain	Hu37D3-H9.v28.A4	WO2016196726 SEQ ID NO: 340	4005
TAU1059	Tau	heavy chain	Hu37D3-H9.v28.A4 IgG4-S228P.YTE	WO2016196726 SEQ ID NO: 348	4006
TAU1060	Tau	heavy chain	Hu37D3-H9.v28.A4 IgG4-S228P.YTE des-K	WO2016196726 SEQ ID NO: 602	4007
TAU1061	Tau	heavy chain	Hu37D3-H9.v5	WO2016196726 SEQ ID NO: 290	4008
TAU1062	Tau	heavy chain	Hu94B2.HC1	WO2016196726 SEQ ID NO: 452	4009
TAU1063	Tau	heavy chain	Hu94B2.HC2	WO2016196726 SEQ ID NO: 453	4010
TAU1064	Tau	heavy chain	Hu94B2.HC3	WO2016196726 SEQ ID NO: 454	4011
TAU1065	Tau	heavy chain	Hu94B2.HC4	WO2016196726 SEQ ID NO: 455	4012
TAU1066	Tau	heavy chain	Hu94B2.HC5	WO2016196726 SEQ ID NO: 456	4013
TAU1067	Tau	heavy chain	Hu94B2.HC6	WO2016196726 SEQ ID NO: 457	4014

TAU1068	Tau	heavy chain	Hu94B2.HC7	WO2016196726 SEQ ID NO: 458	4015
TAU1069	Tau	heavy chain	Hu94B2.HC8	WO2016196726 SEQ ID NO: 459	4016
TAU1070	Tau	heavy chain	Hu94B2.v105	WO2016196726 SEQ ID NO: 300	4017
TAU1071	Tau(pS422)	heavy chain	MAb086	WO2015197735 SEQ ID NO: 11	4018
TAU1072	Tau	heavy chain		WO2016137811 SEQ ID NO: 2	4019
TAU1073	Tau	heavy chain		WO2016137811 SEQ ID NO: 12	4020
TAU1074	Tau (pS422)	heavy chain constant regions		WO2015197735 SEQ ID NO: 58	4021
TAU1075	Tau	heavy chain variable domain	DC8E8	WO2016079597 SEQ ID NO: 7	4022
TAU1076	Tau(pS422)	heavy chain variable domain		WO2015197735 SEQ ID NO: 21	4023
TAU1077	Tau	heavy chain variable domain		WO2016137811 SEQ ID NO: 10	4024
TAU1078	Tau & huntingtin	intrabody	A2	WO2014193632 SEQ ID NO: 2	4025
TAU1079	Tau & huntingtin	intrabody	E10	WO2014193632 SEQ ID NO: 3	4026
TAU1080	Tau & huntingtin	intrabody	H8	WO2014193632 SEQ ID NO: 4	4027
TAU1081	Tau & huntingtin	intrabody	TNT41	WO2014193632 SEQ ID NO: 1	4028
TAU1082	Tau & huntingtin	intrabody		WO2014193632 SEQ ID NO: 5	4029
TAU1083	Tau(pS422)	Ig-kappa light chain constant region		WO2015197735 SEQ ID NO: 59	4030
TAU1084	Tau(pS422)	Ig-kappa light chain constant region		WO2015197735 SEQ ID NO: 60	4031
TAU1085	Tau	light chain	1 A6	WO2016137950 SEQ ID NO: 48	4032
TAU1086	Tau	light chain	113F5-F7	WO2016196726 SEQ ID NO: 91	4033
TAU1087	Tau	light chain	11E10-B8	WO2016196726 SEQ ID NO: 31	4034
TAU1088	Tau	light chain	123E9-A1	WO2016196726 SEQ ID NO: 141	4035
TAU1089	Tau	light chain	125B11-H3	WO2016196726 SEQ ID NO: 81	4036
TAU1090	Tau	light chain	126F11-G11	WO2016196726 SEQ ID NO: 181	4037
TAU1091	Tau	light chain	12A10-E8	WO2016196726 SEQ ID NO: 251	4038
TAU1092	Tau	light chain	14F5-D9	WO2016196726 SEQ ID NO: 211	4039
TAU1093	Tau	light chain	15C6-A7	WO2016196726 SEQ ID NO: 151	4040
TAU1094	Tau	light chain	17H3.2	WO2016112078 SEQ ID NO: 21	4041
TAU1095	Tau	light chain	19F8-B1	WO2016196726 SEQ ID NO: 161	4042
TAU1096	Tau	light chain	19H6-F7	WO2016196726 SEQ ID NO: 61	4043
TAU1097	Tau	light chain	22G7-C9	WO2016196726 SEQ ID NO: 231	4044
TAU1098	Tau	light chain	24A11-D5	WO2016196726 SEQ ID NO: 171	4045
TAU1099	Tau	light chain	26C1-B11	WO2016196726 SEQ ID NO: 101	4046
TAU1100	Tau	light chain	26C1-C8	WO2016196726 SEQ ID NO: 111	4047

TAU1101	Tau	Light chain	29H2.10	WO2016112078 SEQ ID NO: 24	4048
TAU1102	Tau	light chain	30G1-B2	WO2016196726 SEQ ID NO: 121	4049
TAU1103	Tau	light chain	37D3-H9	WO2016196726 SEQ ID NO: 11	4050
TAU1104	Tau	light chain	37D3-H9b	WO2016196726 SEQ ID NO: 21	4051
TAU1105	Tau	light chain	3A4-H4	WO2016196726 SEQ ID NO: 51	4052
TAU1106	Tau	Light chain	4G11	WO2016137950 SEQ ID NO: 44	4053
TAU1107	Tau	light chain	52F6-F11	WO2016196726 SEQ ID NO: 271	4054
TAU1108	Tau	light chain	54C1-H11 and 61E7-C4	WO2016196726 SEQ ID NO: 41	4055
TAU1109	Tau	light chain	55E7-F11	WO2016196726 SEQ ID NO: 261	4056
TAU1110	Tau	light chain	66F5-A1	WO2016196726 SEQ ID NO: 131	4057
TAU1111	Tau	light chain	73H6-B8	WO2016196726 SEQ ID NO: 221	4058
TAU1112	Tau	light chain	7A11-C12	WO2016196726 SEQ ID NO: 241	4059
TAU1113	Tau	light chain	89F4-A1	WO2016196726 SEQ ID NO: 191	4060
TAU1114	Tau	light chain	93A8-D2	WO2016196726 SEQ ID NO: 201	4061
TAU1115	Tau	light chain	94B2-C1	WO2016196726 SEQ ID NO: 71	4062
TAU1116	Tau ps410	light chain	hACI-36-3A8-Ab1	US20150175682 SEQ ID NO: 12	4063
TAU1117	Tau	light chain	hu125B11-H3.LC1	WO2016196726 SEQ ID NO: 442	4064
TAU1118	Tau	light chain	hu125B11-H3.LC2	WO2016196726 SEQ ID NO: 443	4065
TAU1119	Tau	light chain	hu125B11-H3.LC3	WO2016196726 SEQ ID NO: 444	4066
TAU1120	Tau	light chain	hu125B11-H3.LC4	WO2016196726 SEQ ID NO: 445	4067
TAU1121	Tau	light chain	Hu37D3.v39	WO2016196726 SEQ ID NO: 561	4068
TAU1122	Tau	light chain	Hu37D3.v40	WO2016196726 SEQ ID NO: 571	4069
TAU1123	Tau	light chain	Hu37D3.v41	WO2016196726 SEQ ID NO: 581	4070
TAU1124	Tau	light chain	Hu37D3-H9.v1	WO2016196726 SEQ ID NO: 281	4071
TAU1125	Tau	light chain	Hu37D3-H9.v28.A4	WO2016196726 SEQ ID NO: 341	4072
TAU1126	Tau	light chain	Hu37D3-H9.v28.A4 IgG4-S228P.YTE	WO2016196726 SEQ ID NO: 349	4073
TAU1127	Tau	light chain	Hu37D3-H9.v5	WO2016196726 SEQ ID NO: 291	4074
TAU1128	Tau	light chain	Hu94B2.LC10	WO2016196726 SEQ ID NO: 461	4075
TAU1129	Tau	light chain	Hu94B2.LC11	WO2016196726 SEQ ID NO: 462	4076
TAU1130	Tau	light chain	Hu94B2.LC12	WO2016196726 SEQ ID NO: 463	4077
TAU1131	Tau	light chain	Hu94B2.LC13	WO2016196726 SEQ ID NO: 464	4078
TAU1132	Tau	light chain	Hu94B2.LC14	WO2016196726 SEQ ID NO: 465	4079
TAU1133	Tau	light chain	Hu94B2.LC15	WO2016196726 SEQ ID NO: 466	4080
TAU1134	Tau	light chain	Hu94B2.LC16	WO2016196726 SEQ ID NO: 467	4081
TAU1135	Tau	light chain	Hu94B2.LC9	WO2016196726 SEQ ID NO: 460	4082
TAU1136	Tau	light chain	Hu94B2.v105	WO2016196726 SEQ ID NO: 301	4083
TAU1137	Tau(pS422)	light chain	MAb086	WO2015197735 SEQ ID NO: 07	4084
TAU1138	Tau	light chain		WO2016137811 SEQ ID NO: 1	4085
TAU1139	Tau	light chain		WO2016137811 SEQ ID NO: 11	4086

TAU1140	Tau	light chain		US8940272B2 SEQ ID NO: 11	4087
TAU1141	Tau ps411	light chain	hACI-36-2B6-Ab1	US20150175682 SEQ ID NO: 13	4088
TAU1142	Tau	light chain variable domain	DC8E8	WO2016079597 SEQ ID NO: 8	4089
TAU1143	Tau	light chain variable domain		WO2016137811 SEQ ID NO: 9	4090
TAU1144	Tau	single domain antibody	Tau15	WO2016055941 SEQ ID NO: 7	4091
TAU1145	Tau	single domain antibody	Tau81	WO2016055941 SEQ ID NO: 8	4092
TAU1146	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 8	4093
TAU1147	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 10	4094
TAU1148	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 14	4095
TAU1149	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 15	4096
TAU1150	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 16	4097
TAU1151	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 20	4098
TAU1152	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 21	4099
TAU1153	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 22	4100
TAU1154	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 23	4101
TAU1155	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 24	4102
TAU1156	pTau (pS198/pS199/ pS202/pT205)	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 25	4103
TAU1157	Tau	Heavy chain	AB1	WO2017005732A1 SEQ ID NO: 27	4104
TAU1158	pTAU (pS396)	Heavy Chain	C10.2	US20170015738A1 SEQ ID NO: 16	4105
TAU1159	Tau	heavy chain	C2N-8E12	WO2016201434A2 SEQ ID NO: 14	4106
TAU1160	pTAU (pS396)	Heavy Chain	C5.2	US20170015738A1 SEQ ID NO: 24	4107
TAU1161	pTAU (pS396)	Heavy Chain	C8.3	US20170015738A1 SEQ ID NO: 32	4108
TAU1162	pTAU (pS396)	Heavy Chain	D1.2	US20170015738A1 SEQ ID NO: 8	4109
TAU1163	pTAU (pS396)	Heavy Chain	humanized C10.2	US20170015738A1 SEQ ID NO: 35	4110
TAU1164	Tau	Heavy chain	mFab AB 1	WO2017005734A1 SEQ ID NO: 20	4111
TAU1165	Tau	Heavy chain	mFab AB1	WO2017005734A1 SEQ ID NO: 8	4112
TAU1166	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 10	4113
TAU1167	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 11	4114
TAU1168	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 12	4115
TAU1169	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 13	4116

TAU1170	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 22	4117
TAU1171	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 23	4118
TAU1172	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 54	4119
TAU1173	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 55	4120
TAU1174	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 15	4121
TAU1175	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 16	4122
TAU1176	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 17	4123
TAU1177	Tau	Heavy chain		WO2017005734A1 SEQ ID NO: 18	4124
TAU1178	Tau	Heavy chain (VH1)	C2N-8E12	WO2016201434A2 SEQ ID NO: 15	4125
TAU1179	Tau	Heavy chain (VH2)	C2N-8E12	WO2016201434A2 SEQ ID NO: 16	4126
TAU1180	Tau	Heavy chain (VH3)	C2N-8E12	WO2016201434A2 SEQ ID NO: 17	4127
TAU1181	Tau	Heavy chain (VH4)	C2N-8E12	WO2016201434A2 SEQ ID NO: 18	4128
TAU1182	Tau (421)	Heavy chain variable domain	1G10D2	WO2017027685A2 SEQ ID NO: 12	4129
TAU1183	Tau (421)	Heavy chain variable domain	1G11A10	WO2017027685A2 SEQ ID NO: 20	4130
TAU1184	Tau pS404	Heavy chain variable domain	4E6G7	WO2017027691A1 SEQ ID NO: 13	4131
TAU1185	Tau (421)	Heavy chain variable domain	5G2A3	WO2017027685A2 SEQ ID NO: 40	4132
TAU1186	Tau	Heavy chain variable region	IPN001 VH	US9567395 SEQ ID NO: 18	4133
TAU1187	Tau	Heavy chain variable region	IPN002 VH	US9567395 SEQ ID NO: 20	4134
TAU1188	Tau	Heavy chain variable region (VH)	ACI-35-1D2-Ab1	US9540434 SEQ ID NO: 86	4135
TAU1189	Tau	Heavy chain variable region (VH)	ACI-35-2A1-Ab1, ACI-35-2A1-Ab2, and ACI-35-4A6-Ab2	US9540434 SEQ ID NO: 109	4136
TAU1190	Tau	Heavy chain variable region (VH)	ACI-35-2G5-AB1	US9540434 SEQ ID NO: 111	4137
TAU1191	Tau	Heavy chain variable region (VH)	ACI-35-2G5-AB2 and ACI-35-2G5-AB3	US9540434 SEQ ID NO: 113	4138
TAU1192	Tau	Heavy chain variable region (VH)	ACI-35-4A6-Ab1	US9540434 SEQ ID NO: 84	4139
TAU1193	Tau	Heavy chain variable region, humanized	IPN002 VH variant 1	US9567395 SEQ ID NO: 28	4140
TAU1194	Tau	Heavy chain variable region, humanized	IPN002 VH variant 2	US9567395 SEQ ID NO: 29	4141

TAU1195	Tau	Heavy chain variable region, humanized	IPN002 VH variant 3	US9567395 SEQ ID NO: 30	4142
TAU1196	Tau	Heavy chain variable region, humanized	IPN002 VH variant 4	US9567395 SEQ ID NO: 31	4143
TAU1197	Tau (pS422)	Heavy chain variant 16	VH35H5	US20160376352A1 SEQ ID NO: 65	4144
TAU1198	Tau	Heavy chain variant gVH1	C2N-8E12	WO2016201434A2 SEQ ID NO: 1	4145
TAU1199	Tau	Heavy chain variant gVH2	C2N-8E12	WO2016201434A2 SEQ ID NO: 2	4146
TAU1200	Tau	Heavy chain variant gVH3	C2N-8E12	WO2016201434A2 SEQ ID NO: 3	4147
TAU1201	Tau	Heavy chain variant gVH4	C2N-8E12	WO2016201434A2 SEQ ID NO: 4	4148
TAU1202	Tau (421)	Heavy Chain VL2 Variable Domain	5B3C11	WO2017027685A2 SEQ ID NO: 32	4149
TAU1203	Tau	Heavy chain; humanized		WO2017005734A1 SEQ ID NO: 25	4150
TAU1204	Tau	Heavy chain; humanized		WO2017005734A1 SEQ ID NO: 26	4151
TAU1205	Tau	Heavy chain; humanized		WO2017005734A1 SEQ ID NO: 56	4152
TAU1206	Tau	Heavy chain; humanized		WO2017005734A1 SEQ ID NO: 57	4153
TAU1207	Tau	Heavy chain; humanized		WO2017005732A1 SEQ ID NO: 32	4154
TAU1208	Tau	Heavy chain; humanized		WO2017005732A1 SEQ ID NO: 33	4155
TAU1209	Tau	Heavy chain; humanized		WO2017005732A1 SEQ ID NO: 36	4156
TAU1210	Tau	Heavy chain; humanized		WO2017005732A1 SEQ ID NO: 37	4157
TAU1211	Tau	Heavy chain; humanized		WO2017005732A1 SEQ ID NO: 38	4158
TAU1212	Tau	Heavy chain; humanized		WO2017005732A1 SEQ ID NO: 39	4159
TAU1213	pTau (pS198/pS199/ pS202/pT205)	Light chain	AB1	WO2017005732A1 SEQ ID NO: 7	4160
TAU1214	pTau (pS198/pS199/ pS202/pT205)	Light chain	AB1	WO2017005732A1 SEQ ID NO: 9	4161
TAU1215	pTau (pS198/pS199/ pS202/pT205)	Light chain	AB1	WO2017005732A1 SEQ ID NO: 11	4162
TAU1216	pTau (pS198/pS199/ pS202/pT205)	Light chain	AB1	WO2017005732A1 SEQ ID NO: 12	4163
TAU1217	pTau (pS198/pS199/ pS202/pT205)	Light chain	AB1	WO2017005732A1 SEQ ID NO: 13	4164
TAU1218	pTau (pS198/pS199/ pS202/pT205)	Light chain	AB1	WO2017005732A1 SEQ ID NO: 17	4165

TAU1219	pTau (pS198/pS199/ pS202/pT205)	Light chain	AB1	WO2017005732A1 SEQ ID NO: 18	4166
TAU1220	pTau (pS198/pS199/ pS202/pT205)	Light chain	AB1	WO2017005732A1 SEQ ID NO: 19	4167
TAU1221	Tau	Light chain	AB1	WO2017005732A1 SEQ ID NO: 26	4168
TAU1222	pTAU (pS396)	Light Chain	C10.2	US20170015738A1 SEQ ID NO: 15	4169
TAU1223	Tau	light chain	C2N-8E12	WO2016201434A2 SEQ ID NO: 9	4170
TAU1224	pTAU (pS396)	Light Chain	C5.2	US20170015738A1 SEQ ID NO: 23	4171
TAU1225	pTAU (pS396)	Light Chain	C8.3	US20170015738A1 SEQ ID NO: 31	4172
TAU1226	pTAU (pS396)	Light Chain	D1.2	US20170015738A1 SEQ ID NO: 7	4173
TAU1227	pTAU (pS396)	Light Chain	D1.2*	US20170015738A1 SEQ ID NO: 34	4174
TAU1228	pTAU (pS396)	Light Chain	humanized C10.2	US20170015738A1 SEQ ID NO: 36	4175
TAU1229	Tau	Light chain	mFab AB 1	WO2017005734A1 SEQ ID NO: 19	4176
TAU1230	Tau	Light chain	mFab AB1	WO2017005734A1 SEQ ID NO: 7	4177
TAU1231	Tau	Light chain		WO2017005734A1 SEQ ID NO: 9	4178
TAU1232	Tau	Light chain		WO2017005734A1 SEQ ID NO: 14	4179
TAU1233	Tau	Light chain		WO2017005734A1 SEQ ID NO: 21	4180
TAU1234	Tau	Light chain (VK1)	C2N-8E12	WO2016201434A2 SEQ ID NO: 10	4181
TAU1235	Tau	Light chain (VK2)	C2N-8E12	WO2016201434A2 SEQ ID NO: 11	4182
TAU1236	Tau	Light chain (VK3)	C2N-8E12	WO2016201434A2 SEQ ID NO: 12	4183
TAU1237	Tau	Light chain (VK4)	C2N-8E12	WO2016201434A2 SEQ ID NO: 13	4184
TAU1238	Tau (421)	Light Chain Variable Domain	1G10D2	WO2017027685A2 SEQ ID NO: 8	4185
TAU1239	Tau (421)	Light Chain Variable Domain	1G11A10	WO2017027685A2 SEQ ID NO: 16	4186
TAU1240	Tau pS404	Light chain variable domain	4E6G7	WO2017027691A1 SEQ ID NO: 9	4187
TAU1241	Tau (421)	Light Chain Variable Domain	5G2A3	WO2017027685A2 SEQ ID NO: 36	4188
TAU1242	Tau	Light chain variable region	IPN001 VL	US9567395 SEQ ID NO: 17	4189
TAU1243	Tau	Light chain variable region	IPN002 VL	US9567395 SEQ ID NO: 19	4190
TAU1244	Tau	Light chain variable region (VK)	ACI-35-1D2-Ab1	US9540434 SEQ ID NO: 87	4191
TAU1245	Tau	Light chain variable region (VK)	ACI-35-2A1-Ab1	US9540434 SEQ ID NO: 117	4192
TAU1246	Tau	Light chain variable region (VK)	ACI-35-2A1-Ab2	US9540434 SEQ ID NO: 110	4193
TAU1247	Tau	Light chain variable region (VK)	ACI-35-2G5-AB1	US9540434 SEQ ID NO: 112	4194

TAU1248	Tau	Light chain variable region (VK)	ACI-35-2G5-AB2 and ACI-35-2G5-AB3	US9540434 SEQ ID NO: 114	4195
TAU1249	Tau	Light chain variable region (VK)	ACI-35-4A6-Ab1	US9540434 SEQ ID NO: 85	4196
TAU1250	Tau	Light chain variable region (VK)	ACI-35-4A6-Ab2	US9540434 SEQ ID NO: 119	4197
TAU1251	Tau	Light chain variable region, humanized	IPN002 Vk variant 1	US9567395 SEQ ID NO: 32	4198
TAU1252	Tau	Light chain variable region, humanized	IPN002 Vk variant 2	US9567395 SEQ ID NO: 33	4199
TAU1253	Tau	Light chain variable region, humanized	IPN002 Vk variant 3	US9567395 SEQ ID NO: 34	4200
TAU1254	Tau	Light chain variable region, humanized	IPN002 Vk variant 4	US9567395 SEQ ID NO: 35	4201
TAU1255	Tau (pS422)	Light chain variant 18	VL31A1	US20160376352A1 SEQ ID NO: 66	4202
TAU1256	Tau (pS422)	Light chain variant 19	VL49G1	US20160376352A1 SEQ ID NO: 67	4203
TAU1257	Tau (pS422)	Light chain variant 20	VL35F2	US20160376352A1 SEQ ID NO: 68	4204
TAU1258	Tau (pS422)	Light chain variant 21	VL53A2	US20160376352A1 SEQ ID NO: 69	4205
TAU1259	Tau (pS422)	Light chain variant 22	VL35G4	US20160376352A1 SEQ ID NO: 78	4206
TAU1260	Tau (pS422)	Light chain variant 24	VL4G1	US20160376352A1 SEQ ID NO: 86	4207
TAU1261	Tau	Light chain variant gVL1	C2N-8E12	WO2016201434A2 SEQ ID NO: 5	4208
TAU1262	Tau	Light chain variant gVL2	C2N-8E12	WO2016201434A2 SEQ ID NO: 6	4209
TAU1263	Tau	Light chain variant gVL3	C2N-8E12	WO2016201434A2 SEQ ID NO: 7	4210
TAU1264	Tau	Light chain variant gVL4	C2N-8E12	WO2016201434A2 SEQ ID NO: 8	4211
TAU1265	Tau (421)	Light chain VL1 variable domain	5B3C11	WO2017027685A2 SEQ ID NO: 24	4212
TAU1266	Tau (421)	Light chain VL2 variable domain	5B3C11	WO2017027685A2 SEQ ID NO: 28	4213
TAU1267	Tau	Light chain; humanized		WO2017005734A1 SEQ ID NO: 24	4214
TAU1268	Tau	Light chain; humanized		WO2017005732A1 SEQ ID NO: 30	4215
TAU1269	Tau	Light chain; humanized		WO2017005732A1 SEQ ID NO: 31	4216
TAU1270	Tau	Light chain; humanized		WO2017005732A1 SEQ ID NO: 34	4217

TAU1271	Tau	Light chain; humanized		WO2017005732A1 SEQ ID NO: 35	4218
TAU1272	Tau (421)	scFv	1G10D2	WO2017027685A2 SEQ ID NO: 47	4219
TAU1273	Tau (421)	scFv	1G10D2	WO2017027685A2 SEQ ID NO: 48	4220
TAU1274	Tau (421)	scFv	1G10D2	WO2017027685A2 SEQ ID NO: 49	4221
TAU1275	Tau (421)	scFv	1G10D2	WO2017027685A2 SEQ ID NO: 50	4222
TAU1276	Tau (421)	scFv	1G10D2	WO2017027685A2 SEQ ID NO: 51	4223
TAU1277	Tau (421)	scFv	1G10D2	WO2017027685A2 SEQ ID NO: 52	4224
TAU1278	Tau (421)	scFv	1G10D2	WO2017027685A2 SEQ ID NO: 53	4225
TAU1279	Tau (421)	scFv	1G10D2	WO2017027685A2 SEQ ID NO: 54	4226
TAU1280	Tau (421)	scFv	1G10D2	WO2017027685A2 SEQ ID NO: 55	4227
TAU1281	Tau (421)	scFv	1G10D2	WO2017027685A2 SEQ ID NO: 56	4228
TAU1282	Tau (421)	scFv	1G11A10	WO2017027685A2 SEQ ID NO: 57	4229
TAU1283	Tau (421)	scFv	1G11A10	WO2017027685A2 SEQ ID NO: 58	4230
TAU1284	Tau (421)	scFv	1G11A10	WO2017027685A2 SEQ ID NO: 59	4231
TAU1285	Tau (421)	scFv	1G11A10	WO2017027685A2 SEQ ID NO: 60	4232
TAU1286	Tau (421)	scFv	1G11A10	WO2017027685A2 SEQ ID NO: 61	4233
TAU1287	Tau (421)	scFv	1G11A10	WO2017027685A2 SEQ ID NO: 62	4234
TAU1288	Tau (421)	scFv	1G11A10	WO2017027685A2 SEQ ID NO: 63	4235
TAU1289	Tau (421)	scFv	1G11A10	WO2017027685A2 SEQ ID NO: 64	4236
TAU1290	Tau (421)	scFv	1G11A10	WO2017027685A2 SEQ ID NO: 65	4237
TAU1291	Tau (421)	scFv	1G11A10	WO2017027685A2 SEQ ID NO: 66	4238
TAU1292	Tau pS404	scFv	4E6G7	WO2017027691A1 SEQ ID NO: 17	4239
TAU1293	Tau (421)	scFv	5B3C11 (VL1)	WO2017027685A2 SEQ ID NO: 67	4240
TAU1294	Tau (421)	scFv	5B3C11 (VL1)	WO2017027685A2 SEQ ID NO: 68	4241
TAU1295	Tau (421)	scFv	5B3C11 (VL1)	WO2017027685A2 SEQ ID NO: 69	4242
TAU1296	Tau (421)	scFv	5B3C11 (VL1)	WO2017027685A2 SEQ ID NO: 70	4243
TAU1297	Tau (421)	scFv	5B3C11 (VL1)	WO2017027685A2 SEQ ID NO: 71	4244
TAU1298	Tau (421)	scFv	5B3C11 (VL1)	WO2017027685A2 SEQ ID NO: 72	4245
TAU1299	Tau (421)	scFv	5B3C11 (VL1)	WO2017027685A2 SEQ ID NO: 73	4246
TAU1300	Tau (421)	scFv	5B3C11 (VL1)	WO2017027685A2 SEQ ID NO: 74	4247
TAU1301	Tau (421)	scFv	5B3C11 (VL1)	WO2017027685A2 SEQ ID NO: 75	4248
TAU1302	Tau (421)	scFv	5B3C11 (VL1)	WO2017027685A2 SEQ ID NO: 76	4249
TAU1303	Tau (421)	scFv	5B3C11 (VL2)	WO2017027685A2 SEQ ID NO: 77	4250
TAU1304	Tau (421)	scFv	5B3C11 (VL2)	WO2017027685A2 SEQ ID NO: 78	4251
TAU1305	Tau (421)	scFv	5B3C11 (VL2)	WO2017027685A2 SEQ ID NO: 79	4252
TAU1306	Tau (421)	scFv	5B3C11 (VL2)	WO2017027685A2 SEQ ID NO: 80	4253
TAU1307	Tau (421)	scFv	5B3C11 (VL2)	WO2017027685A2 SEQ ID NO: 81	4254
TAU1308	Tau (421)	scFv	5B3C11 (VL2)	WO2017027685A2 SEQ ID NO: 82	4255
TAU1309	Tau (421)	scFv	5B3C11 (VL2)	WO2017027685A2 SEQ ID NO: 83	4256
TAU1310	Tau (421)	scFv	5B3C11 (VL2)	WO2017027685A2 SEQ ID NO: 84	4257
TAU1311	Tau (421)	scFv	5B3C11 (VL2)	WO2017027685A2 SEQ ID NO: 85	4258
TAU1312	Tau (421)	scFv	5B3C11 (VL2)	WO2017027685A2 SEQ ID NO: 86	4259
TAU1313	Tau (421)	scFv	5G2A3	WO2017027685A2 SEQ ID NO: 87	4260
TAU1314	Tau (421)	scFv	5G2A3	WO2017027685A2 SEQ ID NO: 88	4261
TAU1315	Tau (421)	scFv	5G2A3	WO2017027685A2 SEQ ID NO: 89	4262
TAU1316	Tau (421)	scFv	5G2A3	WO2017027685A2 SEQ ID NO: 90	4263
TAU1317	Tau (421)	scFv	5G2A3	WO2017027685A2 SEQ ID NO: 91	4264
TAU1318	Tau (421)	scFv	5G2A3	WO2017027685A2 SEQ ID NO: 92	4265
TAU1319	Tau (421)	scFv	5G2A3	WO2017027685A2 SEQ ID NO: 93	4266
TAU1320	Tau (421)	scFv	5G2A3	WO2017027685A2 SEQ ID NO: 94	4267
TAU1321	Tau (421)	scFv	5G2A3	WO2017027685A2 SEQ ID NO: 95	4268
TAU1322	Tau (421)	scFv	5G2A3	WO2017027685A2 SEQ ID NO: 96	4269

[00274] In one embodiment, the payload region of the AAV particle comprises a nucleic acid sequence encoding a polypeptide which is an antibody, an antibody-based composition, or a

fragment thereof. As a non-limiting example, the antibody may be one or more of the polypeptides listed in Table 3. As another non-limiting example, the antibody may be one or more of the heavy chain sequences listed in Table 3. As a non-limiting example, the antibody may be one or more of the light chain sequences listed in Table 3.

[00275] In one embodiment, the payload region of the AAV particle comprises a nucleic acid sequence encoding a polypeptide comprising a heavy chain and a light chain sequence listed in Table 3. The payload region may also comprise a linker between the heavy and light chain sequences. The linker may be a sequence known in the art or described in Table 2.

[00276] In one embodiment, the payload region of the AAV particle comprises a nucleic acid sequence encoding a polypeptide comprising a heavy chain and a light chain sequence listed in Table 3, where the heavy chain sequence is from a different antibody than the light chain sequence. The payload region may also comprise a linker between the heavy and light chain sequences. The linker may be a sequence known in the art or described in Table 2.

[00277] In one embodiment, the payload region comprises, in the 5' to 3' direction, an antibody light chain sequence, a linker and a heavy chain sequence.

[00278] In one embodiment, the payload region comprises a nucleic acid sequence encoding, in the 5' to 3' direction, an antibody light chain sequence from Table 3, a linker from Table 2 and a heavy chain sequence from Table 3. Non-limiting examples are included in Table 4.

[00279] In one embodiment, the payload region comprises, in the 5' to 3' direction, an antibody heavy chain sequence, a linker and a light chain sequence.

[00280] In one embodiment, the payload region comprises a nucleic acid sequence encoding, in the 5' to 3' direction, an antibody heavy chain sequence from Table 3, a linker from Table 2, and a light chain sequence from Table 3. Non-limiting examples are included in Table 4.

[00281] In one embodiment, the payload region comprises a nucleic acid sequence encoding a single heavy chain. As a non-limiting example, the heavy chain is an amino acid sequence or fragment thereof described in Table 3.

[00282] Shown in Table 3 are a listing of antibodies and their polynucleotides and/or polypeptides sequences. These sequences may be encoded by or included in the AAV particles of the present invention. Variants or fragments of the antibody sequences described in Table 3 may be utilized in the AAV particles of the present invention.

[00283] In some embodiments, the AAV particles may comprise codon-optimized versions of the nucleic acids encoding the polypeptides listed in Table 3. In some cases, the payload region of the AAV particles of the invention may encode one or more isoforms or variants of these heavy and light chain antibody domains. Such variants may be humanized or optimized antibody

domains comprising one or more complementarity determining regions (CDRs) from the heavy and light chains listed in Table 3. CDRs of the antibodies encoded by the viral genomes of the present invention may be 50%, 60%, 70%, 80%, 90%, 95% identical to CDRs listed in or incorporated in the sequences of Table 3. Methods of determining CDRs are well known in the art and are described herein. Payload regions may encode antibody variants with one or more heavy chain variable domain (V_H) or light chain variable domain (V_L) derived from the antibody sequences in Table 3. In some cases, such variants may include bispecific antibodies. Bispecific antibodies encoded by payload regions of the invention may comprise variable domain pairs from two different antibodies.

[00284] In one embodiment, the AAV particles may comprise a heavy and a light chain of an antibody described herein and two promoters. As a non-limiting example, the AAV particles may comprise a nucleic acid sequence of a genome as described in Figure 1 or Figure 2 of US Patent Publication No. US20030219733, the contents of which are herein incorporated by reference in its entirety. As another non-limiting example, the AAV particles may be a dual-promoter AAV for antibody expression as described by Lewis et al. (J. of. Virology, Sept 2002, Vol. 76(17), p 8769-8775; the contents of which are herein incorporated by reference in its entirety).

[00285] Payload regions of the viral genomes of the invention may encode any anti-tau antibodies, or tau-associated antibodies, not limited to those described in Table 3, including antibodies that are known in the art and/or antibodies that are commercially available. This may include fragments of such antibodies or antibodies that have been developed to comprise one or more of such fragments [e.g., variable domains or complementarity determining regions (CDRs)]. Anti-tau antibodies that may be encoded by payloads of the invention include, but are not limited to, AT8 ($pSer^{202}/pThr^{202}$; ThermoFisher, Waltham, MA; described in International Publication No. WO1995017429, the contents of which are herein incorporated in their entirety), AT100 ($pSer^{212}/pSer^{214}$; ThermoFisher, Waltham, MA; described in United States Patent No US6121003, the contents of which are herein incorporated in their entirety), AT180 ($pThr^{231}$; ThermoFisher, Waltham, MA; described in International Publication No. WO1995017429, the contents of which are herein incorporated by reference in their entirety), MC-1 ($Tau^{2-18/312-342}$ conformational antibody; as described in International Publication WO199620218, the contents of which are herein incorporated by reference in their entirety), MC-6 ($pSer^{235}$; described in United States Patent No 5811310, the contents of which are herein incorporated in their entirety), TG-3 ($pThr^{231}$; described in Jicha, GA et al., 1997 J Neurochem 69(5):2087-95, the contents of which are herein incorporated by reference in their entirety), CP13 ($pSer^{202}$), CP27 (human

Tau$^{130-150}$), Tau12 (human Tau$^{9-18}$; Abcam, Cambridge, MA), TG5 (Tau $^{220-242}$; described in United States Patent No US5811310), DA9 (Tau$^{102-140}$; described in United States Patent No US5811310), PHF-1 (pSer^{396}/pSer^{404}; described in International Publication WO199620218), Alz50 (Tau$^{7-9}$ and Tau$^{312-342}$ conformational epitope; described in United States Patent No US5811310 and Carmel, G et al 1996 J Biol Chem 271(51):32780-32795 and Jicha, GA et al, 1997 J Neurosci Res 48(2):128-132, the contents of each of which are herein incorporated by reference in their entirety), Tau-1 (de-phosphorylated Ser^{195}/Ser^{198}/Ser^{199}/Ser^{202}; ThermoFisher, Waltham, MA), Tau46 (Tau$^{404-441}$; Abcam, Cambridge, MA), pS199 (ThermoFisher, Waltham, MA), pT205, pS396 (ThermoFisher, Waltham, MA; described in United States Patent No. US8647631, the contents of which are herein incorporated by reference in their entirety), pS404 (ThermoFisher, Waltham, MA; described in United States Patent No. US8647631, the contents of which are herein incorporated by reference in their entirety), pS422 (ThermoFisher, Waltham, MA), A0024 (hTau$^{243-441}$; Dako, Glostrup, Denmark), HT7 (hTau$^{159-163}$; ThermoFisher, Waltham, MA), Tau2 (hTau$^{52-68}$; Abcam, Cambridge, MA), AD2 (pSer^{396}/pSer^{404}; Bio-Rad Laboratories, Hercules, CA), AT120 (hTau$^{216-224}$; described in United States Patent No. 5843779, the contents of which are herein incorporated by reference in their entirety), AT270 (pThr^{181}; ThermoFisher, Waltham, MA), 12E8 (pSer^{262} and/or Ser^{356}), K9JA (hTau$^{243-441}$; Dako, Caprinteria, CA), TauC3 (hTau Asp441; Santa Cruz Biotechnology, Dallas, TX; described in United States Patent Publication US20120244174 and Gamblin, TC et al 2003 PNAS 100(17):10032-7, the contents of each of which are herein incorporated by reference in their entirety), 4E6G7 (pSer^{396}/pSer^{404}; described in United States Patent Publication No. US2010316564 and Congdon, E.E. et al., 2016. Molecular Neurodegeneration Aug 30;11(1):62, the contents of which are herein incorporated by reference in their entirety), 6B2 and variants thereof, described in International Patent Publication WO2016007414, the contents of which are herein incorporated by reference in their entirety, RZ3 (pThr^{231}), PG5 (pSer^{409}), BT2 (pS$^{199/202}$), DA31 (Tau$^{150-190}$), CP9 (pThr^{231}) Ta1505 (phospho site between Tau$^{410-421}$, particularly pSer^{413} as described in United States Patent Publication US20150183854 and Umeda, T. et al., 2015. Ann Clin Trans Neurol 2(3): 241-255, the contents of each of which are herein incorporated by reference in their entirety), PHF-6 (pThr^{231}, as described in Hoffman R et al., 1997. Biochemistry 36;8114-8124, the contents of which are herein incorporated by reference in their entirety), PHF-13 (pSer^{396}, as described in Hoffman R et al., 1997. Biochemistry 36;8114-8124), 16B5 (Tau$^{25-46}$, as described in United States Publication US20160031976, the contents of which are herein incorporated by reference in their entirety), DC8E8 (as described in United States Patent Publication US20150050215, the contents of which are herein incorporated by reference in their

entirety), PT1 or PT3 (as described in United States Patent US9371376, the contents of which are herein incorporated by reference in their entirety), 4G11 (Tau^{57-64}, as described in International Publication WO2016137950, the contents of which are herein incorporated by reference in their entirety), 1A6 (Tau^{7-17} and $Tau^{215-220}$, as described in International Publication WO2016137950), Tau15 or Tau81 (as described in International Publication WO2016055941, the contents of which are herein incorporated by reference in their entirety), TOC-1 (dimerized or aggregated tau, as described in International Publication WO2012149365, the contents of which are herein incorporated by reference in their entirety), pS404IgG2a/k (Neotope Biosciences, South San Francisco, CA; as described in Ittner et al., 2015. Neurochemistry 132:135-145, the contents of which are herein incorporated by reference in their entirety), TOMA (tau oligomer monoclonal antibody; as described in United States Patent Nos. US8778343 and US9125846, International Publications WO2012051498 and WO2011026031, or United States Publication Nos. US20150004169 and US20150322143, and Castillo-Carranza, DL et al., 2014 J Neurosci 34(12)4260-72, the contents of each of which are herein incorporated by reference in their entirety), TTC-99 (oligomeric tau), BMS-986168 (as described in United States Patent Publication US2014294831, International Publication WO2015081085 and United States Patent US8980271, the contents of which are herein incorporated by reference in their entirety), 3H3 (pan-amyloid epitope; described in Levites, Y et al 2015 J Neurosci 35(16)6265-76, the contents of which are herein incorporated by reference in their entirety), cis-pT231 (described in International Publications WO2012149334 and WO2011056561, the contents of which are herein incorporated by reference in their entirety), CP-3 ($pSer^{214}$; described in Jicha et al 1999 J Neurosci 19(17):7486-94, the contents of which are herein incorporated by reference in their entirety), TNT1 (Tau^{2-18}, as described in United States Patent Publication 20160031978, the contents of which are herein incorporated by reference in their entirety), Tau-nY29 ($nTyr^{29}$; described in Reynolds MR, et al., 2006 J Neurosci 26(42):10636-45, the contents of which are herein incorporated by reference in their entirety), Tau-nY197 ($nTyr^{197}$; described in Reyes, JF et al., 2012 Acta Neuropathol 123(1):119-32, the contents of which are herein incorporated by reference in their entirety), Tau-nY394 ($nTyr^{394}$; described in Reyes, JF et al 2012), 4E4 ($Tau^{337-343}$ $Tau^{387-397}$; described in International Publication WO2012049570 and United States Patent Publication US20150252102, the contents of each of which are herein incorporated by reference in their entirety), ADx210 (described in United States Patent Publication US20140161875, the contents of which are herein incorporated by reference in their entirety), ADx215 (described in United States Patent Publication US20140161875), ADx202 (as described in International Publication WO2015004163, the contents of which are herein incorporated by reference in their

entirety), AP422 (pSer^{422}; described in Hasegawa, M et al 1996 FEBS Lett 384:25-30, the contents of which are herein incorporated by reference in their entirety), Tau5 (Tau$^{210-241}$), RTA2 (Tau$^{273-283}$), RTAC (Tau$^{426-441}$), RTA1 (Tau$^{257-274}$), T46 (Tau$^{395-432}$), T49, MIGT4, O.BG.15, 525, 3-39, 4F1, MapTau (Tau$^{95-108}$; SMI Covance), T1, HYB33801 (Tau$^{5-12}$), Tau13 (Tau$^{2-18}$), B11E8, 5J20 (14-3-3 tau), DC25 (Tau$^{347-353}$), DC39N1 (Tau$^{45-73}$), DC-11 (Tau$^{321-391}$; described in United States Patent US7746180, the contents of which are herein incorporated by reference in their entirety), DC39 (Tau$^{401-411}$), DC4R, n847 (nitrated tau), SPM452, TI4, 1E1/A6 (Tau$^{275-291}$), 5E2, 8E6/C11 (Tau$^{209-224}$), 2E12 (pT231), NFT200, 248E5 (Tau$^{3-214}$), IG2 (Thr^{175}, Thr^{181}, Thr^{231}; as described in International Publication WO2016041553, the contents of which are herein incorporated by reference in their entirety), YP3 (as described in WO2007019273, the contents of which are herein incorporated by reference in their entirety), YP4 (as described in WO2007019273) and 14-3-3 Tau (pSer 14-3-3 binding motif; Abcam, Cambridge, MA). Further, anti-tau antibodies may be any of those listed in the antibody section of Alzforum.org or at the Antibody Resource Page.com, the contents of each of which are herein incorporated by reference in their entirety. Further, anti-tau antibodies may be any commercially available anti-tau antibody. Additional antibodies may include any of those taught in Petry, F.R. et al., 2014. PLoS One 9(5): e94251, the contents of which are herein incorporated by reference in their entirety. In one example, such antibodies may include any of those described in Jicha, G.A. et al., 1997. Journal of Neuroscience Research 48:128--132, the contents of which are herein incorporated by reference in their entirety. One such antibody, MC-1, recognizes distinct conformations of tau that are associated with neurological disease.

[00286] In some embodiments, payloads may encode anti-tau antibodies (or fragments thereof) taught in United States Publication No. US2014294831, the contents of which are herein incorporated by reference in their entirety. Such antibodies may include IPN001 and/or IPN002 antibodies or fragments of such antibodies. In some cases, variable domains of IPN002 as presented in Figures 2A and 2B of US2014294831 may be used (e.g., incorporated into another antibody). In some cases, CDR regions of IPN002 as underlined in Figures 2A and 2B may be used (e.g., incorporated into another antibody or used to prepare humanized versions of IPN002). In some cases, anti-tau antibodies may include any of the IPN001 or IPN002 antibody variants taught in US2014294831 (e.g., in Figures 9-16 of that publication). In one embodiment, this antibody is also referred to as BMS-986168.

