THERAPEUTIC ADENO-ASSOCIATED VIRUS USING CODON OPTIMIZED NUCLEIC ACID ENCODING ALPHA-GLUCOSIDASE (GAA) FOR TREATING POMPE DISEASE, WITH SIGNAL PEPTIDE MODIFICATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 63/321,336 filed March 18, 2022, U.S. Provisional Application No. 63/348,862 filed June 3, 2022 and U.S. Provisional Application No. 63/444,804 filed February 10, 2023, the contents of each of which are incorporated herein by reference in their entireties.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing as Table 9 herein, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present invention relates to methods to treat Pompe disease by administering adeno-associated virus (AAV) particles, virions and vectors for expression of an alpha-glucosidase (GAA) polypeptide, where the nucleic acid encoding GAA can be codon optimized or truncated. The compositions as disclosed herein can be used in methods to treat Pompe disease, including without the clinical need for administration of long-term GAA enzyme replacement therapy (ERT) for an extended period of time.

BACKGROUND

[0004] Pompe disease (Glycogen storage disease type II; acid maltase deficiency; MIM 232300) is caused by recessive mutations of the GAA gene leading to complete or partial deficiency of the lysosomal enzyme acid α-glucosidase (GAA). Absence of GAA leads to the progressive accumulation of glycogen in the lysosomes of many tissues, particularly skeletal muscle and cardiomyocytes. Impaired energy metabolism then leads secondarily to severely disrupted muscle architecture, dysfunction, autophagy, and in adults, significant fatty replacement of skeletal muscle myocytes.

[0005] Clinically, the condition ranges from a fulminant infantile-onset Pompe disease (IOPD) typically leading to death before 12 months of age to a late-onset Pompe disease (LOPD), which is slowly progressive leading to myopathy causing loss of mobility and typically death from respiratory failure 5-15 years after diagnosis. Infantile-onset patients have cardiomyopathy often noted even at birth or even antenatally, with elevated creatine kinase (CK) and then within weeks to the first months of life develop severe hypotonia, respiratory insufficiency requiring ventilator support and massive cardiomegaly. Deaths are most often the result of cardiorespiratory failure, aspiration pneumonia or ventricular arrhythmias. Late-onset Pompe Disease (LOPD) patients (mostly adults, some juveniles)

experience slowly progressive muscle weakness often leading to delayed diagnosis, extensive fatty replacement of trunk and proximal limb muscles, progressing to respiratory failure which is the primary cause of death (Carlier et al. 2011). Basilar artery aneurysms occur and can be life threatening if they rupture (El-Gharbawy et al. 2011; Hobson-Webb et al. 2012). As an alternative or adjunct to enzyme therapy, the feasibility of gene therapy approaches to treat GSD-II have been investigated (Amalfitano, A., et al., (1999) *Proc. Natl. Acad. Sci. USA* 96:8861-8866, Ding, E., et al. (2002) *Mol. Ther.* 5:436-446, Fraites, T. J., et al., (2002) *Mol. Ther.* 5:571-578, Tsujino, S., et al. (1998) *Hum. Gene Ther.* 9:1609-1616).

[0006] MYOZYME® (alglucosidase alfa) was the first US approved product (2006) for the treatment of Pompe disease; LUMIZYME® (alglucosidase alfa) was approved in 2010 and is the current standard-of-care (SOC) treatment for infantile-onset and late-onset Pompe patients. Alglucosidase alfa is administered intravenously every 2 weeks as an infusion at a dose of 20 mg/Kg (LUMIZYME Prescribing Information 2014). Alglucosidase alfa provides an exogenous source of GAA. Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen. Although this enzyme replacement therapy (ERT) prolongs survival in most patients with infantile Pompe disease, a subset have either died, suffered ongoing muscle weakness or remained profoundly hypotonic requiring mechanical ventilator support despite compliance with SOC ERT. For late-onset patients, ERT moderately improves muscle function and pulmonary function parameters, initially, followed by stable function or decline and remains far from an ideal therapy (Schoser et al. 2017).

[0007] For infantile-onset patients, especially those with severe or null mutations (cross-reacting immune material [CRIM])-negatives), high and sustained anti-rhGAA Immunoglobulin G (IgG)-mediated immunity against the GAA enzyme is a primary reason for impaired or inadequate response to ERT. That is, ERT is known to provoke an antibody response in the form of both IgG and IgE and can also lead to infusion-associated reactions (Kishnani et al. 2007; Kishnani et al. 2010). Current practice is to initiate immune modulation with ERT for patients with LOPD at risk for antibody formation.

[0008] Additionally, enzyme replacement therapy (ERT) with alglucosidase alfa (MYOZYME®/LUMIZYME®) is delivered as an onerous every other week, or weekly infusion, and is the only treatment currently available. For those with infantile-onset Pompe disease (IOPD), GAA is absent (CRIM negative) or minimal (~1% of normal) and causes rapidly progressive cardiorespiratory failure and death by the age of 2 years if left untreated (Parini et al. 2018). Subjects with a marked deficiency of GAA present as juveniles or adults (Late-Onset Pompe disease [LOPD]) with less severe symptoms and slower progression. Moreover, missing biweekly treatments can result in significant setbacks requiring many months of ERT to return to the same levels.

[0009] Accordingly, despite temporary therapeutic success, alglucosidase alfa ERT leaves a clear unmet medical need in both IOPD and LOPD. Longitudinal data in subjects confirm that ERT does not lead to complete correction or normalization of patients with Pompe disease. Ultimately subjects typically still decline, albeit at a slower rate, delaying the inevitable progression to death (Kuperus et al. 2017; Parini et al. 2018). While alglucosidase alfa prolongs survival for subjects with both IOPD and LOPD (LUMIZYME Prescribing Information, 2014) the antibody responses to the GAA and decline in effect poses several drawbacks.

[0010] Therefore, from a clinical perspective, long-term treatment of Pompe patients with ERT has had limited success. In the IOPD subset of patients, many experience high, sustained anti-rhGAA antibody titers (HSAT). Pompe patients who lack any residual GAA protein are deemed CRIM-negative. CRIM negative patients develop HSAT, and a subset of CRIM positive patients who also develop high or sustained intermediate titers suffer greatly increased mortality (Banugaria et al. 2011). Furthermore, the use of immunosuppression to prevent antibody formation in patients at risk for HSAT significantly prolonged survival and confirmed the clinical relevance of HSAT (Mendelsohn et al. 2009; Banugaria et al. 2011). Moreover, literature indicates that only about ~1% of ERT is pharmacologically active.

[0011] Therefore, while enzyme therapy has demonstrated reasonable efficacy for severe infantile GSD II, the benefit of GAA enzyme therapy is limited by the need for frequent infusions as well as the subject developing inhibitor or neutralizing antibodies against recombinant hGAA protein (Amalfitano, A., et al. (2001) *Genet. In Med.* 3:132-138), there is a need for improved methods and alternative therapies to treat patients with Pompe disease. Adeno-associated virus (AAV) vector-mediated gene transfer provides an appropriate and feasible alternative.

SUMMARY OF THE INVENTION

[0012] The technology described herein relates generally to a recombinant adenovirus associated (rAAV) vector comprising in its genome: (a) 5' and 3' AAV inverted terminal repeats (ITR) sequences, and (b) located between the 5' and 3' ITRs, a heterologous nucleic acid sequence encoding all or a portion of an endogenous GAA signal peptide, a heterologous signal peptide and an alpha-glucosidase (GAA) polypeptide, wherein the GAA polypeptide comprises amino acid residues 28-952 of SEQ ID NO: 1, 57-952 of SEQ ID NO: 1, or comprises a N-terminal GAA polypeptide fragment, such as comprising amino acids 28, 28-29, 28-30, 28-31, 28-32, or 28-33 of SEQ ID NO: 1 and a deletion of any number of amino acids from the next about 5 amino acids to about 40 amino acids after the N terminal GAA polypeptide fragment of SEQ ID NO: 1, and wherein the heterologous signal peptide can be inserted immediately at or after the N-terminal GAA polypeptide fragment and before the remaining amino acids of the GAA polypeptide, e.g., wherein the heterologous signal peptide is optionally fused at position 57 of the remaining amino acids of the GAA polypeptide, and where the GAA polypeptide can extend to amino acid 952 of SEQ ID NO: 1, or a functional fragment

thereof, and wherein the nucleic acid sequence encoding the GAA polypeptide can be codon optimized, and wherein the heterologous nucleic acid is operatively linked to a liver-specific promoter. In certain embodiments, the homologous GAA signal peptide or a fragment thereof can be present.

[0013] A recombinant adenovirus associated (rAAV) vector comprising in its genome: (a) 5' and 3' AAV inverted terminal repeats (ITR) sequences, and (b) located between the 5' and 3' ITRs, optionally, a heterologous nucleic acid sequence encoding all or a portion of an endogenous GAA signal peptide, a heterologous signal peptide and an alpha-glucosidase (GAA) polypeptide, wherein the GAA polypeptide comprises amino acid residues 28-952 of SEQ ID NO: 1, amino acids 57-952 of SEQ ID NO: 1, or comprises a N-terminal GAA polypeptide fragment, for example, comprising amino acids 28, 28-29, 28-30, 28-31, 28-32, or 28-33 of SEQ ID NO: 1 and a deletion can be any number of amino acids from about 5 amino acids to about 40 amino acids after the N terminal GAA polypeptide fragment of SEQ ID NO: 1, and wherein the heterologous signal peptide can be inserted immediately before the remaining amino acids of the GAA polypeptide. In one embodiment, the heterologous signal peptide is optionally fused at position 57 of the remaining amino acids of the GAA polypeptide, and where the GAA polypeptide can extend to amino acid 952 of SEQ ID NO: 1, or a functional fragment thereof, and wherein the nucleic acid sequence encoding the GAA polypeptide can be wild-type or codon optimized, and wherein the heterologous nucleic acid is operatively linked to a liver-specific promoter.

[0014] In some embodiments, the nucleic acid sequence that encodes an endogenous GAA-signal peptide encodes at least 1-5, or at least 1-10, or at least 1-20, or at least about 1-23, or at least about 1-24, or at least about 1-25, or at least about 1-26, or at least about 1-27 concecutive amino acids of the endogenous GAA signal peptide of SEQ ID NO: 59. In some embodiments, the nucleic acid sequence encoding an GAA-signal peptide encodes a modified GAA signal peptide that comprises a deletion of at least 1, or at least 2, or at least 3, or at least 4, or at least 5, or at least 6, or at least 7, or at least 8, or at least 9, or at least 10, or at least 11, or at least 12, or at least 13, or at least 14, or at least 15, or at least 16, or at least 17, or at least 18, or at least 19, or at least 20 amino acids of SEQ ID NO: 59, where the deletions can be concecutive, or non-concecutive deletions.

[0015] In some embodiments, the nucleic acid sequence that encodes a GAA-signal peptide encodes at least 1-5, or at least 1-10, or at least 1-20, or at least about 1-23, or at least about 1-24, or at least about 1-25, or at least about 1-26, or at least about 1-27 concecutive amino acids of the endogenous GAA signal peptide.

[0016] In one embodiment of any aspect herein, there is codon optimized nucleic acid sequence encoding the GAA polypeptide is selected from the group consisting of SEQ ID NO: 1-18, or functional fragment thereofs.

[0017] In one embodiment of any aspect herein, the nucleic acid encoding SEQ ID NO: 3 is wildtype.

[0018] In one embodiment of any aspect herein, the vector comprises the nucleic acid sequence of

SEQ ID NO: 23, or a functional variant thereof.

[0019] In one embodiment of any aspect herein, the heterologous nucleic acid sequence encodes a GAA protein comprising a signal peptide fused to the GAA polypeptide, wherein the signal peptide is an endogenous GAA signal peptide, or a heterologous signal peptide, or a combination thereof.

[0020] In one embodiment of any aspect herein, the AAV genome comprises, in the 5' to 3' direction: (a) a 5' ITR, (b) a liver-specific promoter sequence, (c) an 5' UTR sequence, (d) a nucleic acid encoding a portion or all of the endogenous GAA signal peptide, (e) a nucleic acid encoding a heterologous signal peptide or the N-terminal GAA polypeptide fragment, (f) a nucleic acid encoding an alpha-glucosidase (GAA) polypeptide, wherein the GAA polypeptide can be whole or a fragment thereof that is functionally active, (g) a poly A sequence, and (h) a reverse RNA pol II terminator sequence.

[0021] In one embodiment of any aspect herein, wherein the vector further comprises at least one of a UTR or a reverse RNA polII terminator sequence.

[0022] In one embodiment of any aspect herein, the UTR is 5' or 3'.

[0023] In one embodiment of any aspect herein, the nucleic acid encoding the signal peptide encodes a signal sequence is selected from any of: an endogenous GAA signal peptide, a fibronectin signal peptide (FN1), a IL-2 wt signal peptide, modified IL-2 signal peptide, IL2(1-3) signal peptide, IgG signal peptide, a AAT signal peptide, a A2M signal peptide, or a PZP signal peptide, or an active fragment thereof having signal peptide activity.

[0024] In one embodiment of any aspect herein, the nucleic acid sequence encodes a GAA polypeptide having the amino acid sequence of SEQ ID NO: 1, or a polypeptide having at least 80% sequence identity to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).

[0025] In one embodiment of any aspect herein, the nucleic acid sequence encoding the GAA polypeptide is SEQ ID NO: 3, or a nucleic acid sequence having at least 80%, or at least 85%, or at least 90% sequence identity to SEQ ID NO: 3 that encodes a GAA polypeptide having at least 80% sequence identity to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).

[0026] In one embodiment of any aspect herein, the 5' UTR sequence comprises SEQ ID NO: 41, or a nucleic acid having at least 80% sequence identity to SEQ ID NO: 41.

[0027] In one embodiment of any aspect herein, the 5' UTR sequence comprises SEQ ID NO: 40, or a nucleic acid having at least 80% sequence identity to SEQ ID NO: 40.

[0028] In one embodiment of any aspect herein, the vector further comprises an intron sequence located 5' of the nucleic acid sequence encoding the signal peptide, and 3' of the promoter.

[0029] In one embodiment of any aspect herein, the intron sequence is selected from the group consisting of: MVM sequence, a HBB2 sequence, an CMVIE intron sequence, or a UBC intron sequence or a SV40 sequence.

[0030] In one embodiment of any aspect herein, the GAA polypeptide is a N-terminal truncated GAA polypeptide selected from any disclosed in Table 1.

[0031] In one embodiment of any aspect herein, the vector further comprises at least one polyA sequence located 3' of the nucleic acid encoding the GAA gene and 5' of the 3' ITR sequence.

[0032] In one embodiment of any aspect herein, the heterologous nucleic acid sequence further comprises a 3' UTR sequence, wherein the 3' UTR sequence is located 3' of the nucleic acid encoding the GAA polypeptide and 5' of the 3' ITR sequence, or is located between the nucleic acid encoding a GAA polypeptide and the poly A sequence, and can also comprise a RNA pol II terminator sequence.

[0033] In one embodiment of any aspect herein, the heterologous nucleic acid sequence further comprises a 3' intron sequence, wherein the 3' intron sequence is located 3' of the nucleic acid encoding the GAA polypeptide and 5' of the 3' ITR sequence, or is located between the nucleic acid encoding the GAA polypeptide and a poly A sequence and/or a RNA polII terminator sequence.

[0034] In one embodiment of any aspect herein, the ITR comprises an insertion, deletion or substitution.

[0035] In one embodiment of any aspect herein, one or more CpG islands in the ITR are removed.

[0036] In one embodiment of any aspect herein, the nucleic acid encoding the signal peptide is selected from any of the group consisting of: AAT signal peptide (e.g., SEQ ID NO: 67), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 67; a fibronectin signal peptide (FN1) (e.g., SEQ ID NO: 73-75), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 73-75; an endogenous GAA signal peptide (SEQ ID NO: 51), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 51; an hIGF2 signal peptide (e.g., SEQ ID NO: 72), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 72; a IgG1 (201) signal peptide (SEQ ID NO: 54), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 54; wtIL2 leader peptide (SEQ ID NO: 55), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 55; mutant IL2 leader peptide (SEQ ID NO: 56) or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99%

sequence identity to SEQ ID NO: 56; and the nucleic acid encoding the GAA polypeptide is selected from any of the group consisting of: SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 or a nucleic acid sequence having at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% sequence identity to SEQ ID NOS: 1-18.

[0037] In one embodiment of any aspect herein, the nucleic acid encoding the GAA polypeptide is selected from SEQ ID NO: 3 or fragment thereof having functional GAA activity, or a nucleic acid sequence having at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 3 which encodes a GAA polypeptide at least 85% sequence identity to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).

[0038] In one embodiment of any aspect herein, the nucleic acid encoding the GAA polypeptide encodes a GAA polypeptide beginning at any of amino acid residues 35, 40, 50, 57, 60, 68, 69, 70, 72, 74, 779, 790, 791, 792, 793, or 796 of SEQ ID NO: 1 or a sequence 80% identical to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).

[0039] In one embodiment of any aspect herein, the GAA polypeptide has an endogenous GAA signal peptide or fragment thereof attached, and a heterologous signal peptide attached to or after the N-terminal of the GAA polypeptide, wherein the endogenous signal peptide has the amino acid sequence of SEQ ID NO: 59 or a sequence at least 80% sequence identity to SEQ ID NO: 59, and the heterologous signal peptide is selected from the group consisting of: SEQ ID NO: 60 (201 IgG signal peptide), or an IL2 wild type signal peptide (SEQ ID NO: 61), modified IL2 signal peptide (SEQ ID NO: 62), A2M signal peptide (SEQ ID NO: 63), or PZP signal peptide (SEQ ID NO: 64), or artificial signal peptide (SEQ ID NO: 65), or cathpetsin L signal peptide (SEQ ID NO: 66) or signal peptides at least 90% sequence identity to SEQ ID NOS: 60-66.

[0040] In one embodiment of any aspect herein, the liver specific promoter is selected from any of: SEQ ID NOS: 86, 88, 91-96, 146-150 or 439-441, or a liver specific promoter having at least 80% sequence identity to SEQ ID NOs: 86, 88, 91-96, 146-150 or 439-441.

[0041] In one embodiment of any aspect herein, the liver specific promoter is selected from any of: SEQ ID NOS: 98 or 99, or a liver specific promoter having at least 80% sequence identity to SEQ ID NOs: 98 or 99.

[0042] In one embodiment of any aspect herein, the liver specific promoter is SEQ ID NOS: 97, or a liver specific promoter having at least 80% sequence identity to SEQ ID NO: 97.

[0043] In one embodiment of any aspect herein, the recombinant vector is manufactured from the plasmid of SEQ ID NO: 27.

[0044] In one embodiment of any aspect herein, the nucleic acid comprises SEQ ID NO: 25, or a

functional fragment thereof.

[0045] In one embodiment of any aspect herein, the recombinant AAV vector is a chimeric AAV vector, haploid AAV vector, a hybrid AAV vector or polyploid AAV vector.

[0046] In one embodiment of any aspect herein, the recombinant AAV vector is a rational haploid vector, a mosaic AAV vector, a chemically modified AAV vector, or a AAV vector from any AAV serotypes.

[0047] In one embodiment of any aspect herein, the recombinant AAV vector is selected from the group consisting of: a AAVXL32 vector, a AAVXL32.1 vector, a AAV8 vector, or a haploid AAV8 vector comprising at least one AAV8 capsid protein. In one embodiment of any aspect herein, the serotype is AAV3b. In one embodiment of any aspect herein, the AAV3b serotype comprises one or mutations in a capsid protein selected from any of: 265D, 549A, Q263Y. In one embodiment of any aspect herein, the AAV3b serotype is selected from any of: AAV3b265D, AAV3b265D549A, AAV3b549A or AAV3bQ263Y, or AAV3bSASTG.

[0048] In one embodiment of any aspect herein, the poly A sequence is a full length HGF poly A sequence. Ine one embodiment, it can be a functional fragment of the hGH polyA sequence.

[0049] In one embodiment of any aspect herein, the poly A sequence is selected from SEQ ID NO: 42, 43 or 44, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 42-44.

[0050] In one embodiment of any aspect herein, the reverse RNA pol II terminator sequence comprises SEQ ID NO: 45, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NO: 45. In one embodiment, it is those sequences.

[0051] Another aspect described herein provides a pharmaceutical composition comprising any of the recombinant AAV vectors described herein in a pharmaceutically acceptable carrier.

[0052] Another aspect described herein provides a method to treat a subject with Pompe Disease, or a glycogen storage disease type II (GSD II, Acid Maltase Deficiency) or having a deficiency in alpha-glucosidase (GAA) polypeptide, comprising administering any of the recombinant AAV vector, or any of the rAAV genome or nucleic acid sequence described herein to the subject.

[0053] In one embodiment of any aspect herein, the AAV vector manufactured from the plasmid of SEQ ID NO: 27.

[0054] In one embodiment of any aspect herein, the recombinant AAV vector comprises the nucleic acid sequence of SEQ ID NO: 3, or a functional fragment thereof.

[0055] In one embodiment of any aspect herein, the recombinant AAV vector comprises the nucleic acid sequence of SEQ ID NO: 23, or a functional variant thereof.

[0056] In one embodiment of any aspect herein, the GAA polypeptide is secreted from the subject's liver and there is uptake of the secreted GAA by skeletal muscle tissue, cardiac muscle tissue, diaphragm muscle tissue or a combination thereof, wherein uptake of the secreted GAA results in a reduction in lysosomal glycogen stores in the tissue(s).

[0057] In one embodiment of any aspect herein, the administering to the subject is selected from any

of: intramuscular, sub-cutaneous, intraspinal, intracisternal, intrathecal, intravenous administration.

[0058] In one embodiment of any aspect herein, the recombinant AAV vector is a chimeric AAV vector, haploid AAV vector, a hybrid AAV vector or polyploid AAV vector.

[0059] In one embodiment of any aspect herein, the recombinant AAV vector is a rational haploid vector, a mosaic AAV vector, a chemically modified AAV vector, or a AAV vector from any AAV serotypes.

[0060] In one embodiment of any aspect herein, the recombinant AAV vector is a AAVXL32 vector or a AAVXL32.1 vector or a AAV8 vector, or a haploid AAV8 vector comprising at least one AAV8 capsid protein.

[0061] In one embodiment of any aspect herein, the recombinant AAV vector is a AAV8 vector.

[0062] In one embodiment of any aspect herein, the recombinant AAV vector is administered at a dosage range of between 1.0E9vg/kg and 5.0E13 vg/kg. For example, 1.0E9vg/kg and 5.0E12 vg/kg; 5.0E9vg/kg and 5.0E12 vg/kg; 5.0E9vg/kg and 1.0E12 vg/kg; 5.0E9vg/kg and 5.0E11 vg/kg; 5.0E9vg/kg and 5.0E10 vg/kg; and 1.0E9vg/kg and 1.0E10 vg/kg.

[0063] In one embodiment of any aspect herein, the method further comprises receiving GAA protein enzyme replacement therapy, and withdrawing GAA protein enzyme replacement therapy (ERT) on the same day, a day after or, any time between day 1 and 26 weeks after administration of the recombinant AAV vector.

[0064] Another aspect described herein provides a nucleic acid construct comprising SEQ ID NO: 3, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 3.

[0065] In one embodiment of any aspect herein, the expression of the nucleic acid sequence of SEQ ID NO: 3 or a nucleic acid having 80% sequence identity thereto encodes a GAA polypeptide having at least 80% sequence identity to SEQ ID NO: 1 and wherein there is R at position 199, a H at position 223 and I at position 780.

[0066] Another aspect described herein provides a nucleic acid construct comprising SEQ ID NO: 23, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NO: 23.

[0067] In one embodiment of any aspect herein, the nucleic acid comprises SEQ ID NO: 3 or SEQ ID NO: 25, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 3 or 25.

[0068] In one embodiment of any aspect herein, the expression of the nucleic acid sequence of SEQ ID NO: 3 or a nucleic acid having 80% sequence identity thereto encodes a GAA polypeptide having at least 80% sequence identity to SEQ ID NO: 1 and wherein there is R at position 199, a H at position 223 and I at position 780.

[0069] Another aspect described herein provides a recombinant AAV comprising any of the nucleic acid constructs described herein.

[0070] In one embodiment of any aspect herein, the AAV lacks at least 1 amino acids of the GAA N terminus.

[0071] In one embodiment of any aspect herein, the AAV lacks at least 5, 10, 15, 20, 25, 30, 35, 40,

45, 50, 55 or mor amino acids of the GAA N terminus.

[0072] In one embodiment of any aspect herein, the heterologous signal peptide is inserted immediately after the endogenous GAA signal peptide or a potion thereof.

[0073] Aspects of the present invention teach certain benefits in construction and use which give rise to the exemplary advantages described below. Other features and advantages of aspects of the present invention will become apparent from the following more detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, the principles of aspects of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0074] This application file contains at least one drawing executed in color. Copies of this patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee. The accompanying drawings illustrate aspects of the present invention. In such drawings:

[0075] FIGs 1A-1D show serum GAA protein quantification by western blot densitometry. Serum GAA protein was measured by western blot densitometry at week 1 (Fig. 1A), week 2 (Fig. 1B). week 3 (Fig. 1C) and week 4 (cardiac serum) (Fig. 1D). Serum GAA was normalized to total protein (A-D).

[0076] FIGs 2A-2D show serum GAA activity by 4MU assay. Serum GAA activity was measured by 4MU assay at week 1 (Fig. 2A), week 2 (Fig. 2B). week 3 (Fig. 2C) and week 4 (cardiac serum) (Fig. 2D).

[0077] FIGs 3A-3C show target organ GAA protein quantification by western blot densitometry. GAA protein was measured 4 weeks post dosing by western blot densitometry in Heart (Fig. 3A), Diaphragm (Fig. 3B) and Liver (Fig. 3C). GAA was normalized to total protein.

[0078] FIGs 4A-4D show target organ GAA activity by 4MU assay. GAA activity was measured by 4MU assay 4 weeks post dosing in Heart (Fig. 4A), Diaphragm (Fig. 4B), Quad (Fig. 4C) and Liver (Fig. 4D).

[0079] FIGs 5A-5D show target organ Glycogen content. Glycogen content was measured 4 weeks post dosing in Heart (Fig. 5A), Diaphragm (Fig. 5B), Quad (Fig. 5C) and Liver (Fig. 5D).

[0080] FIGs 6A-6C show serum GAA protein quantification by western blot densitometry for 3-week sacrifice animals. Serum GAA protein was measured by western blot densitometry at week 1 (Fig. 6A), week 2 (Fig. 6B) and week 3 (Fig. 6C). Serum GAA was normalized to total protein.

[0081] FIGs 7A-7C show serum GAA activity by 4MU assay for 3-week sacrifice animals. Serum GAA activity was measured by 4MU assay at week 1 (Fig. 7A), week 2 (Fig. 7B) and week 3 (Fig. 7C).

[0082] FIGs 8A-8C show target organ GAA activity by 4MU assay for 3-week sacrifice animals. GAA activity was measured by 4MU assay 3 weeks post dosing in Heart (Fig. 8A), Diaphragm (Fig. 8B) and Liver (Fig. 8C).

[0083] FIGs 9A-9C show target organ Glycogen content for 3-week sacrifice animals. Glycogen content was measured 3 weeks post dosing in Heart (Fig. 9A), Diaphragm (Fig. 9B) and Liver (Fig. 9C).

[0084] FIGs 10A-10H show serum GAA protein quantification by western blot densitometry for 8-week sacrifice animals. Serum GAA protein was measured by western blot densitometry at week 1 (Fig. 10A), week 2 (Fig. 10B). week 3 (Fig. 10C) and week 4 (Fig. 10D), week 5 (Fig. 10E), week 6 (Fig. 10F), week 7 (Fig. 10G), week 8 (Fig. 10H). Serum GAA was normalized to total protein.