[00287] In some cases, payloads may encode anti-tau antibodies (or fragments thereof) taught in Otvos, L. et al., 1994. J Neurosci. Res 39(6):669-73, the contents of which are herein incorporated by reference in their entirety. Such antibodies may include monoclonal antibody

PHF-1 or fragments thereof. The PHF-1 antibody binds to tau paired helical filaments, a pathological conformation of tau, found in certain neurological disorders, including Alzheimer's disease. Further, antibody affinity is increased when either serine 396 or serine 404 of tau is phosphorylated and even further increased when both are phosphorylated.

[00288] In some embodiments, payloads may encode anti-tau antibodies (or fragments thereof) taught in US Patent Number US5811310, the contents of which are herein incorporated by reference in their entirety. Such embodiments may include monoclonal antibodies PHF-1 or MC-1 or fragments thereof. MC-1 is a conformational antibody binding to the epitopes presented in Jicha, G.A., et al., 1997. J Neurosci Res 48(128-132).

[00289] In some embodiments, payloads may encode anti-tau antibodies (or fragments thereof) taught in International Publication Number WO2015035190, the contents of which are herein incorporated by reference in their entirety. Such embodiments may include, but are not limited to, antibodies PHF-1 or MC-1 or fragments thereof. Viral genomes of the AAV particles of the present invention may comprise or encode any of SEQ ID NO: 1-6 of WO2015035190.

[00290] Anti-tau antibodies (or fragments thereof) encoded by viral genomes of the invention may include antibodies that bind to one or more of the epitopes presented in Otvos, L. et al., 1994. J Neurosci. Res 39(6):669-73 (e.g., any of those presented in Table 1 of that publication).

[00291] In some embodiments, payloads may encode anti-tau antibodies (or fragments thereof) taught in US Patent Number US7746180, the contents of which are herein incorporated by reference in their entirety. Such embodiments may include antibody DC-11 or fragments thereof.

[00292] In some embodiments, the antibodies encoded by the viral genomes of the present invention may target any of the antigenic regions or epitopes described in United States Patent Publication No US2008050383 or US20100316564, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the antibody targets pS396/pS404. Such embodiments may include antibody 4E6 and/or variants or fragments thereof. The affinity of antibody 4E6 for soluble PHF and its ability to reduce soluble phospho tau has been described in Congdon, E.E. et al., 2016. Molecular Neurodegeneration Aug 30;11(1):62, the contents of which are herein incorporated by reference in their entirety.

[00293] In some embodiments, the antibodies encoded by the viral genomes of the present invention may target any of the antigenic regions or epitopes described in International Patent Publication WO1998022120, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the antibody may be PHF-6 (pT231), or fragments or variants thereof. In another embodiment, the antibody may be PHF-13 (pS396), or a fragment of variant

thereof. These antibodies are further described in Hoffman et al., 1997. Biochemistry 36: 8114-8124, the contents of which are herein incorporated by reference in their entirety.

[00294] In some embodiments, the antibodies encoded by the viral genomes of the present invention may target any of the antigenic regions or epitopes described in International Publication WO2016126993, the contents of which are herein incorporated by reference in their entirety. The antibodies may be derived from any of the tau epitopes described in Table A of WO2016126993. In one embodiment, the antibody of the present invention may comprise any of the sequences listed in Table B or Table 1 of WO2016126993.

[00295] In some embodiments, the antibodies encoded by the viral genomes of the present invention may target any of the antigenic regions or epitopes described in United States Patent Publication US20120244174, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the antibody may bind to caspase-cleaved tau. In one embodiment, the epitope for antibodies targeting caspase cleaved tau is aspartic acid 421. In another embodiment, the epitope for antibodies targeting caspase cleaved tau may be the C-terminus after glutamic residue Glu391. In yet another embodiment, the epitope for antibodies targeting caspase cleaved tau may be at the N-terminus at aspartic acid residue 13. In another embodiment, the antibody may be TauC3.

[00296] In some embodiments, the antibodies encoded by the viral genomes of the present invention may target any of the antigenic regions or epitopes described in United States Patent Publication US20160031978, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the antibody may bind to tau N-terminal residues associated with the PP1/GSK3 signaling cascade. In one embodiment, the antibody may be TNT1.

[00297] In some embodiments, the antibodies encoded by the viral genomes of the present invention may be any of those described in d'Abramo, C et al., 2015. PLOS One 10(8):e0135774, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the antibody may be CP13 (pS202), or a fragment or variant thereof. In another embodiment, the antibody may be RZ3 (pT231), or a fragment or variant thereof. In another embodiment, the antibody may be PG5 (pS409), or a fragment or variant thereof.

[00298] Anti-tau antibodies or fragments thereof encoded by the viral genomes of the present invention may target tau in any antigenic form. As non-limiting examples, antigenic tau may be an unphosphorylated or unmodified tau protein, a phosphorylated or otherwise post-translationally modified tau protein (O-GlnAcylated, or nitrosylated), an oligomeric species of tau protein, a soluble species of tau protein, an insoluble species of tau protein, a

conformationally abnormal species of tau protein, a neuropathological form of tau protein and/or a neurofibrillary tangle or a precursor thereof.

[00299] Anti-tau antibodies or fragments thereof encoded by the viral genomes of the invention, may target any antigenic region or epitope along the full length of any of the six human tau protein isoforms. As non-limiting examples, the targeted antigenic peptides of the tau protein may be any of the following phosphorylated sites pT50, pS396, pS396-pS404, pS404, pS396-pS404-pS422, pS409, pS413, pS422, pS198, pS199, pS199-pS202, pS202, pT205, pT212, pS214, pT212-pS214, pT181, pT231, cis-pT231, pS235, pS238, pT245, pS262, pY310, pY394, pS324, pS356, $pTau^{177-187}$, pY18, pS610, pS622, nitrosylated tau (nY18, nY29), methylated tau (di-meK281, dimeK311), O-GlnAcylated tau at S400, any of the following acetylated sites acK174, acK274, acK280, acK281 and/or any combination thereof. Acetylated tau proteins and associated antigenic peptides are described in Min et al., 2010, Neuron., 67, 953-966, Min et al., 2015, Nature Medicine., 10, 1154-1162, Cohen et al., 2011, Nature Communications., 2, 252, Gorsky et al., 2016, Scientific Report., 6, 22685, Tracy et al., 2016, Neuron., 90, 245-260, the contents of each of which are herein incorporated by reference in their entirety. Phosphorylated tau proteins and associated antigenic peptides are described in Asuni et al., 2007, J Neurosci., 27, 9115-9129, Boutajangout et al., 2010, J Neurosci., 30, 16559-16566, Boutajangout et al., 2011, J Neurochem., 118, 658-667, Chai et al., 2011, J Biol Chem., 286, 34457-34467, Gu et al., 2011, J Biol Chem., 288, 33081-33095, Sankaranarayanan et al., 2015, PloS One, 10, e0125614, Ittner et al., 2015, J Neurochem., 132, 135-145, D'Abramo et al., 2016, Neurobiol Aging., 37, 58-65, Collin et al., 2014, Brain., 137, 2834-2846, Kondo et al., 2015, Nature., 523, 431-436, the contents of each of which are herein incorporated by reference in their entirety.

[00300] In one embodiment, the antibody encoded by the viral genomes of the present invention may be a pS409 targeting antibody as described in Lee et al., 2016, Cell Reports, 16, 1690-1700, or International Patent Publication WO2013151762, the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, this antibody may be RG6100 or R071057 or variants or fragments thereof.

[00301] In one embodiment, the antibody encoded by the viral genomes of the present invention may be a pS413 targeting antibody as described in Umeda et al., 2015, Ann Clin Trans Neurol., 2(3), 241-255 or International Patent Publication WO2013180238, the contents of each of which are herein incorporated by reference in their entirety. In one embodiment, the antibody is Ta1505 or variants or fragments thereof.

[00302] In one embodiment, the antibody encoded by the viral genomes of the present invention may target a tau epitope with amino acid residues 210-275, more specifically pS238 and/or pT245, as described in International Publication WO2011053565, the contents of which are herein incorporated by reference in their entirety.

[00303] In one embodiment, the CDRs of an antibody encoded by the viral genomes of the present invention may be any of those listed in or incorporated in the antibody sequences of Table 3. In one embodiment, the CDRs may be any of those described in International Publication WO2015122922, the contents of which are herein incorporated by reference in their entirety. In one embodiment, a CDR may be any of those chosen from the group of SEQ ID NO: 41, 49, or 57 of WO2015122922. Further a CDR of an antibody encoded by the viral genomes of the present invention may have 50%, 60%, 70%, 80%, 90%, or 95% identity to SEQ ID NO: 41, 49, or 57 of WO2015122922.

[00304] In one embodiment, the antibodies encoded by the viral genomes of the present invention may be any of those described in International Publication WO2016097315, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the antibody may have an amino acid sequence as shown by SEQ ID NO: 2, 11, 20, 29, 38, 47, 56, 65, 74, 83, 92, 101, 110, 119, 128, 137, 146, 155, 164, 173, 182, 191, 209, 218, 226, or 227 of WO2016097315.

[00305] In one embodiment, the antibodies encoded by the viral genomes of the present invention may be a multispecific blood brain barrier receptor antibody that also targets tau, as described in International Publication WO2016094566, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the antibody may have a sequence as shown by SEQ ID NO: 1, 2, 17, 18, 33, 34, 49, 50, 65, 66, 81, 82, 9-16, 25-32, 41-48, 57-64, 73-80, 89-96 of WO2016094566.

[00306] In some embodiments, the antibodies (or fragments thereof) encoded by the viral genomes of the present invention may be any of those taught in United States Patent Nos. US8778343 and US9125846, International Publications WO2012051498 and WO2011026031, or United States Publication Nos. US20150004169 and US20150322143, the contents of each of which are herein incorporated by reference in their entirety. Such antibodies may include those that bind to oligomeric species of tau. Further, such an antibody may be referred to as TOMA (tau oligomer monoclonal antibody), as described in Castillo-Carranza et at (Castillo-Carranza, DL et al., 2014 J Neurosci 34(12)4260-72) the contents of which are herein incorporated by reference in their entirety. In one embodiment, the antibody that binds oligomeric tau may be TTC-99.

[00307] In some embodiments, the antibodies (or fragments thereof) encoded by the viral genomes of the present invention may be any of those taught in International Publications WO2014059442, the contents of which are herein incorporated by reference in their entirety. Such antibodies may include those that bind to oligomeric species of tau.

[00308] In some embodiments, the antibodies (or fragments thereof) encoded by the viral genomes of the present invention may be any of those taught in the International Publications WO2014008404 and WO2016126993, United States Patent Publication US20150183855, Yanamandra, K et al., 2013 Neuron 80(2):402-14 and Yanamandra, K et al 2015 Ann Clin Transl Neurol 2(3):278-88, the contents of each of which are herein incorporated by reference in their entirety. Such antibodies may block tau seeding. Non-limiting examples of antibodies described in these publications include HJ8.1.1, HJ8.1.2, HJ8.2, HJ8.3, HJ8.4, HJ8.5, HJ8.7, HJ8.8, HJ9.1, HJ9.2, HJ9.3, HJ9.4, HJ9.5, and variants thereof. Non-limiting examples of targeted epitopes of tau may include amino acids 22-34, 385-391, 405-411, 3-6, 118-122, 386-401, 7-13, and/or 272-281 of human tau.

[00309] In some embodiments, the antibodies (or fragments thereof) encoded by the viral genomes of the present invention may be any of those taught in the International Publications WO2002062851, the contents of which are herein incorporated by reference in their entirety.

[00310] In some embodiments, the antibodies (or fragments thereof) encoded by the viral genomes of the present invention may be as described in Bright, J et al., 2015 Neurobiol of Aging 36:693-709; Pedersen, JT and Sigurdsson EM, 2015 Trends Mol Med 21(6):394-402; Levites, Y et al 2015 J Neurosci 35(16)6265-76; Jicha et al 1999 J Neurosci 19(17):7486-94; Reyes JF et al., 2012 Acta Neuropathol 123(1):119-32; Reynolds MR, et al., 2006 J Neurosci 26(42):10636-45; Gamblin, TC et al 2003 PNAS 100(17):10032-7; Castillo-Carranza, DL et al., 2014 J Neurosci 34(12)4260-72; Walls, KC et al., 2014 Neurosci Lett 575:96-100; Yanamandra, K et al., 2013 Neuron 80(2):402-14; Yanamandra, K et al 2015 Ann Clin Transl Neurol 2(3):278-88; Allen B, et al., 2002 J Neurosci 22(21):9340-51; Gotz, J et al., 2010 Biochem Biophys Acta 1802(10):860-71; Hasegawa, M et al 1996 FEBS Lett 384:25-30; Carmel, G et al 1996 J Biol Chem 271(51):32780-32795; Jicha, GA et al, 1997 J Neurosci Res 48(2):128-132; Jicha, GA et al., 1997 J Neurochem 69(5):2087-95; the contents of each of which are herein incorporated by reference in their entirety.

[00311] Anti-tau antibodies or fragments thereof encoded by the viral genomes of the present invention may be any commercially available anti-tau antibody known in the art or developed by a person with skill in the art. Non-limiting examples of commercially available anti-tau antibodies include EPR2396(2) ($pThr^{50}$; Abcam, Cambridge, MA), 5H911 ($pThr^{181}$;

ThermoFisher, Waltham, MA), M7004D06 (pThr^{181}; BioLegend, San Diego, CA), 1E7 (pThr^{181}; EMD Millipore, Billerica, MA), EPR2400 (pSer^{198}; Abcam, Cambridge, MA), EPR2401Y (pSer^{199}; Abcam, Cambridge, MA), 2H23L4 (pSer^{199}; ThermoFisher, Waltham, MA), EPR2402 (pSer^{202}; Abcam, Cambridge, MA), 10F8 (pSer^{202}; Abcam, Cambridge, MA), EPR2403(2) (pThr^{205}; Abcam, Cambridge, MA), EPR1884(2) (pSer^{214}; Abcam, Cambridge, MA), EPR2488 (pThr^{231}; Abcam, Cambridge, MA), 1H6L6 (pThr^{231}; ThermoFisher, Waltham, MA), 3G3 (pThr^{231}, pSer^{235}; Abcam, Cambridge, MA), EPR2452 (pSer^{235}; Abcam, Cambridge, MA), 12G10 (pSer^{238}; Abcam, Cambridge, MA), EPR2454 (pSer^{262}; Abcam, Cambridge, MA), EPR2457(2) (pSer^{324}; Abcam, Cambridge, MA), EPR2603 (pSer^{356}; Abcam, Cambridge, MA), EPR2731 (pSer^{396}; Abcam, Cambridge, MA), EPR2605 (pSer^{404}; Abcam, Cambridge, MA), EPR2866 (pSer^{422}; Abcam, Cambridge, MA), 1A4 (pTau$^{177-187}$; Origene, Rockville, MD), 7G9 (pTau$^{177-187}$; Origene, Rockville, MD), 9B4 (pTau$^{177-187}$; Origene, Rockville, MD), 2A4 (pTau$^{177-187}$; Origene, Rockville, MD), 9G3 (pTyr^{18}; NovusBio, Littleton, CO), EPR2455(2) (pSer^{610}; Abcam, Cambridge, MA), EP2456Y (pSer^{622}; Abcam, Cambridge, MA; EMD Millipore, Billerica, MA), SMI 51 (PHF Tau$^{95-108}$; BioLegend, San Diego, CA), TOMA-1 (Oligomeric Tau; EMD Millipore, Billerica, MA), Tau-nY18 (nTyr^{18}; Origene, Rockville, MD; BioLegend, San Diego, CA; EMD Millipore, Billerica, MA), Tau-nY29 (nTyr^{29}; BioLegend, San Diego, CA; EMD Millipore, Billerica, MA; Abcam, Cambridge, MA), 1C9.G6 (di-methyl-Lys^{281}; BioLegend, San Diego, CA), 7G5.F4 (di-methyl-Lys^{311}; BioLegend, San Diego, CA), TNT-1 (Tau$^{2-18}$; EMD Millipore, Billerica, MA), TNT-2 (Tau$^{2-18}$; EMD Millipore, Billerica, MA), 7B8 (Tau$^{5-12}$; Abcam, Cambridge, MA), Tau-13 (Tau$^{20-35}$; BioLegend, San Diego, CA), 1-100 (Tau$^{1-100}$; BioLegend, San Diego, CA), 2G9.F10 (Tau$^{157-168}$; BioLegend, San Diego, CA; Origene, Rockville, MD), 39E10 (Tau$^{189-195}$; BioLegend, San Diego, CA; Origene, Rockville, MD), 77E9 (Tau$^{185-195}$; BioLegend, San Diego, CA; Origene, Rockville, MD), AT8 (pSer^{202}, pSer^{205}; ThermoFisher, Waltham, MA), AT100 (pSer^{212}, pSer^{214}; ThermoFisher, Waltham, MA), PHF-6 (pThr^{231}; NovusBio, Littleton, CO; EMD Millipore, Billerica, MA; BioLegend, San Diego, CA; ThermoFisher, Waltham, MA), AT180 (pThr^{231}; ThermoFisher, Waltham, MA), AT270 (pThr^{181}; ThermoFisher, Waltham, MA), PHF-13 (pSer^{396}; ThermoFisher, Waltham, MA; BioLegend, San Diego, CA), TauC3 (Asp^{421}; BioLegend, San Diego, CA; EMD Millipore, Billerica, MA; ThermoFisher, Waltham, MA), Tau12 (Tau$^{6-18}$; BioLegend, San Diego, CA; EMD Millipore, Billerica, MA), Tau5 (Tau$^{210-241}$; BioLegend, San Diego, CA; EMD Millipore, Billerica, MA; Abcam, Cambridge MA; ThermoFisher, Waltham, MA), HT7 (Tau$^{159-163}$; ThermoFisher, Waltham, MA), 77G7 (Tau$^{316-355}$; BioLegend, San Diego, CA), Tau46 (Tau$^{404-441}$; BioLegend, San Diego, CA; NovusBio, Littleton, CO; Abcam, Cambridge, MA), UMAB239

(Tau$^{623-758}$; Origene, Rockville, MD), OTI6G3 (Tau$^{623-758}$; Origene, Rockville, MD), OTI13E11 (Tau$^{623-758}$; Origene, Rockville, MD), OTI13B5 (Tau$^{623-758}$; Origene, Rockville, MD), E178 (Tau$^{700-800}$; Abcam, Cambridge, MA), SP70 (N-terminal Tau; Origene, Rockville, MD; NovusBio, Littleton, CO; ThermoFisher, Waltham, MA; Abcam, Cambridge, MA), C45 (N-terminal Tau; Origene, Rockville, MD), Tau7 (C-terminal Tau; EMD Millipore, Billerica, MA), S.125.0 (C-terminal Tau; ThermoFisher, Waltham, MA), 8E6/C11 (Three-repeat Tau$^{209-224}$; EMD Millipore, Billerica, MA), 1E1/A6 (Four-repeat Tau$^{275-291}$; EMD Millipore, Billerica, MA), 7D12.1 (Four-repeat Tau$^{275-291}$; EMD Millipore, Billerica, MA), 5C7 (Four-repeat Tau$^{267-278}$; BioLegend, San Diego, CA; Origene, Rockville, MD), 5F9 (Four-repeat Tau$^{275-291}$; BioLegend, San Diego, CA; Origene, Rockville, MD), 3H6.H7 (0N Tau$^{39-50}$; BioLegend, San Diego, CA; Origene, Rockville, MD), 4H5.B9 (1N Tau$^{68-79}$; BioLegend, San Diego, CA; Origene, Rockville, MD), 71C11 (2N Tau; BioLegend, San Diego, CA), PC1C6 (unphosphorylated tau; EMD Millipore, Billerica, MA), Tau2 (BioLegend, San Diego, CA; Origene, Rockville, MD; EMD Millipore, Billerica, MA), 2E9 (Origene, Rockville, MD; NovusBio, Littleton, CO), 4F1 (Origene, Rockville, MD; NovusBio, Littleton, CO), 5B10 (NovusBio, Littleton, CO); 5E2 (EMD Millipore, Billerica, MA), Tau-93 (Origene, Rockville, MD), T14 (ThermoFisher, Waltham, MA), T46 (ThermoFisher, Waltham, MA), BT2 (ThermoFisher, Waltham, MA) and/or variants or derivates thereof.

[00312] In one embodiment, the antibodies encoded by the viral genomes of the present invention may be multispecific antibodies for transferrin receptor and a brain antigen, wherein the brain antigen may be tau, as described in International Publication WO2016081643, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the antibody may have a sequence as given by SEQ ID NO: 160 or 161 of WO2016081643.

[00313] In one embodiment, the antibodies encoded by the viral genomes of the present invention are any of those described in United States Patent Nos. US8871447, US8420613, International Publication No. WO2014193935, WO2010011999, or in United States Publication Nos. US20110250217, US20110020237, US20100316590, or US20120225864, the contents of each of which are herein incorporated by reference in their entirety. In one embodiment, the antibody recognizes an amyloidogenic or aggregating protein.

Disease Specific Epitopes, Innate Defense Regulator Peptides, Cyclic Peptides

[00314] In one embodiment, the viral genomes of the AAV particles may comprise nucleic acids which have been engineered to enable expression of antibodies binding to disease-specific epitopes of proteins. Such antibodies may be used to diagnose, prevent, and/or treat the corresponding medical conditions by targeting epitopes of the protein presented by or accessible

on native or non-native forms (e.g., misfolded forms of native proteins) of the target. Such epitopes may be specific to diseases involved with misfolding of a protein due to pathologic condition and resulting in misfolded aggregates. The disease-specific proteins are considered to be toxic to neurons and to have a role in neuronal cell death and dysfunction in neurodegenerative diseases including, but not limited to, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease, dementia by Lewy body (DLB), and prion diseases, e.g. Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS), kuru, and fatal familial insomnia (FFI).

[00315] In one embodiment, the encoded disease-specific epitopes may include epitopes on SOD1 that are revealed as SOD1 (Superoxide dismutase [Cu-Zn]) dissociates from its homodimeric, normal state. The SOD epitopes may be selectively presented or accessible in non-native SOD1 forms including misfolded SOD1 monomer, misfolded SOD1 dimer, and the epitopes selectively presented or accessible in SOD1 aggregates. Such epitopes may be specific to neurodegenerative diseases including, but not limited to, amyotrophic lateral sclerosis (ALS), Alzheimer's (AD), Parkinson's (PD), and Lewy body diseases (LBD).

[00316] In one embodiment, the expressed antibodies may bind to epitopes presented by or accessible on non-native forms of SOD1, such as those presented by SED ID NO: 2, 3, 5, 6, and 7 of US Patent No. US7977314 (the contents of which are herein incorporated by reference in its entirety), or presented by or accessible on monomeric forms of SOD1, such as those presented by SEQ ID NO: 1 and 4 of US Patent No. US7977314, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the expressed antibodies may comprise isolated peptides corresponding to such epitopes, such as those presented in SEQ ID NO: 1-8 or SEQ ID NO: 8-16, or epitopes presented by SEQ ID NO: 34-63, 65-79 of US Patent No. US7977314, the contents of which are herein incorporated by reference in their entirety.

[00317] In one embodiment, the encoded disease-specific epitopes may be specific to diseases associated with prion protein (PrP); familial amyloid polyneuropathy or senile systemic amyloidosis or a disease related by the presence of misfolded transthyretine (TTR); renal accumulation of β2 microglobulin amyloid deposits or a disease related by the presence of misfolded β2 microglobulin, amyotrophic lateral sclerosis (ALS) or a disease related by the presence of misfolded SOD1; leukemias or myelomas or a disease related by the presence of misfolded cluster of differentiation 38 (CD38); colon cancer metastasis and or a disease related by the presence of misfolded cluster of differentiation (CD44); tumors associated with tumor necrosis factor receptor (TNFR); cancers including cervical, head and neck, endometrial, lung and breast carcinomas, pleural mesotheliomas, malignant melanomas, Hodgkin lymphomas,

anaplastic large cell non-Hodgkin lymphomas, or a disease related by the presence of misfolded Notch homolog 1 (NOTCH1) e.g. acute myeloid leukemias and B-cell chronic lymphoid leukemias; cancer in which Fas receptor (FasR) is implicated; cancers and related disorders in which misfolded epidermal growth factor (EGFR) is implicated; and/or other related diseases, disorders and conditions.

[00318] In one embodiment, the encoded disease specific epitopes may include epitopes that are revealed as the proteins misfold. In one embodiment, the expressed antibodies may bind to predicted epitopes of human PrP, such as those presented by SEQ ID NO: 1-10 of US Patent Publication No. US20100233176; bovine PrP, such as those presented by SEQ ID NO: 11-15 of US Patent Publication No. US20100233176, TTR, such as those presented by SEQ ID NO: 16-22 of US Patent Publication No. US20100233176; beta-2 microglobulin, such as those presented by SEQ ID NO: 23-26 of US Patent Publication No. US20100233176; SOD1, such as those presented by SEQ ID NO: 27-40 of US Patent Publication No. US20100233176; CD38, such as those presented by SEQ ID NO: 41-45 of US Patent Publication No. US20100233176; CD44, such as those presented by 46-50 of US Patent Publication No. US20100233176; TNFR, such as those presented by 51-55 of US Patent Publication No. US20100233176; notch protein, such as those presented in SEQ ID NO: 56-60 of US Patent Publication No. US20100233176; FasR, such as those presented by SEQ ID NO: 61-65 of US Patent Publication No. US20100233176; and EGFR, such as those presented by SEQ ID NO: 66-80 of US Patent Publication No. US20100233176; the contents of which are herein incorporated by reference in their entirety.

[00319] In one embodiment, the expressed antibodies may comprise peptides corresponding to such epitopes. In one embodiment, the expressed antibodies may comprise prion-specific peptides, such as those presented by SEQ ID NO: 81-88 of US Patent Publication No. US20100233176, the contents of which are herein incorporated by reference in their entirety, and variations thereof.

[00320] In one embodiment, the encoded disease-specific epitopes may be specific to prion diseases, including transmissible spongiform encephalopathies (TSEs) or other prion diseases. In one embodiment, the expressed antibodies may bind to predicted epitopes of PrP, such as those presented by SEQ ID NO: 24, 26, 28, 30, 32, 34, 36, 39-43, of US Patent Publication No. US20150004185, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the expressed antibodies may comprise prion-specific peptides or peptide fusions, such as those presented by SEQ ID NO: 12-23, 25, 27, 29, 31, 33, 35, 37, 38, 43, and 44-48 of US Patent Publication No. US20150004185, the contents of which are herein incorporated by reference in their entirety.

[00321] In one embodiment, the expressed antibodies may comprise prion peptides binding to prion specific abnormal isoform of the prion protein, such as those presented by SEQ ID NO: 2-10 of US Patent Publication No. US20040072236, the contents of which are herein incorporated by reference in their entirety.

[00322] In one embodiment, the viral genomes of the AAV particles may comprise nucleic acids which have been engineered to express innate defense regulator (IDR) peptides. IDRs are immunomodulatory peptides that act directly on cells to affect an innate immune response. Such IDRs may be used to treat neurodegenerative diseases associated with neuroinflammation, e.g. amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Friedreich's ataxia, Huntington's disease, Lewy body disease, Parkinson's disease, spinal muscular atrophy, and multiple sclerosis (MS) and other neurodegenerative diseases. In one embodiment, IDRs may be those presented by SEQ ID NO: 1-969, and 973-1264 of International Publication No. WO2013034982, the contents of which are herein incorporated by reference in their entirety, or analogs, derivatives, amidated variations and conservative variations thereof.

[00323] In one embodiment, the viral genomes of the AAV particles may comprise nucleic acids which have been engineered to express antibodies binding to an epitope of the Tropomyosin receptor kinase (TrkC) receptor. Such antibodies may comprise a peptide, such as one presented by SEQ ID NO: 1 of US Patent No. US9200080, the contents of which are herein incorporated by reference in their entirety.

[00324] In some embodiments, the viral genomes of the AAV particles may comprise nucleic acids which have been engineered to express cyclic peptides with an amino acid sequence SNK. Non-limiting examples of other cyclic peptides include SEQ ID NO: 1-7 of US Patent No. US9216217, the contents of which are herein incorporated by reference in their entirety. The method of preparing the antibodies may include hyperimmune preparation method, as described in US Patent No. US9216217, the contents of which are herein incorporated by reference in their entirety.

Prions

[00325] In one embodiment, the viral genomes of the AAV particles may comprise a nucleic acid sequence encoding antibodies comprising prion peptides comprising prion epitopes, and fusions and repeats thereof, such as those presented by SEQ ID NO: 8-32, 35, and 36 of US Patent No. US9056918, the contents of which are herein incorporated by reference in their entirety.

[00326] In one embodiment, the viral genomes of the AAV particles may comprise a nucleic acid sequence encoding prion binding proteins (PrPBP). In one embodiment, the PrPBPs are

cadherins, such as those presented by SEQ ID NO: 1 and 2 of International Publication WO1997/045746, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the PrPBPs are cadherins, such as those presented by SEQ ID NO: 2 and 7-9 of International Publication No. WO2001000235, the contents of which are herein incorporated by reference in their entirety.

The nature of the polypeptides and variants

[00327] Antibodies encoded by payload regions of the viral genomes of the invention may be translated as a whole polypeptide, a plurality of polypeptides or fragments of polypeptides, which independently may be encoded by one or more nucleic acids, fragments of nucleic acids or variants of any of the aforementioned. As used herein, "polypeptide" means a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. In some instances, the polypeptide encoded is smaller than about 50 amino acids and the polypeptide is then termed a peptide. If the polypeptide is a peptide, it will be at least about 2, 3, 4, or at least 5 amino acid residues long. Thus, polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. They may also comprise single chain or multichain polypeptides and may be associated or linked. The term polypeptide may also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid.

[00328] The term "polypeptide variant" refers to molecules which differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. Ordinarily, variants will possess at least about 50% identity (homology) to a native or reference sequence, and preferably, they will be at least about 80%, more preferably at least about 90% identical (homologous) to a native or reference sequence.

[00329] In some embodiments "variant mimics" are provided. As used herein, the term "variant mimic" is one which contains one or more amino acids which would mimic an activated sequence. For example, glutamate may serve as a mimic for phosphoro-threonine and/or phosphoro-serine. Alternatively, variant mimics may result in deactivation or in an inactivated product containing the mimic, e.g., phenylalanine may act as an inactivating substitution for tyrosine; or alanine may act as an inactivating substitution for serine.

[00330] The term "amino acid sequence variant" refers to molecules with some differences in their amino acid sequences as compared to a native or starting sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence. "Native" or "starting" sequence should not be confused with a wild type sequence. As used herein, a native or starting sequence is a relative term referring to an original molecule against which a comparison may be made. "Native" or "starting" sequences or molecules may represent the wild-type (that sequence found in nature) but do not have to be the wild-type sequence.

[00331] Ordinarily, variants will possess at least about 70% homology to a native sequence, and preferably, they will be at least about 80%, more preferably at least about 90% homologous to a native sequence. "Homology" as it applies to amino acid sequences is defined as the percentage of residues in the candidate amino acid sequence that are identical with the residues in the amino acid sequence of a second sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology. Methods and computer programs for the alignment are well known in the art. It is understood that homology depends on a calculation of percent identity but may differ in value due to gaps and penalties introduced in the calculation.

[00332] By "homologs" as it applies to amino acid sequences is meant the corresponding sequence of other species having substantial identity to a second sequence of a second species.

[00333] "Analogs" is meant to include polypeptide variants which differ by one or more amino acid alterations, e.g., substitutions, additions, or deletions of amino acid residues that still maintain the properties of the parent polypeptide.

[00334] Sequence tags or amino acids, such as one or more lysines, can be added to the peptide sequences of the invention (e.g., at the N-terminal or C-terminal ends). Sequence tags can be used for peptide purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences. Certain amino acids (e.g., C-terminal or N-terminal residues) may alternatively be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence which is soluble, or linked to a solid support.

[00335] "Substitutional variants" when referring to proteins are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. The substitutions may be single, where only one amino acid in

the molecule has been substituted, or they may be multiple, where two or more amino acids have been substituted in the same molecule.

[00336] As used herein the term "conservative amino acid substitution" refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine, and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine, or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

[00337] "Insertional variants" when referring to proteins are those with one or more amino acids inserted immediately adjacent to an amino acid at a particular position in a native or starting sequence. "Immediately adjacent" to an amino acid means connected to either the alpha-carboxy or alpha-amino functional group of the amino acid.

[00338] "Deletional variants" when referring to proteins, are those with one or more amino acids in the native or starting amino acid sequence removed. Ordinarily, deletional variants will have one or more amino acids deleted in a particular region of the molecule.

[00339] As used herein, the term "derivative" is used synonymously with the term "variant" and refers to a molecule that has been modified or changed in any way relative to a reference molecule or starting molecule. In some embodiments, derivatives include native or starting proteins that have been modified with an organic proteinaceous or non-proteinaceous derivatizing agent, and post-translational modifications. Covalent modifications are traditionally introduced by reacting targeted amino acid residues of the protein with an organic derivatizing agent that is capable of reacting with selected side-chains or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. The resultant covalent derivatives are useful in programs directed at identifying residues important for biological activity, for immunoassays, or for the preparation of anti-protein antibodies for immunoaffinity purification of the recombinant glycoprotein. Such modifications are within the ordinary skill in the art and are performed without undue experimentation.

[00340] Certain post-translational modifications are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues may be present in the proteins used in accordance with the present invention.

[00341] Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)).

[00342] "Features" when referring to proteins are defined as distinct amino acid sequence-based components of a molecule. Features of the proteins of the present invention include surface manifestations, local conformational shape, folds, loops, half-loops, domains, half-domains, sites, termini or any combination thereof.

[00343] As used herein when referring to proteins the term "surface manifestation" refers to a polypeptide based component of a protein appearing on an outermost surface.

[00344] As used herein when referring to proteins the term "local conformational shape" means a polypeptide based structural manifestation of a protein which is located within a definable space of the protein.

[00345] As used herein when referring to proteins the term "fold" means the resultant conformation of an amino acid sequence upon energy minimization. A fold may occur at the secondary or tertiary level of the folding process. Examples of secondary level folds include beta sheets and alpha helices. Examples of tertiary folds include domains and regions formed due to aggregation or separation of energetic forces. Regions formed in this way include hydrophobic and hydrophilic pockets, and the like.

[00346] As used herein the term "turn" as it relates to protein conformation means a bend which alters the direction of the backbone of a peptide or polypeptide and may involve one, two, three or more amino acid residues.

[00347] As used herein when referring to proteins the term "loop" refers to a structural feature of a peptide or polypeptide which reverses the direction of the backbone of a peptide or polypeptide and comprises four or more amino acid residues. Oliva et al. have identified at least 5 classes of protein loops (J. Mol Biol 266 (4): 814-830; 1997).

[00348] As used herein when referring to proteins the term "half-loop" refers to a portion of an identified loop having at least half the number of amino acid residues as the loop from which it is derived. It is understood that loops may not always contain an even number of amino acid

residues. Therefore, in those cases where a loop contains or is identified to comprise an odd number of amino acids, a half-loop of the odd-numbered loop will comprise the whole number portion or next whole number portion of the loop (number of amino acids of the loop/2+/-0.5 amino acids). For example, a loop identified as a 7-amino acid loop could produce half-loops of 3 amino acids or 4 amino acids (7/2=3.5+/-0.5 being 3 or 4).

[00349] As used herein when referring to proteins the term "domain" refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (e.g., binding capacity, serving as a site for protein-protein interactions).

[00350] As used herein when referring to proteins the term "half-domain" means portion of an identified domain having at least half the number of amino acid residues as the domain from which it is derived. It is understood that domains may not always contain an even number of amino acid residues. Therefore, in those cases where a domain contains or is identified to comprise an odd number of amino acids, a half-domain of the odd-numbered domain will comprise the whole number portion or next whole number portion of the domain (number of amino acids of the domain/2+/-0.5 amino acids). For example, a domain identified as a 7-amino acid domain could produce half-domains of 3 amino acids or 4 amino acids (7/2=3.5+/-0.5 being 3 or 4). It is also understood that sub-domains may be identified within domains or half-domains, these subdomains possessing less than all of the structural or functional properties identified in the domains or half domains from which they were derived. It is also understood that the amino acids that comprise any of the domain types herein need not be contiguous along the backbone of the polypeptide (i.e., nonadjacent amino acids may fold structurally to produce a domain, half-domain or subdomain).

[00351] As used herein when referring to proteins the terms "site" as it pertains to amino acid based embodiments is used synonymous with "amino acid residue" and "amino acid side chain". A site represents a position within a peptide or polypeptide that may be modified, manipulated, altered, derivatized or varied within the polypeptide based molecules of the present invention.

[00352] As used herein the terms "termini or terminus" when referring to proteins refers to an extremity of a peptide or polypeptide. Such extremity is not limited only to the first or final site of the peptide or polypeptide but may include additional amino acids in the terminal regions. The polypeptide based molecules of the present invention may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group (NH2)) and a C-terminus (terminated by an amino acid with a free carboxyl group (COOH)). Proteins of the invention are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These sorts of proteins will have multiple N- and C-

termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

[00353] Once any of the features have been identified or defined as a component of a molecule of the invention, any of several manipulations and/or modifications of these features may be performed by moving, swapping, inverting, deleting, randomizing, or duplicating. Furthermore, it is understood that manipulation of features may result in the same outcome as a modification to the molecules of the invention. For example, a manipulation which involves deleting a domain would result in the alteration of the length of a molecule just as modification of a nucleic acid to encode less than a full-length molecule would.

[00354] Modifications and manipulations can be accomplished by methods known in the art such as site directed mutagenesis. The resulting modified molecules may then be tested for activity using in vitro or in vivo assays such as those described herein or any other suitable screening assay known in the art.

AAV Production

[00355] The present invention provides methods for the generation of parvoviral particles, e.g. AAV particles, by viral genome replication in a viral replication cell.

[00356] In accordance with the invention, the viral genome comprising a payload region encoding an antibody, an antibody-based composition or fragment thereof, will be incorporated into the AAV particle produced in the viral replication cell. Methods of making AAV particles are well known in the art and are described in e.g., United States Patent Nos. US6204059, US5756283, US6258595, US6261551, US6270996, US6281010, US6365394, US6475769, US6482634, US6485966, US6943019, US6953690, US7022519, US7238526, US7291498 and US7491508, US5064764, US6194191, US6566118, US8137948; or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353, and WO2001023597; Methods In Molecular Biology, ed. Richard, Humana Press, NJ (1995); O'Reilly et al., Baculovirus Expression Vectors, A Laboratory Manual, Oxford Univ. Press (1994); Samulski et al., *J. Vir.*63:3822-8 (1989); Kajigaya et al., *Proc. Nat'l. Acad. Sci. USA* 88: 4646-50 (1991); Ruffing et al., *J. Vir.* 66:6922-30 (1992); Kimbauer et al., *Vir.*, 219:37-44 (1996); Zhao et al., *Vir.*272:382-93 (2000); the contents of each of which are herein incorporated by reference in their entirety. In one embodiment, the AAV particles are made using the methods described in WO2015191508, the contents of which are herein incorporated by reference in their entirety.

[00357] Viral replication cells commonly used for production of recombinant AAV viral vectors include but are not limited to 293 cells, COS cells, HeLa cells, KB cells, and other

mammalian cell lines as described in U.S. Pat. Nos. US6156303, US5387484, US5741683, US5691176, and US5688676; U.S. patent publication No. 2002/0081721, and International Patent Publication Nos. WO 00/47757, WO 00/24916, and WO 96/17947, the contents of each of which are herein incorporated by reference in their entireties.

[00358] In some embodiments, the present invention provides a method for producing an AAV particle having enhanced (increased, improved) transduction efficiency comprising the steps of: 1) co-transfecting competent bacterial cells with a bacmid vector and either a viral construct vector and/or AAV payload construct vector, 2) isolating the resultant viral construct expression vector and AAV payload construct expression vector and separately transfecting viral replication cells, 3) isolating and purifying resultant payload and viral construct particles comprising viral construct expression vector or AAV payload construct expression vector, 4) co-infecting a viral replication cell with both the AAV payload and viral construct particles comprising viral construct expression vector or AAV payload construct expression vector, and 5) harvesting and purifying the AAV particle comprising a viral genome.

[00359] In some embodiments, the present invention provides a method for producing an AAV particle comprising the steps of 1) simultaneously co-transfecting mammalian cells, such as, but not limited to HEK293 cells, with a payload region, a construct expressing rep and cap genes and a helper construct, and 2) harvesting and purifying the AAV particle comprising a viral genome.

[00360] In some embodiments, the viral genome of the AAV particle of the invention optionally encodes a selectable marker. The selectable marker may comprise a cell-surface marker, such as any protein expressed on the surface of the cell including, but not limited to receptors, CD markers, lectins, integrins, or truncated versions thereof.

[00361] In some embodiments, selectable marker reporter genes are selected from those described in International Application No. WO 96/23810; Heim et al., Current Biology 2:178-182 (1996); Heim et al., Proc. Natl. Acad. Sci. USA (1995); or Heim et al., Science 373:663-664 (1995); WO 96/30540, the contents of each of which are incorporated herein by reference in their entireties).

II. FORMULATION AND DELIVERY

Pharmaceutical Compositions

[00362] According to the present invention the AAV particles may be prepared as pharmaceutical compositions. It will be understood that such compositions necessarily comprise one or more active ingredients and, most often, a pharmaceutically acceptable excipient.

[00363] Relative amounts of the active ingredient (e.g. AAV particle), a pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in

accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.1% and 100%, e.g., between .5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

[00364] In some embodiments, the AAV particle pharmaceutical compositions described herein may comprise at least one payload. As a non-limiting example, the pharmaceutical compositions may contain an AAV particle with 1, 2, 3, 4 or 5 payloads. In one embodiment, the pharmaceutical composition may contain a nucleic acid encoding a payload construct encoding proteins selected from antibodies and/or antibody-based compositions.

[00365] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, e.g., to non-human animals, e.g. non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, dogs, mice, rats, birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

[00366] In some embodiments, compositions are administered to humans, human patients, or subjects.

Formulations

[00367] The AAV particles of the invention can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection or transduction; (3) permit the sustained or delayed expression of the payload; (4) alter the biodistribution (e.g., target the viral particle to specific tissues or cell types); (5) increase the translation of encoded protein; (6) alter the release profile of encoded protein; and/or (7) allow for regulatable expression of the payload.

[00368] Formulations of the present invention can include, without limitation, saline, liposomes, lipid nanoparticles, polymers, peptides, proteins, cells transfected with viral vectors (e.g., for transfer or transplantation into a subject) and combinations thereof.

[00369] Formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. As used herein the term "pharmaceutical composition" refers to compositions comprising at least one active ingredient and optionally one or more pharmaceutically acceptable excipients.

[00370] In general, such preparatory methods include the step of associating the active ingredient with an excipient and/or one or more other accessory ingredients. As used herein, the phrase "active ingredient" generally refers either to an AAV particle carrying a payload region encoding the polypeptides of the invention or to the antibody or antibody-based composition encoded by a viral genome of by an AAV particle as described herein.

[00371] Formulations of the AAV particles and pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

[00372] A pharmaceutical composition in accordance with the present disclosure may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" refers to a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[00373] In one embodiment, the AAV particles of the invention may be formulated in PBS with 0.001% of pluronic acid (F-68) at a pH of about 7.0.

[00374] Relative amounts of the active ingredient (e.g. AAV particle), the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.1% and 100%, e.g., between 0.5 and 50%, between 1-30%, between 5-80%, or at least 80% (w/w) active ingredient.