[0085] FIGs 11A-11H show serum GAA activity by 4MU assay for 8-week sacrifice animals. Serum GAA activity was measured by 4MU assay at week 1 (Fig. 11A), week 2 (Fig. 11B). week 3 (Fig. 11C) and week 4 (Fig. 11D), week 5 (Fig. 11E), week 6 (Fig. 11F), week 7 (Fig. 11G), week 8 (Fig. 11H).

[0086] FIGs 12A-12C show target organ GAA protein quantification by western blot densitometry for 8-week sacrifice animals. GAA protein was measured 8 weeks post dosing by western blot densitometry in Heart (Fig. 12A), Diaphragm (Fig. 12B), and Liver (Fig. 12C).

[0087] FIGs 13A-13C show target organ GAA activity by 4MU assay for 8-week sacrifice animals. GAA activity was measured by 4MU assay 8 weeks post dosing in Heart (Fig. 13A), Diaphragm (Fig. 13B) and Liver (Fig. 13C).

[0088] FIGs 14A-14F show target organ Glycogen content for 8-week sacrifice animals. Glycogen content was measured 8 weeks post dosing in Heart (Figs 14A, 14D), Diaphragm (Figs 14B, 14E) and Liver (Figs 14C, 14F) and expressed normalized to dose per kg body weight (Figs 14D-14F).

[0089] FIG. 15 shows a schematic of the Actus, M3 and M4 constructs. The Actus comprises the liver promoter of SEQ ID NO: 97, the M3 construct is similar to the M2 construct, with the M3 contruct comprsing the promoter of SEQ ID NO: 99, whereas the M2 construction comprises the promter of SEQ ID NO: 98, which comprises mutations within the muscle transcription factor binding site. The coding sequence in the M3 construct was modified to remove predicted alternative open reading frames and known immune stimulatory hexanucleotide CpG motifs. In the M4 construct, all CG dinucleotide were removed from the entire coding sequence. Alternative frames were not removed in selected M4 constructs. Amino acid sequence is identical to sequence found in Actus 101 (myozyme/lumizyme amino acid sequence) across the M3 and M4 constructs.

[0090] FIGs 16A and **16B** show analyses of hGAA target tissue uptake. Fig. 16A shows expression of GAA activity (top graph) following administrations of M4 as compared to Actus 101 and a vehicle control (VC) in the liver, heart and diaphragm, as well as glycogen levels (bottom graph). Fig. 16B shows expression of GAA activity (top graph) following administrations of M4 from two different lots as compared to Actus 101 and a vehicle control (VC) in the liver, heart and diaphragm, as well as glycogen levels (bottom graph).

[0091] FIGs 17A and **17B** show analyses of serum hGAA expressed by Actus 101 and M4. FIG. 17A shows protein expression of hGAA expressed from Actus 101, M4, and a vehicle control (VC). hGAA protein is 2.48 fold higher when expressed from M4 as compared to Actus 101. Fig. 17B

shows total protein of hGAA activity present in the serum following administrations of M4 from two different lots as compared to Actus 101 and a vehicle control (VC) 4 weeks post injection.

[0092] FIGs 18A-18C show performance of wild type (pM3-NCBI) & Actus 101 hGAA proteins in mouse heart at 4 weeks post vector injection. Fig. 18A is a bar graph showing the hGAA uptake following administration of the indicated constructs. Fig. 18B is a bar graph showing the hGAA activity following administration of the indicated constructs. Fig. 18C is a bar graph showing the glycogen levels following administration of the indicated constructs. Actus 101 performs better than the M3 construct in mouse hGAA activity (Fig. 18B) and glycogen reduction (Fig. 18C) in heart; this is in stark contrast to the M4 construct, which performs better than Actus 101.

[0093] FIG. 19 shows 4MU activity assay for hGAA activity at 4 weeks post transduction in mouse sera with the indicated construct. M4 performs better that Actus 101 in promoting GAA activity.

[0094] FIG. 20 shows liver retention observed following injection with saline (control), Actus 101, or M4. Liver retention appeared to be comparable between Actus 101 and M4.

[0095] FIGs 21A-21D show analyses of hGAA target tissue uptake. Fig. 21A shows expression of GAA activity following administrations of M4, Actus 101 and a saline control in the heart. Fig. 21B shows expression of GAA activity following administrations of M4, Actus 101 and a saline control in the diaphragm. Fig. 21C shows expression of GAA activity following administrations of M4, Actus 101 and a saline control in the quadriceps muscle. Fig. 21D shows expression of GAA activity following administrations of M4, Actus 101 and a saline control in the soleus muscle.

[0096] FIG. 22 presents western blots showing the hGAA expression from vehicle control (VC), Actus 101, and various M4 constructs, Seq12 (SEQ ID NO: 30), Seq99 (SEQ ID NO: 29), Seq3 (SEQ ID NO:28), and Seq100 (SEQ ID NO: 27) at 7, 14 and 21 days post infection. Low and high doses (as indicated) were administered to GAA-KO mice. Levels were assessed at the days indicated. Seq100 results in a higher expression level that persists for a longer period of time as compared to VC, Actus 101 and the other indicated M4 constructs. "H ST 1" and "H ST 2" refer to HIGH DOSE STUDY 1 and HIGH DOSE STUDY 2, respectively. SEQ ID NO: 27, 28, 29, 30 are the plasmids for expression of the rAAV vectors expressing a GAA polypeptide having the sequence of SEQ ID NO: 1, where the rAAV vectors comprise codon optimized nucleic acid sequences selected from: SEQ ID NO: 3 (Seq100), SEQ ID NO: 4 (Seq3), SEQ ID NO:7 (Seq12), SEQ ID NO:13 (Seq99).

[0097] FIG. 23 shows hGAA levels in GAA-KO mouse at 21 days post administration of the indicated constructs. Seq100 results in a higher expression level of hGAA in the sera (top western blot) and liver (bottom western blot) at 21 days post administration as compared to VC, Actus 101 and the other indicated M4 constructs.

[0098] FIG. 24 shows normalized hGAA RNA levels in the liver of GAA-KO mice at 21 days post administration with the indicated constructs. Seq100 results in a higher expression level of hGAA RNA in the sera at 21 days post administration as compared to VC, Actus 101 and the other indicated M4 constructs.

[0099] FIG. 25 presents a western blot showing GAA uptake in the indicated target tissue (i.e., heart or diaphragm) at 21 days post administration with the indicated constructs. Seq100 results in a higher expression level of hGAA in each tissue at 21 days post administration as compared to VC, Actus 101 and the other indicated M4 constructs.

[00100] FIGs 26A and **26B** present bar graphs showing GAA and glycogen levels in the indicated tissue of GAA-KO mice at 21 days post administration FIG. 26A shows GAA activity in the indicated tissue of GAA-KO mice at 21 days post administration with the indicated constructs. Seq100 results in a higher expression level of hGAA in each tissue at 21 days post administration as compared to VC, Actus 101 and the other indicated M4 constructs. FIG. 26B shows glycogen in the indicated tissue of GAA-KO mice at 21 days post administration mice with the indicated constructs. Seq100 results in a higher level of glycogen clearance in each tissue at 21 days post administration as compared to VC, Actus 101 and the other indicated M4 constructs.

[00101] FIG. 27 presents a western blot showing hGAA expression in GAA-KO mice over time. Seq100 results in a higher expression level of hGAA in at day 7 and 14 post administration as compared to VC, Actus 101 and the other indicated M4 constructs.

[00102] FIG. 28 presents a bar graph showing the results of a 4MU assay in GAA-KO mice 21 days post administration. Seq100 results in a higher expression level of hGAA in at day 21 post administration as compared to VC, Actus 101 and the other indicated M4 constructs.

[00103] FIG. 29 is a schematic that shows a number of modified GAAs, showing a construct comprising (i) a GAA-signal peptide, or portion thereof, and (ii) a heterologous signal peptide, attached to (iii) a GAA polypeptide. A N-terminal truncated GAA polypeptide beginning at amino acid 57 is shown as an exemplary GAA polypeptide, however, any N-terminal truncated GAA polypeptide disclosed in Table 1 can be used.

[00104] FIG. 30 presents a western blot showing hGAA expression in GAA-KO mice 4 weeks following administration of the indicated constructs. Balck arrow indicates GAA expression. Gray triangle indicates a non-specific band.

[00105] FIG. 31 presents a bar graph showing total GAA protein in serum of GAA-KO mice 4 weeks following administration of the indicated constructs. Saline is used a control.

[00106] FIG. 32 presents a bar graph showing total GAA activity in serum of GAA-KO mice 4 weeks following administration of the indicated constructs. Saline is used a control. 4MU activity in the serum is consistent with GAA expression levels.

[00107] FIG. 33 presents a bar graph showing total GAA activity in the heart of GAA-KO mice 4 weeks following administration of the indicated constructs. Saline is used a control. 4MU activity in the heart is consistent with GAA expression levels and expression of the construct achieved wild-type levels.

[00108] FIG. 34 presents a bar graph showing total glycogen levels in the heart of GAA-KO mice 4 weeks following administration of the indicated constructs. Saline is used a control. Glycogen levels

in the heart is consistent with GAA expression levels and expression of the construct achieved wild-type levels.

[00109] FIG. 35A presents a western blot showing total GAA activity in the liver of GAA-KO mice 4 weeks following administration of the indicated constructs. **FIG. 35B** presents a bar graph showing total GAA activity in the heart of GAA-KO mice 4 weeks following administration of the indicated constructs. Saline is used a control. Reduced retention of modified GAA in the liver is observed.

[00110] FIG. 36 presents a table showing the level of GAA in serum, GAA activity in serum and heart, glycogen level in heart, and GAA levels retained in liver in mice following administration of indicated AAV (left column).

[00111] FIG. 37 presents a schematic of modified constructs. Mod-Actus is the Actus construct modified to remove wtAAV DNA sequences 5' and 3' to the ITRs. Mod-P072 is the P072 construct modified to replace the 5'UTR with a 5'UTR+intron sequence, remove the 3'UTR, and add a SV40 bi-directional polyA sequence. Mod-P092 is the P092 construct modified to replace the 5'UTR with a 5'UTR+intron sequence, remove the 3'UTR, and add a SV40 bi-directional polyA sequence. Mod-072 and mod-092 are also modified to remove wtAAV DNA sequences 5' and 3' to the ITRs.

[00112] FIGs 38A and 38B present bar graphs showing GAA expression in huh7 cell culture for indicated AAVs. **FIG. 38A** shows GAA activity in huh7 cell lysates. **FIG. 38B** shows GAA activity in huh7 cell supernatants. Mod-P072 secretes that highlest level of GAA into the supernatant. Mod-Actus promotes that highest GAA activity in cells.

[00113] FIGs 39A-39C present data showing *in vivo* expression of indicated AAVs at various levels in wild type mice (C57BL/6J). **FIG. 39A** is a graph showing GAA activity in serum at various weeks post administration in male mice. **FIG. 39B** is a graph showing GAA activity in serum at various weeks post administraton in female mice. **FIG. 39C** is a graph showing GAA activity in serum at various weeks post administraton in male and female mice (total). Mod-P072 achieves the highest GAA activity levels in serum of mice 4 weeks post administration.

[00114] FIGs 40A-40C present bar graphs representing semi-quantitative analysis of GAA level western blots in liver, heart and quadriceps tissue following *in vivo* expression of indicated AAVs at various levels in wild type mice (C57BL/6J). **FIG. 40A** is a graph showing GAA levels in liver tissue in male and female mice. **FIG. 40B** is a graph showing GAA levels in heart tissue in male and female mice. **FIG. 40C** is a graph showing GAA levels in quadriceps tissue in male and female mice. Mod-Actus achieves the highest GAA uptake in liver tissue post administration. Mod-P072 achieves the highest GAA uptake in heart and quadriceps tissue post administration.

[00115] FIG. 41 present a bar graph glycogen levels in heart tissue following administration of Actus 101, pP110, and pP113 at the indicated dose. A greater reduction in glycogen in the cells was observed following administration of pP110 as compared to Actus 101 or pP113. Saline is used a control.

[00116] FIG. 42 present a bar graph glycogen levels in heart tissue following administration of M4,

pP065, pP072 and pP092 at the indicated dose. Higher doses of pP065 and pP072 resulted in the greatest reduction of glycogen levels in the cell. Saline is used a control.

[00117] The above described figures illustrate aspects of the invention in at least one of its exemplary embodiments, which are further defined in detail in the following description. Features, elements, and aspects of the invention that are referenced by the same numerals in different figures represent the same, equivalent, or similar features, elements, or aspects, in accordance with one or more embodiments.

DETAILED DESCRIPTION

[00118] The technology described herein is directed to recombinant AAV (rAAV) vectors and constructs for rAAV for delivering a GAA polypeptide to a subject in the methods to treat Pompe Disease, where the heterologous nucleic acid encoding GAA polypeptide is codon optimized to reduce an immune response and for enhanced and improved efficiency of expression in human subjects. That is, the rAAV constructs described herein for delivering a GAA polypeptide to a subject comprise improvements, such as but not limited to, a codon optimized nucleic acid sequence encoding a GAA polypeptide, where the codon optimized nucleic acid sequence encoding the GAA polypeptide is modified include features for example, (i) enhanced expression *in vivo*, (ii) to reduce CpG islands and/or to eliminate CG dinucleotide content, (iii) modification of STOP sequences or elimination of alternative reading frames (ARF), and (iv) to reduce the innate immune response. Or using a wildtype GAA modified to enhance expression. Furthermore, the rAAV constructs described herein for delivering a GAA polypeptide to a subject comprise improvements such as, e.g., incorporation of a 5' UTR located between the nucleic acid expressing the GAA polypeptide and the liver specific promoter, and use of specific terminator sequences 3' nucleic acid expressing the GAA polypeptide, such as, e.g., specific poly A sequences and/or terminator sequences, multiple polyA sequences, etc.

[00119] The technology described herein relates to improved recombinant AAV (rAAV) vectors and constructs for rAAV for delivering a GAA polypeptide to a subject in the methods to treat Pompe Disease to those previously disclosed in International Patent Application WO2020102645 and WO2021102107, both of which are incorporated herein in their entirety by reference.

[00120] In particular, described herein are targeted viral vectors, e.g., using rAAV vectors as an exemplary example, that comprise a nucleotide sequence containing inverted terminal repeats (ITRs), a liver specific promoter, a heterologous gene, a poly-A tail and potentially other regulator elements for use to treat Pompe disease, where the heterologous gene is human GAA, and wherein the vector, e.g., rAAV can be administered to a patient in a therapeutically effective dose that is delivered to the appropriate tissue and/ or organ for expression of the heterologous gene and treatment of the disease, e.g., Pompe disease.

[00121] One aspect described herein provides a recombinant adenovirus associated (AAV) vector

comprising in its genome: (a) 5' and 3' AAV inverted terminal repeats (ITR) sequences, and (b) located between the 5' and 3' ITRs, a heterologous nucleic acid sequence encoding a polypeptide comprising an alpha-glucosidase (GAA) polypeptide, wherein the heterologous nucleic acid is operatively linked to a liver-specific promoter as disclosed herien.

[00122] In one embodiment of any aspect herein, the heterologous nucleic acid sequence encodes a GAA polypeptide comprising a secretory signal fused to the GAA polypeptide, wherein the secretory signal (also referred to herein as "signal peptide") is the endogenous GAA polypeptide, or an exogenous GAA polypeptide.

[00123] In one embodiment of any aspect herein, the nucleic acid sequence encoding the GAA polypeptide is the human GAA gene or a human codon optimized GAA gene (coGAA) or a modified GAA nucleic acid sequence. As disclosed herein, the nucleic acid encoding the human GAA protein is selected from any of SEQ ID NO: 1-18, or a functional variant having least 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 98% sequence identity to any of SEQ ID NO: 1-18.

[00124] In some embodiments, GAA expressed that comprises at least a signal peptide that promotes secretion of GAA polypeptide from the liver. In some embodiments, the GAA polypeptide, or modified GAA, is expressed as a fusion protein comprising at least a signal peptide that promotes secretion of the GAA polypeptide from the liver.

[00125] In all aspects of all embodiments of the technology described herein, the liver specific promoter expresses the hGAA polypeptide preferentially in the liver. In all aspects of all embodiments of the technology described herein, in some embodiments where the AAV vector comprises at least one capsid protein targeting the liver.

I. Recombinant AAV expressing GAA

[00126] As disclosed herein, one aspect of the technology relates to a method to treat Pompe disease using a rAAV vector comprising a capsid, and within its capsid, a nucleotide sequence referred to as the "rAAV vector genome". The rAAV vector genome (also referred to as "rAAV genome) includes multiple elements, including, but not limited to two inverted terminal repeats (ITRs, e.g., the 5'-ITR and the 3'-ITR), and located between the ITRs are additional elements, including a promoter, a heterologous gene encoding a GAA polypeptide and a poly-A tail, where the heterologous gene encoding a GAA polypeptide is codon optimized, e.g., including but not limited to, reducing CpGs, reduced CpG islands, and minimizing or eliminating internal start codons.

[00127] In some embodiments, the rAAV genome disclosed herein comprises a 5' ITR and 3' ITR sequence, and located between the 5'ITR and the 3' ITR, a promoter, e.g., a liver specific promoter sequence as disclosed herein, which operatively linked to a heterologous nucleic acid encoding a nucleic acid encoding an alpha-glucosidase (GAA) polypeptide, where the heterologous nucleic acid is codon optimized as disclosed herein, and where there is a 5' UTR located between the nucleic acid

encoding a GAA polypeptide and the liver specific promoter sequence. In some instances, there is also a 3' UTR. Further, the UTR can contain an intron. In one embodiment, the heterologous nucleic acid sequence can optionally further comprise one or more of the following elements: an intron sequence, a nucleic acid encoding a secretory signal peptide, which can be an endogenous signal peptide (SP) or a heterologous SP as disclosed herein, a poly A sequence, and a terminator sequence. In some embodiments, the 5' UTR sequence comprises SEQ ID NO: 41, or comprises SEQ ID NO: 40, or a sequence having at least 85%, or at least 90% or more sequence identity to SEQ ID NOs: 40 or 41. In some embodiments, the poly A sequence is a full length HGH poly A sequence comprising SEQ ID NO: 42, or a sequence having at least 85%, or at least 90% or more sequence identity to SEQ ID NO: 42. In some embodiments, the terminator sequence is a reverse RNA pol II terminator sequence. In some embodiments, a reverse RNA pol II terminator sequence comprises sequence SEQ ID NO: 45, or a sequence having at least 85%, or at least 90% or more sequence identity to SEQ ID NO: 45.

[00128] In some embodiments, the nucleic acid encoding an alpha-glucosidase (GAA) polypeptide encodes a full-length GAA polypeptide, e.g., beginning at residue 28 of SEQ ID NO: 1. In some embodiments, the nucleic acid encoding an alpha-glucosidase (GAA) polypeptide encodes a truncated GAA polypeptide, such as, for example, beginning at amino acid residues 35, 40, 50, 57, 60, 68, 69, 70, 72, 74 and/or a C-terminal truncation beginning at residues 779, 790, 791, 792, 793 and 796 of SEQ ID NO: 1, or a GAA polypeptide that has at least 80%, or at least 85%, or at least 90% or at least 95% sequence identity to SEQ ID NO: 1 over the amino acid residues 35-952, 40-952, 50-952, 57-952, 60-952, 68-952, 69-952, 70-952, 72-952, 74-952, 779-952, 790-952, 791-952, 792-952, 793-952 and 796-952 of SEQ ID NO: 1.

[00129] In some embodiments, the nucleic acid encoding an alpha-glucosidase (GAA) polypeptide encodes a full-length GAA polypeptide (e.g., residues 28-952 of SEQ ID NO: 1), or a truncated GAA polypeptide, e.g., a GAA polypeptide beginning at any of residues 35, 40, 50, 57, 60, 68, 69, 70, 72, 74 of SEQ ID NO: 1 and/or a second truncation starting at residues 779, 790, 791, 792, 793 and 796 of SEQ ID NO: 1) that has an endogenous GAA signal peptide attached to the N-terminal of the GAA polypeptide, e.g., comprises endogenous signal peptide comprising residues of SEQ ID NO: 59. For example, SEQ ID NO: 1 and only a heterologous or homologous signal peptide. In alternative embodiments, the nucleic acid encoding an alpha-glucosidase (GAA) polypeptide encodes a full-length GAA polypeptide (e.g., residues 28-952 of SEQ ID NO: 1), or a truncated GAA polypeptide, e.g., a GAA polypeptide beginning at any of residues 35, 40, 50, 57, 60, 68, 69, 70, 72, 74, 779, 790, 791, 792, 793 and 796 of SEQ ID NO: 1, that has a heterologous signal peptide attached to the N-terminal of the full-length, or truncated GAA polypeptide.

[00130] In alternative embodiments, the nucleic acid encoding an alpha-glucosidase (GAA) polypeptide encodes a full-length GAA polypeptide (e.g., residues 28-952 of SEQ ID NO: 1), or a N-terminal truncated GAA polypeptide, e.g., a GAA polypeptide beginning at any of residues 35, 40, 50,

57, 60, 68, 69, 70, 72, 74, 779, 790, 791, 792, 793 and 796 of SEQ ID NO: 1, and also encodes a GAA-signal peptide or a portion or fragment thereof, and a heterologous signal peptide attached to the N-terminal of the full-length, or truncated GAA polypeptide. In some embodiments, the GAA polypeptide is a N-terminal truncated GAA polypeptide, with the truncation beginning at any amino acids 29-35 of SEQ ID NO: 1. In some embodiments, the nucleic acid encoding an alpha-glucosidase (GAA) polypeptide comprises (i) a GAA-signal peptide, or a portion thereof, e.g., a N-terminal portion thereof, (ii) a portion of the GAA polypeptide, (e.g., any portion of residues 28-56 of SEQ ID NO: 1) (iii) a heterologous signal peptide as disclosed herein, and (iv) a GAA polypeptide, e.g., a N-terminal truncated GAA polypeptide, e.g., a GAA polypeptide beginning at any of residues 35, 40, 50, 57, 60, 68, 69, 70, 72, 74, 779, 790, 791, 792, 793 and 796 of SEQ ID NO: 1. In some embodiments, the GAA polypeptide can comprise a C-terminal truncation of at least 1, or at least 2, or at least 3, or at least 4, or at least 5, or at least between 5-10, or between 10-20, or between 20-30 amino residues at the C-termins of the GAA polypeptide. Exemplary heterologous signal peptides are disclosed herein, including, but not limited to, signal peptides comprising amino acids selected from any of SEQ ID NO: 60-78. In some embodiments, the signal peptide attached to the N-terminal of SEQ ID NOs: 60, 61, 62, 63 and 64.

A. Alpha-glucosidase (GAA) polypeptide

[00131] The GAA gene (NM_000152.3) is approximately 18.3 kilobases (kb) long and contains 20 exons (Dasouki et al. 2014). Its complementary DNA has 2,859 nucleotides of coding sequence which encode the immature 952 amino acid enzyme. GAA is synthesized as a membrane bound, catalytically inactive (with respect to the natural substrate glycogen) precursor which is sequestered in the endoplasmic reticulum. It undergoes sugar chain modification in the Golgi complex, followed by transport into the (minor) secretory pathway, or into lysosomes where it is trimmed in a stepwise process at both the amino-and carboxyl-termini. Phosphorylation of mannose residues ensures efficient transport of the enzyme to the lysosomes via the mannose 6-phosphate receptor. In the lysosomes, GAA catalyzes the hydrolysis of α1→4 glucosidic linkages in glycogen in the low potential hydrogen (pH) environment to glucose. Specificity for the natural substrate (glycogen) is gained during its maturation.

[00132] Many normal allelic variants exist in GAA and are responsible for the three known alloenzymes (GAA1, GAA2, and GAA4). More than 450 mutations in GAA have been reported in individuals with Pompe disease. Nonsense mutations, large and small gene rearrangements, and splicing defects have been observed with many mutations being potentially specific to families, geographic regions, or ethnicities. Combinations of mutations that result in either complete or nearly complete absence of GAA enzyme activity (typically <1% of normal activity in skin fibroblasts) are seen more commonly in individuals with IOPD, whereas those combinations that allow partial enzyme activity (approximately 2–40% of normal activity in skin fibroblasts) typically have LOPD

presentation. GAA mutations result in messenger RNA instability and/or severely truncated acid α-glucosidase or an enzyme with markedly decreased activity. Dysfunction or absence of GAA leads to the accumulation of glycogen in lysosomes and in the cytoplasm in multiple tissues, resulting in the destruction of skeletal, smooth and cardiac muscle. The effect of the enzyme deficiency may extend to vesicle systems that are linked to lysosomes and may also affect receptors, such as glucose transporter 4, that cycle through these organelles. Evidence has also shown a failure of productive autophagy and the progressive accumulation of autophagosomes that disrupt the contractile apparatus in muscle fibers, which correlated with a lack of correction of skeletal muscle during ERT.

[00133] Alpha-glucosidase (GAA) polypeptide is a member of family 31 of glycoside hydrolyases. Human GAA is synthesized as a 110 kDal precursor (Wisselaar et al. (1993) J. Biol. Chem. 268(3): 2223-31). The mature form of the enzyme is a mixture of monomers of 70 and 76 kDal (Wisselaar et al. (1993) J. Biol. Chem. 268(3): 2223-31). The precursor enzyme has seven potential glycosylation sites and four of these are retained in the mature enzyme (Wisselaar et al. (1993) J. Biol. Chem. 268(3): 2223-31). The proteolytic cleavage events which produce the mature enzyme occur in late endosomes or in the lysosome (Wisselaar et al. (1993) J. Biol. Chem. 268(3): 2223-31).

[00134] The rAAV vector genome can encode a GAA polypeptide can include, for example, amino acid residues 40-952 of human GAA, or a smaller portion, such as amino acid residues 40-790.

[00135] The C-terminal 160 amino acids are absent from the mature 70 and 76 kDal GAA polypeptide species. However, certain Pompe alleles resulting in the complete loss of GAA activity map to this region, for example Val949Asp (Becker et al. (1998) J. Hum. Genet. 62:991). The phenotype of this mutant indicates that the C-terminal portion of the protein, although not part of the 70 or 76 kDal species, plays an important role in the function of the protein. It has also been reported that the C-terminal portion of the protein, although cleaved from the rest of the protein during processing, remains associated with the major species (Moreland et al. (Nov. 1, 2004) J. Biol. Chem., Manuscript 404008200). Accordingly, the C-terminal residues could play a direct role in the catalytic activity of the protein, and/or may be involved in promoting proper folding of the N-terminal portions of the protein.

[00136] The native GAA gene encodes a precursor polypeptide which possesses a signal sequence and an adjacent putative trans-membrane domain, a trefoil domain (PFAM PF00088) which is a cysteine-rich domain of about 45 amino acids containing 3 disulfide linkages (Thim (1989) FEBS Lett. 250:85), the domain defined by the mature 70/76 kDal polypeptide, and the C-terminal domain. It has been reported that both the trefoil domain and the C-terminal domain are required for the production of functional GAA, and that it is possible that the C-terminal domain interacts with the trefoil domain during protein folding perhaps facilitating appropriate disulfide bond formation in the trefoil domain.

[00137] In some embodiments of the methods and compositions as disclosed herein, the human GAA protein expressed by the AAV comprises amino acids of SEQ ID NO: 1, or a protein at least 60%, or

70%, or 80%, 85% or 90% or 95%, or 98%, or 99% identical to SEQ ID NO: 1.

[00138] In some embodiments, the hGAA polypeptide comprises a signal peptide (SP). One of ordinary skill in the art can appreciate particular positions of GAA to which a signal peptide (SP) can be fused.