[00375] In some embodiments, the AAV formulations described herein may contain sufficient AAV particles for expression of at least one expressed functional antibody or antibody-based

composition. As a non-limiting example, the AAV particles may contain viral genomes encoding 1, 2, 3, 4, or 5 functional antibodies.

[00376] According to the present invention AAV particles may be formulated for CNS delivery. Agents that cross the brain blood barrier may be used. For example, some cell penetrating peptides that can target molecules to the brain blood barrier endothelium may be used for formulation (e.g., Mathupala, *Expert Opin Ther Pat.*, 2009, 19, 137-140; the content of which is incorporated herein by reference in its entirety).

Excipients and Diluents

[00377] The AAV particles of the invention can be formulated using one or more excipients or diluents to (1) increase stability; (2) increase cell transfection or transduction; (3) permit the sustained or delayed release; (4) alter the biodistribution (e.g., target the viral particle to specific tissues or cell types); (5) increase the translation of encoded protein in vivo; (6) alter the release profile of encoded protein in vivo; and/or (7) allow for regulatable expression of the polypeptides of the invention.

[00378] In some embodiments, a pharmaceutically acceptable excipient may be at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use for humans and for veterinary use. In some embodiments, an excipient may be approved by United States Food and Drug Administration. In some embodiments, an excipient may be of pharmaceutical grade. In some embodiments, an excipient may meet the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

[00379] Excipients, as used herein, include, but are not limited to, any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, and the like, as suited to the particular dosage form desired. Various excipients for formulating pharmaceutical compositions and techniques for preparing the composition are known in the art (see Remington: The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro, Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference in its entirety). The use of a conventional excipient medium may be contemplated within the scope of the present disclosure, except insofar as any conventional excipient medium may be incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

[00380] Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen

phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, *etc.*, and/or combinations thereof.

Inactive Ingredients

[00381] In some embodiments, AAV particle formulations may comprise at least one inactive ingredient. As used herein, the term "inactive ingredient" refers to one or more agents that do not contribute to the activity of the active ingredient of the pharmaceutical composition included in formulations. In some embodiments, all, none or some of the inactive ingredients which may be used in the formulations of the present invention may be approved by the US Food and Drug Administration (FDA).

[00382] In one embodiment, the AAV particle pharmaceutical compositions comprise at least one inactive ingredient such as, but not limited to, 1,2,6-Hexanetriol; 1,2-Dimyristoyl-Sn-Glycero-3-(Phospho-S-(1-Glycerol)); 1,2-Dimyristoyl-Sn-Glycero-3-Phosphocholine; 1,2-Dioleoyl-Sn-Glycero-3-Phosphocholine; 1,2-Dipalmitoyl-Sn-Glycero-3-(Phospho-Rac-(1-Glycerol)); 1,2-Distearoyl-Sn-Glycero-3-(Phospho-Rac-(1-Glycerol)); 1,2-Distearoyl-Sn-Glycero-3-Phosphocholine; 1-O-Tolylbiguanide; 2-Ethyl-1,6-Hexanediol; Acetic Acid; Acetic Acid, Glacial; Acetic Anhydride; Acetone; Acetone Sodium Bisulfite; Acetylated Lanolin Alcohols; Acetylated Monoglycerides; Acetylcysteine; Acetyltryptophan, DL-; Acrylates Copolymer; Acrylic Acid-Isooctyl Acrylate Copolymer; Acrylic Adhesive 788; Activated Charcoal; Adcote 72A103; Adhesive Tape; Adipic Acid; Aerotex Resin 3730; Alanine; Albumin Aggregated; Albumin Colloidal; Albumin Human; Alcohol; Alcohol, Dehydrated; Alcohol, Denatured; Alcohol, Diluted; Alfadex; Alginic Acid; Alkyl Ammonium Sulfonic Acid Betaine; Alkyl Aryl Sodium Sulfonate; Allantoin; Allyl .Alpha.-Ionone; Almond Oil; Alpha-Terpineol; Alpha-Tocopherol; Alpha-Tocopherol Acetate, Dl-; Alpha-Tocopherol, Dl-; Aluminum Acetate; Aluminum Chlorhydroxy Allantoinate; Aluminum Hydroxide; Aluminum Hydroxide - Sucrose, Hydrated; Aluminum Hydroxide Gel; Aluminum Hydroxide Gel F 500; Aluminum Hydroxide Gel F 5000; Aluminum Monostearate; Aluminum Oxide; Aluminum Polyester; Aluminum Silicate; Aluminum Starch Octenylsuccinate; Aluminum Stearate; Aluminum Subacetate; Aluminum Sulfate Anhydrous; Amerchol C; Amerchol-Cab; Aminomethylpropanol; Ammonia; Ammonia Solution; Ammonia Solution, Strong; Ammonium Acetate; Ammonium Hydroxide; Ammonium Lauryl Sulfate; Ammonium Nonoxynol-4 Sulfate; Ammonium Salt Of C-12-C-15 Linear Primary Alcohol Ethoxylate; Ammonium Sulfate; Ammonyx; Amphoteric-2; Amphoteric-9; Anethole; Anhydrous Citric Acid; Anhydrous Dextrose; Anhydrous Lactose; Anhydrous Trisodium Citrate; Aniseed Oil; Anoxid Sbn; Antifoam; Antipyrine; Apaflurane;

Apricot Kernel Oil Peg-6 Esters; Aquaphor; Arginine; Arlacel; Ascorbic Acid; Ascorbyl Palmitate; Aspartic Acid; Balsam Peru; Barium Sulfate; Beeswax; Beeswax, Synthetic; Beheneth-10; Bentonite; Benzalkonium Chloride; Benzenesulfonic Acid; Benzethonium Chloride; Benzododecinium Bromide; Benzoic Acid; Benzyl Alcohol; Benzyl Benzoate; Benzyl Chloride; Betadex; Bibapcitide; Bismuth Subgallate; Boric Acid; Brocrinat; Butane; Butyl Alcohol; Butyl Ester Of Vinyl Methyl Ether/Maleic Anhydride Copolymer (125000 Mw); Butyl Stearate; Butylated Hydroxyanisole; Butylated Hydroxytoluene; Butylene Glycol; Butylparaben; Butyric Acid; C20-40 Pareth-24; Caffeine; Calcium; Calcium Carbonate; Calcium Chloride; Calcium Gluceptate; Calcium Hydroxide; Calcium Lactate; Calcobutrol; Caldiamide Sodium; Caloxetate Trisodium; Calteridol Calcium; Canada Balsam; Caprylic/Capric Triglyceride; Caprylic/Capric/Stearic Triglyceride; Captan; Captisol; Caramel; Carbomer 1342; Carbomer 1382; Carbomer 934; Carbomer 934p; Carbomer 940; Carbomer 941; Carbomer 980; Carbomer 981; Carbomer Homopolymer Type B (Allyl Pentaerythritol Crosslinked); Carbomer Homopolymer Type C (Allyl Pentaerythritol Crosslinked); Carbon Dioxide; Carboxy Vinyl Copolymer; Carboxymethylcellulose; Carboxymethylcellulose Sodium; Carboxypolymethylene; Carrageenan; Carrageenan Salt; Castor Oil; Cedar Leaf Oil; Cellulose; Cellulose, Microcrystalline; Cerasynt-Se; Ceresin; Ceteareth-12; Ceteareth-15; Ceteareth-30; Cetearyl Alcohol/Ceteareth-20; Cetearyl Ethylhexanoate; Ceteth-10; Ceteth-2; Ceteth-20; Ceteth-23; Cetostearyl Alcohol; Cetrimonium Chloride; Cetyl Alcohol; Cetyl Esters Wax; Cetyl Palmitate; Cetylpyridinium Chloride; Chlorobutanol; Chlorobutanol Hemihydrate; Chlorobutanol, Anhydrous; Chlorocresol; Chloroxylenol; Cholesterol; Choleth; Choleth-24; Citrate; Citric Acid; Citric Acid Monohydrate; Citric Acid, Hydrous; Cocamide Ether Sulfate; Cocamine Oxide; Coco Betaine; Coco Diethanolamide; Coco Monoethanolamide; Cocoa Butter; Coco-Glycerides; Coconut Oil; Coconut Oil, Hydrogenated; Coconut Oil/Palm Kernel Oil Glycerides, Hydrogenated; Cocoyl Caprylocaprate; Cola Nitida Seed Extract; Collagen; Coloring Suspension; Corn Oil; Cottonseed Oil; Cream Base; Creatine; Creatinine; Cresol; Croscarmellose Sodium; Crospovidone; Cupric Sulfate; Cupric Sulfate Anhydrous; Cyclomethicone; Cyclomethicone/Dimethicone Copolyol; Cysteine; Cysteine Hydrochloride; Cysteine Hydrochloride Anhydrous; Cysteine, Dl-; D&C Red No. 28; D&C Red No. 33; D&C Red No. 36; D&C Red No. 39; D&C Yellow No. 10; Dalfampridine; Daubert 1-5 Pestr (Matte) 164z; Decyl Methyl Sulfoxide; Dehydag Wax Sx; Dehydroacetic Acid; Dehymuls E; Denatonium Benzoate; Deoxycholic Acid; Dextran; Dextran 40; Dextrin; Dextrose; Dextrose Monohydrate; Dextrose Solution; Diatrizoic Acid; Diazolidinyl Urea; Dichlorobenzyl Alcohol; Dichlorodifluoromethane; Dichlorotetrafluoroethane; Diethanolamine; Diethyl Pyrocarbonate;

Diethyl Sebacate; Diethylene Glycol Monoethyl Ether; Diethylhexyl Phthalate; Dihydroxyaluminum Aminoacetate; Diisopropanolamine; Diisopropyl Adipate; Diisopropyl Dilinoleate; Dimethicone 350; Dimethicone Copolyol; Dimethicone Mdx4-4210; Dimethicone Medical Fluid 360; Dimethyl Isosorbide; Dimethyl Sulfoxide; Dimethylaminoethyl Methacrylate - Butyl Methacrylate - Methyl Methacrylate Copolymer; Dimethyldioctadecylammonium Bentonite; Dimethylsiloxane/Methylvinylsiloxane Copolymer; Dinoseb Ammonium Salt; Dipalmitoylphosphatidylglycerol, Dl-; Dipropylene Glycol; Disodium Cocoamphodiacetate; Disodium Laureth Sulfosuccinate; Disodium Lauryl Sulfosuccinate; Disodium Sulfosalicylate; Disofenin; Divinylbenzene Styrene Copolymer; Dmdm Hydantoin; Docosanol; Docusate Sodium; Duro-Tak 280-2516; Duro-Tak 387-2516; Duro-Tak 80-1196; Duro-Tak 87-2070; Duro-Tak 87-2194; Duro-Tak 87-2287; Duro-Tak 87-2296; Duro-Tak 87-2888; Duro-Tak 87-2979; Edetate Calcium Disodium; Edetate Disodium; Edetate Disodium Anhydrous; Edetate Sodium; Edetic Acid; Egg Phospholipids; Entsufon; Entsufon Sodium; Epilactose; Epitetracycline Hydrochloride; Essence Bouquet 9200; Ethanolamine Hydrochloride; Ethyl Acetate; Ethyl Oleate; Ethylcelluloses; Ethylene Glycol; Ethylene Vinyl Acetate Copolymer; Ethylenediamine; Ethylenediamine Dihydrochloride; Ethylene-Propylene Copolymer; Ethylene-Vinyl Acetate Copolymer (28% Vinyl Acetate); Ethylene-Vinyl Acetate Copolymer (9% Vinylacetate); Ethylhexyl Hydroxystearate; Ethylparaben; Eucalyptol; Exametazime; Fat, Edible; Fat, Hard; Fatty Acid Esters; Fatty Acid Pentaerythriol Ester; Fatty Acids; Fatty Alcohol Citrate; Fatty Alcohols; Fd&C Blue No. 1; Fd&C Green No. 3; Fd&C Red No. 4; Fd&C Red No. 40; Fd&C Yellow No. 10 (Delisted); Fd&C Yellow No. 5; Fd&C Yellow No. 6; Ferric Chloride; Ferric Oxide; Flavor 89-186; Flavor 89-259; Flavor Df-119; Flavor Df-1530; Flavor Enhancer; Flavor Fig 827118; Flavor Raspberry Pfc-8407; Flavor Rhodia Pharmaceutical No. Rf 451; Fluorochlorohydrocarbons; Formaldehyde; Formaldehyde Solution; Fractionated Coconut Oil; Fragrance 3949-5; Fragrance 520a; Fragrance 6.007; Fragrance 91-122; Fragrance 9128-Y; Fragrance 93498g; Fragrance Balsam Pine No. 5124; Fragrance Bouquet 10328; Fragrance Chemoderm 6401-B; Fragrance Chemoderm 6411; Fragrance Cream No. 73457; Fragrance Cs-28197; Fragrance Felton 066m; Fragrance Firmenich 47373; Fragrance Givaudan Ess 9090/1c; Fragrance H-6540; Fragrance Herbal 10396; Fragrance Nj-1085; Fragrance P O Fl-147; Fragrance Pa 52805; Fragrance Pera Derm D; Fragrance Rbd-9819; Fragrance Shaw Mudge U-7776; Fragrance Tf 044078; Fragrance Ungerer Honeysuckle K 2771; Fragrance Ungerer N5195; Fructose; Gadolinium Oxide; Galactose; Gamma Cyclodextrin; Gelatin; Gelatin, Crosslinked; Gelfoam Sponge; Gellan Gum (Low Acyl); Gelva 737; Gentisic Acid; Gentisic Acid Ethanolamide; Gluceptate Sodium; Gluceptate Sodium Dihydrate; Gluconolactone;

Glucuronic Acid; Glutamic Acid, Dl-; Glutathione; Glycerin; Glycerol Ester Of Hydrogenated Rosin; Glyceryl Citrate; Glyceryl Isostearate; Glyceryl Laurate; Glyceryl Monostearate; Glyceryl Oleate; Glyceryl Oleate/Propylene Glycol; Glyceryl Palmitate; Glyceryl Ricinoleate; Glyceryl Stearate; Glyceryl Stearate - Laureth-23; Glyceryl Stearate/Peg Stearate; Glyceryl Stearate/Peg-100 Stearate; Glyceryl Stearate/Peg-40 Stearate; Glyceryl Stearate-Stearamidoethyl Diethylamine; Glyceryl Trioleate; Glycine; Glycine Hydrochloride; Glycol Distearate; Glycol Stearate; Guanidine Hydrochloride; Guar Gum; Hair Conditioner (18n195-1m); Heptane; Hetastarch; Hexylene Glycol; High Density Polyethylene; Histidine; Human Albumin Microspheres; Hyaluronate Sodium; Hydrocarbon; Hydrocarbon Gel, Plasticized; Hydrochloric Acid; Hydrochloric Acid, Diluted; Hydrocortisone; Hydrogel Polymer; Hydrogen Peroxide; Hydrogenated Castor Oil; Hydrogenated Palm Oil; Hydrogenated Palm/Palm Kernel Oil Peg-6 Esters; Hydrogenated Polybutene 635-690; Hydroxide Ion; Hydroxyethyl Cellulose; Hydroxyethylpiperazine Ethane Sulfonic Acid; Hydroxymethyl Cellulose; Hydroxyoctacosanyl Hydroxystearate; Hydroxypropyl Cellulose; Hydroxypropyl Methylcellulose 2906; Hydroxypropyl-Beta-cyclodextrin; Hypromellose 2208 (15000 Mpa.S); Hypromellose 2910 (15000 Mpa.S); Hypromelloses; Imidurea; Iodine; Iodoxamic Acid; Iofetamine Hydrochloride; Irish Moss Extract; Isobutane; Isoceteth-20; Isoleucine; Isooctyl Acrylate; Isopropyl Alcohol; Isopropyl Isostearate; Isopropyl Myristate; Isopropyl Myristate - Myristyl Alcohol; Isopropyl Palmitate; Isopropyl Stearate; Isostearic Acid; Isostearyl Alcohol; Isotonic Sodium Chloride Solution; Jelene; Kaolin; Kathon Cg; Kathon Cg II; Lactate; Lactic Acid; Lactic Acid, Dl-; Lactic Acid, L-; Lactobionic Acid; Lactose; Lactose Monohydrate; Lactose, Hydrous; Laneth; Lanolin; Lanolin Alcohol - Mineral Oil; Lanolin Alcohols; Lanolin Anhydrous; Lanolin Cholesterols; Lanolin Nonionic Derivatives; Lanolin, Ethoxylated; Lanolin, Hydrogenated; Lauralkonium Chloride; Lauramine Oxide; Laurdimonium Hydrolyzed Animal Collagen; Laureth Sulfate; Laureth-2; Laureth-23; Laureth-4; Lauric Diethanolamide; Lauric Myristic Diethanolamide; Lauroyl Sarcosine; Lauryl Lactate; Lauryl Sulfate; Lavandula Angustifolia Flowering Top; Lecithin; Lecithin Unbleached; Lecithin, Egg; Lecithin, Hydrogenated; Lecithin, Hydrogenated Soy; Lecithin, Soybean; Lemon Oil; Leucine; Levulinic Acid; Lidofenin; Light Mineral Oil; Light Mineral Oil (85 Ssu); Limonene, (+/-)-; Lipocol Sc-15; Lysine; Lysine Acetate; Lysine Monohydrate; Magnesium Aluminum Silicate; Magnesium Aluminum Silicate Hydrate; Magnesium Chloride; Magnesium Nitrate; Magnesium Stearate; Maleic Acid; Mannitol; Maprofix; Mebrofenin; Medical Adhesive Modified S-15; Medical Antiform A-F Emulsion; Medronate Disodium; Medronic Acid; Meglumine; Menthol; Metacresol; Metaphosphoric Acid; Methanesulfonic Acid; Methionine; Methyl Alcohol; Methyl Gluceth-10;

Methyl Gluceth-20; Methyl Gluceth-20 Sesquistearate; Methyl Glucose Sesquistearate; Methyl Laurate; Methyl Pyrrolidone; Methyl Salicylate; Methyl Stearate; Methylboronic Acid; Methylcellulose (4000 Mpa.S); Methylcelluloses; Methylchloroisothiazolinone; Methylene Blue; Methylisothiazolinone; Methylparaben; Microcrystalline Wax; Mineral Oil; Mono and Diglyceride; Monostearyl Citrate; Monothioglycerol; Multisterol Extract; Myristyl Alcohol; Myristyl Lactate; Myristyl-.Gamma.-Picolinium Chloride; N-(Carbamoyl-Methoxy Peg-40)-1,2-Distearoyl-Cephalin Sodium; N,N-Dimethylacetamide; Niacinamide; Nioxime; Nitric Acid; Nitrogen; Nonoxynol Iodine; Nonoxynol-15; Nonoxynol-9; Norflurane; Oatmeal; Octadecene-1/Maleic Acid Copolymer; Octanoic Acid; Octisalate; Octoxynol-1; Octoxynol-40; Octoxynol-9; Octyldodecanol; Octylphenol Polymethylene; Oleic Acid; Oleth-10/Oleth-5; Oleth-2; Oleth-20; Oleyl Alcohol; Oleyl Oleate; Olive Oil; Oxidronate Disodium; Oxyquinoline; Palm Kernel Oil; Palmitamine Oxide; Parabens; Paraffin; Paraffin, White Soft; Parfum Creme 45/3; Peanut Oil; Peanut Oil, Refined; Pectin; Peg 6-32 Stearate/Glycol Stearate; Peg Vegetable Oil; Peg-100 Stearate; Peg-12 Glyceryl Laurate; Peg-120 Glyceryl Stearate; Peg-120 Methyl Glucose Dioleate; Peg-15 Cocamine; Peg-150 Distearate; Peg-2 Stearate; Peg-20 Sorbitan Isostearate; Peg-22 Methyl Ether/Dodecyl Glycol Copolymer; Peg-25 Propylene Glycol Stearate; Peg-4 Dilaurate; Peg-4 Laurate; Peg-40 Castor Oil; Peg-40 Sorbitan Diisostearate; Peg-45/Dodecyl Glycol Copolymer; Peg-5 Oleate; Peg-50 Stearate; Peg-54 Hydrogenated Castor Oil; Peg-6 Isostearate; Peg-60 Castor Oil; Peg-60 Hydrogenated Castor Oil; Peg-7 Methyl Ether; Peg-75 Lanolin; Peg-8 Laurate; Peg-8 Stearate; Pegoxol 7 Stearate; Pentadecalactone; Pentaerythritol Cocoate; Pentasodium Pentetate; Pentetate Calcium Trisodium; Pentetic Acid; Peppermint Oil; Perflutren; Perfume 25677; Perfume Bouquet; Perfume E-1991; Perfume Gd 5604; Perfume Tana 90/42 Scba; Perfume W-1952-1; Petrolatum; Petrolatum, White; Petroleum Distillates; Phenol; Phenol, Liquefied; Phenonip; Phenoxyethanol; Phenylalanine; Phenylethyl Alcohol; Phenylmercuric Acetate; Phenylmercuric Nitrate; Phosphatidyl Glycerol, Egg; Phospholipid; Phospholipid, Egg; Phospholipon 90g; Phosphoric Acid; Pine Needle Oil (Pinus Sylvestris); Piperazine Hexahydrate; Plastibase-50w; Polacrilin; Polidronium Chloride; Poloxamer 124; Poloxamer 181; Poloxamer 182; Poloxamer 188; Poloxamer 237; Poloxamer 407; Poly(Bis(P-Carboxyphenoxy)Propane Anhydride):Sebacic Acid;
Poly(Dimethylsiloxane/Methylvinylsiloxane/Methylhydrogensiloxane) Dimethylvinyl Or Dimethylhydroxy Or Trimethyl Endblocked; Poly(Dl-Lactic-Co-Glycolic Acid), (50:50; Poly(Dl-Lactic-Co-Glycolic Acid), Ethyl Ester Terminated, (50:50; Polyacrylic Acid (250000 Mw); Polybutene (1400 Mw); Polycarbophil; Polyester; Polyester Polyamine Copolymer; Polyester Rayon; Polyethylene Glycol 1000; Polyethylene Glycol 1450; Polyethylene Glycol

1500; Polyethylene Glycol 1540; Polyethylene Glycol 200; Polyethylene Glycol 300; Polyethylene Glycol 300-1600; Polyethylene Glycol 3350; Polyethylene Glycol 400; Polyethylene Glycol 4000; Polyethylene Glycol 540; Polyethylene Glycol 600; Polyethylene Glycol 6000; Polyethylene Glycol 8000; Polyethylene Glycol 900; Polyethylene High Density Containing Ferric Oxide Black (<1%); Polyethylene Low Density Containing Barium Sulfate (20-24%); Polyethylene T; Polyethylene Terephthalates; Polyglactin; Polyglyceryl-3 Oleate; Polyglyceryl-4 Oleate; Polyhydroxyethyl Methacrylate; Polyisobutylene; Polyisobutylene (1100000 Mw); Polyisobutylene (35000 Mw); Polyisobutylene 178-236; Polyisobutylene 241-294; Polyisobutylene 35-39; Polyisobutylene Low Molecular Weight; Polyisobutylene Medium Molecular Weight; Polyisobutylene/Polybutene Adhesive; Polylactide; Polyols; Polyoxyethylene - Polyoxypropylene 1800; Polyoxyethylene Alcohols; Polyoxyethylene Fatty Acid Esters; Polyoxyethylene Propylene; Polyoxyl 20 Cetostearyl Ether; Polyoxyl 35 Castor Oil; Polyoxyl 40 Hydrogenated Castor Oil; Polyoxyl 40 Stearate; Polyoxyl 400 Stearate; Polyoxyl 6 And Polyoxyl 32 Palmitostearate; Polyoxyl Distearate; Polyoxyl Glyceryl Stearate; Polyoxyl Lanolin; Polyoxyl Palmitate; Polyoxyl Stearate; Polypropylene; Polypropylene Glycol; Polyquaternium-10; Polyquaternium-7 (70/30 Acrylamide/Dadmac; Polysiloxane; Polysorbate 20; Polysorbate 40; Polysorbate 60; Polysorbate 65; Polysorbate 80; Polyurethane; Polyvinyl Acetate; Polyvinyl Alcohol; Polyvinyl Chloride; Polyvinyl Chloride-Polyvinyl Acetate Copolymer; Polyvinylpyridine; Poppy Seed Oil; Potash; Potassium Acetate; Potassium Alum; Potassium Bicarbonate; Potassium Bisulfite; Potassium Chloride; Potassium Citrate; Potassium Hydroxide; Potassium Metabisulfite; Potassium Phosphate, Dibasic; Potassium Phosphate, Monobasic; Potassium Soap; Potassium Sorbate; Povidone Acrylate Copolymer; Povidone Hydrogel; Povidone K17; Povidone K25; Povidone K29/32; Povidone K30; Povidone K90; Povidone K90f; Povidone/Eicosene Copolymer; Povidones; Ppg-12/Smdi Copolymer; Ppg-15 Stearyl Ether; Ppg-20 Methyl Glucose Ether Distearate; Ppg-26 Oleate; Product Wat; Proline; Promulgen D; Promulgen G; Propane; Propellant A-46; Propyl Gallate; Propylene Carbonate; Propylene Glycol; Propylene Glycol Diacetate; Propylene Glycol Dicaprylate; Propylene Glycol Monolaurate; Propylene Glycol Monopalmitostearate; Propylene Glycol Palmitostearate; Propylene Glycol Ricinoleate; Propylene Glycol/Diazolidinyl Urea/Methylparaben/Propylparben; Propylparaben; Protamine Sulfate; Protein Hydrolysate; Pvm/Ma Copolymer; Quaternium-15; Quaternium-15 Cis-Form; Quaternium-52; Ra-2397; Ra-3011; Saccharin; Saccharin Sodium; Saccharin Sodium Anhydrous; Safflower Oil; Sd Alcohol 3a; Sd Alcohol 40; Sd Alcohol 40-2; Sd Alcohol 40b; Sepineo P 600; Serine; Sesame Oil; Shea Butter; Silastic Brand Medical Grade Tubing; Silastic Medical Adhesive,Silicone Type A; Silica,

Dental; Silicon; Silicon Dioxide; Silicon Dioxide, Colloidal; Silicone; Silicone Adhesive 4102; Silicone Adhesive 4502; Silicone Adhesive Bio-Psa Q7-4201; Silicone Adhesive Bio-Psa Q7-4301; Silicone Emulsion; Silicone/Polyester Film Strip; Simethicone; Simethicone Emulsion; Sipon Ls 20np; Soda Ash; Sodium Acetate; Sodium Acetate Anhydrous; Sodium Alkyl Sulfate; Sodium Ascorbate; Sodium Benzoate; Sodium Bicarbonate; Sodium Bisulfate; Sodium Bisulfite; Sodium Borate; Sodium Borate Decahydrate; Sodium Carbonate; Sodium Carbonate Decahydrate; Sodium Carbonate Monohydrate; Sodium Cetostearyl Sulfate; Sodium Chlorate; Sodium Chloride; Sodium Chloride Injection; Sodium Chloride Injection, Bacteriostatic; Sodium Cholesteryl Sulfate; Sodium Citrate; Sodium Cocoyl Sarcosinate; Sodium Desoxycholate; Sodium Dithionite; Sodium Dodecylbenzenesulfonate; Sodium Formaldehyde Sulfoxylate; Sodium Gluconate; Sodium Hydroxide; Sodium Hypochlorite; Sodium Iodide; Sodium Lactate; Sodium Lactate, L-; Sodium Laureth-2 Sulfate; Sodium Laureth-3 Sulfate; Sodium Laureth-5 Sulfate; Sodium Lauroyl Sarcosinate; Sodium Lauryl Sulfate; Sodium Lauryl Sulfoacetate; Sodium Metabisulfite; Sodium Nitrate; Sodium Phosphate; Sodium Phosphate Dihydrate; Sodium Phosphate, Dibasic; Sodium Phosphate, Dibasic, Anhydrous; Sodium Phosphate, Dibasic, Dihydrate; Sodium Phosphate, Dibasic, Dodecahydrate; Sodium Phosphate, Dibasic, Heptahydrate; Sodium Phosphate, Monobasic; Sodium Phosphate, Monobasic, Anhydrous; Sodium Phosphate, Monobasic, Dihydrate; Sodium Phosphate, Monobasic, Monohydrate; Sodium Polyacrylate (2500000 Mw); Sodium Pyrophosphate; Sodium Pyrrolidone Carboxylate; Sodium Starch Glycolate; Sodium Succinate Hexahydrate; Sodium Sulfate; Sodium Sulfate Anhydrous; Sodium Sulfate Decahydrate; Sodium Sulfite; Sodium Sulfosuccinated Undecyclenic Monoalkylolamide; Sodium Tartrate; Sodium Thioglycolate; Sodium Thiomalate; Sodium Thiosulfate; Sodium Thiosulfate Anhydrous; Sodium Trimetaphosphate; Sodium Xylenesulfonate; Somay 44; Sorbic Acid; Sorbitan; Sorbitan Isostearate; Sorbitan Monolaurate; Sorbitan Monooleate; Sorbitan Monopalmitate; Sorbitan Monostearate; Sorbitan Sesquioleate; Sorbitan Trioleate; Sorbitan Tristearate; Sorbitol; Sorbitol Solution; Soybean Flour; Soybean Oil; Spearmint Oil; Spermaceti; Squalane; Stabilized Oxychloro Complex; Stannous 2-Ethylhexanoate; Stannous Chloride; Stannous Chloride Anhydrous; Stannous Fluoride; Stannous Tartrate; Starch; Starch 1500, Pregelatinized; Starch, Corn; Stearalkonium Chloride; Stearalkonium Hectorite/Propylene Carbonate; Stearamidoethyl Diethylamine; Steareth-10; Steareth-100; Steareth-2; Steareth-20; Steareth-21; Steareth-40; Stearic Acid; Stearic Diethanolamide; Stearoxytrimethylsilane; Steartrimonium Hydrolyzed Animal Collagen; Stearyl Alcohol; Sterile Water For Inhalation; Styrene/Isoprene/Styrene Block Copolymer; Succimer; Succinic Acid; Sucralose; Sucrose; Sucrose Distearate; Sucrose Polyesters; Sulfacetamide

Sodium; Sulfobutylether .Beta.-Cyclodextrin; Sulfur Dioxide; Sulfuric Acid; Sulfurous Acid; Surfactol Qs; Tagatose, D-; Talc; Tall Oil; Tallow Glycerides; Tartaric Acid; Tartaric Acid, Dl-; Tenox; Tenox-2; Tert-Butyl Alcohol; Tert-Butyl Hydroperoxide; Tert-Butylhydroquinone; Tetrakis(2-Methoxyisobutylisocyanide)Copper(I) Tetrafluoroborate; Tetrapropyl Orthosilicate; Tetrofosmin; Theophylline; Thimerosal; Threonine; Thymol; Tin; Titanium Dioxide; Tocopherol; Tocophersolan; Total parenteral nutrition, lipid emulsion; Triacetin; Tricaprylin; Trichloromonofluoromethane; Trideceth-10; Triethanolamine Lauryl Sulfate; Trifluoroacetic Acid; Triglycerides, Medium Chain; Trihydroxystearin; Trilaneth-4 Phosphate; Trilaureth-4 Phosphate; Trisodium Citrate Dihydrate; Trisodium Hedta; Triton 720; Triton X-200; Trolamine; Tromantadine; Tromethamine (TRIS); Tryptophan; Tyloxapol; Tyrosine; Undecylenic Acid; Union 76 Amsco-Res 6038; Urea; Valine; Vegetable Oil; Vegetable Oil Glyceride, Hydrogenated; Vegetable Oil, Hydrogenated; Versetamide; Viscarin; Viscose/Cotton; Vitamin E; Wax, Emulsifying; Wecobee Fs; White Ceresin Wax; White Wax; Xanthan Gum; Zinc; Zinc Acetate; Zinc Carbonate; Zinc Chloride; and Zinc Oxide.

[00383] Pharmaceutical composition formulations of AAV particles disclosed herein may include cations or anions. In one embodiment, the formulations include metal cations such as, but not limited to, Zn2+, Ca2+, Cu2+, Mn2+, Mg+ and combinations thereof. As a non-limiting example, formulations may include polymers and complexes with a metal cation (*See e.g.*, U.S. Pat. Nos. 6265389 and 6555525, each of which is herein incorporated by reference in its entirety).

[00384] Formulations of the invention may also include one or more pharmaceutically acceptable salts. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form (e.g., by reacting the free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, acetic acid, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzene sulfonic acid, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate,

stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids.

[00385] Solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N,N'*-dimethylformamide (DMF), *N,N'*-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is referred to as a "hydrate."

III. ADMINISTRATION AND DOSING

Administration

[00386] The AAV particles of the present invention may be administered by any delivery route which results in a therapeutically effective outcome. These include, but are not limited to, enteral (into the intestine), gastroenteral, epidural (into the dura mater), oral (by way of the mouth), transdermal, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intra-arterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraparenchymal (into brain tissue), intraperitoneal (infusion or injection into the peritoneum), intravesical infusion, intravitreal (through the eye), intracavernous injection (into a pathologic cavity) intracavitary (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival, cutaneous, dental (to a tooth or teeth), electro-osmosis, endocervical, endosinusial, endotracheal,

extracorporeal, hemodialysis, infiltration, interstitial, intra-abdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracoronal, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the corporus cavernosa of the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within the stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone), intrameningeal (within the meninges), intramyocardial (within the myocardium), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aurus media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique (topical route administration which is then covered by a dressing which occludes the area), ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), soft tissue, subarachnoid, subconjunctival, submucosal, topical, transplacental (through or across the placenta), transtracheal (through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photopheresis, and spinal.

[00387] In some embodiments, compositions may be administered in a way which allows them to cross the blood-brain barrier, vascular barrier, or other epithelial barrier. The AAV particles of the present invention may be administered in any suitable form, either as a liquid solution or

suspension, as a solid form suitable for liquid solution or suspension in a liquid solution. The AAV particles may be formulated with any appropriate and pharmaceutically acceptable excipient.

[00388] In one embodiment, the AAV particles of the present invention may be delivered to a subject via a single route administration.

[00389] In one embodiment, the AAV particles of the present invention may be delivered to a subject via a multi-site route of administration. A subject may be administered at 2, 3, 4, 5, or more than 5 sites.

[00390] In one embodiment, a subject may be administered the AAV particles of the present invention using a bolus infusion.

[00391] In one embodiment, a subject may be administered the AAV particles of the present invention using sustained delivery over a period of minutes, hours, or days. The infusion rate may be changed depending on the subject, distribution, formulation or another delivery parameter.

[00392] In one embodiment, the AAV particles of the present invention may be delivered by intramuscular delivery route. (See, e.g., U. S. Pat. No. 6506379; the content of which is incorporated herein by reference in its entirety). Non-limiting examples of intramuscular administration include an intravenous injection or a subcutaneous injection.

[00393] In one embodiment, the AAV particles of the present invention may be delivered by oral administration. Non-limiting examples of oral administration include a digestive tract administration and a buccal administration.

[00394] In one embodiment, the AAV particles of the present invention may be delivered by intraocular delivery route. A non-limiting example of intraocular administration include an intravitreal injection.

[00395] In one embodiment, the AAV particles of the present invention may be delivered by intranasal delivery route. Non-limiting examples of intranasal delivery include administration of nasal drops or nasal sprays.

[00396] In some embodiments, the AAV particles that may be administered to a subject by peripheral injections. Non-limiting examples of peripheral injections include intraperitoneal, intramuscular, intravenous, conjunctival, or joint injection. It was disclosed in the art that the peripheral administration of AAV vectors can be transported to the central nervous system, for example, to the motor neurons (e.g., U. S. Patent Publication Nos. US20100240739 and US20100130594; the content of each of which is incorporated herein by reference in their entirety).

[00397] In one embodiment, the AAV particles may be delivered by injection into the CSF pathway. Non-limiting examples of delivery to the CSF pathway include intrathecal and intracerebroventricular administration.

[00398] In one embodiment, the AAV particles may be delivered by systemic delivery. As a non-limiting example, the systemic delivery may be by intravascular administration.

[00399] In one embodiment, the AAV particles of the present invention may be administered to a subject by intracranial delivery (See, e.g., US Pat. No. 8119611; the content of which is incorporated herein by reference in its entirety).

[00400] In one embodiment, the AAV particles of the present invention may be administered to a subject by intraparenchymal administration.

[00401] In one embodiment, the AAV particles of the present invention may be administered to a subject by intramuscular administration.

[00402] In one embodiment, the AAV particles of the present invention are administered to a subject and transduce muscle of a subject. As a non-limiting example, the AAV particles are administered by intramuscular administration.

[00403] In one embodiment, the AAV particles of the present invention may be administered to a subject by intravenous administration.

[00404] In one embodiment, the AAV particles of the present invention may be administered to a subject by subcutaneous administration.

[00405] In one embodiment, the AAV particles of the present invention may be administered to a subject by topical administration.

[00406] In one embodiment, the AAV particles may be delivered by direct injection into the brain. As a non-limiting example, the brain delivery may be by intrastriatal administration.

[00407] In one embodiment, the AAV particles may be delivered by more than one route of administration. As non-limiting examples of combination administrations, AAV particles may be delivered by intrathecal and intracerebroventricular, or by intravenous and intraparenchymal administration.

Parenteral and injectable administration

[00408] In some embodiments, pharmaceutical compositions, AAV particles of the present invention may be administered parenterally. Liquid dosage forms for oral and parenteral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and/or elixirs. In addition to active ingredients, liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl

alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and/or perfuming agents. In certain embodiments for parenteral administration, compositions are mixed with solubilizing agents such as CREMOPHOR®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and/or combinations thereof. In other embodiments, surfactants are included such as hydroxypropylcellulose.

[00409] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing agents, wetting agents, and/or suspending agents. Sterile injectable preparations may be sterile injectable solutions, suspensions, and/or emulsions in nontoxic parenterally acceptable diluents and/or solvents, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid can be used in the preparation of injectables.

[00410] Injectable formulations may be sterilized, for example, by filtration through a bacterial-retaining filter, and/or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00411] In order to prolong the effect of active ingredients, it is often desirable to slow the absorption of active ingredients from subcutaneous or intramuscular injections. This may be accomplished by the use of liquid suspensions of crystalline or amorphous material with poor water solubility. The rate of absorption of active ingredients depends upon the rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Rectal and vaginal administration

[00412] In some embodiments, pharmaceutical compositions, AAV particles of the present invention may be administered rectally and/or vaginally. Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing compositions with suitable non-irritating excipients such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

Oral administration

[00413] In some embodiments, pharmaceutical compositions, AAV particles of the present invention may be administered orally. Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, an active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate and/or fillers or extenders (*e.g.* starches, lactose, sucrose, glucose, mannitol, and silicic acid), binders (*e.g.* carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia), humectants (*e.g.* glycerol), disintegrating agents (*e.g.* agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate), solution retarding agents (*e.g.* paraffin), absorption accelerators (*e.g.* quaternary ammonium compounds), wetting agents (*e.g.* cetyl alcohol and glycerol monostearate), absorbents (*e.g.* kaolin and bentonite clay), and lubricants (*e.g.* talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate), and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

Topical or transdermal administration

[00414] As described herein, pharmaceutical compositions, AAV particles of the present invention may be formulated for administration topically. The skin may be an ideal target site for delivery as it is readily accessible. Three routes are commonly considered to deliver pharmaceutical compositions, AAV particles of the present invention to the skin: (i) topical application (*e.g.* for local/regional treatment and/or cosmetic applications); (ii) intradermal injection (*e.g.* for local/regional treatment and/or cosmetic applications); and (iii) systemic delivery (*e.g.* for treatment of dermatologic diseases that affect both cutaneous and extracutaneous regions). Pharmaceutical compositions, AAV particles of the present invention can be delivered to the skin by several different approaches known in the art.

[00415] In some embodiments, the invention provides for a variety of dressings (e.g., wound dressings) or bandages (e.g., adhesive bandages) for conveniently and/or effectively carrying out methods of the present invention. Typically dressing or bandages may comprise sufficient

amounts of pharmaceutical compositions, AAV particles of the present invention described herein to allow users to perform multiple treatments.

[00416] Dosage forms for topical and/or transdermal administration may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, active ingredients are admixed under sterile conditions with pharmaceutically acceptable excipients and/or any needed preservatives and/or buffers. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of pharmaceutical compositions, AAV particles of the present invention to the body. Such dosage forms may be prepared, for example, by dissolving and/or dispensing pharmaceutical compositions, AAV particles in the proper medium. Alternatively, or additionally, rates may be controlled by either providing rate controlling membranes and/or by dispersing pharmaceutical compositions, AAV particles in a polymer matrix and/or gel.

[00417] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions.

[00418] Topically-administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of active ingredient may be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

Depot administration

[00419] As described herein, in some embodiments, pharmaceutical compositions, AAV particles of the present invention are formulated in depots for extended release. Generally, specific organs or tissues ("target tissues") are targeted for administration.

[00420] In some aspects of the invention, pharmaceutical compositions, AAV particles of the present invention are spatially retained within or proximal to target tissues. Provided are methods of providing pharmaceutical compositions, AAV particles, to target tissues of mammalian subjects by contacting target tissues (which comprise one or more target cells) with pharmaceutical compositions, AAV particles, under conditions such that they are substantially retained in target tissues, meaning that at least 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the composition is retained in the target tissues. Advantageously, retention is determined by measuring the amount of pharmaceutical compositions, AAV particles, that enter one or more target cells. For example, at least 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.9%, 99.99%, or greater than 99.99% of pharmaceutical compositions, AAV particles, administered to

subjects are present intracellularly at a period of time following administration. For example, intramuscular injection to mammalian subjects may be performed using aqueous compositions comprising pharmaceutical compositions, AAV particles of the present invention and one or more transfection reagents, and retention is determined by measuring the amount of pharmaceutical compositions, AAV particles, present in muscle cells.

[00421] Certain aspects of the invention are directed to methods of providing pharmaceutical compositions, AAV particles of the present invention to a target tissues of mammalian subjects, by contacting target tissues (comprising one or more target cells) with pharmaceutical compositions, AAV particles under conditions such that they are substantially retained in such target tissues. Pharmaceutical compositions, AAV particles comprise enough active ingredient such that the effect of interest is produced in at least one target cell. In some embodiments, pharmaceutical compositions, AAV particles generally comprise one or more cell penetration agents, although "naked" formulations (such as without cell penetration agents or other agents) are also contemplated, with or without pharmaceutically acceptable carriers.

Pulmonary administration

[00422] In some embodiments, pharmaceutical compositions, AAV particles of the present invention may be prepared, packaged, and/or sold in formulations suitable for pulmonary administration. In some embodiments, such administration is via the buccal cavity. In some embodiments, formulations may comprise dry particles comprising active ingredients. In such embodiments, dry particles may have a diameter in the range from about 0.5 nm to about 7 nm or from about 1 nm to about 6 nm. In some embodiments, formulations may be in the form of dry powders for administration using devices comprising dry powder reservoirs to which streams of propellant may be directed to disperse such powder. In some embodiments, self-propelling solvent/powder dispensing containers may be used. In such embodiments, active ingredients may be dissolved and/or suspended in low-boiling propellant in sealed containers. Such powders may comprise particles wherein at least 98% of the particles by weight have diameters greater than 0.5 nm and at least 95% of the particles by number have diameters less than 7 nm. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nm and at least 90% of the particles by number have a diameter less than 6 nm. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00423] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally, propellants may constitute 50% to 99.9% (w/w) of the composition, and active ingredient may constitute 0.1% to 20% (w/w) of the composition. Propellants may further comprise additional ingredients such as liquid non-ionic and/or solid

anionic surfactant and/or solid diluent (which may have particle sizes of the same order as particles comprising active ingredients).

[00424] Pharmaceutical compositions formulated for pulmonary delivery may provide active ingredients in the form of droplets of solution and/or suspension. Such formulations may be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising active ingredients, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. Droplets provided by this route of administration may have an average diameter in the range from about 0.1 nm to about 200 nm.