[00139] In some embodiments of the methods and compositions as disclosed herein, the human GAA protein expressed by the AAV comprises amino acids of SEQ ID NO: 1, or fragments or variants thereof, for example a human GAA protein beginning at any of residues selected from: 40,50, 57, 68, 69, 70, 71, 72, 779, 787, 789, 790, 791, 792, 793, or 796 of SEQ ID NO: 1. Accordingly, in one aspect the invention relates to a GAA protein, where the SP is fused to N-terminal amino acid 40, 50, 57, 68, 69, 70, 71, 72, 779, 787, 789, 790, 791, 792, 793, or 796 of human GAA of SEQ ID NO: 1. In some embodiments, the GAA polypeptide expressed by the AAV vector disclosed herein has at least 80%, or at least 85%, or at least 90% or at least 95% sequence identity to amino acid residues selected from: 28-952, 35-952, 40-952, 50-952, 57-952, 60-952, 68-952, 69-952, 70-952, 72-952, 74-952, 779-952, 790-952, 791-952, 792-952, 793-952 and 796-952 of SEQ ID NO: 1, and can further comprise a N-terminal signal peptide, where the signal peptide can be an endogenous GAA signal peptide, or a heterologous signal peptide as disclosed herein.

[00140] In some embodiments of the methods and compositions as disclosed herein, the human GAA protein expressed by the AAV comprises amino acids is a human GAA protein beginning at any of residues selected from: 40, 50, 57, 68, 69, 70, 71, 72, 779, 787, 789, 790, 791, 792, 793, or 796 of SEQ ID NO: 1, or a protein at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% identical thereto.

(i) Modified GAA (modGAA) polypeptides

[00141] In some embodiments, the modified human GAA protein comprises a polypeptide with at least one modification selected from: H199R, R223H, V780I or H201L of SEQ ID NO: 1, or a variant of at least 80%, 90%, 95%, or 99% homology to at least 500, 550, 600, 650, 700, 750, 800, 850, or 900 amino acids of SEQ ID NO: 1 having at least one of these modification. In some embodiments, the modified human GAA protein comprises a polypeptide comprises at least two modifications selected from: H199R, R223H, V780I or H201L of SEQ ID NO: 1, or a variant of at least 80%, 90%, 95%, or 99% homology to at least 500, 550, 600, 650, 700, 750, 800, 850, or 900 concsecutive amino acids of SEQ ID NO: 1 having at least two of these modifications. In some embodiments, the modified human GAA protein comprises a polypeptide with three modifications selected from: H199R, R223H, V780I and H201L of SEQ ID NO: 1 (GAA-H199R-H201L-R223H or GAA-H199R-H201L-V780I), or a variant of at least 80%, 90%, 95%, or 99% homology to at least 500, 550, 600, 650, 700, 750, 800, 850, or 900 concecutive amino acids of SEQ ID NO: 1 having these three modifications.

[00142] One can use these modified GAA polypeptides and fragments thereof. In some embodiments,

the human modified GAA protein expressed by the AAV comprises a GAA polypeptide of SEQ ID NO: 1 as modified above, or a protein at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% identical to SEQ ID NO: 1, or a nucleic acid encoding such a sequence (SEQ ID NO: 3), or a fragment of SEQ ID NO: 1, wherein the fragment begins at any of residues selected from: 40, 50, 57, 68, 69, 70, 71, 72, 779, 787, 789, 790, 791, 792, 793, or 796 of any of SEQ ID NO: 1 (modGAA; H199R, R223H, V780I) or a protein at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% identical to SEQ ID NO: 1, where there is R at amino acid position 199; a H at amino acid position 223; and I at amino acid position 780. Actus 101 (SEQ ID NO: 1), while comprising three point mutations, is considered a wildtype GAA.

[00143] In some embodiments, GAA is modified to add or remove glycosylation sites such as N-linked glycosylation sites, O-linked glycosylation sites or both. In certain embodiments, the addition or removal of glycosylation sites are achieved by N-terminal deletions, C-terminal deletions, internal deletions, random point mutagenesis, or, site directed mutagenesis. In some embodiments, the exemplary GAA modification involve addition of one or more Asparagine (Asn) residue/s or, one or more mutation to yield Asparagine (Asn) residue/s or, deletion of one or more Asparagine (Asn) residue/s. In certain embodiments, all or some of the N-linked, and/or, O-linked glycosylation sites present in GAA are mutated. In some embodiments, GAA modifications will yield information pertaining to the biological activity, physical structure and/or substrate binding potential of GAA.

[00144] In one embodiment, the modified human GAA protein comprises a deletion of the stretch of amino acids between and inclusive of 29-56 of SEQ ID NO: 1. In one embodiment, a modified human GAA protein comprising a deletion of the stretch of amino acids between and inclusive of 29-56 of SEQ ID NO: 1 is no longer maintained within the cell.

[00145] In one embodiment, the modified human GAA protein comprises a polypeptide with at least one modification selected from Table 12. Modifications listed on Table 12 are commonly identified GAA polymorphisms but are not associated with a disease, e.g., Pompe disease.

Table 12. Common GAA polymorphisms.

Position(S)	Amino Acid No	Mutation
CA401359830	2	G>E
CA294886445	3	V>A
CA401359856	4	R>S
CA401359866	5	H>P
CA401359886	6	P>Q
CA401359883	6	P>S
CA401359899	7	P>T
CA8814758	8	C>Y
CA401359938	9	S>C
CA10604542	9	S>P

CA401359943	10	H>Y
CA8814761	11	R>L
CA8814763	12	L>F
CA8814764	12	L>P
CA401360004	14	A>V
CA8814770	16	C>S
CA401360048	17	A>S
CA8814773	17	A>V
CA401360057	18	L>F
CA401360075	19	V>L
CA8814774	19	V>M
CA8814775	20	S>F
CA401360089	20	S>T
CA401360111	22	A>T
CA8814776	22	A>V
CA8814777	23	T>A
CA294886529	24	A>V
CA8814782	25	A>V
CA8814784	27	L>V
CA401360200	28	G>E
CA294886548	28	G>R
CA10604460	28	G>V
CA294886572	29	H>Y
CA401360231	31	L>V
CA8814786	33	H>R
CA8814788	34	D>Y
CA401360282	39	P>L
CA8814790	39	P>S
CA401360310	44	G>D
CA401360312	45	S>A
CA401360316	45	S>C
CA401360317	45	S>F
CA401360314	45	S>P
CA401360321	46	S>F
CA294886602	47	P>S
CA294886615	51	E>G
CA8814796	53	H>N
CA8814797	53	H>R
CA8814799	54	P>L
CA8814798	54	P>T
CA294886644	56	H>L
CA294886642	56	H>N

CA8814800	56	H>Y
CA294886669	58	Q>H
CA8814803	59	G>E
CA8814802	59	G>R
CA401360401	60	A>D
CA401360398	60	A>T
CA401360410	61	S>R
CA401360414	62	R>K
CA401360423	63	P>L
CA294886682	64	G>E
CA401360435	65	P>L
CA401360432	65	P>S
CA8814806	69	Q>*
CA8814807	69	Q>R
CA8814808	70	A>E
CA401360459	70	A>P
CA8814810	71	H>Q
CA294886764	72	P>T
CA8814813	73	G>S
CA401360481	74	R>C
CA8814815	74	R>P
CA8814817	77	A>P
CA401360499	77	A>V
CA8814819	79	P>S
CA401360524	81	Q>H
CA401360526	82	C>R
CA8814823	83	D>V
CA401360542	84	V>G
CA401360539	84	V>L
CA294886928	86	P>H
CA8814830	87	N>H
CA8814831	87	N>T
CA401360560	88	S>G
CA401360566	88	S>R
CA8814834	90	F>L
VAR_004285	91	D>N
CA241285	91	D>S
CA8814836	91	D>Y
CA401360596	93	A>V
CA401360598	94	P>S
CA401360604	95	D>N
CA401360622	97	A>V

CA401360637	99	T>I
CA8814843	100	Q>E
CA401360641	100	Q>K
CA401360648	100	Q>R
CA401360674	102	Q>*
CA401360696	103	C>W
CA8814847	105	A>D
CA8814848	105	A>V
CA401360722	106	R>S
CA294887102	107	G>C
CA401360737	107	G>D
CA401360749	108	C>*
CA401360751	108	C>W
CA294887113	109	C>R
CA8814851	110	Y>H
CA401360782	111	I>F
CA401360786	111	I>M
CA401360791	112	P>A
CA8814852	114	K>R
CA8814853	116	G>V
CA401360860	118	Q>P
CA8814856	121	Q>*
CA401360891	121	Q>P
CA8814858	122	M>R
CA401360915	123	G>R
CA401360930	124	Q>E
CA401360928	124	Q>K
CA401360953	126	W>R
CA401360983	128	F>V
CA8814862	130	P>L
CA8814861	130	P>S
CA401361020	131	P>S
CA401361016	131	P>T
CA401361042	133	Y>N
CA8814865	134	P>S
CA8814866	135	S>R
CA294887228	139	E>K
CA8814871	142	S>R
CA401361288	143	S>C
CA401361271	143	S>P
CA401361370	146	M>I
CA294887253	150	A>G

CA294887248	150	A>T
CA401361468	151	T>A
CA401361469	151	T>S
CA8814876	154	R>C
CA8814877	154	R>H
CA401361552	156	T>P
CA401361565	156	T>S
CA401361581	157	P>S
CA401361593	158	T>P
CA401361619	159	F>L
CA294887341	161	P>H
CA401361638	162	K>R
CA8814880	163	D>V
CA401361651	164	I>F
CA8814883	168	R>L
CA401361673	168	R>P
CA8814882	168	R>W
CA294887359	170	D>G
CA401361709	171	V>L
CA401361738	172	M>I
CA401361729	172	M>K
CA401361724	172	M>V
CA401361746	173	M>L
CA401361748	173	M>V
CA8814886	174	E>D
CA294887367	176	E>K
CA294887368	177	N>T
CA8814892	181	F>L
CA8814894	182	T>M
CA8814927	183	I>M
CA401362038	184	K>R
CA8814928	187	A>G
CA294888081	188	N>D
CA401362102	189	R>K
CA8814929	190	R>C
CA8814930	190	R>L
CA294888098	191	Y>H
CA8814931	191	Y>N
CA401362134	192	E>K
CA401362165	194	P>L
CA401362170	195	L>V
CA401362184	196	E>Q

CA8814936	197	T>N
CA8814937	198	P>L
CA401362214	198	P>R
CA294888175	198	P>T
VAR_004286	199	H>R
CA8814938	200	V>D
CA401362236	200	V>F
CA401362251	201	H>Y
CA8814941	203	R>Q
CA8814942	204	A>T
CA401362293	205	P>A
CA8814944	206	S>C
CA401362303	206	S>P
RCV001175569	208	L>P
CA294888258	209	Y>H
CA8814952	215	E>K
CA401362453	218	F>L
CA8814953	218	F>S
CA401362473	220	V>E
CA401362477	220	V>G
CA401362502	222	V>G
VAR_004287	223	R>H
CA401362510	223	R>P
CA401362504	223	R>S
CA8814959	226	L>P
CA198772	226	L>V
CA401362586	228	G>D
CA8814963	229	R>H
CA401362611	230	V>L
CA401362640	231	L>P
CA8814993	234	T>A
CA8814994	234	T>M
CA8814996	235	T>A
CA401363061	237	A>E
CA401363074	238	P>S
CA401363168	243	D>N
CA401363204	244	Q>H
CA294889597	245	F>V
CA8815005	246	L>F
CA401363297	250	T>I
CA401363390	255	Q>H
CA401363379	255	Q>R

CA8815011	256	Y>C
CA401363423	258	T>I
CA401363464	262	E>A
CA8815018	263	H>R
CA294889693	264	L>F
CA8815020	265	S>R
CA401363512	268	M>I
CA401363510	268	M>I
CA401363521	270	S>G
CA401363525	270	S>N
CA401363558	272	S>R
CA8815021	273	W>*
CA8815022	274	T>I
CA401363599	276	I>F
RCV001090258	276	I>V
CA401363615	277	T>I
CA401363644	279	W>C
CA8815026	281	R>Q
CA401363673	282	D>N
CA8815027	284	A>T
CA8815030	285	P>L
CA8815032	286	T>M
CA401363807	287	P>L
CA8815071	287	P>S
CA401363883	293	G>V
CA8815081	295	H>N
CA401363965	300	A>E
CA294889969	300	A>V
CA8815087	305	G>R
CA401364038	306	S>A
VAR_068586	310	V>G
CA294891320	310	V>L
CA401364194	311	F>L
CA8815093	312	L>M
CA294891343	315	S>N
CA401364267	317	A>V
CA10606846	318	M>L
CA294891694	320	V>M
CA401364384	321	V>A
CA294891725	321	V>I
CA8815118	324	P>Q
CA8815120	324	P>R

CA294891758	325	S>N
CA401364455	327	A>G
CA8815125	332	S>L
CA10604927	334	G>C
CA294891791	336	I>M
CA8815127	336	I>N
CA294891797	338	D>G
CA401364575	338	D>Y
CA8815129	340	Y>C
CA8815130	341	I>V
CA401364670	346	E>Q
CA401364694	347	P>H
CA8815131	348	K>R
CA401364711	349	S>R
CA294891876	352	Q>*
CA401364773	353	Q>H
CA8815135	353	Q>R
CA401364783	354	Y>S
CA198782	357	V>F
CA8815138	357	V>I
CA401364892	360	Y>S
CA294892083	361	P>S
CA8815165	363	M>R
RCV001194238	363	M>V
CA8815166	364	P>L
CA401364935	364	P>S
CA8815168	365	P>S
CA8815169	366	Y>H
CA294892167	368	G>C
CA8815170	368	G>S
CA8815171	368	G>V
CA401364969	370	G>D
CA401364981	372	H>D
CA401364985	372	H>Q
CA401364995	374	C>Y
CA401365013	377	G>C
CA294892229	378	Y>C
CA294892234	379	S>F
CA294892232	379	S>Y
CA401365044	382	A>G
CA401365057	384	T>I
CA401365055	384	T>N

CA8815184	385	R>H
CA401365065	386	Q>R
CA401365070	387	V>M
CA401365075	388	V>L
CA8815187	388	V>M
CA8815188	389	E>K
CA8815191	391	M>T
VAR_068593	391	M>V
CA294892303	394	A>T
CA8815193	395	H>L
CA8815195	396	F>L
CA8815194	396	F>V
CA8815196	397	P>R
CA8815198	398	L>M
CA401365163	400	V>A
CA401365192	404	D>G
CA10604928	404	D>V
CA8815235	407	Y>C
CA234047	407	Y>H
CA8815237	408	M>L
CA401365214	408	M>L
CA8815241	411	R>Q
CA401365237	412	R>G
CA294892536	412	R>K
CA401365241	412	R>S
CA294892544	415	T>M
CA401365278	417	N>K
CA401365292	419	D>G
CA401365297	420	G>D
CA294892550	420	G>S
CA401365310	422	R>L
CA8815245	422	R>Q
CA401365311	423	D>N
CA8815247	425	P>Q
CA401365327	425	P>T
CA401365338	427	M>V
CA401365382	433	Q>L
CA8815254	435	G>S
CA401365395	435	G>V
CA8815256	436	R>Q
CA294892655	438	Y>S
CA294892670	439	M>I

CA294892660	439	M>V
CA8815259	440	M>T
CA8815287	444	P>S
CA8815289	446	I>L
CA8815292	449	S>L
CA401366333	451	P>S
CA8815295	452	A>S
CA401366343	452	A>T
CA401366358	453	G>W
VAR_068597	458	Y>C
CA8815299	459	D>E
CA294894004	460	E>D
CA401366468	461	G>D
CA401366459	461	G>S
CA8815302	464	R>K
CA401366495	464	R>S
CA401366490	464	R>T
CA401366504	465	G>E
CA401366496	465	G>R
CA401366499	465	G>W
CA8815305	466	V>D
CA401366513	466	V>G
CA8815304	466	V>I
CA401366562	470	N>S
CA8815311	471	E>K
CA401366585	472	T>P
CA401366591	472	T>S
CA401366597	473	G>C
CA401366599	473	G>D
CA294894092	473	G>R
CA294894100	474	Q>L
CA8815314	475	P>L
CA401366647	477	I>M
CA294894127	478	G>V
CA401366662	479	K>E
CA401366767	480	V>A
CA401366766	480	V>E
CA8815347	480	V>I
CA401366761	480	V>L
CA401366772	481	W>R
CA401366810	484	S>A
CA401366817	484	S>C

CA401366822	485	T>A
CA401366836	486	A>S
CA8815351	488	P>A
CA401366926	493	P>S
CA401366956	495	A>V
CA198789	499	W>R
CA401367013	500	E>K
CA401367049	502	M>R
CA401367077	505	E>A
CA401367089	506	F>L
CA401367111	509	Q>L
CA294894901	510	V>G
CA294894906	511	P>L
CA401367148	515	M>T
CA8815364	517	I>V
CA401367191	519	M>I
CA401367186	519	M>V
CA401367197	520	N>S
CA401367224	524	N>K
CA401367222	524	N>S
CA239454	528	G>A
CA401367268	531	D>N
CA294895023	532	G>C
CA294895032	534	P>L
CA401367292	534	P>R
CA401367299	535	N>K
CA401367297	535	N>S
CA401367352	542	P>L
CA8815393	542	P>S
CA401367345	542	P>T
CA401367360	543	Y>C
CA915952253	544	V>M
CA10606111	546	G>V
CA8815423	547	V>M
CA401368749	548	V>A
CA8815424	548	V>G
CA8815426	549	G>W
CA294895748	550	G>W
CA8815428	552	L>I
CA401368824	553	Q>K
CA8815430	553	Q>R
CA401368854	554	A>P

CA401368920	557	I>S
CA401368917	557	I>T
CA8815434	560	S>F
CA401368990	562	H>Q
CA401368994	563	Q>R
CA294895795	567	T>P
CA8815436	569	Y>H
CA401369039	570	N>Y
CA10604317	571	L>P
CA401369052	572	H>P
CA8815438	572	H>Q
CA401369065	573	N>K
CA401369071	574	L>F
CA401369090	575	Y>F
VAR_004300	576	G>S
CA401369106	577	L>P
CA401369103	577	L>V
CA294895849	579	E>Q
CA294895855	580	A>V
CA8815443	581	I>L
CA8815444	581	I>M
CA294895864	582	A>P
CA8815447	584	H>D
CA401369180	584	H>P
CA401369182	584	H>R
VAR_068611	585	R>K
CA294896266	586	A>S
CA8815471	588	V>M
CA8815474	592	G>E
CA401369334	592	G>R
CA8815475	593	T>I
CA401369359	594	R>C
CA401369395	597	V>A
CA294896305	598	I>V
CA401369410	599	S>P
CA401369427	600	R>P
CA401369447	602	T>N
CA8815485	602	T>S
CA401369491	606	H>P
CA294896378	606	H>Q
CA401369512	608	R>G
CA294896401	608	R>L

CA401369519	608	R>P
CA401369524	609	Y>D
CA8815490	609	Y>H
CA401369553	611	G>S
CA401369560	612	H>P
CA8815494	612	H>R
CA401369582	613	W>C
CA401369573	613	W>R
CA401369617	616	D>E
CA294896447	616	D>N
CA401369624	617	V>A
CA294896458	617	V>L
CA401369636	618	W>G
CA401369676	621	W>R
CA401369689	622	E>K
CA401369691	622	E>Q
CA8815502	624	L>F
CA401369722	624	L>V
CA8815504	625	A>T
CA294896504	627	S>F
CA8815506	628	V>L
VAR_068621	629	P>L
CA294896534	629	P>S
CA294896808	630	E>A
CA401369839	633	Q>E
CA401369857	635	N>S
CA401369862	636	L>V
CA8815544	637	L>M
CA401369872	638	G>E
CA401369870	638	G>R
CA401369877	639	V>L
CA401369894	642	V>I
CA294896832	643	G>W
CA10605478	644	A>P
CA8815550	644	A>V
CA8815553	646	V>I
CA401369920	647	C>F
CA401369926	648	G>V
CA294896886	651	G>D
CA401369943	651	G>V
CA8815556	653	T>A
CA8815557	653	T>N

CA401370002	661	W>R
CA401370022	663	Q>H
CA401370023	663	Q>H
CA401370024	664	L>V
CA401370036	666	A>P
CA294896940	666	A>V
CA401370051	668	Y>C
CA401370050	668	Y>S
CA401370056	669	P>A
CA8815563	669	P>R
CA401370055	669	P>S
CA8815562	669	P>T
CA401370068	671	M>L
CA220392	671	M>R
CA8815565	671	M>T
CA8815564	671	M>V
CA401370079	673	N>T
CA401370094	674	H>Y
CA401370115	675	N>D
CA401370120	675	N>S
CA8815567	675	N>T
CA401370175	679	S>R
CA401370294	682	Q>K
CA401370340	684	P>R
CA915952255	686	S>K
CA401370371	686	S>N
CA401370406	688	S>N
CA8815603	688	S>R
CA8815604	688	S>R
CA8815605	689	E>G
VAR_004309	689	E>K
CA401370419	689	E>Q
CA401370430	690	P>R
CA401370433	691	A>S
CA8815608	693	Q>R
CA294897317	698	A>D
CA401370485	698	A>V
CA401370488	699	L>F
CA401370489	699	L>P
CA294897331	700	T>A
CA294897382	703	Y>C
CA401370512	704	A>S

CA401370525	706	L>F
CA401370528	706	L>P
CA294897393	707	P>L
CA8815618	708	H>L
CA8815615	708	H>N
CA401370556	711	T>I
CA401370559	712	L>Q
CA8815622	713	F>L
CA294897442	714	H>R
CA401370585	716	A>P
CA401370586	716	A>S
CA8815630	719	A>V
CA8815631	720	G>E
CA401370625	723	V>G
CA8815635	723	V>M
CA401370630	724	A>D
CA401370627	724	A>T
CA401370639	726	P>L
CA401370648	728	F>I
CA401370659	729	L>P
CA401324684	732	P>S
CA8815654	732	P>T
CA8815655	733	K>R
CA401324707	735	S>F
CA401324703	735	S>T
CA401324719	737	T>I
CA294856435	740	V>L
CA10607034	741	D>V
CA401324761	744	L>P
CA401324773	747	G>E
CA8815667	747	G>R
CA294856500	747	G>W
CA401324808	753	T>A
CA294856528	753	T>I
CA8815670	753	T>N
CA401324824	756	L>F
CA8815672	757	Q>P
CA401324830	757	Q>R
CA8815675	761	A>G
CA401324880	765	G>D
CA294856634	766	Y>N
CA8815680	766	Y>S

CA294856691	771	T>I
CA294856710	774	D>E
CA401324934	774	D>H
CA8815713	778	V>L
CA401324975	779	P>Q
VAR_004313	780	V>I
CA401324977	780	V>L
CA8815715	780	V>L
CA294857110	781	E>K
CA294857130	782	A>V
CA8815716	783	L>F
CA401325035	789	P>L
CA294857155	789	P>Q
CA8815719	789	P>R
CA294857158	790	P>S
CA8815720	791	A>S
CA8815721	791	A>V
CA294857164	794	R>C
CA234052	794	R>G
CA10606072	795	E>K
CA8815725	798	I>V
CA401325138	806	T>A
CA8815733	806	T>P
CA401325151	807	L>P
CA401325165	809	A>P
CA8815740	810	P>L
CA8815739	810	P>S
CA401325221	814	I>T
CA401325227	815	N>D
VAR_004314	816	V>I
CA401325283	817	H>R
CA8815749	823	I>L
CA401325517	823	I>V
CA10604584	825	P>R
RCV001091539	827	Q>*
CA401325545	827	Q>R
CA294857876	828	G>S
CA8815773	829	P>L
CA401325955	830	G>R
CA401325967	831	L>F
CA8815775	833	T>I
CA401325992	834	T>A

CA294857899	836	S>P
CA401326041	839	Q>*
CA294857971	840	P>A
CA401326065	841	M>I
CA294857973	841	M>T
CA8815780	844	A>D
CA401326085	844	A>T
CA401326104	846	A>T
CA401326131	848	T>I
CA8815784	851	G>A
CA8815786	851	G>E
CA8815785	851	G>V
CA8815788	854	R>Q
CA401326195	855	G>R
CA401326193	855	G>R
CA401326213	857	L>M
CA294858045	864	S>N
CA401326319	866	E>A
CA401326321	866	E>D
CA401326364	871	G>E
CA401326408	875	Q>R
CA401326462	879	L>P
CA8815798	879	L>V
CA294858091	880	A>S
CA294858106	880	A>V
CA8815799	881	R>G
CA401326485	881	R>S
CA8815825	884	T>M
CA8815828	886	V>M
CA8815832	891	R>C
CA8815833	891	R>H
CA401326709	892	V>L
CA8815834	892	V>M
CA8815835	897	A>G
CA401326806	897	A>T
CA401326843	898	G>D
CA8815836	901	L>M
CA401326934	903	K>E
CA401326957	904	V>M
CA401326986	906	V>G
RCV001091541	906	V>I
CA401326996	907	L>P

CA8815841	912	A>V
CA401327122	914	Q>P
CA8815849	918	S>C
CA401327196	919	N>H
CA401327211	919	N>S
CA401327260	922	P>L
VAR_004317	927	T>I
CA401327420	930	P>T
CA401327438	931	D>G
CA8815884	935	L>V
CA8815885	937	I>V
CA401327760	940	S>L
CA8815888	943	M>T
CA401327939	947	F>L
CA198803	949	V>I
CA8815891	950	S>N
CA401328038	952	C>G

(ii) Nucleotide sequences: N-terminal GAA polypeptide truncations and nucleic acid sequences encoding GAA polypeptides and N-terminal truncations, with endogenous or heterologous signal peptides.

[00146] As disclosed herein, the nucleic acids encoding a GAA protein disclosed herein, e.g., SEQ ID NOS: 1-18 that are codon optimized GAA nucleic acid sequence, for example, which have been modified from the NCBI GAA sequence of NM_00152.5 to include, any one or more of (i) enhanced expression *in vivo*, (ii) reduce CpG islands or reduction or elimination of CG dinucleotides, (iii) to reduce the innate immune response, and (iv) to reduce or eliminate alternative reading frames (ARF), or open reading frames (ORF). Exemplary codon optimized GAA nucleic sequences encompassed for use in the methods and rAAV compositions as disclosed herein can be selected from any of: SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 or SEQ ID NO: 18 as disclosed herein, or a nucleic acid sequence having at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% sequence identity to SEQ ID NOS: 1-18, where SEQ ID NO: 1-18 or variants of at least 80% sequence identity thereto encode GAA polypeptide, where amino acid at position 199 is R (199R); amino acid at position 233 is H (233H), and amino acid at position 780 is I (780I).

[00147] In some embodiments, codon optimized GAA nucleic sequences encompassed for use in the methods and rAAV compositions as disclosed herein can be selected from any of: SEQ ID NO: 3 or SEQ ID NO: 4, or a nucleic acid sequence having at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 3 or SEQ ID NO: 4.

[00148] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence encoding a signal peptide (SP) fused in frame to the 5′ terminus of a GAA nucleic acid sequence that encodes a GAA polypeptide or N-terminal truncated GAA polypeptide, as disclosed herein. For example, heterologous nucleic acid sequence encoding a signal peptide (SP) is fused in frame to the 5′ terminus of a GAA nucleic acid sequence that encodes the GAA polypeptide or N-terminal truncated GAA polypeptide, so that both polypeptides are expressed from the rAAV genome when the rAAV vector transduces a mammalian cell.

[00149] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence comprising SEQ ID NO: 3, or a portion of SEQ ID NO: 3, where expression of a portion of the nucleic acid of SEQ ID NO: 3 produces a functional hGAA protein, and where the functional hGAA protein can comprise a N-terminal deletion of SEQ ID NO: 1, or a N-terminal and C-terminal truncation of SEQ ID NO: 1 as disclosed herein.

[00150] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence comprising SEQ ID NO: 3, or a nucleotides 82-2859 of SEQ ID NO: 3 or a nucleic acid having at least 85% sequence identity thereto, where nucleotides 1-81 of SEQ ID NO: 3 (corresponding to SEQ ID NO: 53) which encodes for a codon optimized hGAA signal peptide are replaced with the nucleic acid encoding a heterologous signal peptide as disclosed herein, e.g., selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto.

[00151] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that comprises one or more base pair deletions at the 5' of SEQ ID NO: 3.

[00152] For example, in some embodiments, the heterologous nucleic acid sequence in the AAV genome can comprise nucleotides selected from any of: 82-2859 of SEQ ID NO: 3, 82-2859bp of SEQ ID NO: 3, 103-2859bp of SEQ ID NO: 3, 118-2859 of SEQ ID NO: 3, 148-2859bp of SEQ ID NO: 3, 169-2859bp of SEQ ID NO: 3, 199-2859bp of SEQ ID NO: 3, 205-2859bp of SEQ ID NO: 3, 208-2859bp of SEQ ID NO: 3, 214-2859bp of SEQ ID NO: 3, 220-2859bp of SEQ ID NO: 3, 265-2859bp of SEQ ID NO: 3, 2335-2859bp of SEQ ID NO: 3, 2368-2859bp of SEQ ID NO: 3, 2371-2859bp of SEQ ID NO: 3, 2374-2859bp of SEQ ID NO: 3, 2377-2859bp of SEQ ID NO: 3, 2386-2859bp of SEQ ID NO: 3 or a nucleic acid having at least 85% sequence identity thereto, and attached to the 5' of said sequence, nucleotides 1-81 (corresponding to SEQ ID NO: 53 or nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto) of SEQ ID NO: 3, which

encodes for a codon optimized hGAA signal peptide.

[00153] In an alternative embodiment, the heterologous nucleic acid sequence in the AAV genome can comprise nucleotides selected from any of: 82-2859 of SEQ ID NO: 3, 82-2859bp of SEQ ID NO: 3, 103-2859bp of SEQ ID NO: 3, 118-2859 of SEQ ID NO: 3, 148-2859bp of SEQ ID NO: 3, 169-2859bp of SEQ ID NO: 3, 199-2859bp of SEQ ID NO: 3, 205-2859bp of SEQ ID NO: 3, 208-2859bp of SEQ ID NO: 3, 214-2859bp of SEQ ID NO: 3, 220-2859bp of SEQ ID NO: 3, 265-2859bp of SEQ ID NO: 3, 2335-2859bp of SEQ ID NO: 3, 2368-2859bp of SEQ ID NO: 3, 2371-2859bp of SEQ ID NO: 3, 2374-2859bp of SEQ ID NO: 3, 2377-2859bp of SEQ ID NO: 3, 2386-2859bp of SEQ ID NO: 3 or a nucleic acid having at least 85% sequence identity thereto, where nucleotides 1-81 (corresponding to SEQ ID NO: 53) of SEQ ID NO: 3, which encodes for a codon optimized hGAA signal peptide, are replaced with the nucleic acid encoding a heterologous signal peptide as disclosed herein, e.g., selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto.

[00154] The truncated GAA can be wildtype or codon optimized. For example, exemplary 5' deletions of SEQ ID NO: 3 are disclosed in Table 1 herein, which encode for N-terminal truncated GAA polypeptide. In some embodiments, the 5' of the 5' deletions of SEQ ID NO: 3 can be attached to the 3' of a nucleic acid encoding a signal peptide as disclosed herein, e.g., any signal peptide selected from any of SEQ ID NOS: 53-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto.

[00155] Table 1: Table of exemplary N-terminal truncations of GAA polypeptide of SEQ ID NO: 1, and the 5' deletions of nucleic acid sequence of SEQ ID NO: 3.

N-terminal GAA truncation	**Corresponding amino acid residues of SEQ ID NO: 1**	**Corresponding nucleotides of coGAA nucleic acid of SEQ ID NO: 3 (Seq100)**
Signal peptide (which can be removed and replaced with a heterologous signal peptide as disclosed herein)	residues 1-27 of SEQ ID NO: 1 MGVRHPPCSHRLLAVCALVSL ATAALL (SEQ ID NO: 59)	Nucleotides 1-81 of SEQ ID NO: 3 ATGGGGGTGAGGCACCCTCC(TGTTCTCACAGGCTGCTGGCT GTGTGTGCTCTGGTGTCTCTG(CCACTGCTGCCCTGCTG (SEQ ID NO: 53)
hGAA polypeptide starting at residue 28 (removal of GAA signal peptide)	residues 28-952 of SEQ ID NO: 1	82-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 35 (Δ1-34 of SEQ ID NO:1)	residues 35-952 of SEQ ID NO: 1	103-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 40 (Δ1-39 of SEQ ID NO:1)	residues 40-952 of SEQ ID NO: 1	118-2859 of SEQ ID NO: 3

hGAA polypeptide starting at residue 50 (Δ1-49 of SEQ ID NO:1)	residues 50-952 of SEQ ID NO: 1	148-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 57 (Δ1-56 of SEQ ID NO:1)	residues 57-952 of SEQ ID NO: 1	169-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 68 (Δ1-67 of SEQ ID NO:1)	residues 68-952 of SEQ ID NO: 1	199-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 69 (Δ1-68 of SEQ ID NO:1)	residues 69-952 of SEQ ID NO: 1	205-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 70(Δ1-69 of SEQ ID NO:1)	residues 70-952 of SEQ ID NO: 1	208-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 72 (Δ1-71 of SEQ ID NO:1)	residues 72-952 of SEQ ID NO: 1	214-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 74 (Δ1-73 of SEQ ID NO:1)	residues 74-952 of SEQ ID NO: 1	220-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 89 (Δ1-88 of SEQ ID NO:1)	residues 89-952 of SEQ ID NO: 1	265-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 779 (Δ1-778 of SEQ ID NO:1)	residues 779-952 of SEQ ID NO: 1	2335-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 790 (Δ1-789 of SEQ ID NO:1)	residues 790-952 of SEQ ID NO: 1	2368-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 791 (Δ1-790 of SEQ ID NO:1)	residues 791-952 of SEQ ID NO: 1	2371-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 792 (Δ1-791 of SEQ ID NO:1)	residues 792-952 of SEQ ID NO: 1	2374-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 793 (Δ1-792 of SEQ ID NO:1 of SEQ ID NO:1)	residues 793-952 of SEQ ID NO: 1	2377-2859bp of SEQ ID NO: 3
hGAA polypeptide starting at residue 796 (Δ1-795 of SEQ ID NO:1)	residues 796-952 of SEQ ID NO: 1	2386-2859bp of SEQ ID NO: 3

[00156] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that comprises nucleotides 103-2859 of SEQ ID NO: 3, where attached to the 5' of said sequence, there is nucleic acid encoding a wildtype or codon optimized hGAA signal peptide (i.e., a nucleic acid comprising SEQ ID NO: 53), or fragment thereof, or a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein, e.g., a nucleic acid sequence selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least

98%, or at least 99% sequence identity thereto.

[00157] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that comprises nucleotides 118-2859 of SEQ ID NO: 3, where attached to the 5' of said sequence, there is nucleic acid encoding a wildtype or codon optimized hGAA signal peptide (i.e., a nucleic acid comprising SEQ ID NO: 53) or a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein, e.g., a nucleic acid sequence selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto.

[00158] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that comprises nucleotides 148-2859 of SEQ ID NO: 3, where attached to the 5' of said sequence, there is nucleic acid encoding a wildtype or codon optimized hGAA signal peptide (i.e., a nucleic acid comprising SEQ ID NO: 53) or a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein, e.g., a nucleic acid sequence selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto.

[00159] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that comprises nucleotides 169-2859 of SEQ ID NO: 3, attached to the 5' of said sequence, there is nucleic acid encoding, e.g., a codon optimized hGAA signal peptide (i.e., a nucleic acid comprising SEQ ID NO: 53) or a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein, e.g., a nucleic acid sequence selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto.

[00160] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that comprises nucleotides 199-2859 of SEQ ID NO: 3, where attached to the 5' of said sequence, there is nucleic acid encoding a wildtype or codon optimized hGAA signal peptide (i.e., a nucleic acid comprising SEQ ID NO: 53), or fragement thereof and/or a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein, e.g., a nucleic acid sequence selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto.

[00161] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that comprises nucleotides 205-2859 or nucleotides 208-2859, or nucleotides 214-2859 of SEQ ID NO: 3, where attached to the 5' of said sequence, there is nucleic acid encoding a wild-type or codon optimized hGAA signal peptide (i.e., a

nucleic acid comprising SEQ ID NO: 53) and/or a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein, e.g., a nucleic acid sequence selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto.

[00162] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that comprises nucleotides 220-2859 or nucleotides 208-2859, or nucleotides 214-2859 of SEQ ID NO: 3, where attached to the 5' of said sequence, there is nucleic acid encoding a wild-type or codon optimized hGAA signal peptide (i.e., a nucleic acid comprising SEQ ID NO: 53) and/or a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein, e.g., a nucleic acid sequence selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto.

[00163] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that comprises any of: nucleotides 265-2859 of SEQ ID NO: 3, or nucleotides 2335-2859 of SEQ ID NO: 3, or nucleotides 2368-2859 of SEQ ID NO: 3, or nucleotides 2371-2859bp of SEQ ID NO: 3, where attached to the 5' of said sequence, there is nucleic acid encoding a wildtype or codon optimized hGAA signal peptide (i.e., a nucleic acid comprising SEQ ID NO: 53), or fragment thereof, and/or a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein, e.g., a nucleic acid sequence selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity thereto.

[00164] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that encodes a signal sequence as disclosed herein, and a GAA polypeptide or a N-terminal truncated GAA polypeptide, where the GAA polypeptide begins at amino acid residues selected from any of: 28, 35, 40, 50, 57, 57, 68, 69, 70, 72, 74, 89, 779, 790, 791, 792, 793 or 796, and optionally, where the GAA polypeptide also has a C-terminal deletion of at least about 10, or about 20, or about 30, or about 40, or about 50, or about 60, or about 70, or about 80, or about 90, or about 100, or about 110, or more than 110 amino acid residues from the C-terminus of SEQ ID NO: 1. In some embodiment, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that encodes a signal sequence as disclosed herein, and a GAA polypeptide or a N-terminal truncated GAA polypeptide, where the GAA polypeptide begins at amino acid residues selected from any of: 28, 35, 40, 50, 57, 57, 68, 69, 70, 72, 74, 89, 779, 790, 791, 792, 793 or 796, and where the C-terminal of the GAA polypeptide occurs at any residue after amino acid residue 500, 600, 700, 800, 842, 852, 862, 875, 885, 895, 900, 905, 915, 920, 925, 930, 935, 940, 945, 950, 951 of SEQ ID NO. 1.

[00165] In some embodiments, the rAAV genome useful in the methods to treat Pompe Disease as disclosed herein comprises a heterologous nucleic acid sequence that (i) encodes a wildtype or codon

optimized hGAA signal peptide (i.e., a nucleic acid comprising SEQ ID NO: 53), or fragment thereof and/or a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein, e.g., a nucleic acid sequence selected from any of SEQ ID NOS: 54-58, 67, 72 or 75, or a nucleotide sequence having at least 85%, or at least 90%, or at least 95%, or at least 97%, or at least 98%, or at least 99% sequence identity to SEQ ID NOS 53-58, 67, 72 or 65, and (ii) encodes a GAA polypeptide, the GAA polypeptide encoded by a nucleic acid sequence beginning at base pairs selected from any of: 82, 103, 118, 148, 169, 199, 205, 208, 214, 220, 265 of SEQ ID NO: 3, and ending at base pair selected from any of: 2553 (i.e., deletion of 100 C-terimal residues, ends at 851aa), 2583 (i.e., deletion of 90 C-terimal residues, ends at 861aa), 2613 (i.e., deletion of 80 C-terimal residues, ends at 871aa), 2643 (i.e., deletion of 70 C-terimal residues, ends at 871aa), 2673 (i.e., deletion of 60 C-terimal residues, ends at 881aa), 2703 (i.e., deletion of 50 C-terimal residues, ends at 891aa), 2733 (i.e., deletion of 40 C-terimal residues, ends at 901aa), 2763 (i.e., deletion of 30 C-terimal residues, ends at 911aa), 2823 (i.e., deletion of 20 C-terimal residues, ends at 921aa), 2775 (i.e., deletion of 27 C-terimal residues, ends at 925aa), 2826 (i.e., deletion of 10 C-terimal residues, ends at 942aa) of SEQ ID NO: 3, or ending anywhere between base pairs 2553- 2859 of SEQ ID NO: 3.

B. Signal Peptide (SP)

[00166] The native GAA signal peptide is not cleaved in the ER thereby causing native GAA polypeptide to be membrane bound in the ER (Tsuji et al. (1987) Biochem. Int. 15(5):945-952). Disruption of the membrane association of GAA can be accomplished by replacing the endogenous GAA signal peptide (and optionally adjacent sequences) with an alternate signal peptide for GAA.

[00167] Accordingly, in representative embodiments, the rAAV vector and rAAV genome useful in the methods to treat Pompe disease as disclosed herein further comprises a heterologous nucleic acid encoding a GAA polypeptide to be transferred to a target cell, attached to a heterologous nucleic acid sequence that encodes a heterologus signal peptide in the place of the endogenous GAA signal peptide. The heterologous nucleic acid encoding a GAA polypetide, including N-terminal truncations of the GAA polypeptide, which is is operatively associated with the segment encoding the secretory signal peptide, such that upon transcription and translation a fusion polypeptide is produced containing the secretory signal sequence operably associated with (e.g., directing the secretion of) the GAA polypeptide or N-terminal truncated GAA polypeptide.

[00168] In some embodiments, the endogenous signal peptide of hGAA (i.e., amino acids 1-27 of SEQ ID NO: 1 (encoded by a codon optimized nucleic acid sequence corresponding to SEQ ID NO: 59)) is replaced with a heterologous signal peptide (also referred to herein as a "signal sequence" or "leader sequence") of SEQ ID NO: 60 (201 IgG signal peptide), or an IL2 wild type signal peptide (SEQ ID NO: 61), modified IL2 signal peptide (SEQ ID NO: 62), A2M signal peptide (SEQ ID NO: 63), or PZP signal peptide (SEQ ID NO: 64), or artificial signal peptide (SEQ ID NO: 65), or cathpetsin L signal peptide (SEQ ID NO: 66) or signal peptides at least 90% sequence identity to SEQ

ID NOS: 60-66.

[00169] In some embodiments, the AAV vector encodes a GAA polypeptide that comprises the endogenous GAA signal peptide (e.g., amino acids 1-27 of SEQ ID NO: 1 (also referred to as "innate GAA" or "cognate GAA" signal peptide). In some embodiments, the AAV vector encodes a GAA polypeptide that comprises the endogenous GAA signal peptide (e.g., amino acids 1-27 of SEQ ID NO: 1, or a portions thereof) and an additional heterologous (i.e., non native) signal sequence. In some embodiments, the GAA polypeptide or N-terminal GAA polypeptide disclosed herein that lacks the endogenous signal peptide of amino acids 1-27 of GAA of SEQ ID NO: 1 is fused to a heterolous signal peptide (also referred to as "secretory signal peptide").

[00170] In a particular embodiment, the heterologous nucleic acid sequence encodes a GAA polypeptide comprising a signal peptide fused to the GAA polypeptide, wherein the signal peptide is a heterologous GAA polypeptide. In some embodiments, the heterologous nucleic acid encoding a GAA polypeptide fused to a heterologous (e.g., exogenous or non-GAA) signal peptide can further comprise, at the 5' end, a nucleic acid sequence encoding a portion of the cognate (e.g., endogenous) GAA signal peptide, e.g., encoding at least 1-5, or at least 1-10, or at least 1-20, or at least about 1-23, or at least about 1-24, or at least about 1-25, or at least about 1-26, or the entire GAA signal peptide, e.g., or at least about 1-27 concecutive amino acids of the endogenous GAA signal peptide. Stated differently, in some embodiments, the heterologous nucleic acid sequence can comprise, in the 5' to 3' direction, a nucleic acid sequence encoding the entire GAA signal peptide of SEQ ID NO: 59 or a portion of the endogenous GAA signal peptide of SEQ ID NO: 59, a nucleic acid sequence encoding a heterologous signal peptide (e.g., non-GAA signal peptide) and a a nucleic acid sequence encoding a GAA polypeptide, sich as the wild-type nucleic acid sequences, or a sequence encoding at least 1-3 amino acid variants, or a codon-optimized nucleic acid sequence encoding a GAA polypeptide, including N-terminal GAA truncations. For example, in some embodiments, the nucleic acid sequence encoding the GAA polypeptide encodes a N-terminal truncated GAA polypeptide, such as those disclosed in Table 1 herein.

[00171] In some embodiments, the order of the signal peptides are changed, for example, in some embodiments, the heterologous nucleic acid sequence can comprise, in the 5' to 3' direction, a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein, the entire GAA signal peptide of SEQ ID NO: 59 or a portion of the endogenous GAA signal peptide of SEQ ID NO: 59 and a wildtype or codon-optimized nucleic acid sequence encoding a GAA polypeptide, including N-terminal GAA truncations.

[00172] In some embodiments, there can be a portion of the GAA polypeptide, e.g., any 1 amino acid, or 2 amino acids or more than 2 concecutive amino acids located in the region of amino acids 28-56 of SEQ ID NO: 1) located between the GAA signal peptide (or portion thereof), and the heterologous signal peptide and upstream (e.g., N-terminal) of a N-terminal truncated GAA polypeptide. For example, and without wishing to be bound by theory, in some embodiments, the heterologous nucleic

acid sequence can comprise, in the 5' to 3' direction, (i) the entire full length GAA signal peptide or a portion thereof as disclosed herein, (ii) a portion of at the the GAA polypeptide, e.g., amino acids 28-35 of SEQ ID NO: 1, amino acid 28 of SEQ ID NO: 1, or amino acids 28-31 of SEQ ID NO: 1, (iii) a heterologous signal peptide, and (iv) a GAA polypeptide, e.g., a N-terminal truncated GAA polypeptide beginning at amino acid 57 of SEQ ID NO: 1. It is envisioned that the portion of at the the GAA polypeptide located between the GAA polypeptide and the heterologous signal peptide can be any length, e.g., at least 1, 2, 3, 4,5 ,6, 7, 8, 9, 10, 10-12, 12,-14, 14,-16, 16-18, 18-20, or more than 20 amino acids of residues 28-56 of SEQ ID NO: 1, and the N-terminal GAA polypetide does not need to start at the next or sequential amino acid of the earlier GAA polypeptide portion. Certain of the amino acids in this 28-56 amino acid region can cause cellular retention. In one embodiment, those amino acids are removed or replaced.

[00173] In some embodiments, the nucleic acid sequence that encodes a GAA-signal peptide encodes at least 1-5, or at least 1-10, or at least 1-20, or at least about 1-23, or at least about 1-24, or at least about 1-25, or at least about 1-26, or at least about 1-27 concecutive amino acids (i.e., the full GAA signal peptide sequence), or non-concecutive amino acids of the endogenous GAA signal peptide of SEQ ID NO: 59. In some embodiments, the nucleic acid sequence encoding a GAA-signal peptide encodes a GAA signal peptide that comprises at least one deletion of at least 1, or at least 2, or at least 3, or at least 4, or at least 5, or at least 6, or at least 7, or at least 8, or at least 9, or at least 10, or at least 11, or at least 12, or at least 13, or at least 14, or at least 15, or at least 16, or at least 17, or at least 18, or at least 19, or at least 20 amino acids of SEQ ID NO: 59, where the one or more deletions can be concecutive, or non-concecutive deletions.

[00174] In some embodiments, the nucleic acid sequence that encodes a GAA-signal peptide can comprise the entire nucleic acid of SEQ ID NO: 57 (encoding GAA signal peptide comprising amino acids 1-27 of SEQ ID NO: 59). In alternative embodiments, the nucleic acid sequence that encodes a GAA-signal peptide can comprise a portion of the nucleic acid sequence of SEQ ID NO: 53, e.g., portions of SEQ ID NO: 53 that are selected from concecutive bases of SEQ ID NO: 53 having the length of any of: 1-3bp, 1-4bp, 1-5bp, 1-6bp, 1-7bp, 1-8bp, 1-9bp, 1-10bp, 1-11bp, 1-12bp, 1-13bp, 1-14bp, 1-15bp, 1-16bp, 1-17bp, 1-18bp, 1-19bp, 1-20bp, 1-21bp, 1-22bp, 1-23bp, 1-24bp, 1-25bp, 1-26bp, 1-27bp, 1-28bp, 1-29bp, 1-30bp, 1-33bp, 1-36bp, 1-39bp, 1-42bp, 1-45bp, 1-48bp, 1-51bp, 1-54bp, 1-57bp, 1-60bp, 1-63bp, 1-66bp, 1-69bp, 1-72b, 1-75bp and 1-78bp in any region of the nucleic acid sequence of SEQ ID NO: 53. That is, using a 21bp portion of SEQ ID NO: 53 as an exemplary example, the GAA signal peptide can comprise a nucleic acid that is a 21bp portion of SEQ ID NO: 53, where the 21bp can be any 21-concenceutive base pairs of SEQ ID NO: 53. For example, a 1-21bp portion beginning at base pair 1 of SEQ ID NO: 53 would encode for a GAA-signal peptide comprising amino acids 1-7 of SEQ ID NO: 59, whereas a 1-21bp portion beginning at base pair 15 of SEQ ID NO: 53 would encode for a GAA-signal peptide comprising amino acids 5-12 of SEQ ID NO: 59. In some embodiments, a portion of the GAA signal peptide of SEQ ID NO: 59 is the N-

terminal portion of SEQ ID NO: 59 (i.e., has a deletion of at least 1, or at least 2, or at least 3, or at least 4, or at least 5, or at least 6, or at least 7, or at least 8, or at least 9, or at least 10, or at least 11, or at least 12, or at least 13, or at least 14 or at least 15 amino acids, or more than 15 amino acids at the C-terminal of SEQ ID NO: 59).

[00175] In some embodiments, the nucleic acid encoding a heterologous signal peptide as disclosed herein can be inserted into the nucleic acid sequence encoding a GAA-signal peptide. The insertion can occur at any location in the 1-81bp of SEQ ID NO: 53. In some embodiments, a nucleic acid sequence encoding a heterologous signal peptide as disclosed herein is inserted in a portion of the nucleic acid encoding a GAA-signal peptide, e.g., generating a chimeric signal peptide comprising, for example, a 5' nucleic acid sequence encoding a portion of a GAA signal peptide (e.g., a portion of SEQ ID NO: 53, as discussed above) and attached to the 3' of said sequence, a nucleic acid encoding a heterologous signal peptide as disclosed herein. In some embodiments, there can also be a nucleic acid encoding a N-terminal portion of the GAA polypeptide with a deletion of amino acids thereafter, e.g., encoding amino acids 28, 28-29, 28-30, 28-31, 28-32, 28-33 etc., of SEQ ID NO: 1 followed by a deletion of about 4-40 amino acids of SEQ ID NO:1. In some embodiments, a heterologous signal peptiode can be inserted immediately following the N-terminal amino acids, e.g., after position 28, 29, 30, 31, 32 or 33.

[00176] In some embodiments of the compositions and methods described herein, the signal peptides serve a general purpose of assisting the secretion of the GAA polypeptide from the liver cells into the blood, where it can travel and be targeted to the lysosomes of mammalian cells, for example, human cardiac and skeletal muscle cells, as described herein. In some embodiments, a heterologous signal peptide is selected from any of: a AAT signal peptide, a fibronectin signal peptide (FN1), 201 signal peptide, wtIL2 signal peptide, mutIL2 signal peptide, A2M signal peptide, PZP signal peptide, or an active fragment of AAT, FN1, 201, wtIL2, mutIL2, A2M or PZP signal peptide having secretory signal activity.

[00177] In some embodiments, the signal peptide is heterologous to (i.e., foreign or exogenous to) the polypeptide of interest. For example, a heterologous signal peptide is a fibronectin secretory signal peptide, the polypeptide of interest is not fibronectin. In some embodiments, the signal peptide is selected from any of: FN1, 201 signal peptide, wtIL2 signal peptide, mutIL2 signal peptide, A2M signal peptide, PZP signal peptide having secretory signal activity. In alternative embodiments, the signal peptide is not heterologous to GAA, i.e., the signal peptide is the GAA signal peptide (i.e., residues 1-27 of SEQ ID NO: 1, which the endogenous GAA polypeptide).

[00178] In some embodiments, the endogenous GAA signal sequence of amino acids 1-27 of SEQ ID NO: 1 (i.e., MGVRHPPCSHRLLAVCALVSLATAALL, SEQ ID NO: 59) is replaced with a different signal peptide (leader peptide). For example, the endogenous signal peptide of GAA (SEQ ID NO: 59) can be replaced with any of: (i) an IgG1 signal peptide (referred to herein as a "201 signal peptide" or "201lp" having an amino acid sequence of: MEFGLSWVFLVALLKGVQCE (SEQ ID

NO: 60) encoded by nucleic acid sequence SEQ ID NO: 54, (ii) wtIL2 lp: MYRMQLLSCIALSLALVTNS (SEQ ID NO: 61) encoded by nucleic acid sequence SEQ ID NO: 55, or (iii) mutIL2 lp: MYRMQLL***LLI***ALSLALVTNS (SEQ ID NO: 62) encoded by nucleic acid sequence SEQ ID NO: 56, (iv) A2M signal peptide MGKNKLLHPSLVLLLLVLLPTDA (SEQ ID NO: 63) encoded by nucleic acid sequence SEQ ID NO: 57, (iv) PZP signal peptide MRKDRLLHLCLVLLLILLSASDSNS (SEQ ID NO: 64) encoded by nucleic acid sequence SEQ ID NO: 58. In some embodiments, the heterologous signal peptide can be truncated.

[00179] In some embodiments, the endogenous GAA signal peptide (SEQ ID NO: 59) or a fragment or portion thereof remains present, and an additional signal peptide is added, e.g., any one or more of signal peptides AAT, FN1, 201 signal peptide, wtIL2 signal peptide, mutIL2 signal peptide, A2M signal peptide, PZP signal peptide, as disclosed herein. In some embodiments, the endogenous GAA signal peptide of amino acids 1-27 of SEQ ID NO: 1 (i.e., MGVRHPPCSHRLLAVCALVSLATAALL, SEQ ID NO: 59) is replaced with a different or heterologous signal peptide. For example, the endogenous signal peptide of GAA (SEQ ID NO: 59) can be replaced with any of the heterologous signal peptides selected from: (i) an IgG1 signal peptide (referred to herein as a "201 signal peptide" or "201lp" having an amino acid sequence of: MEFGLSWVFLVALLKGVQCE (SEQ ID NO: 60) encoded by nucleic acid sequence SEQ ID NO: 54, (ii) wtIL2 lp: MYRMQLLSCIALSLALVTNS (SEQ ID NO: 61) encoded by nucleic acid sequence SEQ ID NO: 55, or (iii) mutIL2 lp: MYRMQLL***LLI***ALSLALVTNS (SEQ ID NO: 62) encoded by nucleic acid sequence SEQ ID NO: 56, (iv) A2M signal peptide MGKNKLLHPSLVLLLLVLLPTDA (SEQ ID NO: 63) encoded by nucleic acid sequence SEQ ID NO: 57, (iv) PZP signal peptide MRKDRLLHLCLVLLLILLSASDSNS (SEQ ID NO: 64) encoded by nucleic acid sequence SEQ ID NO: 58.