Intranasal, nasal and buccal administration

[00425] In some embodiments, pharmaceutical compositions, AAV particles of the present invention may be administered nasally and/or intranasal. In some embodiments, formulations described herein useful for pulmonary delivery may also be useful for intranasal delivery. In some embodiments, formulations for intranasal administration comprise a coarse powder comprising the active ingredient and having an average particle from about 0.2 μm to 500 μm. Such formulations are administered in the manner in which snuff is taken, *i.e.* by rapid inhalation through the nasal passage from a container of the powder held close to the nose.

[00426] Formulations suitable for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition may be prepared, packaged, and/or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may, for example, 0.1% to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may comprise powders and/or an aerosolized and/or atomized solutions and/or suspensions comprising active ingredients. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may comprise average particle and/or droplet sizes in the range of from about 0.1 nm to about 200 nm, and may further comprise one or more of any additional ingredients described herein.

Ophthalmic or otic administration

[00427] In some embodiments, pharmaceutical compositions, AAV particles of the present invention may be prepared, packaged, and/or sold in formulations suitable for ophthalmic and/or otic administration. Such formulations may, for example, be in the form of eye and/or ear drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in aqueous and/or oily liquid excipients. Such drops may further comprise buffering agents, salts, and/or one or more other of any additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise active ingredients in microcrystalline form and/or in liposomal preparations. Subretinal inserts may also be used as forms of administration.

Delivery

[00428] In one embodiment, the AAV particles or pharmaceutical compositions of the present invention may be administered or delivered using the methods for treatment of disease described in US Patent No. 8,999,948, or International Publication No. WO2014178863, the contents of which are herein incorporated by reference in their entirety.

[00429] In one embodiment, the AAV particles or pharmaceutical compositions of the present invention may be administered or delivered using the methods for delivering gene therapy in Alzheimer's Disease or other neurodegenerative conditions as described in US Application No. 20150126590, the contents of which are herein incorporated by reference in their entirety.

[00430] In one embodiment, the AAV particles or pharmaceutical compositions of the present invention may be administered or delivered using the methods for delivery of a CNS gene therapy as described in US Patent Nos. 6,436,708, and 8,946,152, and International Publication No. WO2015168666, the contents of which are herein incorporated by reference in their entirety.

[00431] In one embodiment, the AAV particle or pharmaceutical compositions of the present invention may be administered or delivered using the methods for delivering proteins using AAV vectors described in European Patent Application No. EP2678433, the contents of which are herein incorporated by reference in their entirety.

[00432] In one embodiment, the AAV particle or pharmaceutical compositions of the present invention may be administered or delivered using the methods for delivering DNA to the bloodstream described in US Patent No. US 6,211,163, the contents of which are herein incorporated by reference in their entirety.

[00433] In one embodiment, the AAV particle or pharmaceutical compositions of the present invention may be administered or delivered using the methods for delivering a payload to the central nervous system described in US Patent No. US 7,588,757, the contents of which are herein incorporated by reference in their entirety.

[00434] In one embodiment, the AAV particle or pharmaceutical compositions of the present invention may be administered or delivered using the methods for delivering a payload described in US Patent No. US 8,283,151, the contents of which are herein incorporated by reference in their entirety.

[00435] In one embodiment, the AAV particle or pharmaceutical compositions of the present invention may be administered or delivered using the methods for delivering a payload using a glutamic acid decarboxylase (GAD) delivery vector described in International Patent Publication No. WO2001089583, the contents of which are herein incorporated by reference in their entirety.

[00436] In one embodiment, the AAV particle or pharmaceutical compositions of the present invention may be administered or delivered using the methods for delivering a payload to neural cells described in International Patent Publication No. WO2012057363, the contents of which are herein incorporated by reference in their entirety.

Delivery to Cells

[00437] The present disclosure provides a method of delivering to a cell or tissue any of the above-described AAV particles, comprising contacting the cell or tissue with said AAV particle or contacting the cell or tissue with a formulation comprising said AAV particle, or contacting the cell or tissue with any of the described compositions, including pharmaceutical compositions. The method of delivering the AAV particle to a cell or tissue can be accomplished in *vitro*, *ex vivo*, or *in vivo*.

Delivery to Subjects

[00438] The present disclosure additionally provides a method of delivering to a subject, including a mammalian subject, any of the above-described AAV particles comprising administering to the subject said AAV particle, or administering to the subject a formulation comprising said AAV particle, or administering to the subject any of the described compositions, including pharmaceutical compositions.

Dose and Regimen

[00439] The present invention provides methods of administering AAV particles in accordance with the invention to a subject in need thereof. The pharmaceutical, diagnostic, or prophylactic AAV particles and compositions of the present invention may be administered to a subject using any amount and any route of administration effective for preventing, treating, managing, or diagnosing diseases, disorders and/or conditions. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like. The subject may be a human, a mammal, or an animal. Compositions in

accordance with the invention are typically formulated in unit dosage form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective, prophylactically effective, or appropriate diagnostic dose level for any particular individual will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific payload employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific AAV particle employed; the duration of the treatment; drugs used in combination or coincidental with the specific AAV particle employed; and like factors well known in the medical arts.

[00440] In certain embodiments, AAV particle pharmaceutical compositions in accordance with the present invention may be administered at dosage levels sufficient to deliver from about 0.0001 mg/kg to about 100 mg/kg, from about 0.001 mg/kg to about 0.05 mg/kg, from about 0.005 mg/kg to about 0.05 mg/kg, from about 0.001 mg/kg to about 0.005 mg/kg, from about 0.05 mg/kg to about 0.5 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic, diagnostic, or prophylactic, effect. It will be understood that the above dosing concentrations may be converted to vg or viral genomes per kg or into total viral genomes administered by one of skill in the art.

[00441] In certain embodiments, AAV particle pharmaceutical compositions in accordance with the present disclosure may be administered at about 10 to about 600 µl/site, 50 to about 500 µl/site, 100 to about 400 µl/site, 120 to about 300 µl/site, 140 to about 200 µl/site, about 160 µl/site. As non-limiting examples, AAV particles may be administered at 50 µl/site and/or 150 µl/site.

[00442] The desired dosage of the AAV particles of the present invention may be delivered only once, three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. As used herein, a "split dose" is the division of "single unit dose" or total daily dose into

two or more doses, *e.g.*, two or more administrations of the "single unit dose". As used herein, a "single unit dose" is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event.

[00443] The desired dosage of the AAV particles of the present invention may be administered as a "pulse dose" or as a "continuous flow". As used herein, a "pulse dose" is a series of single unit doses of any therapeutic administered with a set frequency over a period of time. As used herein, a "continuous flow" is a dose of therapeutic administered continuously for a period of time in a single route/single point of contact, i.e., continuous administration event. A total daily dose, an amount given or prescribed in 24-hour period, may be administered by any of these methods, or as a combination of these methods, or by any other methods suitable for a pharmaceutical administration.

[00444] In one embodiment, delivery of the AAV particles of the present invention to a subject provides neutralizing activity to a subject. The neutralizing activity can be for at least 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 20 months, 21 months, 22 months, 23 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years or more than 10 years.

[00445] In one embodiment, delivery of the AAV particles of the present invention results in minimal serious adverse events (SAEs) as a result of the delivery of the AAV particles.

[00446] In one embodiment, delivery of AAV particles to cells of the central nervous system (e.g., parenchyma) may comprise a total dose between about $1x10^6$ VG and about $1x10^{16}$ VG. In some embodiments, delivery may comprise a total dose of about $1x10^6$, $2x10^6$, $3x10^6$, $4x10^6$, $5x10^6$, $6x10^6$, $7x10^6$, $8x10^6$, $9x10^6$, $1x10^7$, $2x10^7$, $3x10^7$, $4x10^7$, $5x10^7$, $6x10^7$, $7x10^7$, $8x10^7$, $9x10^7$, $1x10^8$, $2x10^8$, $3x10^8$, $4x10^8$, $5x10^8$, $6x10^8$, $7x10^8$, $8x10^8$, $9x10^8$, $1x10^9$, $2x10^9$, $3x10^9$, $4x10^9$, $5x10^9$, $6x10^9$, $7x10^9$, $8x10^9$, $9x10^9$, $1x10^{10}$, $1.9x10^{10}$, $2x10^{10}$, $3x10^{10}$, $3.73x10^{10}$, $4x10^{10}$, $5x10^{10}$, $6x10^{10}$, $7x10^{10}$, $8x10^{10}$, $9x10^{10}$, $1x10^{11}$, $2x10^{11}$, $2.5x10^{11}$, $3x10^{11}$, $4x10^{11}$, $5x10^{11}$, $6x10^{11}$, $7x10^{11}$, $8x10^{11}$, $9x10^{11}$, $1x10^{12}$, $2x10^{12}$, $3x10^{12}$, $4x10^{12}$, $5x10^{12}$, $6x10^{12}$, $7x10^{12}$, $8x10^{12}$, $9x10^{12}$, $1x10^{13}$, $2x10^{13}$, $3x10^{13}$, $4x10^{13}$, $5x10^{13}$, $6x10^{13}$, $7x10^{13}$, $8x10^{13}$, $9x10^{13}$, $1x10^{14}$, $2x10^{14}$, $3x10^{14}$, $4x10^{14}$, $5x10^{14}$, $6x10^{14}$, $7x10^{14}$, $8x10^{14}$, $9x10^{14}$, $1x10^{15}$, $2x10^{15}$, $3x10^{15}$, $4x10^{15}$, $5x10^{15}$, $6x10^{15}$, $7x10^{15}$, $8x10^{15}$, $9x10^{15}$, or $1x10^{16}$ VG. As a non-limiting example, the total dose is $1x10^{13}$ VG. As another non-limiting example, the total dose is $2.1x10^{12}$ VG.

[00447] In one embodiment, delivery of AAV particles to cells of the central nervous system (e.g., parenchyma) may comprise a composition concentration between about $1x10^6$ VG/mL and about $1x10^{16}$ VG/mL. In some embodiments, delivery may comprise a composition

concentration of about $1x10^6$, $2x10^6$, $3x10^6$, $4x10^6$, $5x10^6$, $6x10^6$, $7x10^6$, $8x10^6$, $9x10^6$, $1x10^7$, $2x10^7$, $3x10^7$, $4x10^7$, $5x10^7$, $6x10^7$, $7x10^7$, $8x10^7$, $9x10^7$, $1x10^8$, $2x10^8$, $3x10^8$, $4x10^8$, $5x10^8$, $6x10^8$, $7x10^8$, $8x10^8$, $9x10^8$, $1x10^9$, $2x10^9$, $3x10^9$, $4x10^9$, $5x10^9$, $6x10^9$, $7x10^9$, $8x10^9$, $9x10^9$, $1x10^{10}$, $2x10^{10}$, $3x10^{10}$, $4x10^{10}$, $5x10^{10}$, $6x10^{10}$, $7x10^{10}$, $8x10^{10}$, $9x10^{10}$, $1x10^{11}$, $2x10^{11}$, $3x10^{11}$, $4x10^{11}$, $5x10^{11}$, $6x10^{11}$, $7x10^{11}$, $8x10^{11}$, $9x10^{11}$, $1x10^{12}$, $2x10^{12}$, $3x10^{12}$, $4x10^{12}$, $5x10^{12}$, $6x10^{12}$, $7x10^{12}$, $8x10^{12}$, $9x10^{12}$, $1x10^{13}$, $2x10^{13}$, $3x10^{13}$, $4x10^{13}$, $5x10^{13}$, $6x10^{13}$, $7x10^{13}$, $8x10^{13}$, $9x10^{13}$, $1x10^{14}$, $2x10^{14}$, $3x10^{14}$, $4x10^{14}$, $5x10^{14}$, $6x10^{14}$, $7x10^{14}$, $8x10^{14}$, $9x10^{14}$, $1x10^{15}$, $2x10^{15}$, $3x10^{15}$, $4x10^{15}$, $5x10^{15}$, $6x10^{15}$, $7x10^{15}$, $8x10^{15}$, $9x10^{15}$, or $1x10^{16}$ VG/mL. In one embodiment, the delivery comprises a composition concentration of $1x10^{13}$ VG/mL. In one embodiment, the delivery comprises a composition concentration of $2.1x10^{12}$ VG/mL.

Combinations

[00448] The AAV particles may be used in combination with one or more other therapeutic, prophylactic, research or diagnostic agents. By "in combination with," it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present invention. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, research, or diagnostic compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body.

Measurement of Expression

[00449] Expression of payloads from viral genomes may be determined using various methods known in the art such as, but not limited to immunochemistry (e.g., IHC), *in situ* hybridization (ISH), enzyme-linked immunosorbent assay (ELISA), affinity ELISA, ELISPOT, flow cytometry, immunocytology, surface plasmon resonance analysis, kinetic exclusion assay, liquid chromatography-mass spectrometry (LCMS), high-performance liquid chromatography (HPLC), BCA assay, immunoelectrophoresis, Western blot, SDS-PAGE, protein immunoprecipitation, and/or PCR.

Bioavailability

[00024] The AAV particles, when formulated into a composition with a delivery agent as described herein, can exhibit an increase in bioavailability as compared to a composition lacking a delivery agent as described herein. As used herein, the term "bioavailability" refers to the systemic availability of a given amount of AAV particle or expressed payload administered to a

mammal. Bioavailability can be assessed by measuring the area under the curve (AUC) or the maximum serum or plasma concentration (C_{max}) of the composition following. AUC is a determination of the area under the curve plotting the serum or plasma concentration of a compound (e.g., AAV particles or expressed payloads) along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the AUC for a particular compound can be calculated using methods known to those of ordinary skill in the art and as described in G. S. Banker, Modern Pharmaceutics, Drugs and the Pharmaceutical Sciences, v. 72, Marcel Dekker, New York, Inc., 1996, the contents of which are herein incorporated by reference in its entirety.

[00025] The C_{max} value is the maximum concentration of the AAV particle or expressed payload achieved in the serum or plasma of a mammal following administration of the AAV particle to the mammal. The C_{max} value of can be measured using methods known to those of ordinary skill in the art. The phrases "increasing bioavailability" or "improving the pharmacokinetics," as used herein mean that the systemic availability of a first AAV particle or expressed payload, measured as AUC, C_{max}, or C_{min} in a mammal is greater, when co-administered with a delivery agent as described herein, than when such co-administration does not take place. In some embodiments, the bioavailability can increase by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%.

Therapeutic Window

[00026] As used herein "therapeutic window" refers to the range of plasma concentrations, or the range of levels of therapeutically active substance at the site of action, with a high probability of eliciting a therapeutic effect. In some embodiments, the therapeutic window of the AAV particle as described herein can increase by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%.

Volume of Distribution

[00027] As used herein, the term "volume of distribution" refers to the fluid volume that would be required to contain the total amount of the drug in the body at the same concentration as in the blood or plasma: V_{dist} equals the amount of drug in the body/concentration of drug in

blood or plasma. For example, for a 10 mg dose and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which the drug is present in the extravascular tissue. A large volume of distribution reflects the tendency of a compound to bind to the tissue components compared with plasma protein binding. In a clinical setting, V_{dist} can be used to determine a loading dose to achieve a steady state concentration. In some embodiments, the volume of distribution of the AAV particles as described herein can decrease at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%.

Biological Effect

[00028] In one embodiment, the biological effect of the AAV particles delivered to the animals may be categorized by analyzing the payload expression in the animals. The payload expression may be determined from analyzing a biological sample collected from a mammal administered the AAV particles of the present invention. For example, a protein expression of 50-200 pg/ml for the protein encoded by the AAV particles delivered to the mammal may be seen as a therapeutically effective amount of protein in the mammal.

IV. METHODS AND USES OF THE COMPOSITIONS OF THE INVENTION

[00450] The present disclosure provides a method for treating a disease, disorder and/or condition in a mammalian subject, including a human subject, comprising administering to the subject any of the AAV particles described herein or administering to the subject any of the described compositions, including pharmaceutical compositions, described herein.

[00451] In one embodiment, the AAV particles of the present invention are administered to a subject prophylactically.

[00452] In one embodiment, the AAV particles of the present invention are administered to a subject having at least one of the diseases described herein.

[00453] In one embodiment, the AAV particles of the present invention are administered to a subject to treat a disease or disorder described herein. The subject may have the disease or disorder or may be at-risk to developing the disease or disorder.

[00454] In one embodiment, the AAV particles of the present invention are part of an active immunization strategy to protect against diseases and disorders. In an active immunization strategy, a vaccine or AAV particles are administered to a subject to prevent an infectious disease by activating the subject's production of antibodies that can fight off invading bacteria or viruses.

[00455] In one embodiment, the AAV particles of the present invention are part of a passive immunization strategy. In a passive immunization strategy, antibodies against a particular infectious agent are given directly to the subject.

[00456] In one embodiment, the AAV particles of the present invention may be used for passive immunotherapy of tauopathy, (e.g. Alzheimer Disease or Frontotemporal Dementia), as described in Liu et al, the contents of which are herein incorporated by reference in their entirety (Liu, W et al., 2016 J Neurosci 36(49):12425-12435). As a non-limiting example, the AAV particles of the present invention may encode a PHF1 antibody. Heavy and light chains of the PHF1 antibody may be linked by a *Tav*2A and/or Furin 2A linker sequence. Antibody expression may be under the control of a CAG promoter. The AAV particle may comprise, as a non-limiting example, an AAVrh.10 serotype capsid. Further, these PHF1 encoding AAV particles may be administered by bilateral intraparenchymal delivery directly to the hippocampus. Such treatment with AAV-PHF1 may result in a 50-fold increase in antibody levels in the hippocampus as compared to antibody levels subsequent to systemic administration. Neuropathological tau species in the hippocampus may be reduced as much as 80-90% and hippocampal atrophy may be fully rescued after treatment with AAV particles of the present invention.

[00457] In one embodiment, the AAV particles of the present invention may be used to treat tauopathy as described in Ising et al, the contents of which are herein incorporated by reference in their entirety (Ising, C et al., 2017 J Exp Med April 17, Epub ahead of print). As a non-limiting example, the AAV particles of the present invention may encode an HJ8.5, HJ8.7, or Tau5 antibody or a single chain variable fragment (scFv) derived therefrom. Heavy and light chains of the HJ8.5 antibody or scFv may be linked by variable length linker sequences and may be flexible glycine and/or serine linkers. The AAV particle may comprise, as a non-limiting example, an AAV2/8 serotype. Further, these HJ8.5, HJ8.7 or Tau5 encoding AAV particles may be administered by bilateral intracerebroventricular delivery. Such treatment with HJ8.5, HJ8.7 or Tau5 encoding AAV particles may result in a significant reduction in neuropathological tau species in the hippocampus.

Diseases and toxins

[00458] Various infectious diseases may be treated with pharmaceutical compositions, AAV particles, of the present invention. As used herein, the term "infectious disease" refers to any disorders caused by organisms such as bacteria, viruses, fungi or parasites. As a non-limiting example, the infectious disease may be Acute bacterial rhinosinusitis, 14-day measles, Acne, Acrodermatitis chronica atrophicans (ACA)-(late skin manifestation of latent Lyme disease),

Acute hemorrhagic conjunctivitis, Acute hemorrhagic cystitis, Acute rhinosinusitis, Adult T-cell Leukemia-Lymphoma (ATLL), African Sleeping Sickness, AIDS (Acquired Immunodeficiency Sydrome), Alveolar hydatid, Amebiasis, Amebic meningoencephalitis, Anaplasmosis, Anthrax, Arboviral or parainfectious, Ascariasis -(Roundworm infections), Aseptic meningitis, Athlete's foot (Tinea pedis), Australian tick typhus, Avian Influenza, Babesiosis, Bacillary angiomatosis, Bacterial meningitis, Bacterial vaginosis, Balanitis, Balantidiasis, Bang's disease, Barmah Forest virus infection, Bartonellosis (Verruga peruana; Carrion's disease; Oroya fever), Bat Lyssavirus Infection, Bay sore (Chiclero's ulcer), Baylisascaris infection (Racoon roundworm infection), Beaver fever, Beef tapeworm, Bejel (endemic syphilis), Biphasic meningoencephalitis, Black Bane, Black death, Black piedra, Blackwater Fever, Blastomycosis, Blennorrhea of the newborn, Blepharitis, Boils, Bornholm disease (pleurodynia), Borrelia miyamotoi Disease, Botulism, Boutonneuse fever, Brazilian purpuric fever, Break Bone fever, Brill, Bronchiolitis, Bronchitis, Brucellosis (Bang's disease), Bubonic plague, Bullous impetigo, Burkholderia mallei (Glanders), Burkholderia pseudomallei (Melioidosis), Buruli ulcers (also Mycoburuli ulcers), Busse, Busse-Buschke disease (Cryptococcosis), California group encephalitis, Campylobacteriosis, Candidiasis, Canefield fever (Canicola fever; 7-day fever; Weil's disease; leptospirosis; canefield fever), Canicola fever, Capillariasis, Carate, Carbapenem-resistant Enterobacteriaceae (CRE), Carbuncle, Carrion's disease, Cat Scratch fever, Cave disease, Central Asian hemorrhagic fever, Central European tick, Cervical cancer, Chagas disease, Chancroid (Soft chancre), Chicago disease, Chickenpox (Varicella), Chiclero's ulcer, Chikungunya fever, Chlamydial infection, Cholera, Chromoblastomycosis, Ciguatera, Clap, Clonorchiasis (Liver fluke infection), Clostridium Difficile Infection, ClostriDium Perfringens (Epsilon Toxin), Coccidioidomycosis fungal infection (Valley fever; desert rheumatism), Coenurosis, Colorado tick fever, Condyloma accuminata, Condyloma accuminata (Warts), Condyloma lata, Congo fever, Congo hemorrhagic fever virus, Conjunctivitis, cowpox, Crabs, Crimean, Croup, Cryptococcosis, Cryptosporidiosis (Crypto), Cutaneous Larval Migrans, Cyclosporiasis, Cystic hydatid, Cysticercosis, Cystitis, Czechoslovak tick, D68 (EV-D68), Dacryocytitis, Dandy fever, Darling's Disease, Deer fly fever, Dengue fever (1, 2, 3, and 4), Desert rheumatism, Devil's grip, Diphasic milk fever, Diphtheria, Disseminated Intravascular Coagulation, Dog tapeworm, Donovanosis, Donovanosis (Granuloma inguinale), Dracontiasis, Dracunculosis, Duke's disease, Dum Dum Disease, Durand-Nicholas-Favre disease, Dwarf tapeworm, E. Coli infection (E.Coli), Eastern equine encephalitis, Ebola Hemorrhagic Fever (Ebola virus disease EVD), Ectothrix, Ehrlichiosis (Sennetsu fever), Encephalitis, Endemic Relapsing fever, Endemic syphilis, Endophthalmitis, Endothrix, Enterobiasis (Pinworm infection), Enterotoxin - B Poisoning (Staph

Food Poisoning), Enterovirus Infection, Epidemic Keratoconjunctivitis, Epidemic Relapsing fever, Epidemic typhus, Epiglottitis, Erysipelis, Erysipeloid (Erysipelothricosis), Erythema chronicum migrans, Erythema infectiosum, Erythema marginatum, Erythema multiforme, Erythema nodosum, Erythema nodosum leprosum, Erythrasma, Espundia, Eumycotic mycetoma, European blastomycosis, Exanthem subitum (Sixth disease), Eyeworm, Far Eastern tick, Fascioliasis, Fievre boutonneuse (Tick typhus), Fifth Disease (erythema infectiosum), Filatow-Dukes' Disease (Scalded Skin Syndrome; Ritter's Disease), Fish tapeworm, Fitz-Hugh-Curtis syndrome - Perihepatitis, Flinders Island Spotted Fever, Flu (Influenza), Folliculitis, Four Corners Disease, Four Corners Disease (Human Pulmonary Syndrome (HPS)), Frambesia, Francis disease, Furunculosis, Gas gangrene, Gastroenteritis, Genital Herpes, Genital Warts, German measles, Gerstmann-Straussler-Scheinker (GSS), Giardiasis, Gilchrist's disease, Gingivitis, Gingivostomatitis, Glanders, Glandular fever (infectious mononucleosis), Gnathostomiasis, Gonococcal Infection (Gonorrhea), Gonorrhea, Granuloma inguinale (Donovanosis), Guinea Worm, Haemophilus Influenza disease, Hamburger disease, Hansen's disease - leprosy, Hantaan disease, Hantaan-Korean hemorrhagic fever, Hantavirus Pulmonary Syndrome, Hantavirus Pulmonary Syndrome (HPS), Hard chancre, Hard measles, Haverhill fever - Rat bite fever, Head and Body Lice, Heartland fever, Helicobacterosis, Hemolytic Uremic Syndrome (HUS), Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Herpangina, Herpes- genital, Herpes labialis, Herpes- neonatal, Hidradenitis, Histoplasmosis, Histoplasmosis infection (Histoplasmosis), His-Werner disease, HIV infection, Hookworm infections, Hordeola, Hordeola (Stye), HTLV, HTLV- associated myelopathy (HAM), Human granulocytic ehrlichiosis, Human monocytic ehrlichiosis, Human Papillomarivus (HPV), Human Pulmonary Syndrome, Hydatid cyst, Hydrophobia, Impetigo, Including congenital (German Measles), Inclusion conjunctivitis, Inclusion conjunctivitis - Swimming Pool conjunctivitis- Pannus, Infantile diarrhea, Infectious Mononucleosis, Infectious myocarditis, Infectious pericarditis, Influenza, Isosporiasis, Israeli spotted fever, Japanese Encephalitis, Jock itch, Jorge Lobo disease - lobomycosis, Jungle yellow fever, Junin Argentinian hemorrhagic fever, Kala Azar, Kaposi's sarcoma, Keloidal blastomycosis, Keratoconjunctivitis, Kuru, Kyasanur forest disease, LaCrosse encephalitis, Lassa hemorrhagic fever, Legionellosis (Legionnaires Disease), Legionnaire's pneumonia, Lemierre's Syndrome (Postanginal septicemia), Lemming fever, Leprosy, Leptospirosis (Nanukayami fever; Weil's disease), Listeriosis (Listeria), Liver fluke infection, Lobo's mycosis, Lockjaw, Loiasis, Louping Ill, Ludwig's angina, Lung fluke infection, Lung fluke infection (Paragonimiasis), Lyme disease, Lymphogranuloma venereum infection (LGV), Machupo Bolivian hemorrhagic fever, Madura foot, Mal del pinto, Malaria, Malignant pustule,

Malta fever, Marburg hemorrhagic fever, Masters disease, Maternal Sepsis (Puerperal fever), Measles, Mediterannean spotted fever, Melioidosis (Whitmore's disease), Meningitis, Meningococcal Disease, MERS, Milker's nodule, Molluscum contagiosum, Moniliasis, monkeypox, Mononucleosis, Mononucleosis-like syndrome, Montezuma's Revenge, Morbilli, MRSA (methicillin-resistant Staphylococcus aureus) infection, Mucormycosis- Zygomycosis, Multiple Organ Dysfunction Syndrome or MODS, Multiple-system atrophy (MSA), Mumps, Murine typhus, Murray Valley Encephalitis(MVE), Mycoburuli ulcers, Mycoburuli ulcers-Buruli ulcers, Mycotic vulvovaginitis, Myositis, Nanukayami fever, Necrotizing fasciitis, Necrotizing fasciitis- Type 1, Necrotizing fasciitis- Type 2, Negishi, New world spotted fever, Nocardiosis, Nongonococcal urethritis, Non-Polio (Non-Polio Enterovirus), Norovirus infection, North American blastomycosis, North Asian tick typhus, Norwalk virus infection, Norwegian itch, O'Hara disease, Omsk hemorrhagic fever, Onchoceriasis, Onychomycosis, Opisthorchiasis, Opthalmia neonatorium, Oral hairy leukoplakia, Orf, Oriental Sore, Oriental Spotted Fever, Ornithosis (Parrot fever; Psittacosis), Oroya fever, Otitis externa, Otitis media, Pannus, Paracoccidioidomycosis, Paragonimiasis, Paralytic Shellfish Poisoning (Paralytic Shellfish Poisoning), Paronychia (Whitlow), Parotitis, PCP pneumonia, Pediculosis, Peliosis hepatica, Pelvic Inflammatory Disease, Pertussis (also called Whooping cough), Phaeohyphomycosis, Pharyngoconjunctival fever, Piedra (White Piedra), Piedra(Black Piedra), Pigbel, Pink eye conjunctivitis, Pinta, Pinworm infection, Pitted Keratolysis, Pityriasis versicolor (Tinea versicolor), Plague; Bubonic, Pleurodynia, Pneumococcal Disease, Pneumocystosis, Pneumonia, Pneumonic (Plague), Polio or Poliomyelitis, Polycystic hydatid, Pontiac fever, Pork tapeworm, Posada-Wernicke disease, Postanginal septicemia, Powassan, Progressive multifocal leukencephalopathy, Progressive Rubella Panencephalitis, Prostatitis, Pseudomembranous colitis, Psittacosis, Puerperal fever, Pustular Rash diseases (Small pox), Pyelonephritis, Pylephlebitis, Q-Fever, Quinsy, Quintana fever (5-day fever), Rabbit fever, Rabies, Racoon roundworm infection, Rat bite fever, Rat tapeworm, Reiter Syndrome, Relapsing fever, Respiratory syncytial virus (RSV) infection, Rheumatic fever, Rhodotorulosis, Ricin Poisoning, Rickettsialpox, Rickettsiosis, Rift Valley Fever, Ringworm, Ritter's Disease, River Blindness, Rocky Mountain spotted fever, Rose Handler's disease (Sporotrichosis), Rose rash of infants, Roseola, Ross River fever, Rotavirus infection, Roundworm infections, Rubella, Rubeola, Russian spring, Salmonellosis gastroenteritis, San Joaquin Valley fever, Sao Paulo Encephalitis, Sao Paulo fever, SARS, Scabies Infestation (Scabies) (Norwegian itch), Scalded Skin Syndrome, Scarlet fever (Scarlatina), Schistosomiasis, Scombroid, Scrub typhus, Sennetsu fever, Sepsis (Septic shock), Severe Acute Respiratory Syndrome, Severe Acute Respiratory Syndrome

(SARS), Shiga Toxigenic Escherichia coli (STEC/VTEC), Shigellosis gastroenteritis (Shigella), Shinbone fever, Shingles, Shipping fever, Siberian tick typhus, Sinusitis, Sixth disease, Slapped cheek disease, Sleeping sickness, Smallpox (Variola), Snail Fever, Soft chancre, Southern tick associated rash illness, Sparganosis, Spelunker's disease, Sporadic typhus, Sporotrichosis, Spotted fever, Spring, St. Louis encephalitis, Staphylococcal Food Poisoning, Staphylococcal Infection, Strep. throat, Streptococcal Disease, Streptococcal Toxic-Shock Syndrome, Strongyloiciasis, Stye, Subacute Sclerosing Panencephalitis, Subacute Sclerosing Panencephalitis (SSPE), Sudden Acute Respiratory Syndrome, Sudden Rash, Swimmer's ear, Swimmer's Itch, Swimming Pool conjunctivitis, Sylvatic yellow fever, Syphilis, Systemic Inflammatory Response Syndrome (SIRS), Tabes dorsalis (tertiary syphilis), Taeniasis, Taiga encephalitis, Tanner's disease, Tapeworm infections, Temporal lobe encephalitis, Temporal lobe encephalitis, tetani (Lock Jaw), Tetanus Infection, Threadworm infections, Thrush, Tick, Tick typhus, Tinea barbae, Tinea capitis, Tinea corporis, Tinea cruris, Tinea manuum, Tinea nigra, Tinea pedis, Tinea unguium, Tinea versicolor, Torulopsosis, Torulosis, Toxic Shock Syndrome, Toxoplasmosis, transmissible spongioform (CJD), Traveler's diarrhea, Trench fever 5, Trichinellosis, Trichomoniasis, Trichomycosis axillaris, Trichuriasis, Tropical Spastic Paraparesis (TSP), Trypanosomiasis, Tuberculosis (TB), Tuberculousis, Tularemia, Typhoid Fever, Typhus fever, Ulcus molle, Undulant fever, Urban yellow fever, Urethritis, Vaginitis, Vaginosis, Vancomycin Intermediate (VISA), Vancomycin Resistant (VRSA), Varicella, Venezuelan Equine encephalitis, Verruga peruana, Vibrio cholerae (Cholera), Vibriosis (Vibrio), Vincent's disease or Trench mouth, Viral conjunctivitis, Viral Meningitis, Viral meningoencephalitis, Viral rash, Visceral Larval Migrans, Vomito negro, Vulvovaginitis, Warts, Waterhouse, Weil's disease, West Nile Fever, Western equine encephalitis, Whipple's disease, Whipworm infection, White Piedra, Whitlow, Whitmore's disease, Winter diarrhea, Wolhynia fever, Wool sorters' disease, Yaws, Yellow Fever, Yersinosis, Yersinosis (Yersinia), Zahorsky's disease, Zika virus disease, Zoster, Zygomycosis, John Cunningham Virus (JCV), Human immunodeficiency virus (HIV), Influenza virus, Hepatitis B, Hepatitis C, Hepatitis D, Respiratory syncytial virus (RSV), Herpes simplex virus 1 and 2, Human Cytomegalovirus, Epstein-Barr virus, Varicella zoster virus, Coronaviruses, Poxviruses, Enterovirus 71, Rubella virus, Human papilloma virus, *Streptococcus pneumoniae*, *Streptococcus viridans*, *Staphylococcus aureus (S. aureus)*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-intermediate *Staphylococcus aureus* (VISA), Vancomycin-resistant *Staphylococcus aureus* (VRSA), *Staphylococcus epidermidis (S. epidermidis)*, *Clostridium Tetani*, *Bordetella pertussis*, *Bordetella paratussis*, *Mycobacterium*, *Francisella Tularensis*, *Toxoplasma gondii*,

Candida (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei and C. lusitaniae*), and/or any other infectious diseases, disorders, or syndromes.

[00459] Various toxins may be treated with the pharmaceutical compositions, AAV particles, of the present invention. Non-limited examples of toxins include Ricin, Bacillus anthracis, Shiga toxin and Shiga-like toxin, Botulinum toxins.

[00460] Various tropical diseases may be treated with pharmaceutical compositions, AAV particles, of the present invention. Non-limited examples of tropical diseases include Chikungunya fever, Dengue fever, Chagas disease, Rabies, Malaria, Ebola virus, Marburg virus, West Nile Virus, Yellow Fever, Japanese encephalitis virus, and St. Louis encephalitis virus.

[00461] Various foodborne illnesses and gastroenteritis may be treated with pharmaceutical compositions, AAV particles, of the present invention. Non-limited examples of fooborne illnesses and gastroenteritis include Rotavirus, Norwalk virus (Norovirus), Campylobacter jejuni, Clostridium difficile, Entamoeba histolytica, Helicobacter pyroli, Enterotoxin B of Staphylococcus aureus, Hepatitis A virus (HAV), Hepatitis E, Listeria monocytogenes, Salmonella, Clostridium perfringens, and Salmonella.

[00462] Various infectious agents may be treated with pharmaceutical compositions, AAV particles, of the present invention. Non-limited examples of infectious agents include adenoviruses, *Anaplasma phagocytophilium, Ascaris lumbricoides, Bacillus anthracis, Bacillus cereus, Bacteriodes* sp, Barmah Forest virus, *Bartonella bacilliformis, Bartonella henselae, Bartonella quintana*, beta-toxin of *Clostridium perfringens, Bordetella pertussis, Bordetella parapertussis, Borrelia burgdorferi, Borrelia miyamotoi, Borrelia recurrentis, Borrelia* sp., *Botulinum* toxin, *Brucella* sp., *Burkholderia pseudomallei,* California encephalitis virus, *Campylobacter, Candida albicans*, chikungunya virus, *Chlamydia psittaci, Chlamydia trachomatis, Clonorchis sinensis, Clostridium difficile bacteria, Clostridium tetani,* Colorado tick fever virus, *Corynebacterium diphtheriae, Corynebacterium minutissimum, Coxiella burnetii*, coxsackie A, coxsackie B, Crimean-Congo hemorrhagic fever virus, cytomegalovirus, dengue virus, Eastern Equine encephalitis virus, Ebola viruses, echovirus, *Ehrlichia chaffeensis., Ehrlichia equi., Ehrlichia* sp., *Entamoeba histolytica, Enterobacter sp., Enterococcus feacalis,* Enterovirus 71, Epstein-Barr virus (EBV), *Erysipelothrix rhusiopathiae, Escherichia coli,* Flavivirus, *Fusobacterium necrophorum, Gardnerella vaginalis,* Group B *streptococcus, Haemophilus aegyptius, Haemophilus ducreyi, Haemophilus influenzae*, hantavirus, *Helicobacter pylori,* Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, herpes simplex virus 1 and 2, human herpes virus 6, human herpes Virus 8, human immunodeficiency virus 1 and 2, human T-cell leukemia viruses I and II, influenza viruses (A, B, C), Jamestown

Canyon virus, Japanese encephalitis antigenic, Japanese encephalitis virus, John Cunningham virus, juninvirus, Kaposi's Sarcoma-associated Herpes Virus (KSHV), *Klebsiella granulomatis, Klebsiella sp.*, Kyasanur Forest Disease virus, La Crosse virus, Lassavirus, *Legionella pneumophila, Leptospira interrogans, Listeria monocytogenes*, lymphocytic choriomeningitis virus, lyssavirus, Machupovirus, Marburg virus, measles virus, MERS coronavirus (MERS-CoV), *Micrococcus sedentarius, Mobiluncus sp., Molluscipoxvirus, Moraxella catarrhalis, Morbilli- Rubeola virus*, Mumpsvirus, *Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium ulcerans, Mycoplasma genitalium, Mycoplasma* sp, Nairovirus, *Neisseria gonorrhoeae, Neisseria meningitidis*, *Nocardia*, Norwalk virus, norovirus, Omsk hemorrhagic fever virus, papilloma virus, parainfluenza viruses 1-3, parapoxvirus, parvovirus B19, *Peptostreptococcus* sp., *Plasmodium* sp., polioviruses types I, II, and III, *Proteus* sp., *Pseudomonas aeruginosa*, *Pseudomonas pseudomallei, Pseudomonas* sp., rabies virus, respiratory syncytial virus, ricin toxin, *Rickettsia australis, Rickettsia conori, Rickettsia honei, Rickettsia prowazekii,* Ross River Virus, rotavirus, rubellavirus, Saint Louis encephalitis, *Salmonella Typhi, Sarcoptes scabiei*, SARS-associated coronavirus (SARS-CoV), *Serratia sp.*, Shiga toxin and Shiga-like toxin, *Shigella* sp., Sin Nombre Virus, Snowshoe hare virus, *Staphylococcus aureus, Staphylococcus epidermidis, Streptobacillus moniliformis, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus agalactiae, Streptococcus* group A-H, *Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum subsp. Pallidum, Treponema pallidum var. carateum, Treponema pallidum var. endemicum, Tropheryma whippelii, Ureaplasma urealyticum,* Varicella-Zoster virus, variola virus, *Vibrio cholerae*, West Nile virus, yellow fever virus, *Yersinia enterocolitica, Yersinia pestis*, and Zika virus.

[00463] Various rare diseases may be treated with pharmaceutical compositions, AAV particles, of the present invention. As used herein, the term "rare disease" refers to any disease that affects a small percentage of the population. As a non-limiting example, the rare disease may be Acrocephalosyndactylia, Acrodermatitis, Addison Disease, Adie Syndrome, Alagille Syndrome, Amylose, Amyotrophic Lateral Sclerosis, Angelman Syndrome, Angiolymphoid Hyperplasia with Eosinophilia, Arnold-Chiari Malformation, Arthritis, Juvenile Rheumatoid, Asperger Syndrome, Bardet-Biedl Syndrome, Barrett Esophagus, Beckwith-Wiedemann Syndrome, Behcet Syndrome, Bloom Syndrome, Bowen's Disease, Brachial Plexus Neuropathies, Brown-Sequard Syndrome, Budd-Chiari Syndrome, Burkitt Lymphoma, Carcinoma 256, Walker, Caroli Disease, Charcot-Marie-Tooth Disease, Chediak-Higashi Syndrome, Chiari-Frommel Syndrome, Chondrodysplasia Punctata, Colonic Pseudo-

Obstruction, Colorectal Neoplasms, Hereditary Nonpolyposis, Craniofacial Dysostosis, Creutzfeldt-Jakob Syndrome, Crohn Disease, Cushing Syndrome, Cystic Fibrosis, Dandy-Walker Syndrome, De Lange Syndrome, Dementia, Vascular, Dermatitis Herpetiformis, DiGeorge Syndrome, Diffuse Cerebral Sclerosis of Schilder, Duane Retraction Syndrome, Dupuytren Contracture, Ebstein Anomaly, Eisenmenger Complex, Ellis-Van Creveld Syndrome, Encephalitis, Enchondromatosis, Epidermal Necrolysis, Toxic, Facial Hemiatrophy, Factor XII Deficiency, Fanconi Anemia, Felty's Syndrome, Fibrous Dysplasia, Polyostotic, Fox-Fordyce Disease, Friedreich Ataxia, Fusobacterium, Gardner Syndrome, Gaucher Disease, Gerstmann Syndrome, Giant Lymph Node Hyperplasia, Glycogen Storage Disease Type I, Glycogen Storage Disease Type II, Glycogen Storage Disease Type IV, Glycogen Storage Disease Type V, Glycogen Storage Disease Type VII, Goldenhar Syndrome, Guillain-Barre Syndrome, Hallermann's Syndrome, Hamartoma Syndrome, Multiple, Hartnup Disease, Hepatolenticular Degeneration, Hepatolenticular Degeneration, Hereditary Sensory and Motor Neuropathy, Hirschsprung Disease, Histiocytic Necrotizing Lymphadenitis, Histiocytosis, Langerhans-Cell, Hodgkin Disease, Horner Syndrome, Huntington Disease, Hyperaldosteronism, Hyperhidrosis, Hyperostosis, Diffuse Idiopathic Skeletal, Hypopituitarism, Inappropriate ADH Syndrome, Intestinal Polyps, Isaacs Syndrome, Kartagener Syndrome, Kearns-Sayre Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay-Weber Syndrome, Kluver-Bucy Syndrome, Korsakoff Syndrome, Lafora Disease, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Langer-Giedion Syndrome, Leigh Disease, Lesch-Nyhan Syndrome, Leukodystrophy, Globoid Cell, Li-Fraumeni Syndrome, Long QT Syndrome, Machado-Joseph Disease, Mallory-Weiss Syndrome, Marek Disease, Marfan Syndrome, Meckel Diverticulum, Meige Syndrome, Melkersson-Rosenthal Syndrome, Meniere Disease, Mikulicz' Disease, Miller Fisher Syndrome, Mobius Syndrome, Moyamoya Disease, Mucocutaneous Lymph Node Syndrome, Mucopolysaccharidosis I, Mucopolysaccharidosis II, Mucopolysaccharidosis III, Mucopolysaccharidosis IV, Mucopolysaccharidosis VI, Multiple Endocrine Neoplasia Type 1, Munchausen Syndrome by Proxy, Muscular Atrophy, Spinal, Narcolepsy, Neuroaxonal Dystrophies, Neuromyelitis Optica, Neuronal Ceroid-Lipofuscinoses, Niemann-Pick Diseases, Noonan Syndrome, Optic Atrophies, Hereditary, Osteitis Deformans, Osteochondritis, Osteochondrodysplasias, Osteolysis, Essential, Paget Disease Extramammary, Paget's Disease, Mammary, Panniculitis, Nodular Nonsuppurative, Papillon-Lefevre Disease, Paralysis, Pelizaeus-Merzbacher Disease, Pemphigus, Benign Familial, Penile Induration, Pericarditis, Constrictive, Peroxisomal Disorders, Peutz-Jeghers Syndrome, Pick Disease of the Brain, Pierre Robin Syndrome, Pigmentation Disorders, Pityriasis Lichenoides, Polycystic Ovary Syndrome,

Polyendocrinopathies, Autoimmune, Prader-Willi Syndrome, Pupil Disorders, Rett Syndrome, Reye Syndrome, Rubinstein-Taybi Syndrome, Sandhoff Disease, Sarcoma, Ewing's, Schnitzler Syndrome, Sjogren's Syndrome, Sjogren-Larsson Syndrome, Smith-Lemli-Opitz Syndrome, Spinal Muscular Atrophies of Childhood, Sturge-Weber Syndrome, Sweating, Gustatory, Takayasu Arteritis, Tangier Disease, Tay-Sachs Disease, Thromboangiitis Obliterans, Thyroiditis, Autoimmune, Tietze's Syndrome, Togaviridae Infections, Tolosa-Hunt Syndrome, Tourette Syndrome, Uveomeningoencephalitic Syndrome, Waardenburg's Syndrome, Wegener Granulomatosis, Weil Disease, Werner Syndrome, Williams Syndrome, Wilms Tumor, Wolff-Parkinson-White Syndrome, Wolfram Syndrome, Wolman Disease, Zellweger Syndrome, Zollinger-Ellison Syndrome, and von Willebrand Diseases.