[00180] In some embodiments, the nucleic acid sequences in the rAAV vector or rAAV genome is a sequence selected from SEQ ID NO: 470-515. In one embodiment, the nucleic acid sequences in the rAAV vector or rAAV genome comprises at least a portion of a sequence selected from SEQ ID NO: 470-515 (i.e., a sequence that is at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or more of the sequence of SEQ ID NO: 470-515).

[00181] In some embodiments, exemplary nucleic acid sequences in the rAAV vector or rAAV genome as disclosed herein are shown in exemplary constructs provided herein below:

- pP065, is a plasmid comprising in the 5' to 3' direction: [L-ITR]- [(LSP:Liver Specific Promoter)]-[5'UTR]-[1-28aa GAA-SP]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]- [R-ITR]. See, e.g., SEQ ID NO: 470.
- pP066, is a plasmid comprising in the 5' to 3' direction: [L-ITR]- [(LSP:Liver Specific Promoter)]-[5'UTR]-[1-28aa GAA-SP]-[GAA polypeptide starting at amino acid 57 of SEQ

ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]- [R-ITR]. See, e.g., SEQ ID NO: 471.

· pP067, is a plasmid comprising in the 5' to 3' direction: [L-ITR]- [(LSP:Liver Specific Promoter)]-[5'UTR]-[aa1 from GAA-SP]-[28-31aa GAA]-[IL-2 signal sequence]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 472.

· pP068, is a plasmid comprising in the 5' to 3' direction: [L-ITR]- [(LSP:Liver Specific Promoter)]-[5'UTR]-[aa1 from GAA-SP]-[28-31aa GAA]-[201Ig]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 473.

· pP069, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[aa1 from GAA-SP from seq100]-[28-31aa GAA from seq3]-[IL-2 signal sequence]-[GAA polypeptide starting at amino acid 57 of seq3]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[ITR-neighborhood]-[R-ITR]. See, e.g., SEQ ID NO: 474.

· pP070, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[aa1 from GAA-SP]-[28-31aa GAA]-[201Ig]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 475.

· pP071, is a plasmid comprising in the 5' to 3' direction: [L-ITR]- [(LSP:Liver Specific Promoter)]-[5'UTR]-[1-24aa GAA]-[IL-2 signal sequence]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 476.

· pP072, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-24aa GAA]-[201Ig]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 477.

· pP073, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-24aa GAA]-[IL-2 signal sequence]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 478.

· pP074, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-24aa GAA]-[201Ig]-[GAA polypeptide starting at amino acid 57 of

SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 479.

· pP075, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-23aa GAA]-[IL-2 signal sequence]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 480.

· pP076, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-23aa GAA]-[201Ig]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 481.

· pP077, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-23aa GAA]-[IL-2 signal sequence]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal [R-ITR]. See, e.g., SEQ ID NO: 482.

· pP078, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-23aa GAA]-[201Ig]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 483.

· pP079, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-2aa GAA]-[IL-2 signal sequence (Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 484.

· pP080, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-2aa GAA]-[201Ig(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 485.

· pP081, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-2aa GAA]-[IL-2 signal sequence(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 486.

· pP082, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-2aa GAA]-[201Ig(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 487.

· pP083, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-4aa GAA]-[IL-2 signal sequence(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 488.

· pP084, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-4aa GAA]-[201Ig(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID No:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 489.

· pP085, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-4aa GAA]-[IL-2 signal sequence(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 490.

· pP086, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-4aa GAA]-[201Ig(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID No:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 491.

· pP087, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-10aa GAA]-[IL-2 signal sequence(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 492.

· pP088, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-10aa GAA]-[201Ig(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 493.

· pP089, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-10aa GAA]-[IL-2 signal sequence(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 494.

· pP090, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-10aa GAA]-[201Ig(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO;1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 495.

· pP091, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-27aa GAA]-[IL-2 signal sequence(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 496.

· pP092, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-27aa GAA]-[201Ig(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 497.

· pP093, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-27aa GAA]-[IL-2 signal sequence(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[ITR-neighborhood]-[R-ITR]. See, e.g., SEQ ID NO: 498.

· pP094, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-27aa GAA]-[201Ig(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 499.

· pP098, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-24aa GAA]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 500.

· pP099, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[(LSP:Liver Specific Promoter)]-[5'UTR]-[1-24aa GAA]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA signal and Terminator]-[RNA polymerase II transcriptional pause signal]-[R-ITR]. See, e.g., SEQ ID NO: 501.

· pP110, is a plasmid comprising in the 5' to 3' direction: [ITR2]-[LSP]-[1-28aa GAA]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA]-[ITR2]. See, e.g., SEQ ID NO: 502.

· pP111, is a plasmid comprising in the 5' to 3' direction: [ITR2]-[LSP]-[1-24aa GAA]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA]-[ITR2]. See, e.g., SEQ ID NO: 503.

· pP112, is a plasmid comprising in the 5' to 3' direction: [ITR2]-[LSP]-[1-27aa GAA]-[201lp(Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA]-[ITR2]. See, e.g., SEQ ID NO: 504.

· pP113, is a plasmid comprising in the 5' to 3' direction: [ITR2]-[LSP]-[1-24aa GAA]-[201lp]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA]-[ITR2]. See, e.g., SEQ ID NO: 505.

· pP114, is a plasmid comprising in the 5' to 3' direction: [ITR2]-[LSP]-[1-2aa GAA]-[IL-2 signal sequence (Met1 removed)]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA]-[ITR2]. See, e.g., SEQ ID NO: 506.

· pP150, is a plasmid comprising in the 5' to 3' direction: [ITR2]-[LSP]-[1-24aa GAA]-[201Ip]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA]-[ITR2]. See, e.g., SEQ ID NO: 507.

· pP151, is a plasmid comprising in the 5' to 3' direction: [ITR2]-[LSP]-[5'UTR]-[1-24aa GAA]-[201Ip]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA]-[ITR2]. See, e.g., SEQ ID NO: 508.

· pP152, is a plasmid comprising in the 5' to 3' direction: [ITR2]-[LSP]-[1-24aa GAA]-[201Ip]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA]-[ITR2]. See, e.g., SEQ ID NO: 509.

· pP153, is a plasmid comprising in the 5' to 3' direction: [ITR2]-[LSP]-[5'UTR]-[1-24aa GAA]-[201Ip]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA]-[ITR2]. See, e.g., SEQ ID NO: 510.

· pP155, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[fragment of P5]-[LSP]-[1-24aa GAA]-[201Ip]-[GAA polypeptide starting at amino acid 57 of Seq ID NO;1]-[3'UTR]-[hGH polyA]-[R-ITR]. See, e.g., SEQ ID NO: 511.

· pP157, is a plasmid comprising in the 5' to 3' direction: [L-ITR]-[fragment of P5]-[LSP]-[1-28aa GAA from ACTUS]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO:1]-[3'UTR]-[hGH polyA]-[R-ITR]. See, e.g., SEQ ID NO: 512.

[00182] In some embodiments, the exemplary constructs have codon optimized GAA, including codon optimized GAA signal peptide, or portion thereof, e.g., the GAA and/or GAA signal peptide is encoded by seq 100 (SEQ ID NO:3), or seq3 (SEQ ID NO:4), or a fragment thereof. In some embodiments of the invention, the GAA and/or GAA signal peptides, or portion thereof in the exemplary constructs are not codon optimized, e.g., the GAA and/or GAA signal peptide is encoded by SEQ ID NO:2 or fragment thereof.

[00183] In some embodiments, the exemplary constructs described herein can be in a plasmid DNA backbone, or in a close ended linear duplexed DNA backbone or a precursor plasmid of close ended linear duplexed DNA backbone.

[00184] In some embodiments, the exemplary constructs described herein comprise 5'UTRs as described in the instant application including but not limited to SEQ ID NO:40 or SEQ ID NO:41.

[00185] In some embodiments, the nucleic acid encoding GAA the invention including but not limited to exemplary constructs, have 130 bp ITRs. In some embodiments of the invention, the nucleic acid encoding GAA of the invention including but not limited to exemplary constructs, have 145 bp ITRs.

[00186] In some embodiments, exemplary nucleic acid sequences in the rAAV vector or rAAV genome as disclosed herein are shown in **Table 10.**

[00187] Table 10: Exemplary constructs encoding in a 5' to 3' direction a GAA-signal peptide, or portion thereof, a heterologous signal peptide and a GAA polypeptide (see, e.g., FIG. 29). In Table 10, a GAA polypeptide that begins at amino acid 57 of SEQ ID NO:1 is shown for exemplary purposes, however, any GAA polypeptide is envisoned, including any N-terminal truncation disclosed in Table 1 herein, as well as wild type GAA polypeptide, codon-optimized GAA polypeptides, ACTUS-101 GAA polypeptide, and N-terminal truncations thereof. (Hetero-SP, or SP refers to a heterologous signal peptide as disclosed herein, GAA-SP refers to the endogenous (cognate) signal peptide of GAA of SEQ ID NO: 59, or a portion thereof).

Name	Description	Construct Summary	Amino acid construct	Nucleic acid construct
P026	Delta 2-56	[1aa GAA-SP]-[hetro-SP]-[delta1-56 GAA/M5]	[1aa of SEQ ID NO: 59]-[hetro-SP]-[57-952aa of SEQ ID NO: 1]	[1-3bp of SEQ ID NO: 53]-[SP]-[169-2859bp of SEQ ID NO: 3]
P065	Delta 29-56	[1-27 aa GAA-SP]-[delta 29-56 GAA]	[1-27aa of SEQ ID NO: 59]-[28aa of SEQ ID NO:1][57-952aa of SEQ ID NO: 1]	[1-81bp of SEQ ID NO: 53]-[82-84 of SEQ ID NO: 3][169-2859bp of SEQ ID NO: 3]
P067	Retained 28-31 [28-31aa GAA]-[SP]-[delta32-56])	[1-27 aa GAA-SP]-[28-31aa of GAA]-[hetero-SP]--[delta32-56 GAA]	[1-27aa of SEQ ID NO: 59]-[28-31aa of SEQ ID NO:1]-[hetro-SP]-[57-952aa of SEQ ID NO: 1]	[1-81bp of SEQ ID NO: 53]-[82-94bp of SEQ ID NO: 3]-[SP]-[169-2859bp of SEQ ID NO: 3]
P072	Retained 1-24 [1-24aa GAA-SP]-[SP]-[delta25-56])	[1-24 aa GAA-SP]-[hetero-SP]--[delta25-56 GAA]	[1-24aa of SEQ ID NO: 59]-[hetro-SP]-[57-952aa of SEQ ID NO: 1]	[1-72bp of SEQ ID NO: 53]-[SP]-[169-2859bp of SEQ ID NO: 3]
P075	Retained 1-23 [1-23aa GAA-SP]-[SP]-[delta24-56])	[1-23 aa GAA-SP]-[hetero-SP]--[delta24-56 GAA]	[1-23aa of SEQ ID NO: 59]-[hetro-SP]-[57-952aa of SEQ ID NO: 1]	[1-69bp of SEQ ID NO: 53]-[SP]-[169-2859bp of SEQ ID NO: 3]
P092	Retained 1-27 [1-27aa GAA-	[1-27 aa GAA-SP]-[28aa of GAA]-	[1-27aa of SEQ ID NO: 59]-[hetro-SP]-	1-81bp of SEQ ID NO: 53]-[82-84 of SEQ ID

	SP][28aa GAA]-[SP]-[delta29-56])	[hetero-SP]--[delta 29-56 GAA]	[57-952aa of SEQ ID NO: 1]	NO: 3]-[SP]-[169-2859bp of SEQ ID NO: 3]

[00188] In one embodiment, the contructs described in **Table 10** achieve the titers described in **Table 11** following *in vivo* administration at 4 weeks-post administration.

Table 11. Summary of *in vivo* results 4 weeks post administration.

Group	Serum GAA	Serum 4MU	Heart 4MU	Heart glycogen	Liver retention
GAA KO	3.4e4	2.6e3	59.3	38.0	2.1e4
002/M4	2.0e5	4.5e3	65.0	30.7	2.8e6
026/M5	6.6e6	2.7e4	366.4	21.9	5.5e5
065	6.6e6	1.5e4	343.8	26.1	2.2e5
067	5.9e6	1.9e4	294.9	20.5	1.1e6
072	6.6e6	3.9e4	512.9	18.1	6.4e5
075	5.8e6	2.6e4	626.6	27.6	4.6e5
092	4.2e5	6.6e3	193.2	17.3	4.0e4
WT mice	ND	ND	482.1	20.6	ND

[00189] In **Table 11**, "Serum GAA" descibes the level of GAA expression found in the serum of the injected mice 4 weeks post administration; "Serum 4MU" describes the level of GAA activity found in the serum of the injected mice 4 weeks post administration; "Heart 4MU" describes the level of GAA activity found in the heart of the injected mice 4 weeks post administration; "Heart glycogen" describes the level of glucose found in the heart of the injected mice 4 weeks post administration; and "Liver retention" descibes the level of GAA expression found in the liver of the injected mice 4 weeks post administration.

[00190] In general, the GAA-signal peptide and/or heterologous signal peptide will be at the amino-terminus (N-terminus) of the GAA polypeptide (i.e., the nucleic acid segment encoding the signal peptide is 5′ to the heterologous nucleic acid encoding the GAA peptide in the rAAV vector or rAAV genome as disclosed herein). Alternatively, the signal peptide may be at the carboxyl-terminus or embedded within the GAA polypeptide, as long as the signal peptide is operatively associated therewith and directs secretion of the GAA polypeptide or GAA fusion polypeptide of interest (either with or without cleavage of the signal peptide from the GAA polypeptide) from the cell.

[00191] The signal peptide is operatively associated with the GAA polypeptide, including N-terminal

truncated GAA polypeptides as disclosed in Table 1 herein, is targeted to the secretory pathway. Alternatively stated, the signal peptide is operatively associated with the GAA polypeptide such that the GAA-polypeptide is secreted from the cell at a higher level (i.e., a greater quantity) than in the absence of the secretory signal peptide. In general, typically at least about 20%, 30%, 40%, 50%, 70%, 80%, 85%, 90%, 95% or more of the GAA-polypeptide is secreted from the cell when a signal peptide is attached as compared to in the absence of the attachment of a secretory signal peptide. In other embodiments, essentially all of the detectable polypeptide (alone and/or in the form of the fusion polypeptide) is secreted from the cell.

[00192] By the phrase "secreted from the cell", the polypeptide may be secreted into any compartment (e.g., fluid or space) outside of the cell including but not limited to: the interstitial space, blood, lymph, cerebrospinal fluid, kidney tubules, airway passages (e.g., alveoli, bronchioles, bronchia, nasal passages, etc.), the gastrointestinal tract (e.g., esophagus, stomach, small intestine, colon, etc.), vitreous fluid in the eye, and the cochlear endolymph, and the like.

[00193] Accordingly, in some embodiments, a AAV expressing GAA useful in the methods to treat Pompe Disease as disclosed herein comprises a 5' ITR and 3' ITR sequence, and located between the 5'ITR and the 3' ITR, a liver specific promoter operatively linked to a heterologous nucleic acid encoding a secretory peptide and nucleic acid encoding an alpha-glucosidase (GAA) polypeptide (i.e., the heterologous nucleic acid encodes a GAA polypeptide or N-terminal GAA polypeptide comprising a signal peptide-GAA polypeptide).

[00194] In alternative embodiments, a AAV expressing GAA useful in the methods to treat Pompe Disease as disclosed herein comprises a 5' ITR and 3' ITR sequence, and located between the 5'ITR and the 3' ITR, a promoter operatively linked to a heterologous nucleic acid encoding a secretory peptide and nucleic acid encoding an alpha-glucosidase (GAA) polypeptide.

[00195] Generally, secretory signal peptides are cleaved within the endoplasmic reticulum and, in some embodiments, the signal peptide is cleaved from the GAA polypeptide prior to secretion. It is not necessary, however, that the signal peptide is cleaved as long as secretion of the GAA polypeptide from the cell is enhanced and the GAA polypeptide is functional. Thus, in some embodiments, the signal peptide is partially or entirely retained.

[00196] In some embodiments, the rAAV genome, or an isolated nucleic acid as disclosed herein comprises a nucleic acid encoding a chimeric polypeptide comprising a GAA polypeptide operably linked to a secretory signal peptide, and the chimeric polypeptide is expressed and produced from a cell transduced with the rAAV vector and the GAA polypeptide is secreted from the cell. The GAA polypeptide can be secreted after cleavage of all or part of the secretory signal peptide. Alternatively, the GAA polypeptide can retain the signal peptide (i.e., the signal peptide is not cleaved). Thus, in this context, the "GAA polypeptide" can be a chimeric polypeptide comprising the secretory peptide.

[00197] Other signal peptide as encompassed for use in the methods and compositions as disclosed herein. For example, numerous secreted proteins and sequences that direct secretion from the cell are

known in the art, are disclosed in US Patent 9,873,868, which is incorporated herein in its entirety by reference. Exemplary secreted proteins (and their secretory signals) include but are not limited to: erythropoietin, coagulation Factor IX, cystatin, lactotransferrin, plasma protease C1 inhibitor, apolipoproteins (e.g., APO A, C, E), MCP-1, α-2-HS-glycoprotein, α-1-microgolubilin, complement (e.g., C1Q, C3), vitronectin, lymphotoxin-α, azurocidin, VIP, metalloproteinase inhibitor 2, glypican-1, pancreatic hormone, clusterin, hepatocyte growth factor, insulin, α-1-antichymotrypsin, growth hormone, type IV collagenase, guanylin, properdin, proenkephalin A, inhibin β (e.g., A chain), prealbumin, angiocenin, lutropin (e.g., β chain), insulin-like growth factor binding protein 1 and 2, proactivator polypeptide, fibrinogen (e.g., β chain), gastric triacylglycerol lipase, midkine, neutrophil defensins 1, 2, and 3, α-1-antitrypsin, matrix gla-protein, α-tryptase, bile-salt-activated lipase, chymotrypsinogen B, elastin, IG lambda chain V region, platelet factor 4 variant, chromogranin A, WNT-1 proto-oncogene protein, oncostatin M, β-neoendorphin-dynorphin, von Willebrand factor, plasma serine protease inhibitor, serum amyloid A protein, nidogen, fibronectin, rennin, osteonectin, histatin 3, phospholipase A2, cartilage matrix Protein, GM-CSF, matrilysin, neuroendocrine protein 7B2, placental protein 11, gelsolin, M-CSF, transcobalamin I, lactase-phlorizin hydrolase, elastase 2B, pepsinogen A, MIP 1-β, prolactin, trypsinogen II, gastrin-releasing peptide II, atrial natriuretic factor, secreted alkaline phosphatase, pancreatic α-amylase, secretogranin I, β-casein, serotransferrin, tissue factor pathway inhibitor, follitropin β-chain, coagulation factor XII, growth hormone-releasing factor, prostate seminal plasma protein, interleukins (e.g., 2, 3, 4, 5, 9, 11), inhibin (e.g., alpha chain), angiotensinogen, thyroglobulin, IG heavy or light chains, plasminogen activator inhibitor-1, lysozyme C, plasminogen activator, antileukoproteinase 1, statherin, fibulin-1, isoform B, uromodulin, thyroxine-binding globulin, axonin-1, endometrial α-2 globulin, interferon (e.g., alpha, beta, gamma), β-2-microglobulin, procholecystokinin, progastricsin, prostatic acid phosphatase, bone sialoprotein II, colipase, Alzheimer's amyloid A4 protein, PDGF (e.g., A or B chain), coagulation factor V, triacylglycerol lipase, haptoglobuin-2, corticosteroid-binding globulin, triacylglycerol lipase, prorelaxin H2, follistatin 1 and 2, platelet glycoprotein IX, GCSF, VEGF, heparin cofactor II, antithrombin-III, leukemia inhibitory factor, interstitial collagenase, pleiotrophin, small inducible cytokine A1, melanin-concentrating hormone, angiotensin-converting enzyme, pancreatic trypsin inhibitor, coagulation factor VIII, α-fetoprotein, α-lactalbumin, senogelin II, kappa casein, glucagon, thyrotropin beta chain, transcobalamin II, thrombospondin 1, parathyroid hormone, vasopressin copeptin, tissue factor, motilin, MPIF-1, kininogen, neuroendocrine convertase 2, stem cell factor procollagen α1 chain, plasma kallikrein keratinocyte growth factor, as well as any other secreted hormone, growth factor, cytokine, enzyme, coagulation factor, milk protein, immunoglobulin chain, and the like.

[00198] In one embodiment, the secretory signal peptide is not a secretory signal peptide of α-1-antitrypsin (e.g., amino acids 1-24 of α-1-antitrypsin), chymotrypsinogen B2 (e.g., amino acids 1-20 of chymotrypsinogen B2), iduronate-2-sulphatase (e.g., amino acids 1-25 of iduronate-2- sulphatase),

or protease C1 inhibitor (e.g., amino acids 1-23 of protease CI inhibitor).

[00199] In some embodiments, other secretory signal peptides encoded by the rAAV genome and in the rAAV vector as disclosed herein can be selected from, but are not limited to, the signal peptide sequences from prepro-cathepsin L (e.g., GenBank Accession Nos. KHRTL, NP_037288; NP_034114, AAB81616, AAA39984, P07154, CAA68691; the disclosures of which are incorporated by reference in their entireties herein) and prepro-alpha 2 type collagen (e.g., GenBank Accession Nos. CAA98969, CAA26320, CGHU2S, NP_000080, BAA25383, P08123; the disclosures of which are incorporated by reference in their entireties herein) as well as allelic variations, modifications and functional fragments thereof (as discussed above with respect to the fibronectin signal peptide sequence). Exemplary signal peptide sequences include for preprocathepsin L (Rattus norvegicus, MTPLLLLAVLCLGTALA [SEQ ID NO: 77]; Accession No. CAA68691) and for prepro-alpha 2 type collagen (Homo sapiens, MLSFVDTRTLLLLAVTLCLATC [SEQ ID NO: 78]; Accession No. CAA98969). Also encompassed are longer amino acid sequences comprising the full-length signal peptide sequence from preprocathepsin L and prepro-alpha 2 type collagen or functional fragments thereof (as discussed above with respect to the fibronectin signal peptide sequence).

[00200] In some embodiments, the signal peptide is derived in part or in whole from a secreted polypeptide that is produced by liver cells. In some embodiments, a signal peptide can further be in whole or in part synthetic or artificial. Synthetic or artificial secretory signal peptides are known in the art, see e.g., Barash et al., "Human signal peptide description by hidden Markov model and generation of a strong artificial signal peptide for secreted protein expression," Biochem. Biophys. Res. Comm. 294:835-42 (2002); the disclosure of which is incorporated herein in its entirety. In particular embodiments, the signal peptide comprises, consists essentially of, or consists of the artificial secretory signal: MWWRLWWLLLLLLLLWPMVWA (SEQ ID NO: 65) or variations thereof having 1, 2, 3, 4, or 5 amino acid substitutions (optionally, conservative amino acid substitutions, conservative amino acid substitutions are known in the art).

[00201] Exemplary signal peptides for use in the methods and compositions as disclosed herein can be selected from any signal peptide disclosed in Table 2, or portions thereof or functional variants thereof. Exemplary signal peptides are Fibronectin (FN1), or AAT. In some embodiments of the methods and compositions disclosed herein, the rAAV vector composition comprises the nucleic acid encoding a secretory signal peptide, e.g., encoding a signal peptide selected from an AAT signal peptide (e.g., SEQ ID NO: 67), a fibronectin signal peptide (FN1) (e.g., SEQ ID NO: 68-71), an hIGF2 signal peptide (e.g., SEQ ID NO: 72) or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NOs: 67-72.

[00202] In some embodiments of the methods and compositions as disclosed herein, the nucleic acid encoding the signal peptide is selected from any of SEQ ID NO: 54-58, 67, 72-76 and 72, or a nucleic acid sequence at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity

to any of SEQ ID NOs: 54-58, 67, 72-76 and 72.

[00203] *Fibronectin secretory signal peptide:*

[00204] In some embodiments, the signal peptide is a fibronectin secretory signal peptide or portions thereof or functional variants thereof, which term includes modifications of naturally occurring sequences (as described in more detail below).

[00205] In some embodiments, the signal peptide is a fibronectin signal peptide, e.g., a signal sequence of human fibronectin or a signal sequence from rat fibronectin. Fibronectin (FN1) signal sequences and modified FN1 signal peptides encompassed for use in the rAAV genome and rAAV vectors described herein are disclosed in US patent 7,071,172, which is incorporated herein in its entirety by reference, and in Table 3 of provisional application 62/937,556, filed on November 19, 2019 or International Application WO2021102107, which is incorporated herein in its reference. Examples of exemplary fibronectin signal peptide sequences include, but are not limited to those listed in Table 1 of US patent 7,071,172, which is incorporated herein in its entirety by reference.

[00206] Table 2: Exemplary Fibronectin (FN1) secretory signal peptides

Species	Signal peptide sequence	Nucleic acid sequence
H. Sapiens	MLRGPGPGLLLLAVQCLGTAV PSTGA (SEQ ID NO: 70)	ATG CTT AGG GGT CCG GGG CCC GGG CTG CTG CTG CTG GCC GTC CAG TGC CTG GGG ACA GCG GTG CCC TCC ACG GGA GCC (SEQ ID NO: 75)
R. Norvegicus	MLRGPGPGRLLLLAVLCLGTSV RCTETGKSKR (SEQ ID NO: 68)	5′-ATGCTCAGGGGTCCGGGACCCGGGCGGCT GCTGCTGCTAGCAGTCCTGTGCCTGGGGAC ATCGGTGCGCTGCACCGAAACCGGGAAGA GCAAGAGG-3 (SEQ ID NO: 73)
R. Norvegicus	MLRGPGPGRLLLLAVLCLGTSV RCTETGKSKR ↑ LALQIV (SEQ ID NO: 69)	5′-ATG CTC AGG GGT CCG GGA CCC GGG CGG CTG CTG CTG CTA GCA GTC CTG TGC CTG GGG ACA TCG GTG CGC TGC ACC GAA ACC GGG AAG AGC AAG AGG ↑ CAG GCT CAG CAA ATC GTG-3′. (SEQ ID NO: 74) (↑ denotes the cleavage site)
X. laevis	MRRGALTGLLLVLCLSVVLRA APSATSKKRR (SEQ ID NO: 71)	ATG CGC CGG GGG GCC CTG ACC GGG CTG CTC CTG GTC CTG TGC CTG AGT GTT GTG CTA CGT GCA GCC CCC TCT GCA ACA AGC AAG AAG CGC AGG (SEQ ID NO: 76)

[00207] *Peptidase cleavage sites*

[00208] In some embodiments, one or more exogenous peptidase cleavage site may be inserted into the signal peptide -GAA polypeptide, e.g., between the signal peptide and the GAA polypeptide. In particular embodiments, an autoprotease (e.g., the foot and mouth disease virus 2A autoprotease) is inserted between the signal peptide and the GAA polypeptide. In other embodiments, a protease recognition site that can be controlled by addition of exogenous protease is employed (e.g., Lys—Arg recognition site for trypsin, the Lys—Arg recognition site of the Aspergillus KEX2-like protease, the recognition site for a metalloprotease, the recognition site for a serine protease, and the like).

Modification of the GAA polypeptide to delete or inactivate native protease sites is encompassed herein and disclosed in U.S. Provisional Application 62,937,556, filed on November 19, 2019 and International Application WO2021102107, which is incorporated herein in its reference.