[00464] Various autoimmune diseases and autoimmune-related diseases may be treated with pharmaceutical compositions, AAV particles, of the present invention. As used herein, the term "autoimmune disease" refers to a disease in which the body produces antibodies that attack its own tissues. As a non-limiting example, the autoimmune disease may be Acute Disseminated Encephalomyelitis (ADEM), Acute necrotizing hemorrhagic leukoencephalitis, Addison's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome (APS), Autoimmune angioedema, Autoimmune aplastic anemia, Autoimmune dysautonomia, Autoimmune hepatitis, Autoimmune hyperlipidemia, Autoimmune immunodeficiency, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune thrombocytopenic purpura (ATP), Autoimmune thyroid disease, Autoimmune urticaria, Axonal & neuronal neuropathies, Balo disease, Behcet's disease, Bullous pemphigoid, Cardiomyopathy, Castleman disease, Celiac disease, Chagas disease, Chronic fatigue syndrome**, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal ostomyelitis (CRMO), Churg-Strauss syndrome, Cicatricial pemphigoid/benign mucosal pemphigoid, Crohn's disease, Cogans syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST disease, Essential mixed cryoglobulinemia, Demyelinating neuropathies, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis, Eosinophilic fasciitis, Erythema nodosum, Experimental allergic encephalomyelitis, Evans syndrome, Fibromyalgia**, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis (GPA) (formerly called Wegener's Granulomatosis), Graves' disease, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, Hemolytic

anemia, Henoch-Schonlein purpura, Herpes gestationis, Hypogammaglobulinemia, Idiopathic thrombocytopenic purpura (ITP), IgA nephropathy, IgG4-related sclerosing disease, Immunoregulatory lipoproteins, Inclusion body myositis, Interstitial cystitis, Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis, Kawasaki syndrome, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus (SLE), Lyme disease, chronic, Meniere's disease, Microscopic polyangiitis, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica (Devic's), Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus), Paraneoplastic cerebellar degeneration, Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonnage-Turner syndrome, Pars planitis (peripheral uveitis), Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia, POEMS syndrome, Polyarteritis nodosa, Type I, II, & III autoimmune polyglandular syndromes, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Progesterone dermatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Psoriasis, Psoriatic arthritis, Idiopathic pulmonary fibrosis, Pyoderma gangrenosum, Pure red cell aplasia, Raynauds phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Reiter's syndrome, Relapsing polychondritis, Restless legs syndrome, Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome, Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia, Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome, Transverse myelitis, Ulcerative colitis, Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vesiculobullous dermatosis, Vitiligo, and Wegener's granulomatosis (now termed Granulomatosis with Polyangiitis (GPA).

[00465] Various kidney diseases may be treated with pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the kidney disease Abderhalden–Kaufmann–Lignac syndrome (Nephropathic Cystinosis), Abdominal Compartment Syndrome, Acute Kidney Failure/Acute Kidney Injury, Acute Lobar Nephronia, Acute Phosphate Nephropathy, Acute Tubular Necrosis, Adenine Phosphoribosyltransferase Deficiency, Adenovirus Nephritis, Alport Syndrome, Amyloidosis, ANCA Vasculitis Related to Endocarditis and Other Infections, Angiomyolipoma, Analgesic Nephropathy, Anorexia Nervosa and Kidney Disease, Angiotensin Antibodies and Focal Segmental Glomerulosclerosis, Antiphospholipid

Syndrome, Anti-TNF-α Therapy-related Glomerulonephritis, APOL1 Mutations, Apparent Mineralocorticoid Excess Syndrome, Aristolochic Acid Nephropathy, Chinese Herbal Nephropathy, Balkan Endemic Nephropathy, Bartter Syndrome, Beeturia, β-Thalassemia Renal Disease, Bile Cast Nephropathy, BK Polyoma Virus Nephropathy in the Native Kidney, Bladder Rupture, Bladder Sphincter Dyssynergia, Bladder Tamponade, Border-Crossers' Nephropathy, Bourbon Virus and Acute Kidney Injury, Burnt Sugarcane Harvesting and Acute Renal Dysfunction, Byetta and Renal Failure, C1q Nephropathy, Cannabinoid Hyperemesis Acute Renal Failure, Cardiorenal syndrome, Carfilzomib-Indiced Renal Injury, CFHR5 nephropathy, Charcot–Marie–Tooth Disease with Glomerulopathy, Cherry Concentrate and Acute Kidney Injury, Cholesterol Emboli, Churg–Strauss syndrome, Chyluria, Colistin Nephrotoxicity, Collagenofibrotic Glomerulopathy, Collapsing Glomerulopathy, Collapsing Glomerulopathy Related to CMV, Congenital Nephrotic Syndrome, Conorenal syndrome (Mainzer-Saldino Syndrome or Saldino-Mainzer Disease), Contrast Nephropathy, Copper Sulpfate Intoxication, Cortical Necrosis, Crizotinib-related Acute Kidney Injury, Cryoglobuinemia, Crystalglobulin-Induced Nephropathy, Crystal-Induced Acute Kidney injury, Cystic Kidney Disease, Acquired, Cystinuria, Dasatinib-Induced Nephrotic-Range Proteinuria, Dense Deposit Disease (MPGN Type 2), Dent Disease (X-linked Recessive Nephrolithiasis), Dialysis Disequilibrium Syndrome, Diabetes and Diabetic Kidney Disease, Diabetes Insipidus, Dietary Supplements and Renal Failure, Drugs of Abuse and Kidney Disease, Duplicated Ureter, EAST syndrome, Ebola and the Kidney, Ectopic Kidney, Ectopic Ureter, Edema, Swelling, Erdheim-Chester Disease, Fabry's Disease, Familial Hypocalciuric Hypercalcemia, Fanconi Syndrome, Fraser syndrome, Fibronectin Glomerulopathy, Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy, Fraley syndrome, Focal Segmental Glomerulosclerosis, Focal Sclerosis, Focal Glomerulosclerosis, Galloway Mowat syndrome, Giant Cell (Temporal) Arteritis with Kidney Involvement, Gestational Hypertension, Gitelman Syndrome, Glomerular Diseases, Glomerular Tubular Reflux, Glycosuria, Goodpasture Syndrome, Hair Dye Ingestion and Acute Kidney Injury, Hantavirus Infection Podocytopathy, Hematuria (Blood in Urine), Hemolytic Uremic Syndrome (HUS), Atypical Hemolytic Uremic Syndrome (aHUS), Hemophagocytic Syndrome, Hemorrhagic Cystitis, Hemorrhagic Fever with Renal Syndrome (HFRS, Hantavirus Renal Disease, Korean Hemorrhagic Fever, Epidemic Hemorrhagic Fever, Nephropathis Epidemica), Hemosiderosis related to Paroxysmal Nocturnal Hemoglobinuria and Hemolytic Anemia, Hepatic Glomerulopathy, Hepatic Veno-Occlusive Disease, Sinusoidal Obstruction Syndrome, Hepatitis C-Associated Renal Disease, Hepatorenal Syndrome, Herbal Supplements and Kidney Disease, High Blood Pressure and Kidney Disease, HIV-Associated Nephropathy (HIVAN),

Horseshoe Kidney (Renal Fusion), Hunner's Ulcer, Hyperaldosteronism, Hypercalcemia, Hyperkalemia, Hypermagnesemia, Hypernatremia, Hyperoxaluria, Hyperphosphatemia, Hypocalcemia, Hypokalemia, Hypokalemia-induced renal dysfunction, Hypokalemic Periodic Paralysis, Hypomagnesemia, Hyponatremia, Hypophosphatemia, IgA Nephropathy, IgG4 Nephropathy, Interstitial Cystitis, Painful Bladder Syndrome (Questionnaire), Interstitial Nephritis, Ivemark's syndrome, Ketamine-Associated Bladder Dysfunction, Kidney Stones, Nephrolithiasis, Kombucha Tea Toxicity, Lead Nephropathy and Lead-Related Nephrotoxicity, Leptospirosis Renal Disease, Light Chain Deposition Disease, Monoclonal Immunoglobulin Deposition Disease, Liddle Syndrome, Lightwood-Albright Syndrome, Lipoprotein Glomerulopathy, Lithium Nephrotoxicity, LMX1B Mutations Cause Hereditary FSGS, Loin Pain Hematuria, Lupus, Systemic Lupus Erythematosis, Lupus Kidney Disease, Lupus Nephritis, Lupus Nephritis with Antineutrophil Cytoplasmic Antibody Seropositivity, Lyme Disease-Associated Glomerulonephritis, Malarial Nephropathy, Malignancy-Associated Renal Disease, Malignant Hypertension, Malakoplakia, Meatal Stenosis, Medullary Cystic Kidney Disease, Medullary Sponge Kidney, Megaureter, Melamine Toxicity and the Kidney, Membranoproliferative Glomerulonephritis, Membranous Nephropathy, MesoAmerican Nephropathy, Metabolic Acidosis, Metabolic Alkalosis, Methotrexate-related Renal Failure, Microscopic Polyangiitis, Milk-alkalai syndrome, Minimal Change Disease, MDMA (Molly; Ecstacy; 3,4-Methylenedioxymethamphetamine) and Kidney Failure, Multicystic dysplastic kidney, Multiple Myeloma, Myeloproliferative Neoplasms and Glomerulopathy, Nail-patella Syndrome, Nephrocalcinosis, Nephrogenic Systemic Fibrosis, Nephroptosis (Floating Kidney, Renal Ptosis), Nephrotic Syndrome, Neurogenic Bladder, Nodular Glomerulosclerosis, Non-Gonococcal Urethritis, Nutcracker syndrome, Orofaciodigital Syndrome, Orotic Aciduria, Orthostatic Hypotension, Orthostatic Proteinuria, Osmotic Diuresis, Ovarian Hyperstimulation Syndrome, Page Kidney, Papillary Necrosis, Papillorenal Syndrome (Renal-Coloboma Syndrome, Isolated Renal Hypoplasia), Parvovirus B19 and the Kidney, The Peritoneal-Renal Syndrome, Posterior Urethral Valve, Post-infectious Glomerulonephritis, Post-streptococcal Glomerulonephritis, Polyarteritis Nodosa, Polycystic Kidney Disease, Posterior Urethral Valves, Preeclampsia, Propofol infusion syndrome, Proliferative Glomerulonephritis with Monoclonal IgG Deposits (Nasr Disease), Propolis (Honeybee Resin) Related Renal Failure, Proteinuria (Protein in Urine), Pseudohyperaldosteronism, Pseudohypobicarbonatemia, Pseudohypoparathyroidism, Pulmonary-Renal Syndrome, Pyelonephritis (Kidney Infection), Pyonephrosis, Radiation Nephropathy, Ranolazine and the Kidney, Refeeding syndrome, Reflux Nephropathy, Rapidly Progressive Glomerulonephritis, Renal Abscess, Perinephric Abscess,

Renal Agenesis, Renal Arcuate Vein Microthrombi-Associated Acute Kidney Injury, Renal Artery Aneurysm, Renal Artery Stenosis, Renal Cell Cancer, Renal Cyst, Renal Hypouricemia with Exercise-induced Acute Renal Failure, Renal Infarction, Renal Osteodystrophy, Renal Tubular Acidosis, Renin Secreting Tumors (Juxtaglomerular Cell Tumor), Reset Osmostat, Retrocaval Ureter, Retroperitoneal Fibrosis, Rhabdomyolysis, Rhabdomyolysis related to Bariatric Sugery, Rheumatoid Arthritis-Associated Renal Disease, Sarcoidosis Renal Disease, Salt Wasting, Renal and Cerebral, Schistosomiasis and Glomerular Disease, Schimke immuno-osseous dysplasia, Scleroderma Renal Crisis, Serpentine Fibula-Polycystic Kidney Syndrome, Exner Syndrome, Sickle Cell Nephropathy, Silica Exposure and Chronic Kidney Disease, Sri Lankan Farmers' Kidney Disease, Sjögren's Syndrome and Renal Disease, Synthetic Cannabinoid Use and Acute Kidney Injury, Kidney Disease Following Hematopoietic Cell Transplantation, Kidney Disease Related to Stem Cell Transplantation, Thin Basement Membrane Disease, Benign Familial Hematuria, Trigonitis, Tuberculosis, Genitourinary, Tuberous Sclerosis, Tubular Dysgenesis, Immune Complex Tubulointerstitial Nephritis Due to Autoantibodies to the Proximal Tubule Brush Border, Tumor Lysis Syndrome, Uremia, Uremic Optic Neuropathy, Ureteritis Cystica, Ureterocele, Urethral Caruncle, Urethral Stricture, Urinary Incontinence, Urinary Tract Infection, Urinary Tract Obstruction, Vesicointestinal Fistula, Vesicoureteral Reflux, Volatile Anesthetics and Acute Kidney Injury, Von Hippel-Lindau Disease, Waldenstrom's Macroglobulinemic Glomerulonephritis, Warfarin-Related Nephropathy, Wasp Stings and Acute Kidney Injury, Wegener's Granulomatosis, Granulomatosis with Polyangiitis, West Nile Virus and Chronic Kidney Disease, and Wunderlich syndrome.

[00466] Various cardiovascular diseases may be treated with pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the cardiovascular disease may be Ischemic heart disease also known as coronary artery disease, cerebrovascular disease (Stroke), Peripheral vascular disease, Heart failure, Rheumatic heart disease, and Congenital heart disease.

[00467] Various antibody deficiencies may be treated with pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the antibody deficiencies may be X-Linked Agammaglobulinemia (XLA), Autosomal Recessive Agammaglobulinemia (ARA), Common Variable Immune Deficiency (CVID), IgG (IgG1, IgG2, IgG3 and IgG4) Subclass Deficiency, Selective IgA Deficiency, Specific Antibody Deficiency (SAD), Transient Hypogammaglobulinemia of Infancy, Antibody Deficiency with Normal or Elevated Immunoglobulins, Selective IgM Deficiency, Immunodeficiency with Thymoma (Good's

Syndrome), Transcobalamin II Deficiency, Warts, Hypogammaglobulinemia, Infection, Myelokathexis (WHIM) Syndrome, Drug-Induced Antibody Deficiency, Kappa Chain Deficiency, Heavy Chain Deficiencies, Post-Meiotic Segregation (PMS2) Disorder, and Unspecified Hypogammaglobulinemia.

[00468] Various ocular diseases may be treated with pharmaceutical compositions, i.e. AAV particles, of the present invention. As a non-limiting example, the ocular disease may be thyroid eye disease (TED), Graves' disease (GD) and orbitopathy, Retina Degeneration, Cataract, optic atrophy, macular degeneration, Leber congenital amaurosis, retinal degeneration, cone-rod dystrophy, Usher syndrome, leopard syndrome, photophobia, and photoaversion.

[00469] Various neurological diseases may be treated with pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the neurological disease may be Absence of the Septum Pellucidum, Acid Lipase Disease, Acid Maltase Deficiency, Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, Attention Deficit-Hyperactivity Disorder (ADHD), Adie's Pupil, Adie's Syndrome, Adrenoleukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, Aicardi-Goutieres Syndrome Disorder, AIDS - Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis (ALS), Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Antiphospholipid Syndrome, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia Telangiectasia, Ataxias and Cerebellar or Spinocerebellar Degeneration, Atrial Fibrillation and Stroke, Attention Deficit-Hyperactivity Disorder, Autism Spectrum Disorder, Autonomic Dysfunction, Back Pain, Barth Syndrome, Batten Disease, Becker's Myotonia, Behcet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbospinal Muscular Atrophy, Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL), Canavan Disease, Carpal Tunnel Syndrome, Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Central Pontine Myelinolysis, Cephalic Disorders, Ceramidase Deficiency, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysms, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Cavernous Malformation, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Palsy, Cerebro-Oculo-Facio-Skeletal Syndrome (COFS), Charcot-

Marie-Tooth Disease, Chiari Malformation, Cholesterol Ester Storage Disease, Chorea, Choreoacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain, Cockayne Syndrome Type II, Coffin Lowry Syndrome, Colpocephaly, Coma, Complex Regional Pain Syndrome, Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Cree encephalitis, Creutzfeldt-Jakob Disease, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Dejerine-Klumpke Palsy, Dementia, Dementia -Multi-Infarct, Dementia - Semantic, Dementia -Subcortical, Dementia With Lewy Bodies, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Dravet Syndrome, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic Encephalopathy, Empty Sella Syndrome, Encephalitis, Encephalitis Lethargica, Encephaloceles, Encephalopathy, Encephalopathy (familial infantile), Encephalotrigeminal Angiomatosis, Epilepsy, Epileptic Hemiplegia, Erb's Palsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Essential Tremor, Extrapontine Myelinolysis, Fabry Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia Calcification, Familial Periodic Paralyses, Familial Spastic Paralysis, Farber's Disease, Febrile Seizures, Fibromuscular Dysplasia, Fisher Syndrome, Floppy Infant Syndrome, Foot Drop, Friedreich's Ataxia, Frontotemporal Dementia, Gaucher Disease, Generalized Gangliosidoses, Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker Disease, Giant Axonal Neuropathy, Giant Cell Arteritis, Giant Cell Inclusion Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Glycogen Storage Disease, Guillain-Barré Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-1 Associated Myelopathy, Hughes Syndrome, Huntington's Disease, Hydranencephaly, Hydrocephalus, Hydrocephalus - Normal Pressure, Hydromyelia, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathies, Iniencephaly, Intestinal

Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaacs' Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome, Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome, Krabbe Disease, Kugelberg-Welander Disease, Kuru, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Lateral Femoral Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lipid Storage Diseases, Lipoid Proteinosis, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus - Neurological Sequelae, Lyme Disease - Neurological Complications, Machado-Joseph Disease, Macrencephaly, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic Leukodystrophy, Microcephaly, Migraine, Miller Fisher Syndrome, Mini Stroke, Mitochondrial Myopathy, Moebius Syndrome, Monomelic Amyotrophy, Motor Neuron Diseases, Moyamoya Disease, Mucolipidoses, Mucopolysaccharidoses, Multi-Infarct Dementia, Multifocal Motor Neuropathy, Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia - Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myoclonic Encephalopathy of Infants, Myoclonus, Myopathy, Myopathy- Congenital, Myopathy -Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological Complications of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis Optica, Neuromyotonia, Neuronal Ceroid Lipofuscinosis, Neuronal Migration Disorders, Neuropathy- Hereditary, Neurosarcoidosis, Neurosyphilis, Neurotoxicity, Nevus Cavernosus, Niemann-Pick Disease, O'Sullivan-McLeod Syndrome, Occipital Neuralgia, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, Overuse Syndrome, Pain -Chronic, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Periodic Paralyses, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Post-Polio Syndrome, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Postural Hypotension,

Postural Orthostatic Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal Leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear Palsy, Prosopagnosia, Pseudo-Torch syndrome, Pseudotoxoplasmosis syndrome, Pseudotumor Cerebri, Psychogenic Movement, Ramsay Hunt Syndrome I, Ramsay Hunt Syndrome II, Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease - Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Rheumatic Encephalitis, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease, Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Severe Myoclonic Epilepsy of Infancy (SMEI), Shaken Baby Syndrome, Shingles, Shy-Drager Syndrome, Sjögren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Atrophy, Spinocerebellar Degeneration, Steele-Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, Short-lasting, Unilateral, Neuralgiform (SUNCT) Headache, Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis, Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Tourette Syndrome, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Troyer Syndrome, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis Syndromes of the Central and Peripheral Nervous Systems, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson Disease, Wolman's Disease, X-Linked Spinal, and Bulbar Muscular Atrophy.

[00470] Various psychological disorders may be treated with pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the psychological disorders may be Aboulia, Absence epilepsy, Acute stress Disorder, Adjustment Disorders, Adverse effects of medication NOS, Age related cognitive decline, Agoraphobia, Alcohol Addiction,

Alzheimer's Disease, Amnesia (also known as Amnestic Disorder), Amphetamine Addiction, Anorexia Nervosa, Anterograde amnesia, Antisocial personality disorder (also known as Sociopathy), Anxiety Disorder (Also known as Generalized Anxiety Disorder), Anxiolytic related disorders, Asperger's Syndrome (now part of Autism Spectrum Disorder), Attention Deficit Disorder (Also known as ADD), Attention Deficit Hyperactivity Disorder (Also known as ADHD), Autism Spectrum Disorder (also known as Autism), Autophagia, Avoidant Personality Disorder, Barbiturate related disorders, Benzodiazepine related disorders, Bereavement, Bibliomania, Binge Eating Disorder, Bipolar disorder (also known as Manic Depression, includes Bipolar I and Bipolar II), Body Dysmorphic Disorder, Borderline intellectual functioning, Borderline Personality Disorder, Breathing-Related Sleep Disorder, Brief Psychotic Disorder, Bruxism, Bulimia Nervosa, Caffeine Addiction, Cannabis Addiction, Catatonic disorder, Catatonic schizophrenia, Childhood amnesia, Childhood Disintegrative Disorder (now part of Autism Spectrum Disorder), Childhood Onset Fluency Disorder (formerly known as Stuttering), Circadian Rhythm Disorders, Claustrophobia, Cocaine related disorders, Communication disorder, Conduct Disorder, Conversion Disorder, Cotard delusion, Cyclothymia (also known as Cyclothymic Disorder), Delerium, Delusional Disorder, dementia, Dependent Personality Disorder (also known as Asthenic Personality Disorder), Depersonalization disorder (now known as Depersonalization/Derealization Disorder), Depression (also known as Major Depressive Disorder), Depressive personality disorder, Derealization disorder (now known as Depersonalization / Derealization Disorder), Dermotillomania, Desynchronosis, Developmental coordination disorder, Diogenes Syndrome, Disorder of written expression, Dispareunia, Dissocial Personality Disorder, Dissociative Amnesia, Dissociative Fugue, Dissociative Identity Disorder (formerly known as Multiple Personality Disorder), Down syndrome, Dyslexia, Dyspareunia, Dysthymia (now known as Persistent Depressive Disorder), Eating disorder NOS, Ekbom's Syndrome (Delusional Parasitosis), Emotionally unstable personality disorder, Encopresis, Enuresis (bedwetting), Erotomania, Exhibitionistic Disorder, Expressive language disorder, Factitious Disorder, Female Sexual Disorders, Fetishistic Disorder, Folie à deux, Fregoli delusion, Frotteuristic Disorder, Fugue State, Ganser syndrome, Gambling Addiction, Gender Dysphoria (formerly known as Gender Identity Disorder), Generalized Anxiety Disorder, General adaptation syndrome, Grandiose delusions, Hallucinogen Addiction, Halflose personality disorder, Histrionic Personality Disorder, Primary hypersomnia, Huntington's Disease, Hypoactive sexual desire disorder, Hypochondriasis, Hypomania, Hyperkinetic syndrome, Hypersomnia, Hysteria, Impulse control disorder, Impulse control disorder NOS, Inhalant Addiction, Insomnia,

Intellectual Development Disorder, Intermittent Explosive Disorder, Joubert syndrome, Kleptomania, Korsakoff's syndrome, Lacunar amnesia, Language Disorder, Learning Disorders, Major Depression (also known as Major Depressive Disorder), major depressive disorder, Male Sexual Disorders, Malingering, Mathematics disorder, Medication-related disorder, Melancholia, Mental Retardation (now known as Intellectual Development Disorder), Misophonia, Morbid jealousy, Multiple Personality Disorder (now known as Dissociative Identity Disorder), Munchausen Syndrome, Munchausen by Proxy, Narcissistic Personality Disorder, Narcolepsy, Neglect of child, Neurocognitive Disorder (formerly known as Dementia), Neuroleptic-related disorder, Nightmare Disorder, Non Rapid Eye Movement, Obsessive-Compulsive Disorder, Obsessive-Compulsive Personality Disorder (also known as Anankastic Personality Disorder), Oneirophrenia, Onychophagia, Opioid Addiction, Oppositional Defiant Disorder, Orthorexia (ON), Pain disorder, Panic attacks, Panic Disorder, Paranoid Personality Disorder, Parkinson's Disease, Partner relational problem, Passive-aggressive personality disorder, Pathological gambling, Pedophilic Disorder, Perfectionism, Persecutory delusion, Persistent Depressive Disorder (also known as Dysthymia), Personality change due to a general medical condition, Personality disorder, Pervasive developmental disorder (PDD), Phencyclidine related disorder, Phobic disorder, Phonological disorder, Physical abuse, Pica, Polysubstance related disorder, Postpartum Depression, Post-traumatic embitterment disorder (PTED), Post Traumatic Stress Disorder, Premature ejaculation, Premenstrual Dysphoric Disorder, Psychogenic amnesia, Psychological factor affecting medical condition, Psychoneurotic personality disorder, Psychotic disorder, not otherwise specified, Pyromania, Reactive Attachment Disorder, Reading disorder, Recurrent brief depression, Relational disorder, REM Sleep Behavior Disorder, Restless Leg Syndrome, Retrograde amnesia, Retts Disorder (now part of Autism Spectrum Disorder), Rumination syndrome, Sadistic personality disorder, Schizoaffective Disorder, Schizoid Personality Disorder, Schizophrenia, Schizophreniform disorder, Schizotypal Personality Disorder, Seasonal Affective Disorder, Sedative, Hypnotic, or Anxiolytic Addiction, Selective Mutism, Self-defeating personality disorder, Separation Anxiety Disorder, Sexual Disorders Female, Sexual Disorders Male, Sexual Addiction, Sexual Masochism Disorder, Sexual Sadism Disorder, Shared Psychotic Disorder, Sleep Arousal Disorders, Sleep Paralysis, Sleep Terror Disorder (now part of Nightmare Disorder, Social Anxiety Disorder, Somatization Disorder, Specific Phobias, Stendhal syndrome, Stereotypic movement disorder, Stimulant Addiction, Stuttering (now known as Childhood Onset Fluency Disorder), Substance related disorder, Tardive dyskinesia, Tobacco Addiction, Tourettes Syndrome, Transient tic disorder, Transient

global amnesia, Transvestic Disorder, Trichotillomania, Undifferentiated Somatoform Disorder, Vaginismus, and Voyeuristic Disorder.

[00471] Various lung diseases may be treated with pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the lung diseases may be Asbestosis, Asthma, Bronchiectasis, Bronchitis, Chronic Cough, Chronic Obstructive Pulmonary Disease (COPD), Croup, Cystic Fibrosis, Hantavirus, Idiopathic Pulmonary Fibrosis, Pertussis, Pleurisy, Pneumonia, Pulmonary Embolism, Pulmonary Hypertension, Sarcoidosis, Sleep Apnea, Spirometry, Sudden Infant Death Syndrome (SIDS), Tuberculosis, Alagille Syndrome, Autoimmune Hepatitis, Biliary Atresia, Cirrhosis, ERCP (Endoscopic Retrograde Cholangiopancreatography), and Hemochromatosis. Nonalcoholic Steatohepatitis, Porphyria, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis.

[00472] Various bone diseases may be treated with pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the bone diseases may be osteoporosis, neurofibromatosis, osteogenesis imperfecta (OI), rickets, osteosarcoma, achondroplasia, fracture, osteomyelitis, Ewing tumour of bone, osteomalacia, hip dysplasia, Paget disease of bone, marble bone disease, osteochondroma, bone cancer, bone disease, osteochondrosis, osteoma, fibrous dysplasia, cleidocranial dysostosis, osteoclastoma, bone cyst, metabolic bone disease, melorheostosis, callus, Caffey syndrome, and mandibulofacial dysostosis.

[00473] Various blood diseases may be treated with pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the blood diseases may be Anemia and CKD (for health care professionals), Aplastic Anemia and Myelodysplastic Syndromes, Deep Vein Thrombosis, Hemochromatosis, Hemophilia, Henoch-Schönlein Purpura, Idiopathic Thrombocytopenic Purpura, Iron-Deficiency Anemia, Pernicious Anemia, Pulmonary Embolism, Sickle Cell Anemia, Sickle Cell Trait and Other Hemoglobinopathies, Thalassemia, Thrombotic Thrombocytopenic Purpura, and Von Willebrand Disease.

[00474] Various diseases associated with TNF-alpha may be treated with the pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the disease may be respiratory disorder; asthma; allergic and nonallergic asthma; asthma due to infection; asthma due to infection with respiratory syncytial virus (RSV); chronic obstructive pulmonary disease (COPD); a condition involving airway inflammation; eosinophilia; fibrosis and excess mucus production; cystic fibrosis; pulmonary fibrosis; an atopic disorder; atopic dermatitis; urticaria; eczema; allergic rhinitis; allergic enterogastritis; an inflammatory and/or autoimmune condition of the skin; an inflammatory and/or autoimmune condition of gastrointestinal organs;

inflammatory bowel diseases (IBD); ulcerative colitis; Crohn's disease; an inflammatory and/or autoimmune condition of the liver; liver cirrhosis; liver fibrosis; liver fibrosis caused by hepatitis B and/or C virus; scleroderma; tumors or cancers; hepatocellular carcinoma; glioblastoma; lymphoma; Hodgkin's lymphoma; a viral infection; a bacterial infection; a parasitic infection; HTLV-1 infection; suppression of expression of protective type 1 immune responses, and suppression of expression of a protective type 1 immune response during vaccination, rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, insulin dependent diabetes mellitus, thyroiditis, asthma, allergic diseases, psoriasis, dermatitis scleroderma, graft versus host disease, organ transplant rejection, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpurea, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, heart failure, myocardial infarction, Addison's disease, sporadic, polyglandular deficiency type I and polyglandular deficiency type II, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia greata, seronegative arthropathy, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, chlamydia, yersinia and salmonella associated arthropathy, spondyloarthropathy, atheromatous disease/arteriosclerosis, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, hepatitis B, hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, female infertility, ovarian failure, premature ovarian failure, fibrotic lung disease, cryptogenic fibrosing alveolitis, post-inflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial

lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, Sjögren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, fibrosis, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, postinfectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycaemia, type B insulin resistance with acanthosis nigricans, hypoparathyroidism, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthrosis, primary sclerosing cholangitis, psoriasis type 1, psoriasis type 2, idiopathic leucopaenia, autoimmune neutropaenia, renal disease NOS, glomerulonephritides, microscopic vasculitis of the kidneys, Lyme disease, discoid lupus erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjörgren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopaenia, idiopathic thrombocytopaenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis, vitiligo acute liver disease, chronic liver diseases, alcoholic cirrhosis, alcohol-induced liver injury, choleostasis, idiosyncratic liver disease, drug-Induced hepatitis, non-alcoholic steatohepatitis, allergy and asthma, group B streptococci (GBS) infection, mental disorders (e.g., depression and schizophrenia), Th2 Type and Th1 Type mediated diseases, acute and chronic pain (different forms of pain), and cancers such as lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma) abetalipoproteinemia, acrocyanosis, acute and chronic parasitic or infectious processes, acute leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), acute or chronic bacterial infection, acute pancreatitis, acute renal failure, adenocarcinomas, aerial ectopic beats, AIDS dementia complex, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allograft rejection, alpha-1-antitrypsin deficiency, anyotrophic lateral sclerosis, anemia, angina pectoris, anterior horn cell degeneration, anti-CD3 therapy, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aortic and peripheral aneurysms, aortic dissection, arterial hypertension,

arteriosclerosis, arteriovenous fistula, ataxia, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bundle branch block, Burkitt's lymphoma, burns, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chronic myelocytic leukemia (CML), chronic alcoholism, chronic inflammatory pathologies, chronic lymphocytic leukemia (CLL), chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal carcinoma, congestive heart failure, conjunctivitis, contact dermatitis, corpulmonale, coronary artery disease, Creutzfeldt-Jakob disease, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatologic conditions, diabetes, diabetes mellitus, diabetic arteriosclerotic disease, Diffuse Lewy body disease, dilated congestive cardiomyopathy, disorders of the basal ganglia, Down's Syndrome in middle age, drug-induced movement disorders induced by drugs which block CNS dopamine receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hemophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, fungal sepsis, gas gangrene, gastric ulcer, glomerular nephritis, graft rejection of any organ or tissue, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, hairy cell leukemia, Hallervorden-Spatz disease, Hashimoto's thyroiditis, hay fever, heart transplant rejection, hemochromatosis, hemodialysis, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, hepatitis (A), His bundle arrhythmias, HIV infection/HIV neuropathy, Hodgkin's disease, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hypertension, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic pulmonary fibrosis, antibody mediated cytotoxicity, asthenia, infantile spinal muscular atrophy, inflammation of the aorta, influenza a, ionizing radiation exposure, iridocyclitis/uveitis/optic neuritis, ischemia-reperfusion injury, ischemic stroke, juvenile rheumatoid arthritis (JRA), juvenile spinal muscular atrophy, Kaposi's sarcoma, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions of the corticospinal system, lipedema, liver transplant rejection, lymphedema, malaria, malignant lymphoma, malignant histiocytosis, malignant melanoma, meningitis, meningococcemia, metabolic/idiopathic, migraine headache, mitochondrial multi-system disorder, mixed connective tissue disease,

monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Menzel, Dejerine-Thomas, Shy-Drager, and Machado-Joseph), myasthenia gravis, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodysplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, neurodegenerative diseases, neurogenic I muscular atrophies, neutropenic fever, non-Hodgkins lymphoma, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, OKT3® therapy, orchitis/epidydimitis, orchitis/vasectomy reversal procedures, organomegaly, osteoporosis, pancreas transplant rejection, pancreatic carcinoma, paraneoplastic syndrome/hypercalcemia of malignancy, parathyroid transplant rejection, pelvic inflammatory disease, perennial rhinitis, pericardial disease, peripheral atherosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiotomy syndrome, preeclampsia, progressive supranucleo palsy, primary pulmonary hypertension, radiation therapy, Raynaud's phenomenon and disease, Raynaud's disease, Refsum's disease, regular narrow QRS tachycardia, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, sarcomas, scleroderma, senile chorea, senile dementia of Lewy body type, seronegative arthropathies, shock, sickle cell anemia, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, solid tumors, specific arrhythmias, spinal ataxia, spinocerebellar degenerations, streptococcal myositis, structural lesions of the cerebellum, subacute sclerosing panencephalitis, syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, T-cell or FAB ALL, telangiectasia, thromboangitis obliterans, thrombocytopenia, toxicity, transplants, trauma/hemorrhage, type III hypersensitivity reactions, type IV hypersensitivity, unstable angina, uremia, urosepsis, urticaria, valvular heart diseases, varicose veins, vasculitis, venous diseases, venous thrombosis, ventricular fibrillation, viral and fungal infections, viral encephalitis/aseptic meningitis, viral-associated hemophagocytic syndrome, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, acute coronary syndromes, acute idiopathic polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy, acute ischemia, adult Still's disease, alopecia greata, anaphylaxis, anti-phospholipid antibody syndrome, aplastic anemia, arteriosclerosis, atopic eczema, atopic dermatitis, autoimmune dermatitis, autoimmune disorder associated with streptococcus infection, autoimmune enteropathy, autoimmune hearing loss, autoimmune lymphoproliferative syndrome (ALPS), autoimmune myocarditis, autoimmune premature

ovarian failure, blepharitis, bronchiectasis, bullous pemphigoid, cardiovascular disease, catastrophic antiphospholipid syndrome, celiac disease, cervical spondylosis, chronic ischemia, cicatricial pemphigoid, clinically isolated syndrome (CIS) with risk for multiple sclerosis, conjunctivitis, childhood onset psychiatric disorder, chronic obstructive pulmonary disease (COPD), dacryocystitis, dermatomyositis, diabetic retinopathy, diabetes mellitus, disk herniation, disk prolapse, drug induced immune hemolytic anemia, endocarditis, endometriosis, endophthalmitis, episcleritis, erythema multiforme, erythema multiforme major, gestational pemphigoid, Guillain-Barré syndrome (GBS), hay fever, Hughes syndrome, idiopathic Parkinson's disease, idiopathic interstitial pneumonia, IgE-mediated allergy, immune hemolytic anemia, inclusion body myositis, infectious ocular inflammatory disease, inflammatory demyelinating disease, inflammatory heart disease, inflammatory kidney disease, IPF/UIP, iritis, keratitis, keratojunctivitis sicca, Kussmaul disease or Kussmaul-Meier disease, Landry's paralysis, Langerhan's cell histiocytosis, livedo reticularis, macular degeneration, microscopic polyangiitis, morbus bechterev, motor neuron disorders, mucous membrane pemphigoid, multiple organ failure, myasthenia gravis, myelodysplastic syndrome, myocarditis, nerve root disorders, neuropathy, non-A non-B hepatitis, optic neuritis, osteolysis, ovarian cancer, pauciarticular JRA, peripheral artery occlusive disease (PAOD), peripheral vascular disease (PVD), peripheral artery disease (PAD), phlebitis, polyarteritis nodosa (or periarteritis nodosa), polychondritis, polymyalgia rheumatica, poliosis, polyarticular JRA, polyendocrine deficiency syndrome, polymyositis, polymyalgia rheumatica (PMR), post-pump syndrome, primary Parkinsonism, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma), prostatitis, pure red cell aplasia, primary adrenal insufficiency, recurrent neuromyelitis optica, restenosis, rheumatic heart disease, sapho (synovitis, acne, pustulosis, hyperostosis, and osteitis), scleroderma, secondary amyloidosis, shock lung, scleritis, sciatica, secondary adrenal insufficiency, silicone associated connective tissue disease, Sneddon-Wilkinson dermatosis, spondylitis ankylosans, Stevens-Johnson syndrome (SJS), systemic inflammatory response syndrome, temporal arteritis, toxoplasmic retinitis, toxic epidermal necrolysis, transverse myelitis, TRAPS (tumor necrosis factor receptor associated periodic syndrome), type 1 allergic reaction, type II diabetes, urticaria, usual interstitial pneumonia (UIP), vasculitis, vernal conjunctivitis, viral retinitis, Vogt-Koyanagi-Harada syndrome (VKH syndrome), wet macular degeneration, wound healing, yersinia, or salmonella associated arthropathy.

[00475] Various receptor for advanced glycation endproducts (RAGE) diseases may be treated with the pharmaceutical compositions, AAV particles, of the present invention. As a non-

limiting example, the disease may be Amytropic Lateral Sclerosis, Brachial Plexus Injury, Brain Injury, including traumatic brain injury, Cerebral Palsy, Friedrich's Ataxia, Guillain Barre, Leukodystrophies, Multiple Sclerosis, Post Polio, Spina Bifida, Spinal Cord Injury, Spinal Muscle Atrophy, Spinal Tumors, Stroke, Transverse Myelitits, dementia, senile dementia, mild cognitive impairment, Alzheimer-related dementia, Huntington's chorea, tardive dyskinesia, hyperkinesias, manias, Morbus Parkinson, steel-Richard syndrome, Down's syndrome, myasthenia gravis, nerve trauma, vascular amyloidosis, cerebral hemorrhage I with amyloidosis, brain inflammation, Friedrich's ataxia, acute confusion disorder, amyotrophic lateral sclerosis, glaucoma, Alzheimer's disease, diabetic nephropathy, sepsis, rheumatoid arthritis and related inflammatory diseases.

[00476] Various neurite degenerative diseases may be treated with the pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the disease may be multiple sclerosis, Parkinson's disease, Alzheimer's disease, Tay-Sachs disease, Niemann-Pick disease, Gaucher's disease, Hurler's syndrome, Huntington's disease, amyotrophic lateral sclerosis, idiopathic inflammatory demyelinating diseases, vitamin B12 deficiency, central pontine myelinolysis, tabes dorsalis, transverse myelitis, Devic's disease, progressive multifocal leukoencephalopathy, optic neuritis, traumatic injury to the CNS, an ischemic cerebral stroke, glaucoma, diabetic retinopathy, age-dependent macular degeneration, and a leukodystrophy.

[00477] Various neurological diseases may be treated with the pharmaceutical compositions, AAV particles, of the present invention. As a non-limiting example, the disease may be Amyotrophic Lateral Sclerosis, Brachial Plexus Injury, Brain Injury, including traumatic brain injury, Cerebral Palsy, Guillain Barre, Leukodystrophies, Multiple Sclerosis, Post Polio, Spina Bifida, Spinal Cord Injury, Spinal Muscle Atrophy, Spinal Tumors, Stroke, Transverse Myelitis; dementia, senile dementia, mild cognitive impairment, Alzheimer-related dementia, Huntington's chorea, tardive dyskinesia, hyperkinesias, manias, Morbus Parkinson, steel-Richard syndrome, Down's syndrome, myasthenia gravis, nerve trauma, vascular amyloidosis, cerebral hemorrhage I with amyloidosis, brain inflammation, acute confusion disorder, amyotrophic lateral sclerosis, glaucoma and Alzheimer's disease.

[00478] Various cancers may be treated with pharmaceutical compositions, AAV particles, of the present invention. As used herein, the term "cancer" refers to any of various malignant neoplasms characterized by the proliferation of anaplastic cells that tend to invade surrounding tissue and metastasize to new body sites and also refers to the pathological condition characterized by such malignant neoplastic growths. Cancers may be tumors or hematological

malignancies, and include but are not limited to, all types of lymphomas/leukemias, carcinomas and sarcomas, such as those cancers or tumors found in the anus, bladder, bile duct, bone, brain, breast, cervix, colon/rectum, endometrium, esophagus, eye, gallbladder, head and neck, liver, kidney, larynx, lung, mediastinum (chest), mouth, ovaries, pancreas, penis, prostate, skin, small intestine, stomach, spinal marrow, tailbone, testicles, thyroid and uterus.

[00479] Types of carcinomas which may be treated with the AAV particles of the present invention include, but are not limited to, papilloma/carcinoma, choriocarcinoma, endodermal sinus tumor, teratoma, adenoma/adenocarcinoma, melanoma, fibroma, lipoma, leiomyoma, rhabdomyoma, mesothelioma, angioma, osteoma, chondroma, glioma, lymphoma/leukemia, squamous cell carcinoma, small cell carcinoma, large cell undifferentiated carcinomas, basal cell carcinoma and sinonasal undifferentiated carcinoma.

[00480] Types of sarcomas which may be treated with the AAV particles of the present invention include, but are not limited to, soft tissue sarcoma such as alveolar soft part sarcoma, angiosarcoma, dermatofibrosarcoma, desmoid tumor, desmoplastic small round cell tumor, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, hemangiopericytoma, hemangiosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphosarcoma, malignant fibrous histiocytoma, neurofibrosarcoma, rhabdomyosarcoma, synovial sarcoma, and Askin's tumor, Ewing's sarcoma (primitive neuroectodermal tumor), malignant hemangioendothelioma, malignant schwannoma, osteosarcoma, and chondrosarcoma.