D. Spacer and fusion junction of the GAA polypeptide

[00209] Where GAA is expressed with a heterologous signal peptide, the signal peptide can be fused directly to the GAA polypeptide or can be separated from the GAA polypeptide by a linker. An amino acid linker (also referred to herein as a "spacer") incorporates one or more amino acids other than that appearing at that position in the natural protein. Spacers can be generally designed to be flexible or to interpose a structure, such as an a-helix, between the two protein moieties.

[00210] Accordingly, in some embodiments of the methods and compositions disclosed herein, a recombinant AAV vector comprises a heterologous nucleic acid sequence encoding an GAA polypeptide, wherein the GAA protein further comprises a spacer comprising a nucleotide sequence of at least 1 amino acid in length, which is located N-terminal to the GAA polypeptide.

[00211] In one embodiment, the spacer at least 50% identical to the sequence GGGTVGDDDDK.

[00212] In some embodiments, a spacer or linker can be relatively short, e.g., at least 1, 2, 3, 4 or 5 amino acids, or such as the sequence Gly-Ala-Pro or Gly-Gly-Gly-Gly-Gly-Pro, or can be longer, such as, for example, 5-10 amino acids in length or 10-25 amino acids in length. For example, flexible repeating linkers of 3-4 copies of the sequence (e.g., GGGGS) and a-helical repeating linkers of 2-5 copies of the sequence (e.g., EAAAK) have been described (Arai et al. (2004) Proteins: Structure, Function and Bioinformatics 57:829-838). In some embodiments, a linker comprising GGGTVGDDDDK is also encompassed for use. Linkers incorporating an a-helical portion of a human serum protein can be used to minimize immunogenicity of the linker region. In some embodiments, the spacer is encoded by nucleic acids GGCGCGCCG which encodes the amino acid spacer comprising amino acids GAP or Gly-Ala-Pro.

[00213] The site of a fusion junction in the GAA polypeptide to fuse with either the signal peptide should be selected with care to promote proper folding and activity of each polypeptide in the fusion protein and to prevent premature separation of a signal peptide from a GAA polypeptide.

[00214] In some embodiments, a spacer has a helical structure. In another specific embodiment, a spacer is at least 50% identical to the sequence GGGTVGDDDDK.

[00215] In some embodiments, a signal peptide can be fused, directly or by a spacer, to amino acids of the GAA polypeptide as disclosed in Table 1 herein, permitting expression of the GAA polypeptide or N-terminal truncated GAA polypeptiden, and proper secretion of the GAA polypeptide as described herein in the Examples.

[00216] In order to facilitate folding of the signal peptide, GAA amino acid residues adjacent to the fusion junction can be modified. For example, since it is possible that GAA cysteine residues may interfere with proper folding of the signal peptide, the terminal GAA cysteine 952 can be deleted or

substituted with serine to accommodate a C-terminal signal peptide. The signal peptide can also be fused immediately preceding the final Cys952. The penultimate cys938 can be changed to proline in conjunction with a mutation of the final Cys952 to serine.

F. Liver Specific Promoters (LSP)

[00217] In some embodiments, to achieve appropriate levels of GAA expression, the rAAV genotype comprises a liver specific promoter (LSP). A LSP enables expression of the operatively linked gene in the liver, and can in some embodiments, be and inducible LSP. In an embodiment, a LSP is located upstream 5' and is operatively linked to the heterologous nucleic acid sequence encoding the GAA protein.

[00218] Exemplary liver-specific promoters useful in the AAV to treat Pompe according to the method disclosed herien are disclosed in International WO2020102645 and WO2021102107, which are incorporated herein in their entirity by reference.

[00219] In some embodiments, encompassed herein are any liver-specific promoters disclosed WO2020102645 and WO2021102107, where the LSP has been improved. For example, a liver specific promoter useful in the rAAV vectors as disclosed herein is any LSP disclosed International WO2020102645 and WO2021102107 which has been modified to replace the the sequence of SEQ ID NO: 450 (corresponding to as SEQ ID NO: 126 in WO2021102107 or referred to as CRE0052 or LVR_CRE_0052_G6PC sequence) in any of the LSP sequences in WO2021102107 with a sequence selected from SEQ ID NO: 40 or 41, or a sequence having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto. Using SP131A1 (or LVR131_A1) promoter as an exemplary promoter, which is disclosed as SEQ ID NO: 94 in WO2021102107, in the current application the promoter has been modified to replace SEQ ID NO 450 (corresponding to SEQ ID NO: 126 in WO2021102107) with SEQ ID NO: 40 or 41, or a sequence having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto. Any promoter disclosed in WO2021102107 is encompased for use herein, wherein if the promoter comprises SEQ ID NO 450 (corresponding to SEQ ID NO: 126 in WO2021102107), it can be replaced with SEQ ID NO: 40 or 41, or a sequence having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto.

[00220] In some embodiments, the promoter is a LP1 promoter (SEQ ID NO: 432), or a variant having at least sequence at least 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto.

[00221] In some embodiments of the methods to treat Pompe disease disclosed herein, a synthetic liver-specific promoter useful in the AAV vector is any LSP promoter selected from SEQ ID NOS: 86, 88, 91-96, 146-150, 439-441 as disclosed herein, or any LSP selected from SEQ ID NO: 270-341 or 342-430 as disclosed herein, or a synthetic liver-specific promoter thereof which is able to promote liver-specific transgene expression and has an activity in liver cells which is at least 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350% or 400% of

the activity of the TTR promoter comprising SEQ ID NO: 431 as International Application WO2021102107, or a synthetic promoter which is disclosed in Table 4 of International Application WO2021102107, which is incorporated herein in its entirity by reference.

[00222] In some embodiments, a synthetic liver specific promoter is selected from any of: SEQ ID NOS: 86, 88, 91-96, 146-150, or 270-430 as disclosed herein, or nucleic acid sequence that is at least 80%, or at least 90% or 95% identical thereto or to the source regulatory nucleic acid sequence.

[00223] In some embodiments, a liver-specific promoter (LSP) in a AAV expressing a GAA polypeptide as disclosed herein and useful in the methods to treat Pompe disease as disclosed herien comprises a nucleic acid sequence selected from any promoter listed from SEQ ID NOS: 86 (CRM 0412), SEQ ID NO: 91 (SP0412) or SEQ ID NO: 92 (SP0422), SEQ ID NOS: 93 (SP0239), SEQ ID NO: 94 (SP0265), SEQ ID NO: 95 (SP0240) or SEQ ID NO: 96 (SP0246), or SEQ ID NO: 146 (SP0265-UTR), SEQ ID NO: 147 (SP0239-UTR), SEQ ID NO: 148 (SP0240-UTR), SEQ ID NO: 149 (SP0246-UTR) or SEQ ID NO: 150 (SP0131-A1- UTR), SEQ ID NO: 439 (LVR_0243); SEQ ID NO: 440 (LVR_0412) and SEQ ID NO: 441 (A1 Promoter), as disclosed herein, or a functional fragment or variant of any LSP selected from SEQ ID NO: 270-341 or 342-430, or a functional fragment or variant thereof of SEQ ID NOS: 86, 88, 91-96, or 146-150, 439-441 or 270-430.

[00224] In some embodiments of the methods to treat Pompe disease disclosed herein, a synthetic liver- specific promoter is selected from any or any LSP promoter selected from SEQ ID NOS: 86 (CRM 0412), SEQ ID NO: 91 (SP0412) or SEQ ID NO: 92 (SP0422), SEQ ID NOS: 93 (SP0239), SEQ ID NO: 94 (SP0265), SEQ ID NO: 95 (SP0240) or SEQ ID NO: 96 (SP0246), or SEQ ID NO: 146 (SP0265-UTR), SEQ ID NO: 147 (SP0239-UTR), SEQ ID NO: 148 (SP0240-UTR), SEQ ID NO: 149 (SP0246-UTR) or SEQ ID NO: 150 (SP0131-A1- UTR), SEQ ID NO: 439 (LVR_0243); SEQ ID NO: 440 (LVR_0412) and SEQ ID NO: 441 (A1 Promoter), or any LSP selected from SEQ ID NO: 270-341 or 342-430 as disclosed herein, where the synthetic liver-specific promoter is able to promote liver-specific transgene expression and has an activity in liver cells which is at least 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350% or 400% of the activity of the TBG promoter of SEQ ID NO: 435.

[00225] In some embodiments of the methods to treat Pompe disease disclosed herein, a synthetic liver- specific promoter is selected from any or any LSP promoter selected from any of SEQ ID NO: 97, SEQ ID NO: 98 or SEQ ID NO: 99, or a variant having at least sequence at least 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto.In some embodiments of the methods to treat Pompe disease disclosed herein, a synthetic liver- specific promoter is selected from any or any LSP promoter selected from SEQ ID NO: 97, SEQ ID NO: 98 or SEQ ID NO: 99, or a variant having at least sequence at least 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto, where the synthetic liver-specific promoter is able to promote liver-specific transgene expression and has an activity in liver cells which is at least 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350% or 400% of the activity of the

TBG promoter of SEQ ID NO: 435.

[00226] In some embodiments, to achieve appropriate levels of GAA expression, the rAAV genotype comprises a liver specific promoter (LSP). A LSP enables expression of the operatively linked gene in the liver, and can in some embodiments, be and inducible LSP. In an embodiment, a LSP is located upstream 5' and is operatively linked to the heterologous nucleic acid sequence encoding the GAA protein. Exemplary liver-specific promoters are disclosed herein, and include for example, the M3 liver specific promoter comprising a sequence of SEQ ID NO: 99, or a functional variant have at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more of SEQ ID NO: 99.

[00227] In one embodiment, the liver promoter is a promoter that has some expression in the liver. In one embodiment, the promoter that has some expression in the liver is the M2 liver promoter comprising a sequence of SEQ ID NO: 98, or a functional variant have at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more of SEQ ID NO: 98.

[00228] In some embodiments, the synthetic liver specific promoter comprises SEQ ID NO: 99, or nucleic acid sequence that is at least 50%, preferably 60%, 70%, 80%, 90% or 95% identical to the source regulatory nucleic acid sequence. In some embodiments, a synthetic liver specific promoter comprises SEQ ID NO: 99, or nucleic acid sequence that is at least 80%, or at least 90% or 95% identical to nucleotides 1-26 of SEQ ID NO: 99.

[00229] In some embodiments, a synthetic liver specific promoter that is at least 50%, 60%, 70%, 80%, 90% or 95% identical to SEQ ID NO: 99 comprises a nucleic acid sequence where 2% or 1% or fewer of the nucleotides of SEQ ID NO: 99 are altered. In some embodiments, a synthetic liver-specific promoter useful in the methods and compositions as disclosed herein is the same length, or not substantially altered, or 1, 2, 3, 4, 5, or 6 nucleotides longer or 1, 2, 3, 4, 5, or 6 shorter than the length of SEQ ID NO: 99.

In some embodiments, no nucleotides have been deleted when compared to SEQ ID NO: 99. In some embodiments, no nucleotides are inserted when compared to SEQ ID NO: 99. In some embodiments, all modifications made to SEQ ID NO: 99 are nucleotide substitutions.

[00230] In some embodiments, a synthetic liver specific promoter that is at least 50%, 60%, 70%, 80%, 90% or 95% identical to SEQ ID NO: 99 comprises a source regulatory nucleic acid sequence which is active in liver, and the second type of cell or tissue is muscle; or a source regulatory nucleic acid sequence which is active in liver, and the second type of cell or tissue is CNS; or a source regulatory nucleic acid sequence which is active in muscle, and the second type of cell or tissue is liver; or a source regulatory nucleic acid sequence which is active in muscle, and the second type of cell or tissue is CNS.

[00231] In some embodiments, a liver-specific promoter which is a functional variant of a given promoter element preferably retains at least 80% of its activity, more preferably at least 90% of its activity, more preferably at least 95% of its activity, and yet more preferably 100% of its activity (compared to the reference promoter comprising the unmodified promoter element). Suitable assays for assessing liver-specific promoter activity are disclosed in Examples 12 and 13 of International Application WO2021102107 which is incorporated herein in its entirity by reference.

[00232] In some embodiments, liver specific promoters include, but are not limited to, transthyretin promoter (TTR), LSP promoter (LSP), a synthetic liver specific promoter. For example, in some embodiments of the methods and compositions as disclosed herein, the promoter is a liver specific promoter (LSP), and can be selected from any liver specific promoters including, but not limited to, a transthyretin promoter (TTR), a Liver specific promoter (LSP), for example, as disclosed in 5,863,541 (TTR promoter), or LSP promoter (PNAS; 96: 3906-3910, 1999. See e.g. p. 3906, Materials and Methods, rAAV construction), a synthetic liver promoter, the references which are incorporated herein in their entireties by reference. Other liver promoters can be used, for example, synthetic liver promoters.

[00233] In some embodiments, the TTR promoter is a truncated TTR promoter, e.g., comprising SEQ ID NO: 431, or SEQ ID NO: 12 as disclosed in International WO 2020102645, which is incorporated herein in its entirity by reference, or a variant having at least sequence at least 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto. In some embodiments, the LSP is a TBG promoter, e.g., comprising SEQ ID NO: 435, or a variant having at least sequence at least 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto.

[00234] Other liver specific promoters include, but are not limited to promoters for the LDL receptor, Factor VIII, Factor IX, phenylalanine hydroxylase (PAH), ornithine transcarbamylase (OTC), and a 1 -antitrypsin (hAAT), and HCB promoter. In Other liver specific promoters include the AFP (alpha fetal protein) gene promoter and the albumin gene promoter, as disclosed in EP Patent Publication 0 415 731, the a-1 antitrypsin gene promoter, as disclosed in Rettenger, Proc. Natl. Acad. Sci. 91 (1994) 1460-1464, the fibrinogen gene promoter, the APO-A1 (Apolipoprotein Al) gene promoter, and the promoter genes for liver transference enzymes such as, for example, SGOT, SGPT and g-glutamyle transferase. See also 2001/0051611 and PCT Patent Publications WO 90/07936 and WO 91/02805, which are incorporated herein in their entirety by reference. In some embodiments, the liver specific promoter is a recombinant liver specific promoter, e.g., as disclosed in US20170326256A1, which is incorporated herein in its entirety by reference.

[00235] In some embodiments, a liver specific promoter is the hepatitis B X-gene promoter and the hepatitis B core protein promoter. In some embodiments, liver specific promoters can be used with their respective enhancers. The enhancer element can be linked at either the 5' or the 3' end of the nucleic acid encoding the GAA polypeptide. The hepatitis B X gene promoter and its enhancer can be obtained from the viral genome as a 332 base pair EcoRV-NcoI DNA fragment employing the

methods described in Twu, J Virol. 61 (1987) 3448-3453. The hepatitis B core protein promoter can be obtained from the viral genome as a 584 base pair BamHI-Bglll DNA fragment employing the methods described in Gerlach, Virol 189 (1992) 59-66. It may be necessary to remove the negative regulatory sequence in the BamHI-Bglll fragment prior to inserting it.

[00236] It is envisioned that the liver-specific promoter used to express the GAA polypeptide is selected in combination with, or in conjunction with the selection of the signal sequence. In particular, without wishing to be bound by theory, if a strong liver-specific promoter is selected, the signal sequence should be selected that is sufficient to secrete the expressed GAA out of the cell, in order to avoid GAA accumation in the cell and any associated cell toxicity, and/or to avoid the generation of anti-GAA antibodies.

[00237] It is encompassed that the LSP is selected in conjunction with the signal sequence, so that the strength of the liver specific promoter (LSP) that is operatively linked to the nucleic acid encoding the GAA polypeptide can be counter-balanced with the ability of the cell to secrete the expressed GAA protein. Thus, if the liver specific promoter is strong, the specific signal sequence must be sufficiently effective to allow for the expressed GAA can be secreted from the cell so that GAA does not accumulate and create cell toxicity and/or induce an immune response. Thus, the cell secretory pathway, and the selected signal sequence must be able to match the level of GAA expressed by the AAV, where the level of GAA expression is dependent on both the AAV transduction effiency (determined by AAV dose and capsid) and the strength of the liver specific promoter.

G. UTRs, Regulatory sequences and Intron sequences

[00238] In some embodiments, the liver-specific promoters as set out above are operably linked to one or more additional regulatory sequences. An additional regulatory sequence can, for example, enhance expression compared to the liver-specific promoter which is not operably linked the additional regulatory sequence. Generally, it is preferred that the additional regulatory sequence does not substantively reduce the specificity of the liver-specific promoter.

[00239] For example, the liver-specific promoter can be operably linked to a sequence encoding a UTR (e.g., a 5' and/or 3' UTR), an intron, an UTR (e.g., 5' or 3')+intron, or such. In some embodiments, the liver-specific promoter is operably linked to sequence encoding a UTR, e.g., a 5' UTR. A 5' UTR can contain various elements that can regulate gene expression. The 5' UTR in a natural gene begins at the transcription start site and ends one nucleotide before the start codon of the coding region. It should be noted that 5' UTRs as referred to herein may be an entire naturally occurring 5' UTR or it may be a portion of a naturally occurring 5' UTR. The 5 'UTR can also be partially or entirely synthetic. In eukaryotes, 5' UTRs have a median length of approximately 150 nt, but in some cases they can be considerably longer. Regulatory sequences that can be found in 5' UTRs are disclosed in International Application WO2021102107 which is incorporated herein in its entirity by reference.

[00240] In some embodiments, a 5-UTR sequence is located 3' of a liver specific promoter as disclosed herein, and 5' of the heterologous nucleic acid sequence (e.g., encoding a signal peptide and GAA polypeptide).

[00241] In one embodiment, an exemplary 5-UTR sequence comprises, for example, a 24bp sequence of SEQ ID NO: 41, or a functional variant have at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more of SEQ ID NO: 41.

[00242] In one embodiment, an exemplary 5-UTR sequence comprising SEQ ID NO: 41 is the sequence of SEQ ID NO: 40, or a functional variant have at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more of SEQ ID NO: 40.

[00243] In some embodiments, the 5-UTR sequence comprises SEQ ID NO: 41 or SEQ ID NO: 40, or nucleic acid sequence that is at least 50%, preferably 60%, 70%, 80%, 90% or 95% identical to the source regulatory nucleic acid sequence. In some embodiments, a 5-UTR sequence comprises SEQ ID NO: 41 or SEQ ID NO: 40 or nucleic acid sequence that is at least 80%, or at least 90% or 95% identical to nucleotides of SEQ ID NO: 41 or SEQ ID NO: 40.

[00244] In some embodiments, a 5-UTR that is at least 50%, 60%, 70%, 80%, 90% or 95% identical to SEQ ID NO: 41 or SEQ ID NO: 40 comprises a nucleic acid sequence where 2% or 1% or fewer of the nucleotides of SEQ ID NO: 41 or SEQ ID NO: 40 are altered. In some embodiments, a 5-UTR sequence useful in the methods and compositions as disclosed herein is the same length, or not substantially altered, or 1, 2, 3, 4, 5, or 6 nucleotides longer or 1, 2, 3, 4, 5, or 6 shorter than the length of SEQ ID NO: 41 or SEQ ID NO: 40.

[00245] Introns within 5' UTRs have been linked to regulation of gene expression and mRNA export. In some embodiments, a liver-specific promoter as set out above is operably linked to a sequence encoding a 5' UTR derived from the CMV major immediate gene (CMV-IE gene). For example, the 5' UTR from the CMV-IE gene suitably comprises the CMV-IE gene exon 1 and the CMV-IE gene exon 1, or portions thereof. In some cases, the promoter element may be modified in view of the linkage to the 5 'UTR, for example sequences downstream of the transcription start site (TSS) in the promoter element can be removed (e.g. replaced with the 5' UTR).

[00246] The CMV-IE 5'UTR is described in Simari, et al, Molecular Medicine 4: 700-706, 1998 "Requirements for Enhanced Transgene Expression by Untranslated Sequences from the Human Cytomegalovirus Immediate-Early Gene", which is incorporated herein by reference. Variants of the CMV-IE 5' UTR sequences discussed in Simari, et al. are also set out in W02002/031137, incorporated by reference, and the regulatory sequences disclosed therein can also be used. Other UTRs that can be used in combination with a promoter are known in the art, e.g. in Leppek, K., Das,

R. & Bama, M. "Functional 5' UTR mRNA structures in eukaryotic translation regulation and how to find them". Nat Rev Mol Cell Biol 19, 158-174 (2018), incorporated by reference.

[00247] In some embodiments the sequence encoding the 5' UTR comprises SEQ ID NO: 145 as disclosed herein, or a functional variant thereof. In some embodiments, functional variants may have a sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. SEQ ID NO: 145 as disclosed herein encodes a CMV-IE 5' UTR.

[00248] In some embodiments the sequence encoding the 5' UTR comprises SEQ ID NO: 446 as disclosed herein, or a functional variant thereof. In some embodiments, functional variants may have a sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. SEQ ID NO: 446 as disclosed herein, which is a modified CMV-IE intron sequence.

[00249] In some embodiments the 5' UTR comprises a nucleic acid motif that functions as the protein translation initiation site, e.g. sequences that define a Kozak sequence in the mRNA produced. For example, in some embodiments, the sequence encoding the 5' UTR comprises the sequence motif GCCACC at or near its 3' end. Other Kozak sequences or other protein translation initiation sites can be used, as is known in the art (e.g. Marilyn Kozak, "Point Mutations Define a Sequence Flanking the AUG Initiator Codon That Modulates Translation by Eukaryotic Ribosomes" Cell, Vol. 44, 283-292, January 31, 1986; Marilyn Kozak "At Least Six Nucleotides Preceding the AUG Initiator Codon Enhance Translation in Mammalian Cells" J. Mol. Rid. (1987) 196, 947-950; Marilyn Kozak "An analysis of 5'-noncoding sequences from 699 vertebrate messenger RNAs" Nucleic Acids Research. Vol. 15 (20) 1987, all of which are incorporated herein by reference). The protein translation initiation site (e.g. Kozak sequence) is preferably positioned immediately adjacent to the start codon.

[00250] In some embodiments, a sequence encoding a 5' UTR comprises SEQ ID NO: 438 as disclosed herein, or a functional variant thereof. In some embodiments, functional variants may have a sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This 5' UTR comprises six nucleotides of GCCACC, which define a Kozak sequence at the 3' end of the CMV-IE 5' UTR.

[00251] In some embodiments, the rAAV expressing GAA for use in the methods to treat Pompe as disclosed herien comprises an intron sequence located 3' of the promoter sequence and 5' of the heterologous nucleic acid (i.e., 5' of the nucleic acid encoding the signal peptide and GAA polypeptide). Intron sequences serve to increase one or more of: mRNA stability, mRNA transport out of nucleus and/or expression and/or regulation of the expressed GAA polypeptide. In alternative embodiments, a rAAV genotype does not comprise an intron sequence.

[00252] In one embodiment, a UTR sequence described herein can be used as a 3'UTR.

[00253] A synthetic liver-specific promoter according to the present invention can be operably linked to a sequence encoding a UTR (e.g. a 5' and/or 3' UTR), and/or an intron, or suchlike. In some embodiments, a synthetic liver specific promoter as set herein, is operably linked to a sequence encoding a 5' UTR and an intron. In some embodiments, the 5' UTR and intron is derived from the

CMV major immediate gene (CMV-IE gene). The CMV-IE 5'UTR and intron is described in Simari, et al., Molecular Medicine 4: 700-706, 1998 "Requirements for Enhanced Transgene Expression by Untranslated Sequences from the Human Cytomegalovirus Immediate-Early Gene", which is incorporated herein by reference. Variants of the CMV-IE 5' UTR and intron sequences discussed in Simari, et al. are also set out in WO2002/031137, incorporated by reference, and the regulatory sequences disclosed therein can also be used. In some embodiments the 5' UTR or the 5' UTR and intron suitably comprises a nucleic acid motif that functions as the protein translation initiation site, e.g. sequences that define a Kozak sequence in the mRNA produced. For example, in some embodiments, the sequence encoding the 5' UTR comprises the sequence motif GCCACC at or near its 3' end. Other Kozak sequences or other protein translation initiation sites can be used, as is known in the art (e.g. Marilyn Kozak, "Point Mutations Define a Sequence Flanking the AUG Initiator Codon That Modulates Translation by Eukaryotic Ribosomes" Cell, Vol. 44, 283-292, January 31, 1986; Marilyn Kozak "At Least Six Nucleotides Preceding the AUG Initiator Codon Enhance Translation in Mammalian Cells" J. Mol. Rid. (1987) 196, 947-950; Marilyn Kozak "An analysis of 5''-noncoding sequences from 699 vertebrate messenger RNAs" Nucleic Acids Research. Vol. 15 (20) 1987, all of which are incorporated herein by reference). The protein translation initiation site (e.g. Kozak sequence) is preferably positioned immediately adjacent to the start codon.

[00254] In some embodiments, any one of the promoters described herein, or variants thereof, is linked to a sequence encoding a 5' UTR and/or a 5'UTR and an intron to provide a composite promoter. Herein, such composite promoter may be referred to simply as "composite promoters", or in some cases simply "promoters" for brevity.

[00255] In some embodiments, the intron sequence is a MVM intron sequence, for example, but not limited to intron sequence of SEQ ID NO: 442, or nucleic acid sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto.

[00256] In some embodiments, the intron sequence is a HBB2 intron sequence, for example, but not limited to and intron sequence of SEQ ID NO: 443 or SEQ ID NO: 444 or nucleic acid sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto.

[00257] In some embodiments of the methods and compositions disclosed herein, a recombinant AAV vector comprises a heterologous nucleic acid sequence that further comprises an intron sequence located 5' of the sequence encoding the secretory signal peptide, and 3' of the promoter. In some embodiments, the intron sequence comprises a MVM sequence or a HBB2 sequence, wherein the MVM sequence comprises the nucleic acid sequence of SEQ ID NO: 442, or a nucleic acid sequence at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 442, and the HBB2 sequence comprises the nucleic acid sequence of SEQ ID NO: 443 or SEQ ID NO: 444, or a nucleic acid sequence at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 443 or SEQ ID NO: 444.

[00258] In some embodiments, the intron sequence is a ubiquitin C (UBC) intron sequence, e.g.,

intron 1 from the UBC gene, or a portion thereof, e.g., as disclosed in Bianchi et al, 2009, Gene, 448 (1); 88-101, where the intron 1 sequence of the UBC gene is 812bp and starts at chromosomal location 124,914,586, and ends at 124,913,775. In some embodiments, the intron sequence is a UBC intron, for example, but not limited to intron sequence of SEQ ID NO: 445, or nucleic acid sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity to SEQ ID NO: 445.

[00259] In some embodiments, the rAAV genotype comprises an intron sequence selected in the group consisting of a human beta globin b2 (or HBB2) intron, a FIX intron, a chicken beta-globin intron, a CMVIE intron, a UBC intron, a HBB intron sequence, a MVM sequeocne and a SV40 intron. In some embodiment, the intron is intron 1 from human RNA pol II. In some embodiments, the intron is optionally a modified intron such as a modified HBB2 intron (see, e.g., SEQ ID NO: 17 in of WO2018046774A1): a modified FIX intron (see., e.g., SEQ ID NO: 19 in WO2018046774A1), or a modified chicken beta-globin intron (e.g., see SEQ ID NO: 21 in WO2018046774A1), or modified HBB2 or FIX introns disclosed in WO2015/162302, which are incorporated herein in their entirety by reference.

H. Poly-A sequences and Terminator sequences

[00260] In some embodiments, an rAAV vector genome includes at least one poly-A tail that is located 3' and downstream from the heterologous nucleic acid gene encoding the GAA polypeptide. Any polyA sequence can be used, including but not limited to hGH poly A, BGH poly A, SV40 poly A, synpA polyA and the like. In some embodiments, the polyA is a synthetic polyA sequence. In some embodiments, the rAAV vector genome comprises two poly-A tails, e.g., a hGH poly A sequence and another polyA sequence, where a spacer nucleic acid sequence is located between the two poly A sequences.