[00481] As a non-limiting example, the cancer which may be treated may be Acute granulocytic leukemia, Acute lymphocytic leukemia, Acute myelogenous leukemia, Adenocarcinoma, Adenosarcoma, Adrenal cancer, Adrenocortical carcinoma, Anal cancer, Anaplastic astrocytoma, Angiosarcoma, Appendix cancer, Astrocytoma, Basal cell carcinoma, B-Cell lymphoma), Bile duct cancer, Bladder cancer, Bone cancer, Bowel cancer, Brain cancer, Brain stem glioma, Brain tumor, Breast cancer, Carcinoid tumors, Cervical cancer, Cholangiocarcinoma, Chondrosarcoma, Chronic lymphocytic leukemia, Chronic myelogenous leukemia, Colon cancer, Colorectal cancer, Craniopharyngioma, Cutaneous lymphoma, Cutaneous melanoma, Diffuse astrocytoma, Ductal carcinoma in situ, Endometrial cancer, Ependymoma, Epithelioid sarcoma, Esophageal cancer, Ewing sarcoma, Extrahepatic bile duct cancer, Eye cancer, Fallopian tube cancer, Fibrosarcoma, Gallbladder cancer, Gastric cancer, Gastrointestinal cancer, Gastrointestinal carcinoid cancer, Gastrointestinal stromal tumors, General, Germ cell tumor, Glioblastoma multiforme, Glioma, Hairy cell leukemia, Head and neck cancer, Hemangioendothelioma, Hodgkin lymphoma, Hodgkin's disease, Hodgkin's lymphoma, Hypopharyngeal cancer, Infiltrating ductal carcinoma, Infiltrating lobular carcinoma,

Inflammatory breast cancer, Intestinal Cancer, Intrahepatic bile duct cancer, Invasive / infiltrating breast cancer, Islet cell cancer, Jaw cancer, Kaposi sarcoma, Kidney cancer, Laryngeal cancer, Leiomyosarcoma, Leptomeningeal metastases, Leukemia, Lip cancer, Liposarcoma, Liver cancer, Lobular carcinoma in situ, Low-grade astrocytoma, Lung cancer, Lymph node cancer, Lymphoma, Male breast cancer, Medullary carcinoma, Medulloblastoma, Melanoma, Meningioma, Merkel cell carcinoma, Mesenchymal chondrosarcoma, Mesenchymous, Mesothelioma, Metastatic breast cancer, Metastatic melanoma, Metastatic squamous neck cancer, Mixed gliomas, Mouth cancer, Mucinous carcinoma, Mucosal melanoma, Multiple myeloma, Nasal cavity cancer, Nasopharyngeal cancer, Neck cancer, Neuroblastoma, Neuroendocrine tumors, Non-Hodgkin lymphoma, Non-Hodgkin's lymphoma, Non-small cell lung cancer, Oat cell cancer, Ocular cancer, Ocular melanoma, Oligodendroglioma, Oral cancer, Oral cavity cancer, Oropharyngeal cancer, Osteogenic sarcoma, Osteosarcoma, Ovarian cancer, Ovarian epithelial cancer, Ovarian germ cell tumor, Ovarian primary peritoneal carcinoma, Ovarian sex cord stromal tumor, Paget's disease, Pancreatic cancer, Papillary carcinoma, Paranasal sinus cancer, Parathyroid cancer, Pelvic cancer, Penile cancer, Peripheral nerve cancer, Peritoneal cancer, Pharyngeal cancer, Pheochromocytoma, Pilocytic astrocytoma, Pineal region tumor, Pineoblastoma, Pituitary gland cancer, Primary central nervous system lymphoma, Prostate cancer, Rectal cancer, Renal cell cancer, Renal pelvis cancer, Rhabdomyosarcoma, Salivary gland cancer, Sarcoma, Sarcoma, bone, Sarcoma, soft tissue, Sarcoma, uterine, Sinus cancer, Skin cancer, Small cell lung cancer, Small intestine cancer, Soft tissue sarcoma, Spinal cancer, Spinal column cancer, Spinal cord cancer, Spinal tumor, Squamous cell carcinoma, Stomach cancer, Synovial sarcoma, T-cell lymphoma), Testicular cancer, Throat cancer, Thymoma/thymic carcinoma, Thyroid cancer, Tongue cancer, Tonsil cancer, Transitional cell cancer, Transitional cell cancer, Transitional cell cancer, Triple-negative breast cancer, Tubal cancer, Tubular carcinoma, Ureteral cancer, Ureteral cancer, Urethral cancer, Uterine adenocarcinoma, Uterine cancer, Uterine sarcoma, Vaginal cancer, and Vulvar cancer.

Diagnostic applications

[00482] The AAV particles of the present invention may be used for diagnostic purposes or as diagnostic tools for any of the aforementioned diseases or disorders. As non-limiting examples, the AAV particles of the present invention or the antibodies encoded within the viral genome therein may be used as a biomarker for disease diagnosis. As a second non-limiting example, the AAV particles of the present invention or the antibodies encoded within the viral genome therein may be used for diagnostic imaging purposes, e.g., MRI, PET, CT or ultrasound.

Preventative applications

[00483] The AAV particles of the present invention or the antibodies encoded by the viral genome therein may be used to prevent disease or stabilize the progression of disease. In one embodiment, the AAV particles of the present invention are used to as a prophylactic to prevent a disease or disorder in the future. In one embodiment, the AAV particles of the present invention are used to halt further progression of a disease or disorder. As a non-limiting example, the AAV particles of the invention may be used in a manner similar to that of a vaccine.

Research applications

[00484] The AAV particles of the present invention or the antibodies encoded by the viral genome therein may also be used as research tools. The AAV particles of the invention may be used as in any research experiment, e.g., *in vivo* or *in vitro* experiments. In a non-limiting example, the AAV particles of the invention may be used in cultured cells. The cultured cells may be derived from any origin known to one with skill in the art, and may be as non-limiting examples, derived from a stable cell line, an animal model or a human patient or control subject. In a non-limiting example, the AAV particles of the invention may be used in *in vivo* experiments in animal models (i.e., mouse, rat, rabbit, dog, cat, non-human primate, guinea pig, ferret, c-elegans, drosophila, zebrafish, or any other animal used for research purposes, known in the art). In another non-limiting example, the AAV particles of the invention may be used in human research experiments or human clinical trials.

Combination applications

[00485] The AAV particles of the invention may be used as a combination therapy with any other therapeutic molecule known in the art. The therapeutic molecule may be approved by the US Food and Drug Administration or may be in clinical trial or at the preclinical research stage. The therapeutic molecule may utilize any therapeutic modality known in the art, with non-limiting examples including gene silencing or interference (i.e., miRNA, siRNA, RNAi, shRNA), gene editing (i.e., TALEN, CRISPR/Cas9 systems, zinc finger nucleases), and gene, protein or enzyme replacement.

Therapeutic applications

[00486] The present disclosure additionally provides a method for treating neurological diseases and/or disorders in a mammalian subject, including a human subject, comprising administering to the subject any of the AAV particles of the invention. In some cases, neurological diseases and/or disorders treated according to methods described herein include indications involving irregular expression or aggregation of tau. Such indications may include,

but are not limited to Alzheimer's disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), Frontotemporal lobar degeneration (FTLD), chronic traumatic encephalopathy (CTE), Progressive Supranuclear Palsy (PSP), Down's syndrome, Pick's disease, Corticobasal degeneration (CBD), Amyotrophic lateral sclerosis (ALS), Prion diseases, Creutzfeldt-Jakob disease (CJD), Multiple system atrophy, Tangle-only dementia, and Progressive subcortical gliosis.

[00487] In some embodiments, methods of treating neurological diseases and/or disorders in a subject in need thereof may comprise the steps of: (1) deriving, generating and/or selecting an anti-tau antibody, antibody-based composition or fragment thereof; (2) producing an AAV particle with a viral genome that includes a payload region encoding the selected antibody of (1); and (3) administering the AAV particle (or pharmaceutical composition thereof) to the subject.

[00488] The present disclosure provides a method for administering to a subject in need thereof, including a human subject, a therapeutically effective amount of the AAV particles of the invention to slow, stop or reverse disease progression. As a non-limiting example, disease progression may be measured by cognitive tests such as, but not limited to, the Mini-Mental State Exam (MMSE) or other similar diagnostic tool(s), known to those skilled in the art. As another non-limiting example, disease progression may be measured by change in the pathological features of the brain, CSF or other tissues of the subject, such as, but not limited to a decrease in levels of tau (either soluble or insoluble). In one embodiment levels of insoluble hyperphosphorylated tau are decreased. In one embodiment levels of soluble tau are decreased. In one embodiment both soluble and insoluble tau are decreased. In one embodiment, levels of insoluble hyperphosphorylated tau are increased. In one embodiment levels of soluble tau are increased. In one embodiment both insoluble and soluble tau levels are increased. In one embodiment, neurofibrillary tangles are decreased in size, number, density, or combination thereof. In another embodiment, neurofibrillary tangles are increased in size, number, density or combination thereof.

Alzheimer's disease

[00489] Alzheimer Disease (AD) is a debilitating neurodegenerative disease currently afflicting more than 35 million people worldwide, with that number expected to double in coming decades. Symptomatic treatments have been available for many years but these treatments do not address the underlying pathophysiology. Recent clinical trials using these and other treatments have largely failed and, to date, no known cure has been identified.

[00490] The AD brain is characterized by the presence of two forms of pathological aggregates, the extracellular plaques composed of β-amyloid (Aβ) and the intracellular

neurofibrillary tangles (NFT) comprised of hyperphosphorylated microtubule associated protein tau. Based on early genetic findings, β-amyloid alterations were thought to initiate disease, with changes in tau considered downstream. Thus, most clinical trials have been Aβ-centric. Although no mutations of the tau gene have been linked to AD, such alterations have been shown to result in a family of dementias known as tauopathies, demonstrating that changes in tau can contribute to neurodegenerative processes. Tau is normally a very soluble protein known to associate with microtubules based on the extent of its phosphorylation. Hyperphosphorylation of tau depresses its binding to microtubules and microtubule assembly activity. In tauopathies, the tau becomes hyperphosphorylated, misfolds and aggregates as NFT of paired helical filaments (PHF), twisted ribbons or straight filaments. In AD, NFT pathology, rather than plaque pathology, correlates more closely with neuropathological markers such as neuronal loss, synaptic deficits, severity of disease and cognitive decline. NFT pathology marches through the brain in a stereotyped manner and animal studies suggest a trans-cellular propagation mechanism along neuronal connections.

[00491] Several approaches have been proposed for therapeutically interfering with progression of tau pathology and preventing the subsequent molecular and cellular consequences. Given that NFT are composed of a hyperphosphorylated, misfolded and aggregated form of tau, interference at each of these stages has yielded the most avidly pursued set of targets. Introducing agents that limit phosphorylation, block misfolding or prevent aggregation have all generated promising results. Passive and active immunization with late stage anti-phospho-tau antibodies in mouse models have led to dramatic decreases in tau aggregation and improvements in cognitive parameters. It has also been suggested that introduction of anti-tau antibodies can prevent the trans-neuronal spread of tau pathology.

[00492] The vectored antibody delivery (VAD) of tau disease associated antibodies of the present invention may be used to treat subjects suffering from AD and other tauopathies. In some cases, methods of the present invention may be used to treat subjects suspected of developing AD or other tauopathies.

Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)

[00493] Although Alzheimer's disease is, in part, characterized by the presence of tau pathology, no known mutations in the tau gene have been causally linked to the disease. Mutations in the tau gene have been shown to lead to an autosomal dominantly inherited tauopathy known as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) and demonstrate that alterations in tau can lead to neurodegenerative changes in the brain. Mutations in the tau gene that lead to FTDP-17 are thought to influence splicing patterns,

thereby leading to an elevated proportion of tau with four microtubule binding domains (rather than three). These molecules are considered to be more amyloidogenic, meaning they are more likely to become hyperphosphorylated and more likely to aggregate into NFT (Hutton, M. et al., 1998, Nature 393(6686):702-5). Although physically and behaviorally, FTDP-17 patients can appear quite similar to Alzheimer's disease patients, at autopsy FTDP-17 brains lack the prominent Aβ plaque pathology of an AD brain (Gotz, J. et al., 2012, British Journal of Pharmacology 165(5):1246-59). Therapeutically targeting the aggregates of tau protein may ameliorate and prevent degenerative changes in the brain and potentially lead to improved cognitive ability.

[00494] As of today, there is no treatment to prevent, slow the progression, or cure FTD. Medication may be prescribed to reduce aggressive, agitated or dangerous behavior. There remains a need for therapy affecting the underlying pathophysiology, such as antibody therapies targeting tau protein.

[00495] In some embodiments, the vectored antibody delivery of the present invention may be used to treat subjects suffering from FTDP-17. In some cases, methods of the present invention may be used to treat subjects suspected of developing FTDP-17.

Chronic traumatic encephalopathy

[00496] Unlike the genetically linked tauopathies, chronic traumatic encephalopathy is a degenerative tauopathy linked to repeated head injuries. The disease was first described in boxers whom behaved "punch drunk" and has since been identified primarily in athletes that play American football, ice hockey, wrestling and other contact sports. The brains of those suffering from CTE are characterized by distinctive patterns of brain atrophy accompanied by accumulation of hyperphosphorylated species of aggregated tau in NFT. In CTE, pathological changes in tau are accompanied by a number of other pathobiological processes, such as inflammation (Daneshvar, D.H. et al., 2015 Mol Cell Neurosci 66(Pt B): 81-90). Targeting the tau aggregates may provide reprieve from the progression of the disease and may allow cognitive improvement.

[00497] As of today, there is no medical therapy to treat or cure CTE. The condition is only diagnosed after death, due to lack of in vivo techniques to identify CTE specific biomarkers. There remains a need for therapy affecting the underlying pathophysiology, such as antibody therapies targeting tau protein.

[00498] In some embodiments, the vectored antibody delivery methods of the present invention may be used to treat subjects suffering from CTE. In some cases, methods of the present invention may be used to treat subjects suspected of developing CTE.

Prion diseases

[00499] Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a group of rare progressive conditions affecting the nervous system. The related conditions are rare and are typically caused by mutations in the PRNP gene which enables production of the prion protein. Gene mutations lead to an abnormally structured prion protein. Alternatively, the abnormal prion may be acquired by exposure from an outside source, e.g. by consumption of beef products containing the abnormal prion protein. Abnormal prions are misfolded, causing the brain tissue to degenerate rapidly. Prion diseases include, but are not limited to, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal insomnia (FFI), variably protease-sensitive prionopathy (VPSPr), and kuru. Prion diseases are rare. Approximately 350 cases of prion diseases are diagnosed in the US annually.

[00500] CJD is a degenerative brain disorder characterized by problems with muscular coordination, personality changes including mental impairment, impaired vision, involuntary muscle jerks, weakness and eventually coma. The most common categories of CJD are sporadic, hereditary due to a genetic mutation, and acquired. Sporadic CJD is the most common form affecting people with no known risk factors for the disease. The acquired form of CJD is transmitted by exposure of the brain and nervous system tissue to the prion. As an example, variant CJD (vCDJ) is linked to a bovine spongiform encephalopathy (BSE), also known as a 'mad cow' disease. CJD is fatal and patients typically die within one year of diagnosis.

[00501] Prion diseases are associated with an infectious agent consisting of an alternative conformational isoform of the prion protein, PrPSc. PrPSc replication is considered to occur through an induction of the infectious prion in the normal prion protein (PrPC). The replication occurs without a nucleic acid.

[00502] As of today, there is no therapy to manage or cure CJD, or other prion diseases. Typically, treatment is aimed at alleviating symptoms and increasing comfortability of the patient, e.g. with pain relievers. There remains a need for therapy affecting the underlying pathophysiology, such as antibody therapies targeting the prion protein.

[00503] In some embodiments, vectored antibody delivery methods of the present invention may be used to treat subjects suffering from a prion disease. In some cases, methods of the present invention may be used to treat subjects suspected of developing a prion disease.

Neurodegeneration and stroke

[00504] Neurodegenerative diseases and other diseases of the nervous system share many common features. Neurodegenerative diseases, in particular, are a group of conditions characterized by progressive loss of neuronal structure and function, ultimately leading to

neuronal cell death. Neurons are the building blocks of the nervous system(s) and are generally not able to reproduce and/or be replaced, and therefore neuron damage and/or death is especially devastating. Other, non-degenerating diseases that lead to neuronal cell loss, such as stroke, have similarly debilitating outcomes. Targeting molecules that contribute to the deteriorating cell structure or function may prove beneficial generally for treatment of nervous system diseases, neurodegenerative disease and/or stroke.

[00505] Certain molecules are believed to have inhibitory effects on neurite outgrowth, contributing to the limited ability of the central nervous system to repair. Such molecules include, but are not limited to, myelin associated proteins, such as, but not limited to, RGM (Repulsive guidance molecule), NOGO (Neurite outgrowth inhibitor), NOGO receptor, MAG (myelin associated glycoprotein), and MAI (myelin associated inhibitor). In one embodiment, the vectored antibody delivery of the present invention is utilized to target the aforementioned antigens (e.g., neurite outgrowth inhibitors).

[00506] Many neurodegenerative diseases are associated with aggregation of misfolded proteins, including, but not limited to, alpha synuclein, tau, amyloid β, prion proteins, TDP-43, and huntingtin (see, e.g. De Genst et al., 2014, Biochim Biophys Acta;1844(11):1907-1919, and Yu et al., 2013, Neurotherapeutics.; 10(3): 459–472, references therein). The aggregation results from disease-specific conversion of soluble proteins to an insoluble, highly ordered fibrillary deposit. This conversion is thought to prevent the proper disposal or degradation of the misfolded protein, thereby leading to further aggregation. Conditions associated with alpha synuclein and tau may be referred to as "synucleinopathies" and "tauopathies", respectively. In one embodiment, the vectored antibody delivery of the present invention is utilized to target the aforementioned antigens (e.g., misfolded or aggregated proteins).

Other therapeutic targets

[00507] The AAV particles or pharmaceutical compositions of the present invention useful in preventing or treating tauopathies or tau-associated diseases may alternatively, or in combination, encode an antibody that does not bind to the tau protein (e.g., the antigen is a polypeptide other than tau). Non-limiting examples of other target antigens include any of the following, including fragments or variants thereof, α-synuclein (monomers, oligomers, aggregates, fragments), ABCA1 (ATP-binding cassette, sub-family A, member 1), ABCA4 (ATP-binding cassette, sub-family A, member 4), ABCB1 (ATP-binding cassette, sub-family B, member 1), ACE (angiotensin I converting enzyme), ACKR1 (atypical chemokine receptor 1 (Duffy blood group)), AMPA (DL-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), ACTH (Adrenocorticotropic Hormone), ACVR2A (Activin receptor type-2A), ACVR2B

(Activin receptor type-2B), ADDL (Adducin-Like Protein 70), ADORA2A (adenosine A2a receptor), ADRA2A (adrenoceptor alpha 2A), AIFM1 (apoptosis-inducing factor), AKT1 (RAC-alpha serine/threonine-protein kinase), ALK-1 (activin receptor-like kinase 1), Alpha beta fibril, alpha subunit (basic helix-loop-helix transcription factor), AMT (Aminomethyltransferase), Amyloid β (monomers, oligomers, aggregates, fragments), amyloid or amyloid-like proteins, ANGPTL3 (Angiopoietin-Like 3), ANGTP1 (angiopoitin 1), ANGTP2 (angiopoietin 2), ANK3 (ankyrin 3), ANKG (ankyrin G), Annexin IV, phospholipid, Anx-A1 (annexin A1), APOE (apolipoprotein E), APP (amyloid beta precursor protein), ARSD (Arylsulfatase D), ATM (Ataxia Telangiectasia Mutated serine/threonine kinase), ATXN1 (ataxin 1), ATXN2 (ataxin 2), ATXN3 (ataxin 3), ATXN7 (ataxin 7), B Lymphocyte Stimulator, BDNF (brain-derived neurotrophic factor), beta A4 peptide/Alpha beta 4, beta A4 peptide, Alpha beta 5, bAlpha beta 6, Alpha beta 7, Alpha beta 8, Alpha beta 9, Beta-secretases (BACE), BRAF (B-Raf Proto-Oncogene, Serine/Threonine Kinase), Properdin (factor P), Factors Ba and Bb, C1, C1q (complement component 1, subcomponent q), C2, C3, C4, C3a, C3b, C5, C5a, C5b, C6, C7, C8, C9 and C5b-9 (complement components), CAIX (Carbonic anhydrase IX), CA 125 (cancer antigen 125), CACNA1A (calcium channel voltage-dependent P/Q type alpha 1A subunit), cadherins, CA-IX (carbonic anhydrase 9), CALCA (calcitonin-related polypeptide alpha), CCKBR (cholecystokinin B receptor), CCL11 (eotaxin-1), CCL2 (Chemokine (C-C Motif) Ligand 2), CD11 (integrin alpha component), CD147 (basigin), CD154 (CD40L), CD19 (Cluster of Differentiation 19), CD2 (cluster of differentiation 2), CD20 (B-lymphocyte antigen), CD200 (cluster of differentiation 200), CD22 (cluster of differentiation 22), CD221 (insulin-like growth factor 1 (IGF-1) receptor), CD248 (Endosialin), CD26 (Dipeptidyl peptidase-4), CD27 (antigen precursor), CD274 (cluster of differentiation 274), CD28 (Cluster of Differentiation 28), CD29 (Integrin, Beta 1), CD3 (cluster of differentiation 3), CD30 (cluster of differentiation 30), CD31 (cluster of differentiation 31), CD33 (cluster of differentiation 33), CD37 (Leukocyte antigen), CD38 (cyclic ADP ribose hydrolase), CD3E (T-Cell Surface Antigen T3/Leu-4 Epsilon Chain), CD4 (T-Cell Surface Antigen T4/Leu-3), CD40 (CD40 Molecule, TNF Receptor Superfamily Member 5), CD41 (Integrin, Alpha 2b (Platelet Glycoprotein IIb Of IIb/IIIa Complex, Antigen CD41)), CD44 (cluster of differentiation 44), CD51 (integrin alpha 1), CD52 (Human Epididymis-Specific Protein 5), CD55 (Decay Accelerating Factor For Complement (Cromer Blood Group)), CD58 (lymphocyte function-associated antigen 3), CD59 (MAC-inhibitory protein), CD6 (cluster of differentiation 6), CD70 (cluster of differentiation 70, ligand for CD27), CD74 (HLA class II histocompatibility antigen gamma chain), CD79B (immunoglobulin-associated beta), CEA (Carcinoembryonic antigen), CFHR1 (Complement

Factor H-Related 1), CGRP (Calcitonin gene-related peptide), CHMP2B (charged multivesicular body protein 2B), CHRNA4 (cholinergic receptor nicotinic alpha 4 (neuronal)), CHRNB2 (cholinergic receptor nicotinic beta 2 (neuronal)), CISD2 (CDGSH iron sulfur domain 2), CLEC16A (C-type lectin domain family 16 member A), CLRN1 (clarin 1), CNR1 (cannabinoid receptor 1), CNTNAP2 (contactin associated protein-like 2), COMT (catechol-O-methyltransferase), CRB1 (crumbs family member 1, photoreceptor morphogenesis associated), CRX (cone-rod homeobox), CRY (crystallin), CSF1R (Colony Stimulating Factor 1 Receptor), CSF2 (Colony Stimulating Factor 2 (Granulocyte-Macrophage)), CSF2RA (Colony Stimulating Factor 2 Receptor, Alpha, Low-Affinity), CTGF (Connective Tissue Growth Factor), CTLA4 (Cytotoxic T-Lymphocyte-Associated Protein 4), CXC (chemokine receptor type 4), CXCL10 (Chemokine (C-X-C Motif) Ligand 10), DDC (dopa decarboxylase (aromatic L-amino acid decarboxylase)), DIABLO (IAP-Binding Mitochondrial Protein), differentiation factor 8 (GDF8), DISC1 (disrupted in schizophrenia 1), DLL3 (Delta-Like 3 (Drosophila)), DLL4 (Delta-Like 4 (Drosophila)), DPP4 (dipeptyl-peptidase 4), DPP6 (dipeptidyl-peptidase 6), DR6 (Death receptor 6), DRD1 (dopamine receptor D1), DRD2 (dopamine receptor D2), DRD4 (dopamine receptor D4), DRD5 (dopamine receptor 5), DRD5 (dopamine receptor D5), DTNBP1 (dystrobrevin binding protein 1), EAG1 (Ether-A-Go-Go Potassium Channel 1), EDB (fibronectin extra domain-B), EDNRA (endothelin receptor type A), EFNA1 (Ephrin-A1), EGFL7 (EGF-Like-Domain, Multiple 7), EGFR/ERBB1/HER1 (epidermal growth factor receptor 1), EN2 (Engrailed Homeobox 2), EPCAM (Epithelial cell adhesion molecule), EPHA3 (EPH Receptor A3), episialin (a carcinoma-associated mucin, MUC-1), ERBB2 (epidermal growth factor receptor 2), ERBB3 (epidermal growth factor receptor 3), ESR1 (estrogen receptor 1), F3 (coagulation factor III), F9 (human factor 9), F10 (human factor 10), FAAH (fatty acid amide hydrolase), Factor D C3 proactivator convertase), humanized IgG1, humanized IgG2, FAP (Fibroblast Activation Protein, Alpha), FBN2 (fibrillin 2), FBP (Folate-binding protein), FcγRIIB (Fc receptor gamma B), FcγRIIIA (Fc receptor gamma A), FLT1 (Fms-Related Tyrosine Kinase 1), FOLR1 (folate receptor alpha), Frizzled receptor, FXN (frataxin), FUS/TLS (RNA binding protein), G protein-coupled, GAA (glucosidase alpha acid), Gc-globulin (Vitamin D binding protein), Gangliosides, GD2 (ganglioside G2), GD3 (ganglioside g3), GM2 (monosialotetrahexosylganglioside 2) (GDF-8 (myostatin), GDNF (glial cell derived neurotrophic factor), GDNF (glial cell derived neurotrophic factor), GFAP (glial fibrillary acidic protein), GFRα3 (GDNF family receptor alpha-3), ghrelin, GIT1 (G protein-coupled receptor kinase interacting ArfGAP 1), GJA (Gap junction protein), GLDC Glycine Dehydrogenase (Decarboxylating), glycoprotein NMB (GPNMB), gpA33 (Glycoprotein A33 (Transmembrane)),

GPC3 (glypican 3), GRIN2B (glutamate receptor ionotropic N-methyl D-aspartate 2B), GRN (granulin), GDF8 (growth differentiation factor 8), GTPases (guanosine triphosphate), GSTP1 (glutathione S-transferase pi 1), GUCA1A (guanylate cyclase activator 1A (retina), GUCY2C (anti-GCC), HMCN1 (hemicentin 1), HGF (Hepatocyte Growth Factor), HIF1A (hypoxia inducible factor 1, HINT1 (histidine triad nucleotide binding protein 1), HIST3H3 (Histone H3), histone, HLA-DQB1 (major histocompatibility complex class II DQ beta 1), HLA-DR (MHC class II cell surface receptor), HLA-DRB1 (major histocompatibility complex class II DR beta 1), hNav1.7 (sodium ion channel), HTR1A (5-hydroxytryptamine (serotonin) receptor 1A G protein-coupled), HTR2A (5-hydroxytryptamine (serotonin) receptor 2A, HTR2A (5-hydroxytryptamine (serotonin) receptor 2A G protein-coupled), HTT (huntingtin), IAP-binding mitochondrial protein, IFNAR1 (Interferon (Alpha, Beta And Omega) Receptor 1), IFNB1 (interferon beta 1 fibroblast), IFN-γ (Interferon gamma), IGF-1 receptor, IGF1R (insulin-like growth factor 1 receptor), IGF-I (insulin-like growth factor 1), IGG1 (immunoglobulin subclass 1), IgG2 (immunoglobulin subclass 2), IgG4 (immunoglobulin subclass 4), IGHE (Immunoglobulin Heavy Constant Epsilon), IL 1B (interleukin 1 beta), IL12 (interleukin 12), IL12B (interleukin 12B), IL13 (interleukin 13), IL17A (interleukin 17A), IL17F (interleukin 17F), IL1A (interleukin 1A), IL1B (interleukin 1 beta), IL1-Ri (Interleukin 1 receptor, type I), IL20 (Interleukin 20), IL23A (interleukin 23A), IL-23p19 subunit (interleukin 23 subunit p19), IL2RA (interleukin 2 receptor alpha), IL4R (interleukin 4 receptor alpha, IL6 (interleukin 6), IL6R (interleukin 6 receptor), IL7R (interleukin 7 receptor), ILGF2 (insulin like growth factor 2), INS (insulin), Integrin α5β1, Integrin αVβ3, integrin αIIbβ3/GPIIb/IIIa, IP6K2 (inositol hexakisphosphate kinase 2), ITGA4 (Integrin, Alpha 4 (Antigen CD49D, Alpha 4 Subunit Of VLA-4 Receptor)), ITGB7 (Integrin, Alpha 7 (Antigen CD49D, Alpha 4 Subunit Of VLA-7 Receptor)), ITGAL (integrin alpha L chain), ITGAV ((Vitronectin Receptor, Alpha Polypeptide, Antigen CD51), ITGB3 (Integrin alpha-V/beta-3), KCNQ2 (potassium channel voltage gated KQT-like subfamily Q member 2), KDR (Kinase Insert Domain Receptor), KIR2D (killer immunoglobulin-like receptor (KIR) 2D subtype), KLRC1 (Killer Cell Lectin-Like Receptor Subfamily C, Member 1), LAG-3 (Lymphocyte-activation gene 3), Le (y) (Lewis y) antigen, LINGO (Leucine rich repeat and Immunoglobin-like domain-containing protein 1), LOXL2 (Lysyl oxidase homolog 2), LPG (lysophosphatidylglucoside), LPS (Lipopolysaccharides), LRP1 (low density lipoprotein receptor-related protein 1), LRRC6 (Leucine Rich Repeat Containing 6), LRRK2 (leucine-rich repeat kinase 2), LTA (Lymphotoxin Alpha), MAF (maf avian musculoaponeurotic fibrosarcoma oncogene homolog), MAG (Myelin Associated Glycoprotein), MAI (myelin associated inhibitor), MAOB (monoamine oxidase B), MAPT

(microtubule-associated protein tau), MBP (myelin basic protein), MCAF (monocyte chemotactic and activating factor), MCP-1 (Monocyte chemoattractant protein-1), MBL (mannose binding lectin), mannose, MET (Tyrosine-Protein Kinase Met), MIF (Macrophage Migration Inhibitory Factor (Glycosylation-Inhibiting Factor), MS4A1 (Membrane-Spanning 4-Domains, Subfamily A, Member 1), MSLN (Mesothelin), MST1R (Macrophage Stimulating 1 Receptor), MSTN (myostatin), MUC1/Episialin, MUC5AC (Mucin 5AC, Oligomeric Mucus/Gel-Forming), mucin CanAg (glycoform MUC-1), Mucins, myostatin, myostatin antagonists, N-acetyl glucosamine, NCAM1 (Neural Cell Adhesion Molecule 1), Neu5Gc/ NGNA (Neurogenin A), neuregulin (NRG), neurokinin B, NGF (Nerve growth factor), NMDA (N-methyl-D-aspartate), NOGO (Neurite outgrowth inhibitor), NOGO receptor-1, Nogo-66, NOGOA/NiG (Neurite Outgrowth Inhibitory Fragments of NOGOA), Notch receptor, NOTCH-1 (Notch homolog 1, translocation-associated (Drosophila)), NRG1 (neuregulin 1), NRP1 (Neuropilin 1), NT-3 trkC ligand, N-terminal region of Aβ8-x peptide, OGG1 (8-oxoguanine DNA glycosylase), oligomers of N-terminal truncated Aβ, OPA2 (Optic Atrophy 2), OPA3 (Optic Atrophy 3), oxLDL (Oxidized low-density lipoprotein), P75 (Low-affinity Nerve Growth Factor Receptor), PAND1 9Panic disorder 1), PAND2 (Panic disorder 2), PAND3 9Panic disorder 3), PARK2 (parkin RBR E3 ubiquitin protein ligase), PCSK9 (proprotein convertase subtilisin/kexin type 9), PD-1 (Programmed cell death protein 1), PD-2 (Programmed cell death protein 2), PD-3 (Programmed cell death protein 3), PD-4 (Programmed cell death protein 4), PD-5 (Programmed cell death protein 5), PD-6 (Programmed cell death protein 6), PD-7 (Programmed cell death protein 7), PD-8 (Programmed cell death protein 8), PDGFRA (Platelet-derived growth factor receptor alpha), PDGFRB (Platelet-derived growth factor receptor beta), PD-L1 (Programmed cell death protein 1 ligand), PEX7 (Peroxisomal Biogenesis Factor 7), PHOBS (phobia specific), PhosphatidyL-serine, chimeric IgG1, Phosphatide L-serine, Chimeric IgG2, PINK1 (PTEN induced putative kinase 1), platelet-derived growth factor receptor beta PDGFRB, PLAU (plasminogen activator urokinase), PLP (protelopid protein), PMP22 (peripheral myelin protein 22), POLG (polymerase (DNA directed) gamma), PRDM16 (PR domain containing 16), Prion proteins, PrP, PrPC, PrPSc, PRKCG (protein kinase C gamma), PSEN1 (presenilin 1), PSEN2 (presenilin 2), PSMA (Prostate-specific membrane antigen), PTGS2 (prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)), PTPN11 (Tyrosine-protein phosphatase non-receptor type 11), PVRL4 (Poliovirus Receptor-Related 4), PVRL5 (Poliovirus Receptor-Related 5), pyroglutamated A β, RAf1 (proto-oncogene serine/threonine-protein kinase), RAGE protein, RANKL (Receptor activator of nuclear factor kappa-B ligand), RCAN1 (regulator of calcineurin 1), RDh12 (retinol

dehydrogenase 12 (all-trans/9-cis/11-cis)), RGM A (Repulsive guidance molecule A), RHD (Rh blood group, D antigen), RHO (rhodopsin), RPE65 (retinal pigment epithelium-specific protein 65kDa), RTN4 (Reticulon-4, NOGO), S100B (calcium-binding protein B), S1P4 (Type 4 sphingosine 1-phosphate G protein-coupled receptor), SCN1A (Sodium Channel, Voltage Gated, Type I Alpha Subunit), SDC1 (Syndecan 1), selectin P, SHANK3 (SH3 And Multiple Ankyrin Repeat Domains 3), SLAMF7 (SLAM Family Member 7), SLC18A2 (solute carrier family 18 (vesicular monoamine transporter, member 2), SLC1A2 (solute carrier family 1 (glial high affinity glutamate transporter, member 2), SLC34A2 (Solute Carrier Family 34 (Type II Sodium/Phosphate Cotransporter), SLC6A3 (solute carrier family 6 (neurotransmitter transporter) member 3), SLC6A4 (Solute Carrier Family 6 (Neurotransmitter Transporter), SMN1 (survival of motor neuron 1 telomeric), SMN2 (survival of motor neuron 2 centromeric), SNCA (synuclein alpha (non A4 component of amyloid precursor)), SNCA (synuclein alpha (non A4 component of amyloid precursor), SNCB (synuclein beta), SOD1 (superoxide dismutase 1 soluble), SOST (Sclerostin), sphingosine-1-phosphate, SQSTM1 (sequestosome 1), STEAP1 (Six Transmembrane Epithelial Antigen Of The Prostate 1), SULF2 (Sulfatase 2), TACR1 (tachykinin receptor 1), TAG-72 (Tumor-associated glycoprotein 72), TARDBP (TAR DNA binding protein), tau antigen, tau protein, tau pS422, TDP-43, tenascin, tenascin C, TFPI (Tissue Factor Pathway Inhibitor (Lipoprotein-Associated Coagulation Inhibitor)), TGF beta (Transforming growth factor beta), TH (Tyrosine hydroxylase), TkrC (Tropomyosin receptor kinase C), TMEFF2 (Transmembrane Protein With EGF-Like And Two Follistatin-Like Domains 2), TMEFF3 (Transmembrane Protein With EGF-Like And Two Follistatin-Like Domains 3), TNF (tumor necrosis factor), TNFa (tumor necrosis factor alpha), TNFRSF10B (Tumor Necrosis Factor Receptor Superfamily, Member 10b), TNFRSF12A (Tumor Necrosis Factor Receptor Superfamily, Member 12A), TNFRSF8 (Tumor Necrosis Factor Receptor Superfamily, Member 8), TNFRSF9 (Tumor Necrosis Factor Receptor Superfamily, Member 9), TNFSF11 (Tumor Necrosis Factor Receptor Superfamily, Member 11), TNFSF13B (Tumor Necrosis Factor Receptor Superfamily, Member 13b), TNF-α (Tumor Necrosis Factor alpha)), TNNT2 (troponin T type 2), TOR1A (torsin family 1 member A (torsin A)), TPBG (Trophoblast Glycoprotein), TPH2 (tryptophan hydroxylase 2), TRAILR1 (Death receptor 4), TRAILR2 (Death receptor 5), TrkA (Tropomyosin receptor kinase A), TRPV4 (Transient Receptor Potential Cation Channel, Subfamily V, Member 4), TSC2 (tuberous sclerosis 2), TULP1 (tubby like protein 1), tumor necrosis factor related protein 5, tumor specific glycosylation of MUC1, tumor-associated calcium signal transducer 2, tumor protein p53, TYRP1 (glycoprotein 75), UCHL1 (ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)), UNC-13A (unc-13

homolog A), USH1C (Usher Syndrome 1C), USH2A (Usher Syndrome 2A (Autosomal Recessive, Mild), VEGF (Vascular endothelial growth factor), VEGF A (Vascular endothelial growth factor A), C5, Factor P, Factor D, EPO (Erythropoietin), EPOR (EPO receptor), Interleukins, IL-1β, IL-17A, Il-10, TNFα, FGFR2 (Fibroblast Growth Factor Receptor 2), VEGFR (vascular endothelial growth factor receptor), VEGFR2 (vascular endothelial growth factor receptor 2), vimentin, voltage gated ion channels, VWF (Von Willebrand Factor), WFS1 (Wolfram syndrome 1 (wolframin)), and YES1 (Yamaguchi Sarcoma Viral Oncogene Homolog 1).

[00508] In one embodiment, the AAV particle of the present invention, useful in treating a tauopathy or tau-associated disease, targets an antigen considered to be part of the immune system (i.e., target antigens commonly associated with treatment of cancers or autoimmune diseases).

[00509] In one embodiment, the AAV particle of the present invention, useful in treating a tauopathy or tau-associated disease, targets an antigen considered to be part of the inflammatory system (i.e., target antigens commonly associated with treatment of inflammatory diseases).

[00510] In one embodiment, the AAV particle of the present invention, useful in treating a tauopathy or tau-associated disease, targets an antigen considered to be part of the cell-death signaling cascade.

[00511] In one embodiment, the AAV particle of the present invention, useful in treating a tauopathy or tau-associated disease, targets an antigen considered to be a neuroprotective agent.

[00512] AAV Particles and methods of using the AAV particles described in the present invention may be used to prevent, manage and/or treat tauopathies or tau associated disease. As a non-limiting example, the AAV particles of the present invention comprise a nucleic acid sequence encoding at least one of the sequences described in Table 3 or Table 4 (SEQ ID NO: 2948-4269 and 4276-4320).

V. KITS AND DEVICES

Kits

[00513] In one embodiment, the invention provides a variety of kits for conveniently and/or effectively carrying out methods of the present invention. Typically, kits will comprise sufficient amounts and/or numbers of components to allow a user to perform multiple treatments of a subject(s) and/or to perform multiple experiments.

[00514] Any of the AAV particles of the present invention may be comprised in a kit. In some embodiments, kits may further include reagents and/or instructions for creating and/or synthesizing compounds and/or compositions of the present invention. In some embodiments,

kits may also include one or more buffers. In some embodiments, kits of the invention may include components for making protein or nucleic acid arrays or libraries and thus, may include, for example, solid supports.

[00515] In some embodiments, kit components may be packaged either in aqueous media or in lyophilized form. The container means of the kits will generally include at least one vial, test tube, flask, bottle, syringe or other container means, into which a component may be placed, and preferably, suitably aliquoted. Where there is more than one kit component, (labeling reagent and label may be packaged together), kits may also generally contain second, third or other additional containers into which additional components may be separately placed. In some embodiments, kits may also comprise second container means for containing sterile, pharmaceutically acceptable buffers and/or other diluents. In some embodiments, various combinations of components may be comprised in one or more vial. Kits of the present invention may also typically include means for containing compounds and/or compositions of the present invention, e.g., proteins, nucleic acids, and any other reagent containers in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which desired vials are retained.

[00516] In some embodiments, kit components are provided in one and/or more liquid solutions. In some embodiments, liquid solutions are aqueous solutions, with sterile aqueous solutions being particularly preferred. In some embodiments, kit components may be provided as dried powder(s). When reagents and/or components are provided as dry powders, such powders may be reconstituted by the addition of suitable volumes of solvent. In some embodiments, it is envisioned that solvents may also be provided in another container means. In some embodiments, labeling dyes are provided as dried powders. In some embodiments, it is contemplated that 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 120, 130, 140, 150, 160, 170, 180, 190, 200, 300, 400, 500, 600, 700, 800, 900, 1000 micrograms or at least or at most those amounts of dried dye are provided in kits of the invention. In such embodiments, dye may then be resuspended in any suitable solvent, such as DMSO.

[00517] In some embodiments, kits may include instructions for employing kit components as well the use of any other reagent not included in the kit. Instructions may include variations that may be implemented.

Devices

[00518] In one embodiment, the AAV particles may delivered to a subject using a device to deliver the AAV particles and a head fixation assembly. The head fixation assembly may be, but is not limited to, any of the head fixation assemblies sold by MRI interventions. As a non-

limiting example, the head fixation assembly may be any of the assemblies described in US Patent Nos. 8099150, 8548569, and 9031636 and International Patent Publication Nos. WO201108495 and WO2014014585, the contents of each of which are incorporated by reference in their entireties. A head fixation assembly may be used in combination with an MRI compatible drill such as, but not limited to, the MRI compatible drills described in International Patent Publication No. WO2013181008 and US Patent Publication No. US20130325012, the contents of which are herein incorporated by reference in its entirety.

[00519] In one embodiment, the AAV particles may be delivered using a method, system and/or computer program for positioning apparatus to a target point on a subject to deliver the AAV particles. As a non-limiting example, the method, system and/or computer program may be the methods, systems and/or computer programs described in US Patent No. 8340743, the contents of which are herein incorporated by reference in its entirety. The method may include: determining a target point in the body and a reference point, wherein the target point and the reference point define a planned trajectory line (PTL) extending through each; determining a visualization plane, wherein the PTL intersects the visualization plane at a sighting point; mounting the guide device relative to the body to move with respect to the PTL, wherein the guide device does not intersect the visualization plane; determining a point of intersection (GPP) between the guide axis and the visualization plane; and aligning the GPP with the sighting point in the visualization plane.

[00520] In one embodiment, the AAV particles may be delivered to a subject using a convention-enhanced delivery device. Non-limiting examples of targeted delivery of drugs using convection are described in US Patent Publication Nos. US20100217228, US20130035574, and US 20130035660 and International Patent Publication No. WO2013019830 and WO2008144585, the contents of each of which are herein incorporated by reference in their entireties.

[00521] In one embodiment, a subject may be imaged prior to, during and/or after delivery of the AAV particles. The imaging method may be a method known in the art and/or described herein, such as but not limited to, magnetic resonance imaging (MRI). As a non-limiting example, imaging may be used to assess therapeutic effect. As another non-limiting example, imaging may be used for assisted delivery of AAV particles.

[00522] In one embodiment, the AAV particles may be delivered using an MRI-guided device. Non-limiting examples of MRI-guided devices are described in US Patent Nos. 9055884, 9042958, 8886288, 8768433, 8396532, 8369930, 8374677, and 8175677 and US Patent Application No. US20140024927 the contents of each of which are herein incorporated by

reference in their entireties. As a non-limiting example, the MRI-guided device may be able to provide data in real time such as those described in US Patent Nos. 8886288 and 8768433, the contents of each of which is herein incorporated by reference in its entirety. As another non-limiting example, the MRI-guided device or system may be used with a targeting cannula such as the systems described in US Patent Nos. 8175677 and 8374677, the contents of each of which are herein incorporated by reference in their entireties. As yet another non-limiting example, the MRI-guided device includes a trajectory guide frame for guiding an interventional device as described, for example, in US Patent No. 9055884 and US Patent Application No. US20140024927, the contents of each of which are herein incorporated by reference in their entireties.