[00261] In some embodiments, the polyA signal is 3' of the heterologous nucleic acid sequence encoding the GAA polypeptide. In some embodiments, the rAAV genome comprises 3' of the nucleic acid encoding the GAA polypeptide, a first polyA sequence and a reverse RNA polymerase II terminator sequence (rev RNA PolII terminator sequence), and the 3' ITR. Non limiting examples of first polyA is hGH poly A, BGH poly A, SV40 poly A or, any functional fragment thereof in 5' to 3' orientation. Non limiting examples of reverse RNA polymerase II terminator sequence is hGH poly A, BGH poly A, SV40 poly A or, any functional fragment thereof in 3' to 5' orientation.

[00262] In some embodiments, the rAAV genome comprises 3' of the nucleic acid encoding the GAA polypeptide, a first polyA sequence, a spacer nucleic acid sequence (e.g., of between 100-400bp, or about 100-250bp, or about 250-400bp), a second poly A sequence, a spacer nucleic acid sequence, and the 3' ITR.

[00263] In some embodiments, the first and/or second poly A sequence is a hGH poly A sequence, and in some embodiments, the first and second poly A sequences are a synthetic poly A sequence. In

some embodiments, the first poly A sequence is a hGH poly A sequence and the second poly A sequence is a synthetic sequence, or vice versa – that is, in alternative embodiments, the first poly A sequence is a synthetic poly A sequence and the second poly A sequence is a hGH polyA sequence.

[00264] In some embodiments, the poly A sequence is selected from any of: SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44, where SEQ ID NO: 44 comprises the signal AATAAA, or a poly A nucleic acid sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity to any of SEQ ID NOS: 42, 43 or 44.

[00265] In some embodiments, the poly A sequence is selected from any of: SEQ ID NO: 46 or SEQ ID NO: 47, or a poly A nucleic acid sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity to any of SEQ ID NOS: 46 or 47.

[00266] In some embodiments, the poly A sequence is, for example, SEQ ID NO: 15 as disclosed in International WO2021102107 (hGH poly A sequence), or a poly A nucleic acid sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity to SEQ ID NO: 15 as disclosed in International Application WO2021102107. In some embodiments, the hGHpoly sequence encompassed for use is described in Anderson et al. J. Biol. Chem 264(14); 8222-8229, 1989 (See, e.g., p. 8223, 2nd column, first paragraph) which is incorporated herein in its entirety by reference.

[00267] In one embodiment, the recombinant AAV disclosed herein comprises in its genome a transcriptional terminator signal sequence or a transcriptional pause signal sequence in the reverse orientation between polyA and 3'ITR. In one embodiment, the recombinant AAV disclosed herein comprises in its genome a transcriptional terminator signal sequence or a transcriptional pause signal sequence that is in the 3'-5' orientation between polyA and 3'ITR. Any transcription termination signal can be used including, e.g., inverted natural polyA sequences from any species or synthetic polyA signals or fragments thereof, or other nucleic acid structure terminators known in the art. Exemplary polyA signals and/or transcription terminators include, but are not limited to the polyA signals of BGH, SV40, HGH, Betaglobin, RNA polymerase II transcriptional pause signal from alpha 2 globin gene, transcription termination signal for pol III, or fragments thereof, and in any combination thereof.

[00268] In some embodiments, a transcriptional terminator signal sequence is a reverse RNA polymerase II terminator sequence which is, in a 5' to 3' orientation SEQ ID NO: 45, or a rev RNA PolII terminator sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity to any of SEQ ID NOS: 45, where SEQ ID NO: 45 orientated in a 5' to 3' direction is located between the 3' of the poly A sequence and 5' of the right ITR sequence (or 3' ITR).

[00269] A transcription terminator signal or reverse RNA Polymerase II terminator sequence as described here is also interchangeably be called a "reverse poly A," which refers to a polyA signal sequence placed in a 3'-5' orientation downstream of the nucleic acid encoding GAA and upstream of 3'ITR. Any natural or synthetic poly A in 3'-5' orientation can be used as reverse poly A. In some

embodiments, the reverse poly A is the poly A (pA) as described in International publication no. WO2019143950 and US application publication no. US20200340013, which are incorporated herein by reference in its entirety.

[00270] For the sake of clarity, "reverse poly A," "the double stranded RNA termination element," and "reverse RNA Polymerase II terminator sequence" are used interchangeably herein. In 3' to 5' orientation, the reverse poly A or termination element does not allow transcription from 3'ITR, and hence double stranded RNA is not transcribed from 3'ITR. The reverse poly A or double stranded RNA termination element can be heterologous, e.g., from a different gene, for example, other than the gene of interest, or homologous to, e.g., the same gene as the gene of interest. In various embodiments, the poly A signal comprises the double stranded RNA transcription element or reverse poly A. For example, the poly A signal of several aspects of the invention described herein comprises a full length poly A signal in 5' to 3' orientation and another poly A signal in 3' to 5' orientation. In some embodiments, the 5' end of double stranded RNA termination element or reverse poly A sequence, and the 3' end of poly A signal are immediately next to each other, or at least 1 nucleotide apart, or at least 2 nucleotides apart, or at least 3 nucleotides apart, or at least 4 nucleotides apart, or at least 5 nucleotides apart, or or at least 6 nucleotides apart, or at least 7 nucleotides apart, or at least 8 nucleotides apart, or at least 9 nucleotides apart, or at least 10 nucleotides apart, or more apart. In some embodiments, the poly A signal does not comprise double stranded RNA transcription element or reverse poly A. In some embodiments, the poly A signal comprises AATAAA (SEQ ID NO: 467) or AAUAAA (SEQ ID NO: 468). In some embodiments, the poly A signal comprises at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10 repeats or more of AATAAA (SEQ ID NO: 467) or AAUAAA (SEQ ID NO: 468). In some embodiments, the poly A signal comprises transcription termination signal for Pol III as described in "Delineation of the Exact Transcription Termination Signal for Type 3 Polymerase III. Mol Ther Nucleic Acids. 2018 Mar 2;10:36-44, which is incorporated herein by reference in its entirety. In some embodiments, the one or more transcription termination signals for Pol III is in 3' to 5' orientation. In some embodiments, the poly A signal comprises TTTT. In some embodiments, poly A signal comprises AAAAAAA (SEQ ID NO: 469). The poly A sequences as described in "Definition of an efficient synthetic poly(A) site" Genes Dev. 1989 Jul;3(7):1019-25. doi: 10.1101/gad.3.7.1019., which is incorporated by reference in its entirety. All the above poly A sequences and or terminator sequences described herein can be used as inverted sequence e.g., in 3' to 5' orientation.

[00271] In some aspects of the invention descried herein, the poly A sequence comprises poly A sequence and a terminator sequence, e.g., the poly A sequence comprises hGH Poly A sequence and a Pol III terminator sequence. In various aspects of the invention, the poly A sequence and Pol III terminator sequences are interchangeably referred to as "poly A." In several aspects of the invention described herein, the poly A sequence further comprises a Reverse RNA Polymerase II terminator sequence, or RNA Polymerase II transcriptional pause signal sequence, or reverse poly A. Without

any limitation, an example of Reverse RNA Polymerase II terminator sequence, or RNA Polymerase II transcriptional pause signal sequence, or reverse Poly A, is the 3' sequence of the human hemoglobin alpha gene.

[00272] In some embodiments, a poly-A tail can be engineered to stabilize the RNA transcript that is transcribed from an rAAV vector genome, including a transcript for a heterologous gene, which in one embodiment is a GAA, and in alternative embodiments, the poly-A tail can be engineered to include elements that are destabilizing.

[00273] In one embodiment, the polyA is a bi-directional polyA sequence. Bi-directional polyA sequences are commonly isolated from virual DNA, for example, the SV40 polyA is a bi-directional polyA.

[00274] In some embodiments of the methods to treat Pompe disease as disclosed herein, a recombinant AAV vector comprises at least one polyA sequence located 3' of the nucleic acid encoding the GAA gene and 5' of the 3' ITR sequence. In some embodiments, the poly A is a full length poly A (fl-polyA) sequence. In some embodiments, the polyA is a truncated polyA sequence as disclosed in International WO2021102107, which is incorporated herein in its entirity.

[00275] In an embodiment, a poly-A tail can be engineered to become a destabilizing element by altering the length of the poly-A tail. In an embodiment, the poly-A tail can be lengthened or shortened.

[00276] In some embodiments, there is a 3' untranslated regions (3'UTRs) located between the heterologous gene encoding the GAA polypeptide and the poly-A tail. In some embodiments, there is a 3' UTR located 3' of the nucleic acid sequence encoding the GAA polypeptide. In some embodiments, a 3' untranslated region (3'UTR) comprises GAA 3' UTR (SEQ ID NO: 50) or a 3' UTR (SEQ ID NO: 49) as disclosed herein.

[00277] In another embodiment, a promoter region, or 3' UTR or polyA region can comprise a destabilizing element, is a target sequence for a microRNA (miRNA) that has the ability to silence (repress translation and promote degradation) the RNA transcripts when the miRNA binds to a miRNA target sequence. Accordingly, in some embodiments, addition or deletion of seed regions within the 3-UTR or a poly-A tail can increase or decrease expression of a protein, such as the GAA polypeptide. In some embodiments, the miRNA target region is a synthetic miRNA target region which is targeted by an artificial miRNA (amiRNA) according to methods known in the art.

[00278] In another embodiment, seed regions can also be engineered into the 3' untranslated regions (3'UTRs) located between the heterologous gene and the poly-A tail. In a further embodiment, the destabilizing agent can be an siRNA. The coding region of the siRNA can be included in an rAAV vector genome and is generally located downstream, 3' of the poly-A tail.

[00279] In all aspects of the methods for treating Pompe disease as disclosed herein, the rAAV genome may also comprise a Stuffer DNA nucleic sequence. An exemplary stuffer DNA sequence is SEQ ID NO: 71 as disclosed in International Application WO2021102107, or a nucleic acid sequence

having at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% nucleotide sequence identity thereto. In some embodiments, the stuffer sequence is located 3' of the poly A tail, for example, and is located 5' of the '3 ITR sequence. In some embodiments, the stuffer DNA sequence comprises a synthetic polyadenylation signal in the reverse orientation.

[00280] In some embodiments, a stuffer nucleic acid sequence (also referred to as a "spacer" nucleic acid fragment) can be located between the poly A sequence and the 3' ITR (i.e., a stuffer nucleic acid sequence is located 3' of the polyA sequence and 5' of the 3' ITR). Such a stuffer nucleic acid sequence can be about 30bp, 50pb, 75bp, 100bp, 150bp, 200bp, 250bp, 300bp or longer than 300bp. In some embodiments of the methods and compositions as disclosed herein, a stuffer nucleic acid fragment is between 20-50bp, 50-100bp, 100-200bp, 200-300bp, 300-500bp, or any integer between 20-500bp. Exemplary stuffer (or spacer) nucleic acid sequence can be selected from any of: SEQ ID NO: 16, SEQ ID NO: 71 or SEQ ID NO: 78 as disclosed in International Application WO2021102107, or a nucleic acid sequence at least about 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%, identical to SEQ ID NO: 16 or SEQ ID NO: 71 or SEQ ID NO: 78 as disclosed in International Application WO2021102107.

E. CS sequence

[00281] In some embodiments of the methods and compositions disclosed herein, a recombinant AAV vector comprises a heterologous nucleic acid sequence that can further comprises at collagen stability (CS) sequence located 3' of the nucleic acid encoding the GAA polypeptide and 5' of the 3' ITR sequence. In some embodiments, the rAAV genome disclosed herein comprises a heterologous nucleic acid sequence that can optionally comprise a Collagen stability sequence (CS or CSS), which is positioned 3' of the nucleic acid encoding the GAA polypeptide and 5' of the nucleic acid encoding a polyA signal. In some embodiments, the CS sequence can be replaced by a 3' UTR sequence as disclosed herein.

[00282] Exemplary collagen stability sequences include CCCAGCCCACTTTTCCCCAA or a sequence at least 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity thereto. An exemplary collagen stability sequence can have an amino acid sequence of PSPLFP or an amino acid sequence having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity thereto. CS sequences are disclosed in Holick and Liebhaber, Proc. Nat. Acad. Sci. 94: 2410-2414, 1997 (See, e.g. Figure 3, p. 5205), which is incorporated herein its entirety by reference.

I. AAV ITRs

[00283] The rAAV vector or genome as disclosed herein for use in the methods to treat Pompe disease can comprise AAV ITRs that have desirable characteristics and can be designed to modulate the activities of, and cellular responses to vectors that incorporate the ITRs. In another embodiment, the AAV ITRs are synthetic AAV ITRs that has desirable characteristics and can be designed to manipulate the activities of and cellular responses to vectors comprising one or two synthetic ITRs,

including, as set forth in U.S. Patent No. 9,447433, which is incorporated herein by reference.

[00284] In another embodiment, an ITR exhibits modified transcription activity relative to a naturally occurring ITR, e.g., ITR2 from AAV2. It is known that the ITR2 sequence inherently has promoter activity. It also inherently has termination activity, similar to a poly(A) sequence. The minimal functional ITR of the present invention exhibits transcription activity as shown in the examples, although at a diminished level relative to ITR2. Thus, in some embodiments, the ITR is functional for transcription. In other embodiments, the ITR is defective for transcription. In certain embodiments, the ITR can act as a transcription insulator, e.g., preventing transcription of a transgenic cassette present in the vector when the vector is integrated into a host chromosome.

[00285] One aspect of the invention relates to an rAAV vector genome comprising at least one synthetic AAV ITR, wherein the nucleotide sequence of one or more transcription factor binding sites in the ITR is deleted and/or substituted, relative to the sequence of a naturally occurring AAV ITR such as ITR2. In some embodiments, it is the minimal functional ITR in which one or more transcription factor binding sites are deleted and/or substituted. In some embodiments at least 1 transcription factor binding site is deleted and/or substituted, e.g., at least 5 or more or 10 or more transcription factor binding sites, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 transcription factor binding sites.

[00286] Another embodiment, a rAAV vector, including an rAAV vector genome as described herein comprises a polynucleotide comprising at least one synthetic AAV ITR, wherein one or more CpG islands (a cytosine base followed immediately by a guanine base (a CpG) in which the cytosines in such arrangement tend to be methylated) that typically occur at, or near the transcription start site in an ITR are deleted and/or substituted. In an embodiment, deletion or reduction in the number of CpG islands can reduce the immunogenicity of the rAAV vector. This results from a reduction or complete inhibition in TLR-9 binding to the rAAV vector DNA sequence, which occurs at CpG islands. It is also well known that methylation of CpG motifs results in transcriptional silencing. Removal of CpG motifs in the ITR is expected to result in decreased TLR-9 recognition and/or decreased methylation and therefore decreased transgene silencing. In some embodiments, it is the minimal functional ITR in which one or more CpG islands are deleted and/or substituted. In an embodiment, AAV ITR2 is known to contain 16 CpG islands of which one or more, or all 16 can be deleted.

[00287] In some embodiments, at least 1 CpG motif is deleted and/or substituted, *e.g.*, at least 4 or more or 8 or more CpG motifs, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 CpG motifs.

[00288] In another embodiment, the synthetic ITR comprises, consists essentially of, or consists of one of the nucleotide sequences listed in Table 4. In other embodiments, the synthetic ITR comprises, consist essentially of, or consist of a nucleotide sequence that is at least 80% identical, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to any one of the nucleotide sequences listed in Table 4. In some embodiments, the ITR is a sequence is disclosed in FIG. 1 of Samulski *et al.,* 1983,

Cell, 33; 135-143 (referred to "Samulski *et al,* 1983" as which is incorporated herein in its entirety by reference), which discloses modified ITR sequences in FIG. 1. In some embodiments, the ITR sequence comprises, or consists of a nucleotide sequence that is at least 80% identical, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to one of the ITR sequences in FIG. 1 as disclosed in Samulski *et al,* 1993. In some embodiments, the ITR comprises, or consists of a nucleotide sequence that is at least 80% identical, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% or 99.5% identical to the ITR sequence of pSM 609 right disclosed in the middle panel of FIG. 1 (that lacks the 9bp) disclosed in Samulski *et al,* 1983. In some embodiments, the ITR comprises a nucleotide sequence that is at least 80% identical, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% or 99.5% identical to the ITR sequence of any of SEQ ID NOs: 79-84 and 450-451.

[00289] In some embodiments, the ITR sequence, e.g., Right ITR (or 3' ITR) is SEQ ID NO: 80 or SEQ ID NO: 82 or a nucleotide sequence that is at least 80% identical, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% or 99.5% identical to SEQ ID NO: 80 or SEQ ID NO: 82. In some embodiments, the ITR sequence, e.g., left ITR (or 5' ITR) is SEQ ID NO: 79 or SEQ ID NO: 81 or a nucleotide sequence that is at least 80% identical, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% or 99.5% identical to SEQ ID NO: 79 or SEQ ID NO: 81.

[00290] Table 4: Exemplary synthetic ITR sequences

L-ITR	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTC GGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGA GGGAGTGGCCAACTCCATCACTAGGGGTTCCT (SEQ ID NO: 79)
R-ITR	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCG CTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCC GGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 80)
L-ITR	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTC GGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGA GGGAGTGGCCAACTCCATCACTAGGG (SEQ ID NO: 81)
R-ITR	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCG CTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCC GGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 82)
MH-257	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCG CTCACTGAGGCAATTTGATAAAAATCGTCAAATTATAAACAGGCTTTGCC TGTTTAGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACT CCATCACTAGGGGTTCCT (SEQ ID NO: 83)
MH-258	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCG CTCACTGAGGGATAAAAATCCAGGCTTTGCCTGCCTCAGTGAGCGAGCG AGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCT (SEQ ID NO: 84)
MH Delta 258	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCG CTCACTGAGGGATAAAAATCCAGGCTTTGCCTGCCTCAGTGAGCGAGCG AGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCT (SEQ ID NO: 85)
MH Telomere-1 ITR	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGGGATTGGGATTG CGCGCTCGCTCGCGGGATTGGGATTGGGATTGGGATTGGGATTGGGATTG ATAAAAATCAATCCCAATCCCAATCCCAATCCCAATCCCAATCCCGCGAG CGAGCGCGCAATCCCAATCCCAGAGAGGGAGTGGCCAACTCCATCACTA GGGGTTCCT (SEQ ID NO: 86)

MH Telomere-2 ITR	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCG CTCGGGATTGGGATTGGGATTGGGATTGGGATTGGGATTGATAAAAATC AATCCCAATCCCAATCCCAATCCCAATCCCAATCCCGCGAGCGAGCGCGC AGGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTAAGCTTATTAT A (SEQ ID NO: 87)
MH PolII 258 ITR	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCG CTCACTGAGGGCGCCTATAAAGATAAAAATCCAGGCTTTGCCTGCCTCAG TTAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGG TTCCT (SEQ ID NO: 88)
MH 258 Delta D conservative	CTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGA GGGATAAAAATCCAGGCTTTGCCTGCCTCAGTGAGCGAGCGAGCGCGCA GAGAGGGAGTGGCCAACTCCATCACTAG (SEQ ID NO: 89)
5' ITR	TTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACC AAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAG CGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCT (SEQ ID NO: 104)
3' ITR	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCG CTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCC GGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAA (SEQ ID NO: 105)
ITR (145bp)	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCG CTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCC GGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAA (SEQ ID NO: 448)
ITR (145bp – 1983, lacking 9bp)	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCG CTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCC GGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGG (SEQ ID NO: 449)

II. Vectors and Virions

[00291] In one embodiment, the rAAV vector (also referred to as a rAAV virion) as disclosed herein comprises a capsid protein, and a rAAV genome in the capsid protein. A rAAV capsid of the rAAV virion used to treat Pompe Disease is any of those listed in Table 3 herein, or in Table 1 as disclosed in International Applications WO2020/102645, and WO2020/102667, each of which are incorporated herein in their entirety. In one embodiment, a rAAV capsid of the rAAV virion used to treat Pompe Disease is an AAV8 capsid. In one embodiment, a rAAV vector is an rAAV8 vector.

[00292] Table 3: Table 3: AAV Serotypes and exemplary Published corresponding capsid sequence

TABLE 3	
Serotype and where capsid sequence is published	**Serotype and where capsid sequence is published**
AAV3.3b (See SEQ ID NO:72 in US20030138772)	AAV3-3 (See SEQ ID NO: 200 US20150315612)
AAV3-3 (See SEQ ID NO:217 US20150315612)	AAV3a ((See SEQ ID NO: 5 in US6156303)
AAV3a (See SEQ ID NO: 9 in US6156303)	AAV3b (See SEQ ID NO: 6 in US6156303)
AAV3b (See SEQ ID NO:10 in US6156303)	AAV3b (See SEQ ID NO: 1 in US6156303)

AAV4 (See SEQ ID NO:17 US20140348794)	AAV4 ((See SEQ ID NO:5 in US20140348794)
AAV4 (See SEQ ID NO: 3 in US20140348794)	AAV4 (See SEQ ID NO:14 in US20140348794)
AAV4 (See SEQ ID NO: 15 in US20140348794)	AAV4 (See SEQ ID NO: 19 in US20140348794)
AAV4 (See SEQ ID NO: 12 in US20140348794)	AAV4 (See SEQ ID NO: 13 in US20140348794)
AAV4 (See SEQ ID NO: 7 in US20140348794)	AAV4 (See SEQ ID NO: 8 in US20140348794)
AAV4 (See SEQ ID NO: 9 in US20140348794)	AAV4 (See SEQ ID NO: 2 in US20140348794)
AAV4 (See SEQ ID NO: 10 in US20140348794)	AAV4 (See SEQ ID NO: 11 in US20140348794)
AAV4 (See SEQ ID NO: 18 in US20140348794)	AAV4 (See SEQ ID NO:63 in US20030138772) and US20160017295 SEQ
ID NO: (See SEQ ID NO: 4 in US20140348794)	AAV4 (See SEQ ID NO: 16 in US20140348794)
AAV4 (See SEQ ID NO: 20 in US20140348794)	AAV4 (See SEQ ID NO: 6 in US20140348794)
AAV4 (See SEQ ID NO: 1 in US20140348794)	AAV42.2 (See SEQ ID NO: 9 in US20030138772)
AAV42.2 (See SEQ ID NO: 102 in US20030138772)	AAV42.3b (See SEQ ID NO: 36 in US20030138772)
AAV42.3B (See SEQ ID NO: 107 in US20030138772)	AAV42.4 (See SEQ ID NO: 33 in US20030138772)
AAV42.4 (See SEQ ID NO: 88 in US20030138772)	AAV42.8 (See SEQ ID NO: 27 in US20030138772)
AAV42.8 (See SEQ ID NO: 85 in US20030138772)	AAV43.1 (See SEQ ID NO: 39 in US20030138772)
AAV43.1 (See SEQ ID NO: 92 in US20030138772)	AAV43.12 (See SEQ ID NO: 41 in US20030138772)
AAV43.12 (See SEQ ID NO: 93 in US20030138772)	AAV8 (See SEQ ID NO: 15 in US20150159173)
AAV8 (See SEQ ID NO: 7 in US20150376240)	AAV8 (See SEQ ID NO:4 in US20030138772;US20150315612 SEQ
ID NO: 182	AAV8 (See SEQ ID NO: 95 in US20030138772), US20140359799 SEQ

AAV8 (See SEQ ID NO: 31 in US20150159173)	AAV8 (See, e.g., SEQ ID NO: 8 in US20160017295, or SEQ ID NO:7 in US7198951, or SEQ ID NO: 223 in US20150315612)
AAV8 (See SEQ ID NO: 8 in US20150376240)	AAV8 (See SEQ ID NO: 214 in US20150315612)
AAV-8b (See SEQ ID NO: 5 in US20150376240)	AAV-8b (See SEQ ID NO: 3 in US20150376240)
AAV-8h (See SEQ ID NO: 6 in US20150376240)	AAV-8h (See SEQ ID NO: 4 in US20150376240)
AAV9 (See SEQ ID NO: 5 in US20030138772)	AAV9 (See SEQ ID NO: 1 in US7198951)
AAV9 (See SEQ ID NO: 9 in US20160017295)	AAV9 (See SEQ ID NO: 100 in US20030138772), US7198951 SEQ ID NO: 2
	AAV9 (See SEQ ID NO: 3 in US7198951)
AAV9 (AAVhu.14) (See SEQ ID NO: 3 in US20150315612)	AAV9 (AAVhu.14) (See SEQ ID NO: 123 in US20150315612)
AAVA3.1 (See SEQ ID NO: 120 in US20030138772)	AAVA3.3 (See SEQ ID NO: 57 in US20030138772)
AAVA3.3 (See SEQ ID NO: 66 in US20030138772)	AAVA3.4 (See SEQ ID NO: 54 in US20030138772)
AAVA3.4 (See SEQ ID NO: 68 in US20030138772)	AAVA3.5 (See SEQ ID NO: 55 in US20030138772)
AAVA3.5 (See SEQ ID NO: 69 in US20030138772)	AAVA3.7 (See SEQ ID NO: 56 in US20030138772)
AAVA3.7 (See SEQ ID NO: 67 in US20030138772)	AAV29. (See SEQ ID NO: 11 in (AAVbb. l) 161 US20030138772)
AAVC2 (See SEQ ID NO: 61 in US20030138772)	AAVCh.5 (See SEQ ID NO:46 in US20150159173); US20150315612 SEQ
ID NO: 234	AAVcy.2 (AAV13.3) (See SEQ ID NO: 15 in US20030138772)
AAV24.1 (See SEQ ID NO: 101 in US20030138772)	AAVcy.3 (AAV24.1) (See SEQ ID NO: 16 in US20030138772)
AAV27.3 (See SEQ ID NO: 104 in US20030138772)	AAVcy.4 (AAV27.3) (See SEQ ID NO: 17 in US20030138772)
AAVcy.5 (See SEQ ID NO: 227 in US20150315612)	AAV7.2 (See SEQ ID NO: 103 in US20030138772)
AAVcy.5 (AAV7.2) (See SEQ ID NO: 18 in US20030138772)	AAV16.3 (See SEQ ID NO: 105 in US20030138772)

AAVcy.6 (AAV16.3) (See SEQ ID NO: 10 in US20030138772)	AAVcy.5 (See SEQ ID NO: 8 in US20150159173)
AAVcy.5 (See SEQ ID NO: 24 in US20150159173)	AAVCy.5Rl (See SEQ ID NO: in US20150159173
AAVCy.5R2 (See SEQ ID NO: in US20150159173)	AAVCy.5R3 (See SEQ ID NO: in US20150159173
AAVCy.5R4 (See SEQ ID NO: in US20150159173)	AAVDJ (See SEQ ID NO: 3 in US20140359799) and SEQ ID NO: 2 in US7588772)
	AAVDJ (See SEQ ID NO: 2 in US20140359799; and SEQ ID NO: 1 in US7588772)
	AAVDJ-8 (See SEQ ID NO: in US7588772; Grimm et al 2008
AAVDJ-8 (See SEQ ID NO: in US7588772; Grimm et al 2008	AAVF5 (See SEQ ID NO: 110 in US20030138772)
AAVH2 (See SEQ ID NO: 26 in US20030138772)	AAVH6 (See SEQ ID NO: 25 in US20030138772)
AAVhEl. l (See SEQ ID NO: 44 in US9233131)	AAVhErl.14 (See SEQ ID NO: 46 in US9233131)
AAVhErl.16 (See SEQ ID NO: 48 in US9233131)	AAVhErl.18 (See SEQ ID NO: 49 in US9233131)
AAVhErl.23 (AAVhEr2.29) (See SEQ ID NO: 53 in US9233131)	AAVhErl.35 (See SEQ ID NO: 50 in US9233131)
AAVhErl.36 (See SEQ ID NO: 52 in US9233131)	AAVhErl.5 (See SEQ ID NO: 45 in US9233131)
AAVhErl.7 (See SEQ ID NO: 51 in US9233131)	AAVhErl.8 (See SEQ ID NO: 47 in US9233131)
AAVhEr2.16 (See SEQ ID NO: 55 in US9233131)	AAVhEr2.30 (See SEQ ID NO: 56 in US9233131)
AAVhEr2.31 (See SEQ ID NO: 58 in US9233131)	AAVhEr2.36 (See SEQ ID NO: 57 in US9233131)
AAVhEr2.4 (See SEQ ID NO: 54 in US9233131)	AAVhEr3.1 (See SEQ ID NO: 59 in US9233131)
AAVhu.l (See SEQ ID NO: 46 in US20150315612)	AAVhu.l (See SEQ ID NO: 144 in US20150315612)
AAVhu.lO (AAV16.8) (See SEQ ID NO: 56 in US20150315612)	AAVhu.lO (AAV16.8) (See SEQ ID NO: 156 in US20150315612)