[00523] In one embodiment, the AAV particles may be delivered using an MRI-compatible tip assembly. Non-limiting examples of MRI-compatible tip assemblies are described in US Patent Publication No. US20140275980, the contents of which is herein incorporated by reference in its entirety.

[00524] In one embodiment, the AAV particles may be delivered using a cannula which is MRI-compatible. Non-limiting examples of MRI-compatible cannulas include those taught in International Patent Publication No. WO2011130107, the contents of which are herein incorporated by reference in its entirety.

[00525] In one embodiment, the AAV particles may be delivered using a catheter which is MRI-compatible. Non-limiting examples of MRI-compatible catheters include those taught in International Patent Publication No. WO2012116265, US Patent No. 8825133 and US Patent Publication No. US20140024909, the contents of each of which are herein incorporated by reference in their entireties.

[00526] In one embodiment, the AAV particles may be delivered using a device with an elongated tubular body and a diaphragm as described in US Patent Publication Nos. US20140276582 and US20140276614, the contents of each of which are herein incorporated by reference in their entireties.

[00527] In one embodiment, the AAV particles may be delivered using an MRI compatible localization and/or guidance system such as, but not limited to, those described in US Patent Publication Nos. US20150223905 and US20150230871, the contents of each of which are herein incorporated by reference in their entireties. As a non-limiting example, the MRI compatible localization and/or guidance systems may comprise a mount adapted for fixation to a patient, a targeting cannula with a lumen configured to attach to the mount so as to be able to controllably translate in at least three dimensions, and an elongate probe configured to snugly advance via

slide and retract in the targeting cannula lumen, the elongate probe comprising at least one of a stimulation or recording electrode.

[00528] In one embodiment, the AAV particles may be delivered to a subject using a trajectory frame as described in US Patent Publication Nos. US20150031982 and US20140066750 and International Patent Publication Nos. WO2015057807 and WO2014039481, the contents of each of which are herein incorporated by reference in their entireties.

[00529] In one embodiment, the AAV particles may be delivered to a subject using a gene gun.

VI. DEFINITIONS

[00530] At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges.

[00531] *About:* As used herein, the term "about" means +/- 10% of the recited value.

[00532] *Adeno-associated virus*: The term "adeno-associated virus" or "AAV" as used herein refers to members of the dependovirus genus comprising any particle, sequence, gene, protein, or component derived therefrom.

[00533] *AAV Particle*: As used herein, an "AAV particle" is a virus which comprises a viral genome with at least one payload region and at least one ITR region. AAV vectors of the present disclosure may be produced recombinantly and may be based on adeno-associated virus (AAV) parent or reference sequences. AAV particle may be derived from any serotype, described herein or known in the art, including combinations of serotypes (i.e., "pseudotyped" AAV) or from various genomes (e.g., single stranded or self-complementary). In addition, the AAV particle may be replication defective and/or targeted.

[00534] *Activity:* As used herein, the term "activity" refers to the condition in which things are happening or being done. Compositions of the invention may have activity and this activity may involve one or more biological events.

[00535] *Administered in combination:* As used herein, the term "administered in combination" or "combined administration" means that two or more agents are administered to a subject at the same time or within an interval such that there may be an overlap of an effect of each agent on the patient. In some embodiments, they are administered within about 60, 30, 15, 10, 5, or 1 minute of one another. In some embodiments, the administrations of the agents are spaced sufficiently closely together such that a combinatorial (*e.g.*, a synergistic) effect is achieved.

[00536] *Amelioration*: As used herein, the term "amelioration" or "ameliorating" refers to a lessening of severity of at least one indicator of a condition or disease. For example, in the context of neurodegeneration disorder, amelioration includes the reduction of neuron loss.

[00537] *Animal:* As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans at any stage of development. In some embodiments, "animal" refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically-engineered animal, or a clone.

[00538] *Antibody:* As used herein, the term "antibody" is referred to in the broadest sense and specifically covers various embodiments including, but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g. bispecific antibodies formed from at least two intact antibodies), and antibody fragments (e.g., diabodies) so long as they exhibit a desired biological activity (e.g., "functional"). Antibodies are primarily amino-acid based molecules but may also comprise one or more modifications (including, but not limited to the addition of sugar moieties, fluorescent moieties, chemical tags, etc.). Non-limiting examples of antibodies or fragments thereof include V_H and V_L domains, scFvs, Fab, Fab', $F(ab')_2$, Fv fragment, diabodies, linear antibodies, single chain antibody molecules, multispecific antibodies, bispecific antibodies, intrabodies, monoclonal antibodies, polyclonal antibodies, humanized antibodies, codon-optimized antibodies, tandem scFv antibodies, bispecific T-cell engagers, mAb2 antibodies, chimeric antigen receptors (CAR), tetravalent bispecific antibodies, biosynthetic antibodies, native antibodies, miniaturized antibodies, unibodies, maxibodies, antibodies to senescent cells, antibodies to conformers, antibodies to disease specific epitopes, or antibodies to innate defense molecules.

[00539] *Antibody-based composition:* As used herein, "antibody-based" or "antibody-derived" compositions are monomeric or multi-meric polypeptides which comprise at least one amino-acid region derived from a known or parental antibody sequence and at least one amino acid region derived from a non-antibody sequence, e.g., mammalian protein.

[00540] *Approximately:* As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference

value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[00541] *Associated with:* As used herein, the terms "associated with," "conjugated," "linked," "attached," and "tethered," when used with respect to two or more moieties, means that the moieties are physically associated or connected with one another, either directly or via one or more additional moieties that serves as a linking agent, to form a structure that is sufficiently stable so that the moieties remain physically associated under the conditions in which the structure is used, *e.g.*, physiological conditions. An "association" need not be strictly through direct covalent chemical bonding. It may also suggest ionic or hydrogen bonding or a hybridization based connectivity sufficiently stable such that the "associated" entities remain physically associated.

[00542] *Bifunctional:* As used herein, the term "bifunctional" refers to any substance, molecule or moiety which is capable of or maintains at least two functions. The functions may affect the same outcome or a different outcome. The structure that produces the function may be the same or different.

[00543] *Biocompatible*: As used herein, the term "biocompatible" means compatible with living cells, tissues, organs or systems posing little to no risk of injury, toxicity or rejection by the immune system.

[00544] *Biodegradable*: As used herein, the term "biodegradable" means capable of being broken down into innocuous products by the action of living things.

[00545] *Biologically active*: As used herein, the phrase "biologically active" refers to a characteristic of any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological effect on that organism, is considered to be biologically active. In particular embodiments, an AAV particle of the present invention may be considered biologically active if even a portion of the encoded payload is biologically active or mimics an activity considered biologically relevant.

[00546] *Capsid*: As used herein, the term "capsid" refers to the protein shell of a virus particle.

[00547] *Chimeric antigen receptor (CAR):* As used herein, the term "chimeric antigen receptor" or "CAR" refers to an artificial chimeric protein comprising at least one antigen specific targeting region (ASTR), a transmembrane domain and an intracellular signaling domain, wherein the antigen specific targeting region comprises a full-length antibody or a fragment thereof. As a non-limiting example the ASTR of a CAR may be any of the antibodies listed in Table 3, antibody-based compositions or fragments thereof. Any molecule that is capable of binding a target antigen with high affinity can be used in the ASTR of a CAR. The

CAR may optionally have an extracellular spacer domain and/or a co-stimulatory domain. A CAR may also be used to generate a cytotoxic cell carrying the CAR.

[00548] *Complementary and substantially complementary:* As used herein, the term "complementary" refers to the ability of polynucleotides to form base pairs with one another. Base pairs are typically formed by hydrogen bonds between nucleotide units in antiparallel polynucleotide strands. Complementary polynucleotide strands can form base pair in the Watson-Crick manner (e.g., A to T, A to U, C to G), or in any other manner that allows for the formation of duplexes. As persons skilled in the art are aware, when using RNA as opposed to DNA, uracil rather than thymine is the base that is considered to be complementary to adenosine. However, when a U is denoted in the context of the present invention, the ability to substitute a T is implied, unless otherwise stated. Perfect complementarity or 100% complementarity refers to the situation in which each nucleotide unit of one polynucleotide strand can form hydrogen bond with a nucleotide unit of a second polynucleotide strand. Less than perfect complementarity refers to the situation in which some, but not all, nucleotide units of two strands can form hydrogen bond with each other. For example, for two 20-mers, if only two base pairs on each strand can form hydrogen bond with each other, the polynucleotide strands exhibit 10% complementarity. In the same example, if 18 base pairs on each strand can form hydrogen bonds with each other, the polynucleotide strands exhibit 90% complementarity. As used herein, the term "substantially complementary" means that the siRNA has a sequence (e.g., in the antisense strand) which is sufficient to bind the desired target mRNA, and to trigger the RNA silencing of the target mRNA.

[00549] *Compound:* Compounds of the present disclosure include all of the isotopes of the atoms occurring in the intermediate or final compounds. "Isotopes" refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

[00550] The compounds and salts of the present disclosure can be prepared in combination with solvent or water molecules to form solvates and hydrates by routine methods.

[00551] *Comprehensive Positional Evolution (CPE ™):* As used herein, the term "comprehensive positional evolution" refers to an antibody evolution technology that allows for mapping of the effects of amino acid changes at every position along an antibody variable domain's sequence. This comprehensive mutagenesis technology can be used to enhance one or more antibody properties or characteristics.

[00552] *Comprehensive Protein Synthesis (CPS ™):* As used herein, the term "comprehensive protein synthesis" refers to a combinatorial protein synthesis technology that can be used to

optimize antibody properties or characteristics by combining the best properties into a new, high-performance antibody.

[00553] *Conditionally active:* As used herein, the term "conditionally active" refers to a mutant or variant of a wild-type polypeptide, wherein the mutant or variant is more or less active at physiological conditions than the parent polypeptide. Further, the conditionally active polypeptide may have increased or decreased activity at aberrant conditions as compared to the parent polypeptide. A conditionally active polypeptide may be reversibly or irreversibly inactivated at normal physiological conditions or aberrant conditions.

[00554] *Conserved:* As used herein, the term "conserved" refers to nucleotides or amino acid residues of a polynucleotide sequence or polypeptide sequence, respectively, that are those that occur unaltered in the same position of two or more sequences being compared. Nucleotides or amino acids that are relatively conserved are those that are conserved amongst more related sequences than nucleotides or amino acids appearing elsewhere in the sequences.

[00555] In some embodiments, two or more sequences are said to be "completely conserved" if they are 100% identical to one another. In some embodiments, two or more sequences are said to be "highly conserved" if they are at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be "highly conserved" if they are about 70% identical, about 80% identical, about 90% identical, about 95%, about 98%, or about 99% identical to one another. In some embodiments, two or more sequences are said to be "conserved" if they are at least 30% identical, at least 40% identical, at least 50% identical, at least 60% identical, at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be "conserved" if they are about 30% identical, about 40% identical, about 50% identical, about 60% identical, about 70% identical, about 80% identical, about 90% identical, about 95% identical, about 98% identical, or about 99% identical to one another. Conservation of sequence may apply to the entire length of a polynucleotide or polypeptide or may apply to a portion, region or feature thereof.

[00556] *Control Elements:* As used herein, "control elements", "regulatory control elements", or "regulatory sequences" refers to promoter regions, polyadenylation signals, transcription termination sequences, upstream regulatory domains, origins of replication, internal ribosome entry sites ("IRES"), enhancers, and the like, which provide for the replication, transcription and translation of a coding sequence in a recipient cell. Not all of these control elements need always be present as long as the selected coding sequence is capable of being replicated, transcribed and/or translated in an appropriate host cell.

[00557] *Controlled Release:* As used herein, the term "controlled release" refers to a pharmaceutical composition or compound release profile that conforms to a particular pattern of release to effect a therapeutic outcome.

[00558] *Cytostatic:* As used herein, "cytostatic" refers to inhibiting, reducing, suppressing the growth, division, or multiplication of a cell (*e.g.*, a mammalian cell (*e.g.*, a human cell)), bacterium, virus, fungus, protozoan, parasite, prion, or a combination thereof.

[00559] *Cytotoxic:* As used herein, "cytotoxic" refers to killing or causing injurious, toxic, or deadly effect on a cell (*e.g.*, a mammalian cell (*e.g.*, a human cell)), bacterium, virus, fungus, protozoan, parasite, prion, or a combination thereof.

[00560] *Delivery:* As used herein, "delivery" refers to the act or manner of delivering an AAV particle, a compound, substance, entity, moiety, cargo or payload.

[00561] *Delivery Agent:* As used herein, "delivery agent" refers to any substance which facilitates, at least in part, the *in vivo* delivery of an AAV particle to targeted cells.

[00562] *Destabilized:* As used herein, the term "destable", "destabilize", or "destabilizing region" means a region or molecule that is less stable than a starting, wild-type or native form of the same region or molecule.

[00563] *Detectable label:* As used herein, "detectable label" refers to one or more markers, signals, or moieties which are attached, incorporated or associated with another entity that is readily detected by methods known in the art including radiography, fluorescence, chemiluminescence, enzymatic activity, absorbance and the like. Detectable labels include radioisotopes, fluorophores, chromophores, enzymes, dyes, metal ions, ligands such as biotin, avidin, streptavidin and haptens, quantum dots, and the like. Detectable labels may be located at any position in the peptides or proteins disclosed herein. They may be within the amino acids, the peptides, or proteins, or located at the N- or C- termini.

[00564] *Digest:* As used herein, the term "digest" means to break apart into smaller pieces or components. When referring to polypeptides or proteins, digestion results in the production of peptides.

[00565] *Distal:* As used herein, the term "distal" means situated away from the center or away from a point or region of interest.

[00566] *Dosing regimen:* As used herein, a "dosing regimen" is a schedule of administration or physician determined regimen of treatment, prophylaxis, or palliative care.

[00567] *Encapsulate:* As used herein, the term "encapsulate" means to enclose, surround or encase.

[00568] *Engineered:* As used herein, embodiments of the invention are "engineered" when they are designed to have a feature or property, whether structural or chemical, that varies from a starting point, wild type or native molecule.

[00569] *Effective Amount:* As used herein, the term "effective amount" of an agent is that amount sufficient to effect beneficial or desired results, for example, clinical results, and, as such, an "effective amount" depends upon the context in which it is being applied. For example, in the context of administering an agent that treats cancer, an effective amount of an agent is, for example, an amount sufficient to achieve treatment, as defined herein, of cancer, as compared to the response obtained without administration of the agent.

[00570] *Epitope:* As used herein, an "epitope" refers to a surface or region on a molecule that is capable of interacting with a biomolecule. For example, a protein may contain one or more amino acids, e.g., an epitope, which interacts with an antibody, e.g., a biomolecule. In some embodiments, when referring to a protein or protein module, an epitope may comprise a linear stretch of amino acids or a three-dimensional structure formed by folded amino acid chains.

[00571] *EvoMap™*: As used herein, an EvoMap™ refers to a map of a polypeptide, wherein detailed informatics are presented about the effects of single amino acid mutations within the length of the polypeptide and their influence on the properties and characteristics of that polypeptide.

[00572] *Expression:* As used herein, "expression" of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (*e.g.*, by splicing, editing, 5′ cap formation, and/or 3′ end processing); (3) translation of an RNA into a polypeptide or protein; and (4) post-translational modification of a polypeptide or protein.

[00573] *Feature:* As used herein, a "feature" refers to a characteristic, a property, or a distinctive element.

[00574] *Formulation:* As used herein, a "formulation" includes at least one AAV particle and a delivery agent.

[00575] *Fragment:* A "fragment," as used herein, refers to a portion. For example, fragments of proteins may comprise polypeptides obtained by digesting full-length protein isolated from cultured cells.

[00576] *Functional:* As used herein, a "functional" biological molecule is a biological molecule in a form in which it exhibits a property and/or activity by which it is characterized.

[00577] *Gene expression:* The term "gene expression" refers to the process by which a nucleic acid sequence undergoes successful transcription and in most instances translation to produce a

protein or peptide. For clarity, when reference is made to measurement of "gene expression", this should be understood to mean that measurements may be of the nucleic acid product of transcription, e.g., RNA or mRNA or of the amino acid product of translation, e.g., polypeptides or peptides. Methods of measuring the amount or levels of RNA, mRNA, polypeptides and peptides are well known in the art.

[00578] *Homology*: As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term "homologous" necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). In accordance with the invention, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least about 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. In accordance with the invention, two protein sequences are considered to be homologous if the proteins are at least about 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least about 20 amino acids.

[00579] *Heterologous Region*: As used herein the term "heterologous region" refers to a region which would not be considered a homologous region.

[00580] *Homologous Region*: As used herein the term "homologous region" refers to a region which is similar in position, structure, evolution origin, character, form or function.

[00581] *Identity*: As used herein, the term "identity" refers to the overall relatedness between polymeric molecules, *e.g.*, between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at

corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H. and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., *et al.*, *Nucleic Acids Research*, 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. *et al.*, *J. Molec. Biol.*, 215, 403 (1990)).

[00582] *Inhibit expression of a gene:* As used herein, the phrase "inhibit expression of a gene" means to cause a reduction in the amount of an expression product of the gene. The expression product can be an RNA transcribed from the gene (*e.g.*, an mRNA) or a polypeptide translated from an mRNA transcribed from the gene. Typically, a reduction in the level of an mRNA results in a reduction in the level of a polypeptide translated therefrom. The level of expression may be determined using standard techniques for measuring mRNA or protein.

[00583] *In vitro*: As used herein, the term "*in vitro*" refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, in a Petri dish, *etc.*, rather than within an organism (*e.g.*, animal, plant, or microbe).

[00584] *In vivo*: As used herein, the term "*in vivo*" refers to events that occur within an organism (*e.g.*, animal, plant, or microbe or cell or tissue thereof).

[00585] *Isolated*: As used herein, the term "isolated" refers to a substance or entity that has been separated from at least some of the components with which it was associated (whether in nature or in an experimental setting). Isolated substances may have varying levels of purity in reference to the substances from which they have been associated. Isolated substances and/or entities may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated agents are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "pure" if it is substantially free of other components.

[00586] *Substantially isolated*: By "substantially isolated" is meant that a substance is substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the substance or AAV particles of the present disclosure. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the present disclosure, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

[00587] *Linker*: As used herein "linker" refers to a molecule or group of molecules which connects two molecules, such as a V_H chain and V_L chain or an antibody. A linker may be a nucleic acid sequence connecting two nucleic acid sequences encoding two different polypeptides. The linker may or may not be translated. The linker may be a cleavable linker.

[00588] *MicroRNA (miRNA) binding site*: As used herein, a microRNA (miRNA) binding site represents a nucleotide location or region of a nucleic acid transcript to which at least the "seed" region of a miRNA binds.

[00589] *Modified*: As used herein "modified" refers to a changed state or structure of a molecule of the invention. Molecules may be modified in many ways including chemically, structurally, and functionally.

[00590] *Naturally Occurring*: As used herein, "naturally occurring" or "wild-type" means existing in nature without artificial aid, or involvement of the hand of man.

[00591] *Non-human vertebrate:* As used herein, a "non-human vertebrate" includes all vertebrates except *Homo sapiens*, including wild and domesticated species. Examples of non-human vertebrates include, but are not limited to, mammals, such as alpaca, banteng, bison, camel, cat, cattle, deer, dog, donkey, gayal, goat, guinea pig, horse, llama, mule, pig, rabbit, reindeer, sheep water buffalo, and yak.

[00592] *Off-target:* As used herein, "off target" refers to any unintended effect on any one or more target, gene, or cellular transcript.

[00593] *Open reading frame:* As used herein, "open reading frame" or "ORF" refers to a sequence which does not contain a stop codon in a given reading frame.

[00594] *Operably linked:* As used herein, the phrase "operably linked" refers to a functional connection between two or more molecules, constructs, transcripts, entities, moieties or the like.

[00595] *Particle:* As used herein, a "particle" is a virus comprised of at least two components, a protein capsid and a polynucleotide sequence enclosed within the capsid.

[00596] *Patient:* As used herein, "patient" refers to a subject who may seek or be in need of treatment, requires treatment, is receiving treatment, will receive treatment, or a subject who is under care by a trained professional for a particular disease or condition.

[00597] *Payload:* As used herein, "payload" or "payload region" refers to one or more polynucleotides or polynucleotide regions encoded by or within a viral genome or an expression product of such polynucleotide or polynucleotide region, e.g., a transgene, a polynucleotide encoding a polypeptide or multi-polypeptide or a modulatory nucleic acid or regulatory nucleic acid.

[00598] *Payload construct:* As used herein, "payload construct" is one or more polynucleotide regions encoding or comprising a payload that is flanked on one or both sides by an inverted terminal repeat (ITR) sequence. The payload construct is a template that is replicated in a viral production cell to produce a viral genome.

[00599] *Payload construct vector:* As used herein, "payload construct vector" is a vector encoding or comprising a payload construct, and regulatory regions for replication and expression in bacterial cells.

[00600] *Payload construct expression vector:* As used herein, a "payload construct expression vector" is a vector encoding or comprising a payload construct and which further comprises one or more polynucleotide regions encoding or comprising components for viral expression in a viral replication cell.

[00601] *Peptide:* As used herein, "peptide" is less than or equal to 50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[00602] *Pharmaceutically acceptable*: The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00603] *Pharmaceutically acceptable excipients*: The phrase "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[00604] *Pharmaceutically acceptable salts*: The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form (e.g., by reacting the free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, acetic acid, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzene sulfonic acid, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate,

nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, *Pharmaceutical Salts: Properties, Selection, and Use*, P.H. Stahl and C.G. Wermuth (eds.), Wiley-VCH, 2008, and Berge et al., *Journal of Pharmaceutical Science*, 66, 1-19 (1977), each of which is incorporated herein by reference in its entirety.

[00605] *Pharmaceutically acceptable solvate*: The term "pharmaceutically acceptable solvate," as used herein, means a compound of the invention wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N,N'*-dimethylformamide (DMF), *N,N'*-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is referred to as a "hydrate."

[00606] *Pharmacokinetic*: As used herein, "pharmacokinetic" refers to any one or more properties of a molecule or compound as it relates to the determination of the fate of substances administered to a living organism. Pharmacokinetics is divided into several areas including the extent and rate of absorption, distribution, metabolism and excretion. This is commonly referred

to as ADME where: (A) Absorption is the process of a substance entering the blood circulation; (D) Distribution is the dispersion or dissemination of substances throughout the fluids and tissues of the body; (M) Metabolism (or Biotransformation) is the irreversible transformation of parent compounds into daughter metabolites; and (E) Excretion (or Elimination) refers to the elimination of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

[00607] *Physicochemical:* As used herein, "physicochemical" means of or relating to a physical and/or chemical property.

[00608] *Preventing:* As used herein, the term "preventing" refers to partially or completely delaying onset of an infection, disease, disorder and/or condition; partially or completely delaying onset of one or more symptoms, features, or clinical manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying onset of one or more symptoms, features, or manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying progression from an infection, a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the infection, the disease, disorder, and/or condition.

[00609] *Proliferate:* As used herein, the term "proliferate" means to grow, expand or increase or cause to grow, expand or increase rapidly. "Proliferative" means having the ability to proliferate. "Anti-proliferative" means having properties counter to or inapposite to proliferative properties.

[00610] *Prophylactic:* As used herein, "prophylactic" refers to a therapeutic or course of action used to prevent the spread of disease.

[00611] *Prophylaxis:* As used herein, a "prophylaxis" refers to a measure taken to maintain health and prevent the spread of disease.

[00612] *Protein of interest:* As used herein, the terms "proteins of interest" or "desired proteins" include those provided herein and fragments, mutants, variants, and alterations thereof.

[00613] *Proximal:* As used herein, the term "proximal" means situated nearer to the center or to a point or region of interest.

[00614] *Purified:* As used herein, "purify," "purified," "purification" means to make substantially pure or clear from unwanted components, material defilement, admixture or imperfection. "Purified" refers to the state of being pure. "Purification" refers to the process of making pure.

[00615] *Region:* As used herein, the term "region" refers to a zone or general area. In some embodiments, when referring to a protein or protein module, a region may comprise a linear

sequence of amino acids along the protein or protein module or may comprise a three-dimensional area, an epitope and/or a cluster of epitopes. In some embodiments, regions comprise terminal regions. As used herein, the term "terminal region" refers to regions located at the ends or termini of a given agent. When referring to proteins, terminal regions may comprise N- and/or C-termini. N-termini refer to the end of a protein comprising an amino acid with a free amino group. C-termini refer to the end of a protein comprising an amino acid with a free carboxyl group. N- and/or C-terminal regions may there for comprise the N- and/or C-termini as well as surrounding amino acids. In some embodiments, N- and/or C-terminal regions comprise from about 3 amino acid to about 30 amino acids, from about 5 amino acids to about 40 amino acids, from about 10 amino acids to about 50 amino acids, from about 20 amino acids to about 100 amino acids and/or at least 100 amino acids. In some embodiments, N-terminal regions may comprise any length of amino acids that includes the N-terminus, but does not include the C-terminus. In some embodiments, C-terminal regions may comprise any length of amino acids, which include the C-terminus, but do not comprise the N-terminus.

[00616] In some embodiments, when referring to a polynucleotide, a region may comprise a linear sequence of nucleic acids along the polynucleotide or may comprise a three-dimensional area, secondary structure, or tertiary structure. In some embodiments, regions comprise terminal regions. As used herein, the term "terminal region" refers to regions located at the ends or termini of a given agent. When referring to polynucleotides, terminal regions may comprise 5' and 3' termini. 5' termini refer to the end of a polynucleotide comprising a nucleic acid with a free phosphate group. 3' termini refer to the end of a polynucleotide comprising a nucleic acid with a free hydroxyl group. 5' and 3' regions may there for comprise the 5' and 3' termini as well as surrounding nucleic acids. In some embodiments, 5' and 3' terminal regions comprise from about 9 nucleic acids to about 90 nucleic acids, from about 15 nucleic acids to about 120 nucleic acids, from about 30 nucleic acids to about 150 nucleic acids, from about 60 nucleic acids to about 300 nucleic acids and/or at least 300 nucleic acids. In some embodiments, 5' regions may comprise any length of nucleic acids that includes the 5' terminus, but does not include the 3' terminus. In some embodiments, 3' regions may comprise any length of nucleic acids, which include the 3' terminus, but does not comprise the 5' terminus.

[00617] *RNA or RNA molecule*: As used herein, the term "RNA" or "RNA molecule" or "ribonucleic acid molecule" refers to a polymer of ribonucleotides; the term "DNA" or "DNA molecule" or "deoxyribonucleic acid molecule" refers to a polymer of deoxyribonucleotides. DNA and RNA can be synthesized naturally, e.g., by DNA replication and transcription of DNA, respectively; or be chemically synthesized. DNA and RNA can be single-stranded (i.e., ssRNA

or ssDNA, respectively) or multi-stranded (e.g., double stranded, i.e., dsRNA and dsDNA, respectively). The term "mRNA" or "messenger RNA", as used herein, refers to a single stranded RNA that encodes the amino acid sequence of one or more polypeptide chains.

[00618] *Sample:* As used herein, the term "sample" or "biological sample" refers to a subset of its tissues, cells or component parts (e.g. body fluids, including but not limited to blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen). A sample further may include a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, organs. A sample further refers to a medium, such as a nutrient broth or gel, which may contain cellular components, such as proteins or nucleic acid molecule.

[00619] *Self-complementary viral particle:* As used herein, a "self-complementary viral particle" is a particle comprised of at least two components, a protein capsid and a polynucleotide sequence encoding a self-complementary genome enclosed within the capsid.

[00620] *Signal Sequences:* As used herein, the phrase "signal sequences" refers to a sequence which can direct the transport or localization of a protein.

[00621] *Single unit dose*: As used herein, a "single unit dose" is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event. In some embodiments, a single unit dose is provided as a discrete dosage form (e.g., a tablet, capsule, patch, loaded syringe, vial, etc.).

[00622] *Similarity*: As used herein, the term "similarity" refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art.

[00623] *Split dose*: As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses.

[00624] *Stable:* As used herein "stable" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

[00625] *Stabilized:* As used herein, the term "stabilize", "stabilized," "stabilized region" means to make or become stable.

[00626] *Subject*: As used herein, the term "subject" or "patient" refers to any organism to which a composition in accordance with the invention may be administered, *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans) and/or plants.

[00627] *Substantially*: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[00628] *Substantially equal*: As used herein as it relates to time differences between doses, the term means plus/minus 2%.

[00629] *Substantially simultaneously*: As used herein and as it relates to plurality of doses, the term means within 2 seconds.

[00630] *Suffering from*: An individual who is "suffering from" a disease, disorder, and/or condition has been diagnosed with or displays one or more symptoms of a disease, disorder, and/or condition.

[00631] *Susceptible to*: An individual who is "susceptible to" a disease, disorder, and/or condition has not been diagnosed with and/or may not exhibit symptoms of the disease, disorder, and/or condition but harbors a propensity to develop a disease or its symptoms. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition (for example, cancer) may be characterized by one or more of the following: (1) a genetic mutation associated with development of the disease, disorder, and/or condition; (2) a genetic polymorphism associated with development of the disease, disorder, and/or condition; (3) increased and/or decreased expression and/or activity of a protein and/or nucleic acid associated with the disease, disorder, and/or condition; (4) habits and/or lifestyles associated with development of the disease, disorder, and/or condition; (5) a family history of the disease, disorder, and/or condition; and (6) exposure to and/or infection with a microbe associated with development of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[00632] *Sustained release:* As used herein, the term "sustained release" refers to a pharmaceutical composition or compound release profile that conforms to a release rate over a specific period of time.

[00633] *Synthetic*: The term "synthetic" means produced, prepared, and/or manufactured by the hand of man. Synthesis of polynucleotides or polypeptides or other molecules of the present invention may be chemical or enzymatic.

[00634] *Targeting:* As used herein, "targeting" means the process of design and selection of nucleic acid sequence that will hybridize to a target nucleic acid and induce a desired effect.

[00635] *Targeted Cells:* As used herein, "targeted cells" refers to any one or more cells of interest. The cells may be found *in vitro*, *in vivo*, *in situ* or in the tissue or organ of an organism. The organism may be an animal, preferably a mammal, more preferably a human and most preferably a patient.

[00636] *Therapeutic Agent:* The term "therapeutic agent" refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect.

[00637] *Therapeutically effective amount:* As used herein, the term "therapeutically effective amount" means an amount of an agent to be delivered (*e.g.*, nucleic acid, drug, therapeutic agent, diagnostic agent, prophylactic agent, *etc.*) that is sufficient, when administered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is provided in a single dose. In some embodiments, a therapeutically effective amount is administered in a dosage regimen comprising a plurality of doses. Those skilled in the art will appreciate that in some embodiments, a unit dosage form may be considered to comprise a therapeutically effective amount of a particular agent or entity if it comprises an amount that is effective when administered as part of such a dosage regimen.

[00638] *Therapeutically effective outcome*: As used herein, the term "therapeutically effective outcome" means an outcome that is sufficient in a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[00639] *Total daily dose:* As used herein, a "total daily dose" is an amount given or prescribed in 24 hr period. It may be administered as a single unit dose.

[00640] *Transfection*: As used herein, the term "transfection" refers to methods to introduce exogenous nucleic acids into a cell. Methods of transfection include, but are not limited to, chemical methods, physical treatments and cationic lipids or mixtures.

[00641] *Treating*: As used herein, the term "treating" refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular infection, disease, disorder, and/or condition. For example, "treating" cancer may refer to inhibiting survival, growth, and/or spread of a tumor. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[00642] *Unmodified*: As used herein, "unmodified" refers to any substance, compound or molecule prior to being changed in any way. Unmodified may, but does not always, refer to the wild type or native form of a biomolecule. Molecules may undergo a series of modifications whereby each modified molecule may serve as the "unmodified" starting molecule for a subsequent modification.

[00643] *Vector*: As used herein, a "vector" is any molecule or moiety which transports, transduces or otherwise acts as a carrier of a heterologous molecule. Vectors of the present invention may be produced recombinantly and may be based on and/or may comprise adeno-associated virus (AAV) parent or reference sequence. Such parent or reference AAV sequences may serve as an original, second, third or subsequent sequence for engineering vectors. In non-limiting examples, such parent or reference AAV sequences may comprise any one or more of the following sequences: a polynucleotide sequence encoding a polypeptide or multi-polypeptide, which sequence may be wild-type or modified from wild-type and which sequence may encode full-length or partial sequence of a protein, protein domain, or one or more subunits of a protein; a polynucleotide comprising a modulatory or regulatory nucleic acid which sequence may be wild-type or modified from wild-type; and a transgene that may or may not be modified from wild-type sequence . These AAV sequences may serve as either the "donor" sequence of one or more codons (at the nucleic acid level) or amino acids (at the polypeptide level) or "acceptor" sequences of one or more codons (at the nucleic acid level) or amino acids (at the polypeptide level).

[00644] *Viral genome*: As used herein, a "viral genome" or "vector genome" is a polynucleotide comprising at least one inverted terminal repeat (ITR) and at least one encoded payload. A viral genome encodes at least one copy of the payload.

[00645] Described herein are compositions, methods, processes, kits and devices for the design, preparation, manufacture and/or formulation of AAV particles. In some embodiments, payloads, such as but not limited to AAV polynucleotides, may be encoded by payload constructs or contained within plasmids or vectors or recombinant adeno-associated viruses (AAVs).

[00646] The details of one or more embodiments of the invention are set forth in the accompanying description below. Although any materials and methods similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred materials and methods are now described. Other features, objects and advantages of the invention will be apparent from the description. In the description, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present description will control.

[00647] The present invention is further illustrated by the following non-limiting examples.

VII. EXAMPLES

EXAMPLE 1. Production and Purification of AAV particles

[00648] AAV particles described herein may be produced using methods known in the art, such as, for example, triple transfection or baculovirus mediated virus production. Any suitable permissive or packaging cell known in the art may be employed to produce the vectors. Mammalian cells are often preferred. Also preferred are trans-complementing packaging cell lines that provide functions deleted from a replication-defective helper virus, e.g., 293 cells or other E1a trans-complementing cells.

[00649] The gene cassette may contain some or all of the parvovirus (e.g., AAV) cap and rep genes. Preferably, however, some or all of the cap and rep functions are provided in trans by introducing a packaging vector(s) encoding the capsid and/or Rep proteins into the cell. Most preferably, the gene cassette does not encode the capsid or Rep proteins. Alternatively, a packaging cell line is used that is stably transformed to express the cap and/or rep genes

[00650] Recombinant AAV virus particles are, in some cases, produced and purified from culture supernatants according to the procedure as described in US20160032254, the contents of which are incorporated by reference. Production may also involve methods known in the art

including those using 293T cell, sf9 insect cells, triple transfection or any suitable production method.

[00651] In some cases, 293 cells are transfected with CaPO4 with plasmids required for production of AAV, i.e., AAV2 rep, an adenoviral helper construct and a ITR flanked transgene cassette. The AAV2 rep plasmid also contains the cap sequence of the particular virus being studied. Twenty-four hours after transfection, which occurs in serum containing DMEM, the medium is replaced with fresh medium with or without serum. Three (3) days after transfection, a sample is taken from the culture medium of the 293 adherent cells. Subsequently cells are scraped and transferred into a receptacle. After centrifugation to remove cellular pellet, a second sample is taken from the supernatant after scraping. Next cell lysis is achieved by three consecutive freeze-thaw cycles (-80C. to 37C.). Cellular debris is removed and sample 3 is taken from the medium. The samples are quantified for AAV particles by DNase resistant genome titration by Taqman.TM. PCR. The total production yield from such a transfection is equal to the particle concentration from sample 3.

[00652] AAV vector titers are measured according to genome copy number (genome particles per milliliter). Genome particle concentrations are based on Taqman.RTM. PCR of the vector DNA as previously reported (Clark et al. (1999) Hum. Gene Ther., 10:1031-1039; Veldwijk et al. (2002) Mol. Ther., 6:272-278).

EXAMPLE 2. Tissue specific expression

[00653] To evaluate the expression of various encoded antibody payloads in tissues, a series of AAV particles carrying the encoded antibody sequences driven by a panel of ubiquitous and tissue-specific promoters are made. These particles are administered to the specific tissue, e.g., intramuscularly, via an appropriate route, e.g., a single injection in the gastrocnemius muscle and expression is monitored to determine the relative expression potential of the payload as well as of each promoter in this target tissue. Measurement of antibody production is performed using standard techniques, for example by ELISA.

[00654] In some cases, the cytomegalovirus immediate early promoter (CMV), chimeric chicken-beta-actin (CAG), and ubiquitin C (UBC), CBA, H1 promoters provide robust expression.

EXAMPLE 3. Generation of antibodies

Antibody production by hybridoma technology

[00655] Host animals (e.g. mice, rabbits, goats, and llamas) are immunized by an injection with an antigenic protein (e.g., tau) to elicit lymphocytes that specifically bind to the antigen (e.g., tau). Lymphocytes are collected and fused with immortalized cell lines to generate

hybridomas. Hybridomas are cultured in a suitable culture medium that is enriched with appropriate selection agents to promote growth.

[00656] Antibodies produced by the cultured hybridomas are subjected to analysis to determine binding specificity of the antibodies for the target antigen. Once antibodies with desirable characteristics are identified, corresponding hybridomas are subcloned through limiting dilution procedures and grown by standard methods. Antibodies produced by these cells are isolated and purified using standard immunoglobulin purification procedures.

Recombinant antibody production

[00657] Recombinant antibodies are produced using heavy and light chain variable region cDNA sequences selected from hybridomas or from other sources. Sequences encoding antibody variable domains expressed by hybridomas are determined by extracting RNA molecules from antibody-producing hybridoma cells and producing cDNA by reverse transcriptase polymerase chain reaction (PCR). PCR is used to amplify cDNA using primers specific for heavy and light chain sequences. PCR products are then subcloned into plasmids for sequence analysis. Antibodies are produced by insertion of resulting variable domain sequences into expression vectors.

[00658] Recombinant antibodies are also produced using phage display technology. Target antigens are screened, in vitro, using phage display libraries having millions to billions of phage particles expressing unique single chain variable fragments (scFvs) on their viral coat. Precipitated phage particles are analyzed and sequences encoding expressed scFvs are determined. Sequences encoding antibody variable domains and/or CDRs are inserted into expression vectors for antibody production.

[00659] Recombinant antibodies are further produced using yeast surface display technology, wherein antibody variable domain sequences are expressed on the cell surface of *Saccharomyces cerevisiae*. Recombinant antibodies are developed by displaying the antibody fragment of interest as a fusion to e.g. Aga2p protein on the surface of the yeast, where the protein interacts with proteins and small molecules in a solution. scFvs with affinity towards desired receptors are isolated from the yeast surface using magnetic separation and flow cytometry. Several cycles of yeast surface display and isolation will be done to attain scFvs with desired properties through directed evolution.

EXAMPLE 4. Optimization of the encoded Antibody

[00660] To design an optimal framework for the expression of an antibody, the heavy and light chains of several antibodies separated by an F2A self-processing peptide sequence are cloned into a mammalian expression vector under the control of the CMV promoter. 293T cells or any

suitable cell line transfected with these vectors exhibit secretion of human IgG into the culture supernatant that is then detected by ELISA.

[00661] To increase expression, the antibody chains and/or the processing peptide are codon optimized for mammalian expression. In some instances, a furin cleavage site at the N-terminus is inserted for better processing.

[00662] To improve secretion of the antibody, the endogenous signal sequences are replaced with a sequence which may or may not be codon optimized, derived from any gene. In some cases, the human growth hormone signal sequence is used. Any of the heavy, light or both chains may be driven by any signal sequence, whether the same or different. Antibody expression is confirmed using standard immunohistochemical techniques, including ELISA.

EXAMPLE 5. Vectored Antibodies

[00663] Viral genomes are designed for AAV delivery of antibodies to cells. The viral genome comprises a payload region and at least one inverted terminal repeat (ITR) region. The payload region may optionally encode regulatory elements e.g., a promoter region, an intronic region, or a polyadenylation sequence. The payload region comprises a sequence encoding one or more polypeptides selected from the group consisting of those listed in Table 3. An exemplary payload region comprises a sequence encoding an antibody heavy chain, a region encoding an antibody light chain and a region encoding a linker connecting the heavy and light chain sequences or polypeptides before further processing. A promoter is selected to target the desired tissue or for desired regulation of expression, or both. The promoter may be selected from human EF1α, CMV, CBA, and its derivative CAG, GUSB, UBC, or any other promoter known to one with skill in the art, or combinations thereof. The 5' and 3' ITRs may or may not be of the same serotype as the capsid of the AAV particle.

[00664] Payload regions may optionally encode a linker between light and heavy antibody chain sequences or polypeptides. Sequence encoding linkers are derived from an internal ribosome entry site (IRES; SEQ ID NO: 899), foot and mouth disease virus 2A (F2A; SEQ ID NO: 900), porcine teschovirus-1 virus 2A (P2A; SEQ ID NO: 901), a furin cleavage site (F; SEQ ID NO: 902), or a 5xG4S (SEQ ID NO: 4321 encoded by SEQ ID NO: 903) linker sequence. In various payload regions, the order of heavy and light chains is alternated with respect to 5' to 3' direction. Payloads are further designed to encode protein signal sequences (to aid in protein processing, localization, and/or secretion) as well as an untranslated poly A tail.

[00665] Each viral genome is then incorporated into an AAV cloning vector to create payload expression vectors.

[00666] The payload expression vectors are expressed in e.g. Expi293 cells. The supernatants are collected and expressed antibodies are purified using protein A/G beads. Supernatants are diluted with a loading buffer and applied to a column prepared with A/G beads. Unbound proteins are washed through with loading buffer. Elution buffer is added to the column, fractions collected, and fractions containing proteins of interest are identified with absorption spectroscopy technique, pooled together, and neutralized. Western blotting techniques are used to identify payload regions producing the antibody proteins of interest. Purified antibodies are then tested for their affinity to their specific target by e.g. ELISA essay technique and antibodies with the highest affinity are identified and selected.

[00667] Finally, the rAAVs are produced using, for example, HEK293T cells. The cells are transfected simultaneously with the viral genome of the present invention, a viral genome encoding helper proteins and a viral genome encoding replication and capsid proteins.

EXAMPLE 6. In Vivo Expression and efficacy of antibody payloads

[00668] To determine the efficacy or comparative expression of encoded antibodies, dose-dependent expression is determined at a series of time points. Samples from mice treated with AAV particles encoding antibodies or luciferase at various levels are examined for expression using standard techniques such as nucleic acid analyses for RNA levels, protein analyses for antibody levels and compared to the expression of the luciferase control.

EXAMPLE 7. Treatment of Tau-Associated Disease

[00669] AAV particles of the current invention for delivery of an antibody are administered to a patient who has been diagnosed with a tau associated disease, disorder or condition. The purpose of the treatment may be aimed to manage the disease, prevent or slow the progression of the disease, treat the symptoms associated with the disease and/or cure the disease.

[00670] The AAV particles are administered to a subject by IV, ICV, IPa or IT administration. The administration may include one or more injections over a period of time. The level and distribution of AAV particles and antibody expression is monitored by standard diagnostic techniques known in the art. Such diagnostic techniques include e.g. (e.g. from blood, urine, or saliva), cerebrospinal fluid (CSF) testing, or any other testing useful for monitoring antibody levels in the body.

[00671] Additionally, the progression of the disease and the health of the patient is monitored by standard diagnostic techniques known in the art. Such techniques may include diagnostic imaging (e.g. X-ray, MRI scans, Ultrasound scans, PET scans, Nuclear scans, mammography), biopsy, laboratory tests (e.g. from blood, urine, or saliva), cerebrospinal fluid (CSF) testing, vital signs, clinical tests (cognitive, motor or reflex tests) and other relevant techniques. Treatment

with the AAV particles may results in cure of the tau-associated disease, slowing down or stabilizing the progression of the disease, or have no effect on the progression of the disease. Additionally, the treatment may reduce severity of one or more symptoms associated with the disease, eliminate one or more symptoms associated with the disease or have no effect on the symptoms.

EXAMPLE 8. Payloads for Tau Associated Diseases

[00672] Payloads were designed for viral delivery of anti-tau antibodies MC-1 (with heavy chain of SEQ ID NO: 2948 and light chain of SEQ ID NO: 3153), PHF1 (with heavy chain of SEQ ID NO: 2949 and light chain of SEQ ID NO: 3154) and IPN002 (with heavy chain of SEQ ID NO: 2950 and light chain of SEQ ID NO: 3155) to cells. The viral genome includes, besides the coding region, a 5' ITR (SEQ ID NO: 4270), CB6 promoter (SEQ ID NO: 4271), SV40 intron (SEQ ID NO: 4272), rabbit globin poly A tail (SEQ ID NO: 4273), and 3'ITR (SEQ ID NO: 4274) sequences.

[00673] Payloads were designed to encode a linker between light and heavy antibody chains. Sequence encoding linkers were derived from an internal ribosome entry site (IRES; SEQ ID NO: 899), foot and mouth disease virus 2A (F2A; SEQ ID NO: 900), porcine teschovirus-1 virus 2A (P2A; SEQ ID NO: 901), a furin cleavage site (F; SEQ ID NO: 902), or a 5xG4S (also referred to herein as "G4S5") (SEQ ID NO: 4321 encoded by SEQ ID NO: 903) linker sequence. In various payload regions, the order of heavy and light chains was alternated with respect to 5' to 3' direction. Payloads were further designed to encode protein signal sequences (to aid in protein processing, localization, and/or secretion) as well as an untranslated poly A tail. Payload region sequences included in the prepared viral genomes are listed in Table 4. Each viral genome was then cloned into a pAAVss cloning vector (SEQ ID NO: 4275) to create the AAV particle listed in Table 4.

Table 4. AAV Particle Sequences

Description	Abbreviation	Coding Region SEQ ID	Viral Genome SEQ ID NO	Complete Sequence SEQ ID
pAAVss-CB6-SV40-MC1HIRESL	MC1HIRESL	4276	4292	4291
pAAVss-CB6-SV40-MC1LIRESH	MC1LIRESH	4277	4294	4293
pAAVss-CB6-SV40-MC1HF2AL	MC1HF2AL	4278	4296	4295
pAAVss-CB6-SV40-MC1LF2AH	MC1LF2AH	4279	4298	4297
pAAVss-CB6-SV40-MC1HF.F2AL	MC1HF.F2AL	4280	4300	4299
pAAVss-CB6-SV40-MC1LF.F2AH	MC1LF.F2AH	4281	4302	4301
pAAVss-CB6-SV40-MC1HP2AL	MC1HP2AL	4282	4304	4303
pAAVss-CB6-SV40-MC1LP2AH	MC1LP2AH	4283	4306	4305
pAAVss-CB6-SV40-MC1HF.P2AL	MC1HF.P2AL	4284	4308	4307
pAAVss-CB6-SV40-MC1LF.P2AH	MC1LF.P2AH	4285	4310	4309
pAAVss-CB6-SV40-MC1LG4S5H	MC1LG4S5H	4286	4312	4311
pAAVss-CB6-SV40-IPN002LF2AH	IPN002LF2AH	4287	4314	4313

pAAVss-CB6-SV40-IPN002HF.F2AL	IPN002HF.F2AL	4288	4316	4315
pAAVss-CB6-SV40-PHF-1LF2AH	PHF-1LF2AH	4289	4318	4317
pAAVss-CB6-SV40-PHF-1HF.F2AL	PHF-1HF.F2AL	4290	4320	4319

EXAMPLE 9. Development of ELISA assay to determine affinity to ePHF tau

[00674] An assay was developed to determine the affinity of anti-tau antibodies expressed from various payload coding region constructs for extracellular tau in the form of paired helical filaments (ePHF). The ePHF were first immobilized on a 96-well plate overnight by pre-coating with 1500X of the concentrated PHF tau at 4°C, washed 3 times with PBS then blocked with 3% BSA for 2hrs at room temperature or overnight at 4°C. Supernatants from suspensions of Expi 293 cells transfected with MC-1 payload coding region constructs were collected and loaded onto the plates. Anti-tau antibody MC-1 was diluted in 3% BSA and analyzed separately as a control. Plates were then incubated for 2hrs at room temperature. Wells were washed 5 times with TBS/0.5% Tween 20 wash buffer, then incubated with 1:5000 dilution of anti-mouse antibody labeled with HRP (Thermo Fisher Scientific, Waltham, MA) for 30 min. Plates were then developed by incubating with one-step TMB substrate (Thermo Fisher Scientific, Waltham, MA) for 30 min, stopped by 2N H_2SO_4 and read using a BioTek Synergy H1 hybrid reader (BioTek, Winooski, VT) at 450nm. The concentration of anti-tau antibodies, and their affinity for ePHF tau, was determined using a standard curve. Anti-tau antibodies produced using MC1LIRESH, MC1LF2AH, MC1HF.F2AL, MC1LF.F2AH, and MC1HF.P2AL payload coding region constructs showed similar affinity for ePHF tau as the MC-1 control. Anti-tau antibodies generated using MC1HIRESL, MC1LP2AH and MC1LF.P2AH payload coding region constructs demonstrated lower affinity to ePHF tau than control MC-1.

[00675] According to the same assay, MC1LF2AH, MC1HF.F2AL, IPN002LF2AH, IPN002HF.F2AL, PHF-1LF2AH, and PHF-1HF.F2AL payload coding region constructs were expressed in Expi 293 cells, the supernatants collected and expressed antibodies were tested for affinity to ePHF tau. Antibodies generated using all six constructs tested showed similar affinity for ePHF tau in comparison to their respective control antibodies (MC-1, PHF1 and IPN002 antibodies).

EXAMPLE 10. ELISA assay for detection of expressed antibodies

[00676] Expi 293 cell culture supernatants from cells expressing anti-tau antibodies were tested by sandwich ELISA to detect and determine concentrations of expressed antibodies. Ninety-six well plates were pre-coated with anti-mouse IgG1 overnight at 4°C then washed 3 times with PBS and blocked with 3% BSA for 2hrs at room temperature. Supernatants were diluted in blocking buffer (3% BSA), added to the wells and incubated for 2hrs at room

temperature. Samples were then washed 5 times with TBS/0.5% Tween 20 wash buffer and incubated with 1:5000 dilution of anti-mouse antibody labeled with HRP (Thermo Fisher Scientific, Waltham, MA) for 30 min. Plates were developed by incubating with one-step TMB substrate for 30 min, stopped by 2N H_2SO_4 and read using a BioTek Synergy H1 hybrid reader (BioTek, Winooski, VT) at 450nm. The concentration of expressed MC-1 anti-tau antibodies was then determined for each construct using a standard curve (see Table 5).

Table 5. Concentrations of expressed antibodies

Construct name	Antibody concentration µg/ml
MC1HIRESL	4.42
MC1LIRESH	32.29
MC1LF2AH	10.74
MC1HF.F2AL	12.10
MC1LF.F2AH	12.94
MC1LP2AH	44.12
MC1HF.P2AL	23.79
MC1LF.P2AH	46.43

[00677] Cells expressing MC1LIRESH, MC1LP2AH and MC1LF.P2AH coding region constructs produced the highest concentration of antibodies from transfected cells.

[00678] In a subsequent experiment using the same methods, cell supernatants from Expi 293 cells expressing MC1LF2AH, MC1HF.F2AL, PHF1LF2AH, PHF1HF.F2AL, IPN002LF2AH, or IPN002HF.F2AL coding region constructs were also assessed for concentrations of expressed antibodies by ELISA. Antibody concentrations from supernatants tested are presented in Table 6.

Table 6. Concentrations of expressed antibodies

Construct name	Antibody concentration µg/ml
MC1LF2AH	40.4
MC1HF.F2AL	4.5
PHF1LF2AH	28.3
PHF1HF.F2AL	2.9
IPN002LF2AH	10.2
IPN002HF.F2AL	1.6

[00679] Cells expressing MC1LF2AH, PHF1LF2AH and IPN002LF2AH coding constructs produced the highest concentration of antibodies from transfected cells.

EXAMPLE 11. Western blotting for anti-tau antibody expression

[00680] Anti-tau antibodies expressed using MC1HIRESL, MC1LIRESH, MC1HF2AL, MC1LF2AH, MC1HF.F2AL, MC1LF.F2AH, MC1HP2AL, MC1LP2AH, MC1HF.P2AL, MC1LF.P2AH, and MC1LG4S5H coding region constructs was assessed by Western blotting in both small and large volume (30mL) cell culture experiments. Expi 293 cells expressing MC1HIRESL, MC1LIRESH, MC1HF2AL, MC1LF2AH, MC1HF.F2AL, MC1LF.F2AH,

MC1HP2AL, MC1LP2AH, MC1HF.P2AL, MC1LF.P2AH, or MC1LG4S5H coding region constructs were cultured to produce antibody-rich supernatant. After centrifugation, supernatants were collected and two small samples of each were removed and mixed with equal volumes of Laemunli sample buffer. Samples were then boiled at 95°C for 5 min before loading into two 4-20% polyacrylamide gels along with molecular weight markers. Both gels were run for 1-2hrs at 100V under reducing or non-reducing conditions. Proteins were then transferred to a nitrocellulose membrane for 2hr at 4 °C and stained with anti-mouse IgGs. First membranes were placed in blocking buffer for 1h at room temperature or overnight at 4°C followed by incubation with anti-mouse IgG antibodies in blocking buffer overnight at 4°C. The membranes were then washed three times each for 5min in TBST and incubated with enzyme-labeled secondary antibody in blocking buffer for 1hr at room temperature. Membranes were washed three times each for 5min in TBST then developed using a luminescent substrate.

[00681] Under both reducing and non-reducing conditions, three coding region constructs showed limited expression when initially assessed by Western blot. In normal (reducing) conditions, antibody heavy chains usually run at approximately 50kD, while light chains are evident at 25kD. In supernatant from cells expressing MC1HF2AL and MC1LG4S5H coding regions, only the 25kD species was evident while in supernatant from cells expressing MC1HP2AL, neither species appeared. The remaining supernatants showed the anticipated 25 and 50kD species under reducing conditions and several high molecular weight (80-150kD) bands under non-reducing conditions.

[00682] A similar experiment was conducted using MC1LF2AH, MC1HF.F2AL, IPN002LF2AH, IPN002HF.F2AL, PHF-1LF2AH, and PHF-1HF.F2AL coding region constructs. Western blot showed the expected 25kD and 50kD bands under reducing conditions and high molecular weight triplets under non-reducing conditions, similar to the appropriate controls (MC-1, PHF1 and IPN002 antibodies). LF2AH coding region constructs generated better expression levels for all three antibodies than the HF.F2AL coding region constructs.

[00683] Antibody concentrations from scaled-up culture conditions (30mL) were determined for select constructs (see Table 7).

Table 7. Antibody concentrations from 30 mL cultures

Construct name	Concentration µg/ml
MC1LIRESH	20.3
MC1LF2AH	86.2
MC1HF.F2AL	9.9
MC1LF.F2AH	14.7
MC1HF.P2AL	15.9

[00684] Coding construct MC1LF2AH yielded the highest concentration of antibody from transfected cells.

EXAMPLE 12. Purification of anti-tau antibody constructs

[00685] Anti-tau antibodies expressed in large volumes of Expi 293 cells (30mL) were purified using protein A/G beads. A column was prepared with protein A/G bead resin and washed 3 times with loading buffer. Supernatants were diluted with equal volumes of loading buffer and applied to the column. Unbound proteins were washed through with loading buffer. Elution buffer was added to the column and fractions collected. Fractions containing proteins were identified by absorbance at 280nm, pooled together, neutralized and run on polyacrylamide gels as described in Example 4. Under reducing conditions, antibodies produced using MC1LIRESH, MC1LF2AH, MC1LF.F2AL, MC1LF.F2AH, and MC1HF.P2AL coding region constructs yielded protein bands when examined by Western blotting that were similar to those observed with MC-1 control antibody (bands at 25kD and 50kD). Under non-reducing conditions, all expressed antibodies generated a triplet set of bands between 80-150kD, as did the MC-1 control.

[00686] Purified anti-tau antibodies were then tested for their affinity to ePHF tau by ELISA assay as described in Example 9. Antibodies with the highest affinity for ePHF tau were those produced using MC1LF2AH, MC1HF.F2AL and MC1LF.F2AH coding region constructs. These antibodies all demonstrated affinity for ePHF tau that was similar to that observed with MC-1 control antibody.

EXAMPLE 13. rAAV Production of anti-tau antibodies using HEK293T cells

[00687] HEK293 cells were transfected with three vectors simultaneously: anti-tau antibody encoding viral genomes; vectors expressing rep and cap genes; and a helper vector to generate rAAV9 products. Vector production was the greatest (highest AAV titer Vg/μL) when using MC1F2AH and MC1HF.F2AL viral genomes. These two formats were then utilized to generate rAAV9 particles encoding anti-tau antibodies PHF1 and IPN002.

EXAMPLE 14. Evaluation of Anti-tau antibody constructs in Non-human primates

[00688] Adult Rhesus macaque monkeys, pre-screened for low anti-AAV antibody levels, will receive intraparenchymal (IPa; thalamus and putamen) or intracisternal (CM) administration of anti-tau antibody AAV particles to assess expression, distribution and therapeutic potential.

[00689] Anti-tau antibody AAV particles will be formulated in a solution comprising 180mM sodium chloride, 10mM sodium phosphate, and 0.001% Pluronic Acid. Dosing concentrations will be 2.1×10^{12} vg/ml for IPa administration and 1×10^{13} vg/ml for CM administration. For IPa administration (2.1×10^{12} vg/ml), two animals will each receive bilateral infusions (1-2μL)

into the thalamus (150μL) and putamen (60 μL) by convection enhanced delivery device guided by MRI. An additional three animals will each receive a single 1mL bolus injection into the CSF via the cisterna magna (1×10^{13} vg/ml). Animals will be monitored post-injection(s) for 28 days, with weekly body weight measurements and daily cage-side behavioral, mortality and morbidity checks serving as secondary readouts. Serum and CSF samples will be collected pre-dose and prior to necropsy.

[00690] On day 29, animals will be transcardially perfused with PBS, tissues will be collected and drop fixed in paraformaldehyde for histological analyses or flash frozen for biochemical assay. Tissues processed for histological analysis will be sectioned and immunostained with HRP-labeled mouse IgG1 for presence of the tau antibodies. Further, these samples will be co-immunostained with NeuN, Iba1 or GFAP to identify cell-type. Samples snap frozen for biochemical analyses will be utilized for PCR to detect vector genomes and mRNA, ELISA to detect antibodies and MS to determine protein levels. Blood and CSF samples will be assessed for antibody and AAV levels.

VIII. EQUIVALENTS AND SCOPE

[00691] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[00692] In the claims, articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process.

[00693] It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.

[00694] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or

subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00695] In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (e.g., any antibiotic, therapeutic or active ingredient; any method of production; any method of use; etc.) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[00696] It is to be understood that the words which have been used are words of description rather than limitation, and that changes may be made within the purview of the appended claims without departing from the true scope and spirit of the invention in its broader aspects.

[00697] While the present invention has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with reference to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the invention.

CLAIMS

1. An AAV particle comprising a capsid and a viral genome, said viral genome comprising at least one inverted terminal repeat (ITR) region and a payload region, said payload region comprising a regulatory sequence operably linked to at least a first nucleic acid segment, said first nucleic acid segment encoding one or more polypeptides selected from the group consisting of any member given in Table 3 and fragments thereof.
2. The AAV particle of claim 1, wherein the capsid is selected from the group of serotypes consisting of Table 1.
3. The AAV particle of claim 2, wherein the regulatory sequence comprises a promoter.
4. The AAV particle of claim 3, wherein the promoter is selected from the group consisting of human elongation factor 1α-subunit (EF1α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β-actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC). Tissue-specific expression elements can be used to restrict expression to certain cell types such as, but not limited to, muscle specific promoters, B cell promoters, monocyte promoters, leukocyte promoters, macrophage promoters, pancreatic acinar cell promoters, endothelial cell promoters, lung tissue promoters, astrocyte promoters, or nervous system promoters which can be used to restrict expression to neurons, astrocytes, or oligodendrocytes.
5. The AAV particle of claim 1, wherein the viral genome is single stranded.
6. The AAV particle of claim 1, wherein the viral genome is self-complementary.
7. The AAV particle of claim 1, wherein at least one region of the viral genome is codon-optimized.
8. The AAV particle of claim 7, wherein the first nucleic acid segment is codon-optimized.
9. The AAV particle of any of claims 1-8, wherein the first nucleic acid segment encodes one or more polypeptides selected from the group consisting of an antibody heavy chain, an antibody light chain, a linker, and combinations thereof.
10. The AAV particle of claim 9, wherein any of the polypeptides encoded by first nucleic acid segment of the payload region is humanized.
11. The AAV particle of claim 9, wherein the linker is selected from one or more of the members of the group given in Table 2.

12. The AAV particle of claim 9, wherein the first nucleic acid segment encodes from 5' to 3', an antibody heavy chain, a linker, and an antibody light chain.
13. The AAV particle of claim 9, wherein the first nucleic acid segment encodes from 5' to 3', an antibody light chain, a linker, and an antibody heavy chain.
14. The AAV particle of claim 9, wherein the first nucleic acid segment encodes one or more antibody heavy chains.
15. The AAV particle of claim 14, wherein the first nucleic acid segment encodes one or more antibody heavy chains selected from those listed in Table 3.
16. The AAV particle of claim 9, wherein the first nucleic acid segment encodes one or more antibody light chains.
17. The AAV particle of claim 16, wherein the first nucleic acid segment encodes one or more antibody light chains selected from those listed in Table 3.
18. The AAV particle of claim 9, wherein the first nucleic acid segment encodes one or more antibody heavy chains and one or more antibody light chains and, optionally one or more linkers.
19. The AAV particle of any of claims 9-18, wherein said linker is selected from the group consisting of Table 2 and combinations thereof.
20. The AAV particle of claim 1, wherein the first nucleic acid segment encodes an antibody, having at least 95% identity to any of the sequences selected from the group consisting of SEQ ID NO: 2948-4269 and 4276-4320 (Table 3 and Table 4).
21. An AAV particle comprising a capsid and a viral genome, said viral genome comprising at least one inverted terminal repeat (ITR) region and a payload region comprising a regulatory sequence operably linked to at least a first nucleic acid segment, said first nucleic acid segment encoding a bispecific antibody derived from any of the sequences listed in Tables 3 or 4 or portions or fragments thereof.
22. The AAV particle of claim 21, wherein the bispecific antibody comprises a light and a heavy chain selected from two different starting antibodies selected from the group consisting of SEQ ID NO: 2948-4269and 4276-4320 (Table 3 and Table 4).
23. A method of producing a functional antibody in a subject in need thereof, comprising administering to said subject the AAV particle of any of claims 1-22.
24. The method of claim 23, wherein the level or amount of the functional antibody in the target cell or tissue after administration to the subject is from about .001 ug/mL to 100 mg/mL.

25. The method of claim 23, wherein the functional antibody is encoded by a single first nucleic acid segment of a viral genome within said AAV particle.
26. The method of claim 23, wherein the functional antibody is encoded by two different viral genomes, said two different viral genomes packaged in separate capsids.
27. A pharmaceutical composition comprising an AAV particle of any of the preceding claims in a pharmaceutically acceptable excipient.
28. The pharmaceutical composition of claim 27, wherein the pharmaceutically acceptable excipient is saline.
29. The pharmaceutical composition of claim 27, wherein the pharmaceutically acceptable excipient is 0.001% pluronic in saline.
30. A method of expressing an antibody in a cell or tissue comprising administering the AAV particle of any of claims 1-29 via a delivery route selected from the group consisting of enteral (into the intestine), gastroenteral, epidural (into the dura mater), oral (by way of the mouth), transdermal, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal, (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intra-arterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraparenchymal (into brain tissue), intraperitoneal, (infusion or injection into the peritoneum), intravesical infusion, intravitreal, (through the eye), intracavernous injection (into a pathologic cavity) intracavitary (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), or in ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival, cutaneous, dental (to a tooth or teeth), electro-osmosis, endocervical, endosinusial, endotracheal, extracorporeal, hemodialysis, infiltration, interstitial, intra-abdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracoronal, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the corporus cavernosa of

the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within the stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone), intrameningeal (within the meninges), intramyocardial (within the myocardium), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aurus media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique (topical route administration which is then covered by a dressing which occludes the area), ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), soft tissue, subarachnoid, subconjunctival, submucosal, topical, transplacental (through or across the placenta), transtracheal (through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photopheresis and spinal.

31. The method of claim 30, wherein the delivery route is intramuscular.

32. The method of claim 31, wherein the intramuscular administration is to at least one limb.

33. The method of claim 30, wherein the delivery route is intravascular.

34. The method of claim 30, wherein the delivery route is intrathecal.
35. The method of claim 30, wherein the delivery route is intracerebroventricular.
36. The method of claim 30, wherein the delivery route is intraparenchymal.
37. The method of claim 30, wherein the AAV particle is encapsulated in a nanoparticle.
38. The method of claim 30, wherein the AAV particle is delivered by a device.
39. The method of claim 38, wherein the device is a gene gun.
40. A method of preventing a disease or disorder in a subject comprising administering to said subject the pharmaceutical composition of any of claims 27-29.
41. The method of claim 40, wherein the administration is at a prophylactically effective dose.
42. The method of claim 41, wherein the dose is from about 1 ug/mL to about 500 ug/mL of expressed polypeptide or 1x10e4 to 1x10e16 VG/mL from the pharmaceutical composition.
43. The method of claim 42, wherein the pharmaceutical composition is administered once.
44. The method of claim 42, wherein the pharmaceutical composition is administered more than once.
45. The method of claim 42, wherein the pharmaceutical composition is administered daily, weekly, monthly or yearly.
46. The method of claim 42, wherein the pharmaceutical composition is co-administered as part of a combination therapy.
47. A method of treating a disease or disorder in a subject in need thereof comprising administering to said subject the pharmaceutical composition of any of claims 27-29.
48. The method of claim 47, wherein said disease or disorder is selected from the group consisting of tauopathies, tau-associated diseases, Alzheimer's disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), Frontotemporal lobar degeneration (FTLD), chronic traumatic encephalopathy (CTE), Progressive Supranuclear Palsy (PSP), Down's syndrome, Pick's disease, Corticobasal degeneration (CBD), Amyotrophic lateral sclerosis (ALS), Prion diseases, Creutzfeldt-Jakob disease (CJD), Multiple system atrophy, Tangle-only dementia, and Progressive subcortical gliosis, neurodegenerative disease and stroke.
49. The AAV particle of claim 1, wherein the viral genome comprises 2 ITR regions.
50. The AAV particle of claim 1, wherein the at least one ITR region is derived from the same parental serotype as the capsid.

51. The AAV particle of claim 1, wherein the at least one ITR region is derived from a different serotype as the capsid.
52. The AAV particle of claim 1, wherein the at least one ITR region is derived from AAV2.
53. The AAV particle of claim 1, wherein the at least one ITR region is 100-150 nucleotides in length.
54. The AAV particle of claim 1, wherein the at least one ITR region is 102 nucleotides in length.
55. The AAV particle of claim 1, wherein the at least one ITR region is 140-142 nucleotides in length.
56. The AAV particle of claim 1, wherein the at least one ITR region is 140 nucleotides in length.
57. The AAV particle of claim 1, wherein the at least one ITR region is 141 nucleotides in length.
58. The AAV particle of claim 1, wherein the at least one ITR region is 142 nucleotides in length.
59. The AAV particle of claim 1, wherein the viral genome further comprises an intron or stuffer sequence.
60. A method of producing an antibody in a subject comprising administering the AAV particle of claim 1 to said subject, with the proviso that the antibody is not a virus neutralizing antibody.
61. A method of producing an antibody in a subject comprising administering the AAV particle of claim 1 to said subject, with the proviso that the antibody is not an HIV or HCV virus neutralizing antibody.
62. The AAV particle of claim 1, wherein the payload region of the viral genome comprises a second nucleic acid segment, said second nucleic acid segment encoding an aptamer, siRNA, saRNA, ribozyme, microRNA, mRNA or combination thereof.
63. The AAV particle of claim 62, wherein the second nucleic acid segment encodes an siRNA and said siRNA is designed to target the mRNA that encodes the target of the antibody encoded by the first nucleic acid segment.
64. The AAV particle of claim 62, wherein the second nucleic acid segment encodes a microRNA and said microRNA is selected to target the mRNA that encodes the target of the antibody encoded by the first nucleic acid segment.

65. The AAV particle of claim 62, wherein the second nucleic acid segment encodes an mRNA and said mRNA encodes one or more peptides inhibitors of the same target of the antibody encoded by the first nucleic acid segment.

66. The AAV particle of claim 1 or 62, wherein the payload region of the viral genome comprises a third nucleic acid segment.

67. The AAV particle of claim 66, wherein the third nucleic acid segment encodes a nuclear export signal.

68. The AAV particle of claim 66, wherein the third nucleic acid segment encodes a polynucleotide or polypeptide which acts as a regulator of expression of the viral genome in which it is encoded.

69. The AAV particle of claim 66, wherein the third nucleic acid segment encodes a polynucleotide or polypeptide which acts as a regulator of expression of the payload region of the viral genome in which it is encoded.

70. The AAV particle of claim 66, wherein the third nucleic acid segment encodes a polynucleotide or polypeptide which acts as a regulator of expression of the first nucleic acid segment of the payload region of the viral genome in which it is encoded.

FIG. 1

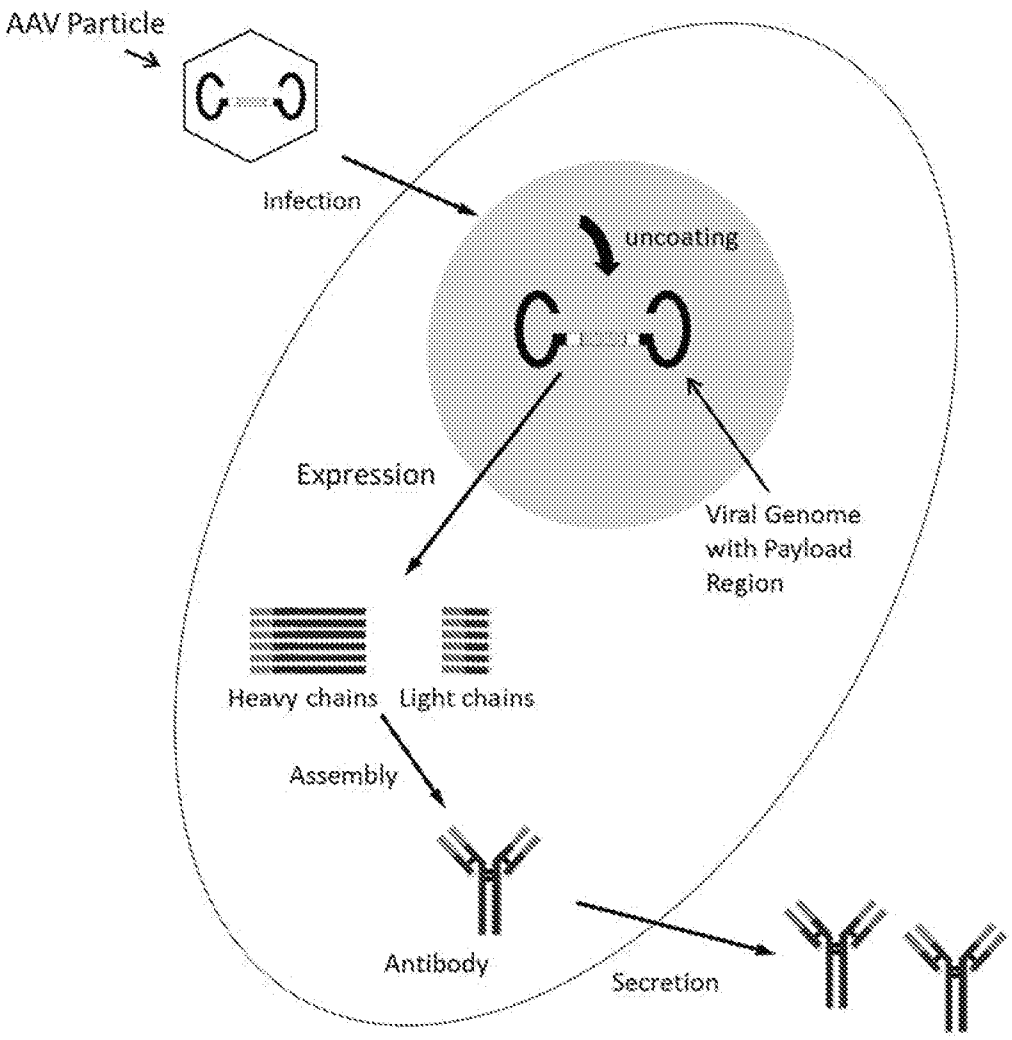

AAV Particle
Infection
uncoating
Expression
Viral Genome with Payload Region
Heavy chains
Light chains
Assembly
Antibody
Secretion

FIG. 2

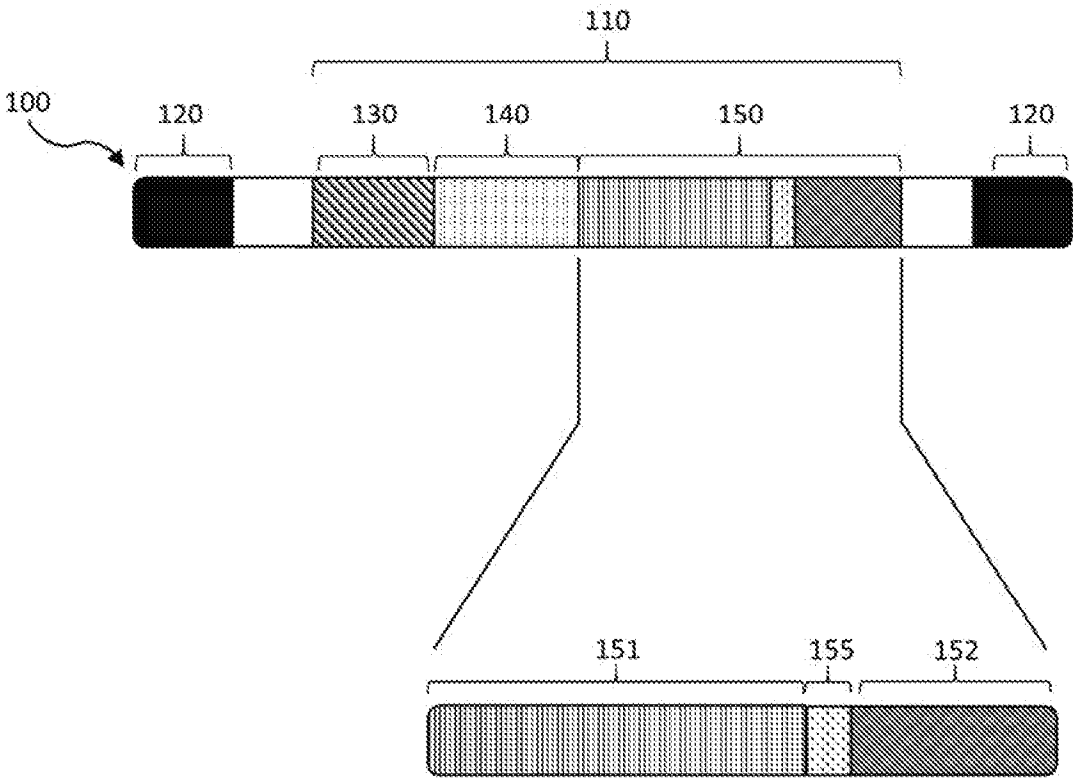
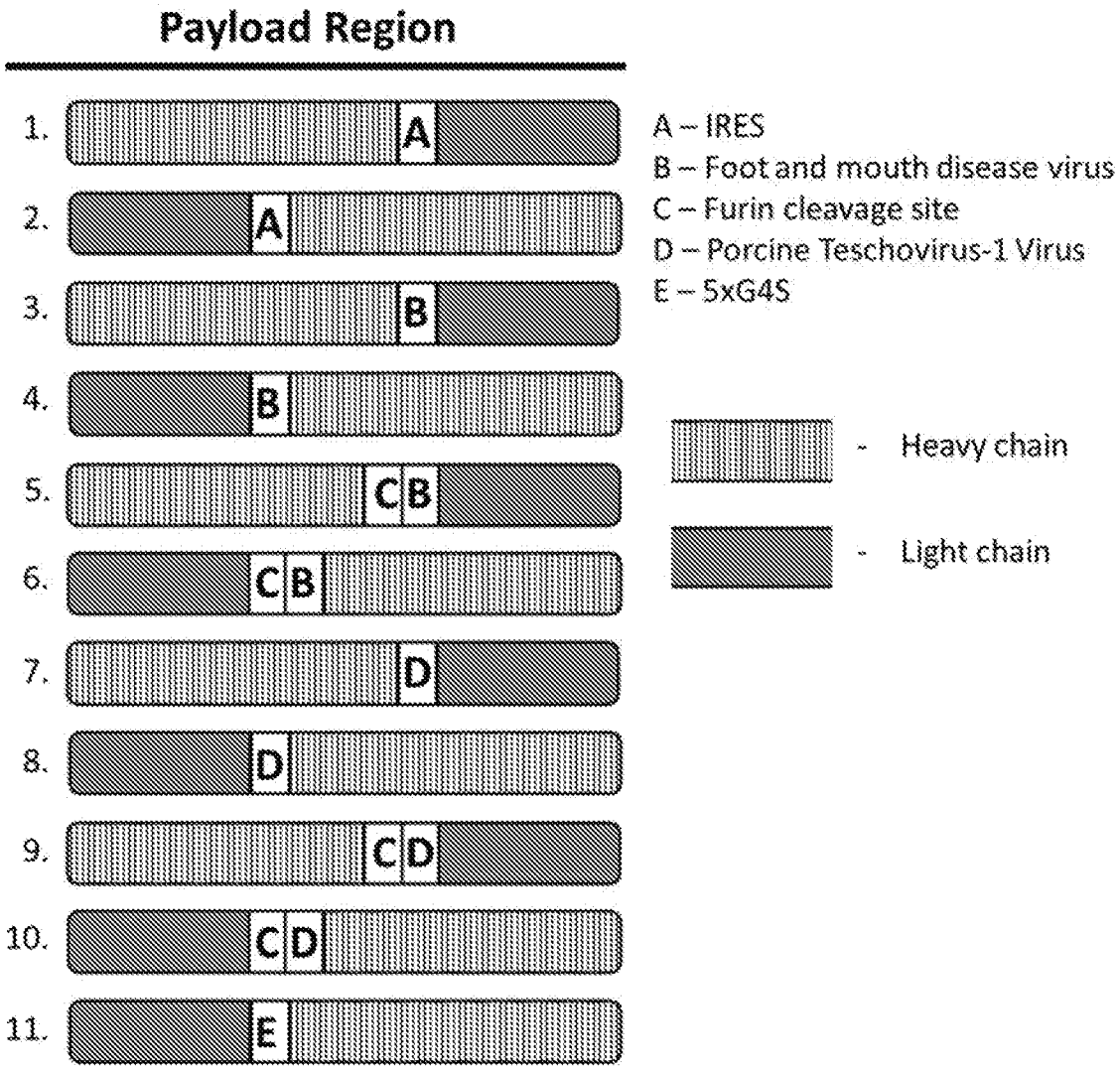


FIG. 3


Payload Region
1.
A
2.
A
3.
B
4.
B
5.
C B
6.
C B
7.
D
8.
D
9.
C D
10.
C D
11.
E
A – IRES
B – Foot and mouth disease virus
C – Furin cleavage site
D – Porcine Teschovirus-1 Virus
E – 5xG4S
- Heavy chain
- Light chain

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/30060

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07K 14/005, 14/47; A61K 48/00; C12N 15/09, 15/86 (2017.01)

CPC - C12N 15/09, 15/86; C07K 14/005, 14/47, A61K 48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2015/035190 A1 (CORNELL UNIVERSITY) March 12, 2015; paragraph [0065]; claim 35; figure 5b	1, 5-8, 9/1, 9/5-8, 10/9/1, 10/9/5-8, 12/9/1, 12/9/5-8, 13/9/1, 13/9/5-8, 14/9/1, 14/9/5-8, 15/14/9/1, 15/14/9/5-8, 16/9/1, 16/9/5-8, 17/16/9/1, 17/16/9/5-8, 18/9/1, 18/9/5-8, 20, 49, 51-53, 59-61, 66/1 ------ 2-4, 9/2-4, 10/9/2-4, 12/9/2-4, 13/9/2-4, 14/9/2-4, 15/14/9/2-4, 16/9/2-4, 17/16/9/2-4, 18/9/2-4, 50, 54-58, 67/66/1
Y	US 2015/0010578 A1 (CALIFORNIA INSITUTE OF TECHNOLOGY) January 8, 2015; paragraphs [0009]-[0010], [0015], [0019], [0020], [0038], [0042], [0075], [0082], [0113], [0208], [0218], claim 1	21
Y	WO 2015/191508 A1 (VOYAGER THERAPEUTICS, INC.) December 17, 2015; paragraphs [0009], [0026], [00148], [00249], [00265], [00275]	1, 62, 66/62, 67/66/62

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2017 (18.09.2017)	27 SEP 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/30060

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0035973 A1 (WALKER, C) February 11, 2010; paragraphs [0010], [0040], [0056], [0059], [0073], [0089]; Claims 1, 4, 14	1, 62-63, 66/62, 67/66/62
Y	US 2015/0183854 A1 (OSAKA CITY UNIVERSITY, et al.) July, 2, 2015; paragraph [0029]	1, 21, 62, 63, 67/66/62
Y	WO 2000/28061 (THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA) May 18, 2000; claim 10	2-4, 9/2-4, 10/9/2-4, 12/9/2-4, 13/9/2-4, 14/9/2-4, 15/14/9/2-4, 16/9/2-4, 17/16/9/2-4, 18/9/2-4
Y	US 7,105,345 (WILSON, JM et al.) September 12, 2006; column 8, lines 47-60	50
Y	US 6,936,466 B2 (FELDHAUS, AL) August 30, 2005; column 7, lines 8-17	54-58
Y	WO 2016/007741 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) January 14, 2016; claims 33, 57-58	63
Y	US 2011/0071214 A1 (ALLEN, GJ) March 24, 2011; paragraphs [0020], [0070]	67/66/1, 67/66/62
A	US 2014/0044794 A1 (OKADA, T et al.) February 13, 2014; abstract	68/66/1, 68/66/62, 69/66/1, 69/66/62, 70/66/1, 70/66/62
A	CN 101186925 A (SUN, D et al.) May 28, 2008; claim 1	11/9/1-8
A	US 2015/0284452 A1 (IOGENETICS, LLC) October 8, 2015; paragraphs [0010]-[0011]	22
A	WO 2014/016737 A1 (PFIZER INC.) January 30, 2014; claim 11	22
A	US 2009/0130114 A1 (QIAN, X et al.) May 21, 2009; pages 28-29	22
A	US 2011/0274691 A1 (ARVEDSON, T et al.) November 10, 2011; paragraph [0061]	22
A	WO 2016/014688 A2 (QIU, J et al.) January 28, 2016; claim 15	22
A	US 2013/0095116 A1 (GURNEY, AL et al.) April 18, 2013; claim 208	22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/30060

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 19, 23-48
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
-***-Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

Groups I+, Claims 1-18, 20-22, 49-70; SEQ ID NOs: 1, 899, 2948, 2949, 3153, 3154, 3495, 3549, 3550, 3698, 3753, 3754, 4131, 4187

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US17/30060

-***-Continuation of Box No. III - Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-18, 20-22, 49-70 and SEQ ID NOs: 1, 899, 2948 and 3154 are directed toward an AAV particle comprising a payload comprising a nucleic acid segment encoding a bispecific antibody; and methods of producing an antibody therewith.

The AAV particles and methods will be searched to the extent they encompass a first cargo nucleic acid segment encoding a heavy chain encompassing SEQ ID NO: 2948 (first exemplary heavy chain) and a light chain encompassing SEQ ID NO: 3154 (first exemplary light chain); and a linker encompassing SEQ ID NO: 899 (first exemplary linker); wherein the AAV has a serotype associated with a sequence encompassing SEQ ID NO: 1 (first exemplary serotype sequence). Applicant is invited to elect additional antibody heavy and/or light chain sequence(s), with specified SEQ ID NO: for each, and/or linker sequence(s), with specified SEQ ID NO: for each, and/or AAV serotype sequence(s), with specified SEQ ID NO: for each, to be searched. Additional antibody heavy and/or light chain sequence(s), and/or linker sequence(s) and/or AAV serotype sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), 3 (in-part), 4 (in-part), 5 (in-part), 6 (in-part), 7 (in-part), 8 (in-part), 9 (in-part), 10 (in-part), 11 (in-part), 12 (in-part), 13 (in-part), 14 (in-part), 15 (in-part), 16 (in-part), 17 (in-part), 18 (in-part), 20 (in-part), 21 (in-part), 22 (in-part), 49 (in-part), 50 (in-part), 51 (in-part), 52 (in-part), 53 (in-part), 54 (in-part), 55 (in-part), 56 (in-part), 57 (in-part), 58 (in-part), 59 (in-part), 60 (in-part), 61 (in-part), 62 (in-part), 63 (in-part), 64 (in-part), 65 (in-part), 66 (in-part), 67 (in-part), 68 (in-part), 69 (in-part) and 70 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 2948 (heavy chain), SEQ ID NO: 3154 (light chain); SEQ ID NO: 899 (linker); and SEQ ID NO: 1 (serotype sequence). Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a serotype sequence encompassing SEQ ID NO: 2 (first exemplary elected serotype sequence).

No technical features are shared between the antibody heavy and/or light chain sequences, and/or the linker sequences, and/or the serotype sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: an AAV particle comprising a capsid and a viral genome, said viral genome comprising at least one inverted terminal repeat (ITR) region and a payload region, said payload region comprising a regulatory sequence operably linked to at least a first nucleic acid segment, said first nucleic acid segment encoding a bispecific antibody derived from an antibody heavy or light chain sequence, or portions or fragments thereof; a method of producing an antibody in a subject comprising administering the AAV particle to said subject, with the proviso that the antibody is not a virus neutralizing antibody.

However, these shared technical features are previously disclosed by WO 2015/175639 A1 to The Trustees of the University of Pennsylvania (hereinafter 'Pennsylvania').

Pennsylvania discloses an AAV particle comprising a capsid and a viral genome (an AAV particle comprising a capsid and a viral *genome; page 4, lines 11-13; page 19, lines 15-19), said viral genome comprising at least one inverted terminal repeat (ITR) region and* a payload region (said viral genome comprising at least one inverted terminal repeat (ITR) region and a payload region; page 2, lines 17-23; page 19, lines 15-19), said payload region comprising a regulatory sequence operably linked to at least a first nucleic acid segment (said payload region comprising a regulatory sequence operably linked to at least a first nucleic acid segment; page 2, lines 17-23; page 19, lines 15-19), said first nucleic acid segment encoding a bispecific antibody derived from an antibody heavy or light chain sequence, or portions or fragments thereof (said first nucleic acid segment encoding a bispecific antibody derived from an antibody heavy or light chain sequence, or portions or fragments thereof; page 2, lines 8-16); and a method of producing an antibody in a subject (a method for delivering an antibody to a subject (producing an antibody in a subject); page 3, lines 1-2) comprising administering the AAV particle to said subject (comprising administering the AAV particle to said subject; page 3, lines 1-2), with the proviso that the *antibody is not a virus neutralizing antibody (wherein the antibodies bind to cancer antigens (comprising administering the AAV particle* to said subject); page 5, lines 30-33; page 6, lines 16-24).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Pennsylvania reference, unity of invention is lacking.