AAVhu.l1 (AAV16.12) (See SEQ ID NO: 57 in US20150315612)	AAVhu.l1 (AAV16.12) (See SEQ ID NO: 153 in US20150315612)
AAVhu.12 (See SEQ ID NO: 59 in US20150315612)	AAVhu.12 (See SEQ ID NO: 154 in US20150315612)
AAVhu.13 (See SEQ ID NO: 16 in US2015015917 and ID NO: 71 in US20150315612)	
AAVhu.13 (See SEQ ID NO: 32 in US20150159173 and ID NO: 129 US20150315612)	
AAVhu.136.1 (See SEQ ID NO: 165 in US20150315612)	AAVhu.140.1 (See SEQ ID NO: 166 in US20150315612)
AAVhu.140.2 (See SEQ ID NO: 167 in US20150315612)	AAVhu.145.6 (See SEQ ID NO: 178 in US20150315612)
AAVhu.15 (See SEQ ID NO: 147 in US20150315612)	AAVhu.15 (AAV33.4) (See SEQ ID NO: 50 in US20150315612)
AAVhu.156.1 (See SEQ ID NO: 179 in US20150315612)	AAVhu.16 (See SEQ ID NO: 148 in US20150315612)
AAVhu.l6 (AAV33.8) (See SEQ ID NO: 51 in US20150315612)	AAVhu.17 (See SEQ ID NO: 83 in US20150315612)
AAVhu.l7 (AAV33.12) (See SEQ ID NO: 4 in US20150315612)	AAVhu.172.1 (See SEQ ID NO: 171 in US20150315612)
AAVhu.172.2 (See SEQ ID NO: 172 in US20150315612)	AAVhu.173.4 (See SEQ ID NO: 173 in US20150315612)
AAVhu.173.8 (See SEQ ID NO: 175 in US20150315612)	AAVhu.18 (See SEQ ID NO: 52 in US20150315612)
AAVhu.18 (See SEQ ID NO: 149 in US20150315612)	AAVhu.19 (See SEQ ID NO: 62 in US20150315612)
AAVhu.19 (See SEQ ID NO: 133 in US20150315612)	AAVhu.2 (See SEQ ID NO: 48 in US20150315612)
AAVhu.2 (See SEQ ID NO: 143 in US20150315612)	AAVhu.20 (See SEQ ID NO: 63 in US20150315612)
AAVhu.20 (See SEQ ID NO: 134 in US20150315612)	AAVhu.21 (See SEQ ID NO: 65 in US20150315612)
AAVhu.21 (See SEQ ID NO: 135 in US20150315612)	AAVhu.22 (See SEQ ID NO: 67 in US20150315612)
AAVhu.22 239 (See SEQ ID NO: 138 in US20150315612)	AAVhu.23 (See SEQ ID NO: 60 in US20150315612)
AAVhu.23.2 (See SEQ ID NO: 137 in US20150315612)	AAVhu.24 (See SEQ ID NO: 66 in US20150315612)

AAVhu.24 (See SEQ ID NO: 136 in US20150315612)	AAVhu.25 (See SEQ ID NO: 49 in US20150315612)
AAVhu.25 (See SEQ ID NO: 146 in US20150315612)	AAVhu.26 (See SEQ ID NO: 17 in US20150159173 and SEQ ID NO: 61 in US20150315612)
	AAVhu.26 (See SEQ ID NO: 33 in US20150159173), US20150315612 SEQ
	AAVhu.27 (See SEQ ID NO: 64 in US20150315612)
AAVhu.27 (See SEQ ID NO: 140 in US20150315612)	AAVhu.28 (See SEQ ID NO: 68 in US20150315612)
AAVhu.28 (See SEQ ID NO: 130 in US20150315612)	AAVhu.29 (See SEQ ID NO: 69 in US20150315612)
AAVhu.29 (See SEQ ID NO: 42 in US20150159173 and SEQ ID NO: 132 in US20150315612)	
AAVhu.29 (See SEQ ID NO: 225 in US20150315612)	AAVhu.29R (See SEQ ID NO: in US20150159173
AAVhu.3 (See SEQ ID NO: 44 in US20150315612)	AAVhu.3 (See SEQ ID NO: 145 in US20150315612)
AAVhu.30 (See SEQ ID NO: 70 in US20150315612)	AAVhu.30 (See SEQ ID NO: 131 in US20150315612)
AAVhu.31 (See SEQ ID NO: 1 in US20150315612)	AAVhu.31 (See SEQ ID NO: 121 in US20150315612)
AAVhu.32 (See SEQ ID NO: 2 in US20150315612)	AAVhu.32 (See SEQ ID NO: 122 in US20150315612)
AAVhu.33 (See SEQ ID NO: 75 in US20150315612)	AAVhu.33 (See SEQ ID NO: 124 in US20150315612)
AAVhu.34 (See SEQ ID NO: 72 in US20150315612)	AAVhu.34 (See SEQ ID NO: 125 in US20150315612)
AAVhu.35 (See SEQ ID NO: 73 in US20150315612)	AAVhu.35 (See SEQ ID NO: 164 in US20150315612)
AAVhu.36 (See SEQ ID NO: 74 in US20150315612)	AAVhu.36 (See SEQ ID NO: 126 in US20150315612)
AAVhu.37 (See SEQ ID NO: 34 in US20150159173 and SEQ ID NO: 88 in US20150315612)	
AAVhu.37 (AAV106.1) (See SEQ ID NO: 10 in US20150315612 and SEQ ID NO: 18 in US20150159173)	

AAVhu.38 (See SEQ ID NO: 161 in US20150315612)	AAVhu.39 (See SEQ ID NO: 102 in US20150315612)
AAVhu.39 (AAVLG-9) (See SEQ ID NO: 24 in US20150315612)	AAVhu.4 (See SEQ ID NO: 47 in US20150315612)
AAVhu.4 (See SEQ ID NO: 141 in US20150315612)	AAVhu.40 (See SEQ ID NO: 87 in US20150315612)
AAVhu.40 (AAV114.3) (See SEQ ID NO: 11 in US20150315612)	AAVhu.41 (See SEQ ID NO: 91 in US20150315612)
AAVhu.41 (AAV127.2) (See SEQ ID NO: 6 in US20150315612)	AAVhu.42 (See SEQ ID NO: 85 in US20150315612)
AAVhu.42 (AAV127.5) (See SEQ ID NO:8 in US20150315612)	AAVhu.43 (See SEQ ID NO: 160 in US20150315612)
AAVhu.43 (See SEQ ID NO: 236 in US20150315612)	AAVhu.43 (AAV128.1) (See SEQ ID NO: 80 in US20150315612)
AAVhu.44 (See SEQ ID NO: 45 in US20150159173 and SEQ ID NO: 158 in US20150315612)	
AAVhu.44 (AAV128.3) (See SEQ ID NO: 81 in US20150315612)	AAVhu.44Rl (See SEQ ID NO: in US20150159173
AAVhu.44R2 (See SEQ ID NO: in US20150159173	AAVhu.44R3 (See SEQ ID NO: in US20150159173
AAVhu.45 (See SEQ ID NO: 76 in US20150315612)	AAVhu.45 (See SEQ ID NO: 127 in US20150315612)
AAVhu.46 (See SEQ ID NO: 82 in US20150315612)	AAVhu.46 (See SEQ ID NO: 159 in US20150315612)
AAVhu.46 (See SEQ ID NO: 224 in US20150315612)	AAVhu.47 (See SEQ ID NO: 77 in US20150315612)
AAVhu.47 (See SEQ ID NO: 128 in US20150315612)	AAVhu.48 (See SEQ ID NO: 38 in US20150159173)
AAVhu.48 (See SEQ ID NO: 157 in US20150315612)	AAVhu.48 (AAV130.4) (See SEQ ID NO: 78 in US20150315612)
AAVhu.48Rl (See SEQ ID NO: in US20150159173	AAVhu.48R2 (See SEQ ID NO: in US20150159173
AAVhu.48R3 (See SEQ ID NO: in US20150159173	AAVhu.49 (See SEQ ID NO: 209 in US20150315612)
AAVhu.49 (See SEQ ID NO: 189 in US20150315612)	AAVhu.5 (See SEQ ID NO: 45 in US20150315612)
AAVhu.5 (See SEQ ID NO: 142 in US20150315612)	AAVhu.51 (See SEQ ID NO: 208 in US20150315612)

AAVhu.51 (See SEQ ID NO: 190 in US20150315612)	AAVhu.52 (See SEQ ID NO: 210 in US20150315612)
AAVhu.52 (See SEQ ID NO: 191 in US20150315612)	AAVhu.53 (See SEQ ID NO: 19 in US20150159173)
AAVhu.53 (See SEQ ID NO: 35 in US20150159173)	AAVhu.53 (AAV145.1) (See SEQ ID NO: 176 in US20150315612)
AAVhu.54 (See SEQ ID NO: 188 in US20150315612)	AAVhu.54 (AAV145.5) (See SEQ ID NO: 177 in US20150315612)
AAVhu.55 (See SEQ ID NO: 187 in US20150315612)	AAVhu.56 (See SEQ ID NO: 205 in US20150315612)
AAVhu.56 (AAV145.6) (See SEQ ID NO: 168 in US20150315612)	AAVhu.56 (AAV145.6) (See SEQ ID NO: 192 in US20150315612)
AAVhu.57 (See SEQ ID NO: 206 in US20150315612)	AAVhu.57 (See SEQ ID NO: 169 in US20150315612)
AAVhu.57 (See SEQ ID NO: 193 in US20150315612)	AAVhu.58 (See SEQ ID NO: 207 in US20150315612)
AAVhu.58 (See SEQ ID NO: 194 in US20150315612)	AAVhu.6 (AAV3.1) (See SEQ ID NO: 5 in US20150315612)
AAVhu.6 (AAV3.1) (See SEQ ID NO: 84 in US20150315612)	AAVhu.60 (See SEQ ID NO: 184 in US20150315612)
AAVhu.60 (AAV161.10) (See SEQ ID NO: 170 in US20150315612)	AAVhu.61 (See SEQ ID NO: 185 in US20150315612)
AAVhu.61 (AAV161.6) (See SEQ ID NO: 174 in US20150315612)	AAVhu.63 (See SEQ ID NO: 204 in US20150315612)
AAVhu.63 (See SEQ ID NO: 195 in US20150315612)	AAVhu.64 (See SEQ ID NO: 212 in US20150315612)
AAVhu.64 (See SEQ ID NO: 196 in US20150315612)	AAVhu.66 (See SEQ ID NO: 197 in US20150315612)
AAVhu.67 (See SEQ ID NO: 215 in US20150315612)	AAVhu.67 (See SEQ ID NO: 198 in US20150315612)
AAVhu.7 (See SEQ ID NO: 226 in US20150315612)	AAVhu.7 (See SEQ ID NO: 150 in US20150315612)
AAVhu.7 (AAV7.3) (See SEQ ID NO: 55 in US20150315612)	AAVhu.71 (See SEQ ID NO: 79 in US20150315612)
AAVhu.8 (See SEQ ID NO: 53 in US20150315612)	AAVhu.8 (See SEQ ID NO: 12 in US20150315612)
AAVhu.8 (See SEQ ID NO: 151 in US20150315612)	AAVhu.9 (AAV3.1) (See SEQ ID NO: 58 in US20150315612)

AAVhu.9 (AAV3.1) (See SEQ ID NO: 155 in US20150315612)	AAV-LK01 (See SEQ ID NO: 2 in US20150376607)
AAV-LK01 (See SEQ ID NO: 29 in US20150376607)	AAV-LK02 (See SEQ ID NO: 3 in US20150376607)
AAV-LK02 (See SEQ ID NO: 30 in US20150376607)	AAV-LK03 (See SEQ ID NO: 4 in US20150376607)
AAV-LK03 (See SEQ ID NO: 12 in WO2015121501 and SEQ ID NO: 31 in US20150376607)	
AAV-LK04 (See SEQ ID NO: 5 in US20150376607)	AAV-LK04 (See SEQ ID NO: 32 in US20150376607)
AAV-LK05 (See SEQ ID NO: 6 in US20150376607)	AAV-LK05 (See SEQ ID NO: 33 in US20150376607)
AAV-LK06 (See SEQ ID NO: 7 in US20150376607)	AAV-LK06 (See SEQ ID NO: 34 in US20150376607)
AAV-LK07 (See SEQ ID NO: 8 in US20150376607)	AAV-LK07 (See SEQ ID NO: 35 in US20150376607)
AAV-LK08 (See SEQ ID NO: 9 in US20150376607)	AAV-LK08 (See SEQ ID NO: 36 in US20150376607)
AAV-LK09 (See SEQ ID NO: 10 in US20150376607)	AAV-LK09 (See SEQ ID NO: 37 in US20150376607)
AAV-LK10 (See SEQ ID NO: 11 in US20150376607)	AAV-LK10 (See SEQ ID NO: 38 in US20150376607)
AAV-LK11 (See SEQ ID NO: 12 in US20150376607)	AAV-LK11 (See SEQ ID NO: 39 in US20150376607)
AAV-LK12 (See SEQ ID NO: 13 in US20150376607)	AAV-LK12 (See SEQ ID NO: 40 in US20150376607)
AAV-LK13 (See SEQ ID NO: 14 in US20150376607)	AAV-LK13 (See SEQ ID NO: 41 in US20150376607)
AAV-LK14 (See SEQ ID NO: 15 in US20150376607)	AAV-LK14 (See SEQ ID NO: 42 in US20150376607)
AAV-LK15 (See SEQ ID NO: 16 in US20150376607)	AAV-LK15 (See SEQ ID NO: 43 in US20150376607)
AAV-LK16 (See SEQ ID NO: 17 in US20150376607)	AAV-LK16 (See SEQ ID NO: 44 in US20150376607)
AAV-LK17 (See SEQ ID NO: 18 in US20150376607)	AAV-LK17 (See SEQ ID NO: 45 in US20150376607)
AAV-LK18 (See SEQ ID NO: 19 in US20150376607)	AAV-LK18 (See SEQ ID NO: 46 in US20150376607)

AAV-LK19 (See SEQ ID NO: 20 in US20150376607)	AAV-LK19 (See SEQ ID NO: 47 in US20150376607)
AAV-PAEC (See SEQ ID NO: 1 in US20150376607)	AAV-PAEC (See SEQ ID NO: 48 in US20150376607)
AAV-PAEC11 (See SEQ ID NO: 26 in US20150376607)	AAV-PAEC11 (See SEQ ID NO: 54 in US20150376607)
AAV-PAEC 12 (See SEQ ID NO: 27 in US20150376607)	AAV-PAEC 12 (See SEQ ID NO: 51 in US20150376607)
AAV-PAEC 13 (See SEQ ID NO: 28 in US20150376607)	AAV-PAEC 13 (See SEQ ID NO: 49 in US20150376607)
AAV-PAEC2 (See SEQ ID NO: 21 in US20150376607)	AAV-PAEC2 (See SEQ ID NO: 56 in US20150376607)
AAV-PAEC4 (See SEQ ID NO: 22 in US20150376607)	AAV-PAEC4 (See SEQ ID NO: 55 in US20150376607)
AAV-PAEC6 (See SEQ ID NO: 23 in US20150376607)	AAV-PAEC6 (See SEQ ID NO: 52 in US20150376607)
AAV-PAEC7 (See SEQ ID NO: 24 in US20150376607)	AAV-PAEC7 (See SEQ ID NO: 53 in US20150376607)
AAV-PAEC8 (See SEQ ID NO: 25 in US20150376607)	AAV-PAEC8 (See SEQ ID NO: 50 in US20150376607)
AAVpi.1 (See SEQ ID NO: 28 in US20150315612)	AAVpi.1 (See SEQ ID NO: 93 in US20150315612; AAVpi.2 408, see SEQ ID NO: 30 in US20150315612)
AAVpi.2 (See SEQ ID NO: 95 in US20150315612)	AAVpi.3 (See SEQ ID NO: 29 in US20150315612)
AAVpi.3 (See SEQ ID NO: 94 in US20150315612)	AAVrh.10 (See SEQ ID NO: 9 in US20150159173)
AAVrh.10 (See SEQ ID NO: 25 in US20150159173)	AAV44.2 (See SEQ ID NO: 59 in US20030138772)
AAVrh.10 (AAV44.2) (See SEQ ID NO: 81 in US20030138772)	AAV42.1B (See SEQ ID NO: 90 in US20030138772)
AAVrh.12 (AAV42.1b) (See SEQ ID NO: 30 in US20030138772)	AAVrh.13 (See SEQ ID NO: 10 in US20150159173)
AAVrh.13 (See SEQ ID NO: 26 in US20150159173)	AAVrh.13 (See SEQ ID NO: 228 in US20150315612)
AAVrh.13R (See SEQ ID NO: in US20150159173	AAV42.3A (See SEQ ID NO: 87 in US20030138772)
AAVrh.14 (AAV42.3a) (See SEQ ID NO: 32 in US20030138772)	AAV42.5A (See SEQ ID NO: 89 in US20030138772)

AAVrh.l7 (AAV42.5a) (See SEQ ID NO: 34 in US20030138772)	AAV42.5B (See SEQ ID NO: 91 in US20030138772)
AAVrh.l8 (AAV42.5b) (See SEQ ID NO: 29 in US20030138772)	AAV42.6B (See SEQ ID NO: 112 in US20030138772)
AAVrh.l9 (AAV42.6b) (See SEQ ID NO: 38 in US20030138772)	AAVrh.2 (See SEQ ID NO: 39 in US20150159173)
AAVrh.2 (See SEQ ID NO: 231 in US20150315612)	AAVrh.20 (See SEQ ID NO: 1 in US20150159173)
AAV42.10 (See SEQ ID NO: 106 in US20030138772)	AAVrh.21 (AAV42.10) (See SEQ ID NO: 35 in US20030138772)
AAV42.11 (See SEQ ID NO: 108 in US20030138772)	AAVrh.22 (AAV42.11) (See SEQ ID NO: 37 in US20030138772)
AAV42.12 (See SEQ ID NO: 113 in US20030138772)	AAVrh.23 (AAV42.12) (See SEQ ID NO: 58 in US20030138772)
AAV42.13 (See SEQ ID NO: 86 in US20030138772)	AAVrh.24 (AAV42.13) (See SEQ ID NO: 31 in US20030138772)
AAV42.15 (See SEQ ID NO: 84 in US20030138772)	AAVrh.25 (AAV42.15) (See SEQ ID NO: 28 in US20030138772)
AAVrh.2R (See SEQ ID NO: in US20150159173	AAVrh.31 (AAV223.1) (See SEQ ID NO: 48 in US20030138772)
AAVC1 (See SEQ ID NO: 60 in US20030138772)	AAVrh.32 (AAVC1) (See SEQ ID NO: 19 in 446 US20030138772)
AAVrh.32/33 (See SEQ ID NO: 2 in US20150159173)	AAVrh.51 (AAV2-5) (See SEQ ID NO: 104 in US20150315612)
AAVrh.52 (AAV3-9) (See SEQ ID NO: 18 in US20150315612)	AAVrh.52 (AAV3-9) (See SEQ ID NO: 96 in US20150315612)
AAVrh.53 (See SEQ ID NO: in US20150315612)	AAVrh.53 (AAV3-11) (See SEQ ID NO: 17 in US20150315612)
AAVrh.53 (AAV3-11) (See SEQ ID NO: 186 in US20150315612)	AAVrh.54 (See SEQ ID NO: 40 in US20150315612)
AAVrh.54 (See SEQ ID NO: 49 in US20150159173 and SEQ ID NO: 116 in US20150315612)	
AAVrh.55 (See SEQ ID NO: 37 in US20150315612)	AAVrh.55 (AAV4-19) (See SEQ ID NO: 117 in US20150315612)
AAVrh.56 (See SEQ ID NO: 54 in US20150315612)	AAVrh.56 (See SEQ ID NO: 152 in US20150315612)
AAVrh.57 (See SEQ ID NO: in 497 US20150315612 SEQ ID NO: 26	AAVrh.57 (See SEQ ID NO: 105 in US20150315612)

AAVrh.58 (See SEQ ID NO: 27 in US20150315612)	AAVrh.58 (See SEQ ID NO: 48 in US20150159173 and SEQ ID NO: 106 in US20150315612)
	AAVrh.58 (See SEQ ID NO: 232 in US20150315612)
AAVrh.59 (See SEQ ID NO: 42 in US20150315612)	AAVrh.59 (See SEQ ID NO: 110 in US20150315612)
AAVrh.60 (See SEQ ID NO: 31 in US20150315612)	AAVrh.60 (See SEQ ID NO: 120 in US20150315612)
AAVrh.61 (See SEQ ID NO: 107 in US20150315612)	AAVrh.61 (AAV2-3) (See SEQ ID NO: 21 in US20150315612)
AAVrh.62 (AAV2-15) (See SEQ ID NO: 33 in US20150315612)	AAVrh.62 (AAV2-15) (See SEQ ID NO: 114 in US20150315612)
AAVrh.64 (See SEQ ID NO: 15 in US20150315612)	AAVrh.64 (See SEQ ID NO: 43 in US20150159173 and SEQ ID NO: 99 in US20150315612)
	AAVrh.64 (See SEQ ID NO: 233 in US20150315612)
AAVRh.64R1 (See SEQ ID NO: in US20150159173	AAVRh.64R2 (See SEQ ID NO: in US20150159173
AAVrh.65 (See SEQ ID NO: 35 in US20150315612)	AAVrh.65 (See SEQ ID NO: 112 in US20150315612)
AAVrh.67 (See SEQ ID NO: 36 in US20150315612)	AAVrh.67 (See SEQ ID NO: 230 in US20150315612)
AAVrh.67 (See SEQ ID NO: 47 in US20150159173 and SEQ ID NO: 47 in US20150315612)	
AAVrh.68 (See SEQ ID NO: 16 in US20150315612)	AAVrh.68 (See SEQ ID NO: 100 in US20150315612)
AAVrh.69 (See SEQ ID NO: 39 in US20150315612)	AAVrh.69 (See SEQ ID NO: 119 in US20150315612)
AAVrh.70 (See SEQ ID NO: 20 in US20150315612)	AAVrh.70 (See SEQ ID NO: 98 in US20150315612)
AAVrh.71 (See SEQ ID NO: 162 in US20150315612)	AAVrh.72 (See SEQ ID NO: 9 in US20150315612)
AAVrh.73 (See SEQ ID NO: 5 in US20150159173)	AAVrh.74 (See SEQ ID NO: 6 in US20150159173)
AAVrh.8 (See SEQ ID NO: 41 in US20150159173)	AAVrh.8 (See SEQ ID NO: 235 in US20150315612)

AAVrh.8R (See SEQ ID NO: 9 in US20150159173, WO2015168666)	AAVrh.8R A586R mutant (See SEQ ID NO: 10 in WO2015168666)
AAVrh.8R R533A mutant (See SEQ ID NO: 11 in WO2015168666)	BAAV (bovine AAV) (See SEQ ID NO: 8 in US9193769)
BAAV (bovine AAV) (See SEQ ID NO: 10 in US9193769)	BAAV (bovine AAV) (See SEQ ID NO: 4 in US9193769)
BAAV (bovine AAV) (See SEQ ID NO: 2 in US9193769)	BAAV (bovine AAV) (See SEQ ID NO: 6 in US9193769)
BAAV (bovine AAV) (See SEQ ID NO: 1 in US9193769)	BAAV (bovine AAV) (See SEQ ID NO: 5 in US9193769)
BAAV (bovine AAV) (See SEQ ID NO: 3 in US9193769)	BAAV (bovine AAV) (See SEQ ID NO: 11 in US9193769)
BAAV (bovine AAV) (See SEQ ID NO: 5 in US7427396)	BAAV (bovine AAV) (See SEQ ID NO: 6 in US7427396)
BAAV (bovine AAV) (See SEQ ID NO: 7 in US9193769)	BAAV (bovine AAV) (See SEQ ID NO: 9 in US9193769)
BNP61 AAV (See SEQ ID NO: 1 in US20150238550)	BNP61 AAV (See SEQ ID NO: 2 in US20150238550)
BNP62 AAV (See SEQ ID NO: 3 in US20150238550)	BNP63 AAV (See SEQ ID NO: 4 in US20150238550)
caprine AAV (See SEQ ID NO: 3 in US7427396)	caprine AAV (See SEQ ID NO: 4 in US7427396)
true type AAV (ttAAV) (See SEQ ID NO: 2 in WO2015121501)	AAAV (Avian AAV) (See SEQ ID NO: 12 in US9238800)
AAAV (Avian AAV) (See SEQ ID NO: 2 in US9238800)	AAAV (Avian AAV) (See SEQ ID NO: 6 in US9238800)
AAAV (Avian AAV) (See SEQ ID NO: 4 in US9238800)	AAAV (Avian AAV) (See SEQ ID NO: 8 in US9238800)
AAAV (Avian AAV) (See SEQ ID NO: 14 in US9238800)	AAAV (Avian AAV) (See SEQ ID NO: 10 in US9238800)
AAAV (Avian AAV) (See SEQ ID NO: 15 in US9238800)	AAAV (Avian AAV) (See SEQ ID NO: 5 in US9238800)
AAAV (Avian AAV) (See SEQ ID NO: 9 in US9238800)	AAAV (Avian AAV) (See SEQ ID NO: 3 in US9238800)
AAAV (Avian AAV) (See SEQ ID NO: 7 in US9238800)	AAAV (Avian AAV) (See SEQ ID NO: 11 in US9238800)
AAAV (Avian AAV) (See SEQ ID NO: in US9238800)	AAAV (Avian AAV) (See SEQ ID NO: 1 in US9238800)

AAV Shuffle 100-1 (See SEQ ID NO: 23 in US20160017295)	AAV Shuffle 100-1 (See SEQ ID NO: 11 in US20160017295)
AAV Shuffle 100-2 (See SEQ ID NO: 37 in US20160017295)	AAV Shuffle 100-2 (See SEQ ID NO: 29 in US20160017295)
AAV Shuffle 100-3 (See SEQ ID NO: 24 in US20160017295)	AAV Shuffle 100-3 (See SEQ ID NO: 12 in US20160017295)
AAV Shuffle 100-7 (See SEQ ID NO: 25 in US20160017295)	AAV Shuffle 100-7 (See SEQ ID NO: 13 in US20160017295)
AAV Shuffle 10-2 (See SEQ ID NO: 34 in US20160017295)	AAV Shuffle 10-2 (See SEQ ID NO: 26 in US20160017295)
AAV Shuffle 10-6 (See SEQ ID NO: 35 in US20160017295)	AAV Shuffle 10-6 (See SEQ ID NO: 27 in US20160017295)
AAV Shuffle 10-8 (See SEQ ID NO: 36 in US20160017295)	AAV Shuffle 10-8 (See SEQ ID NO: 28 in US20160017295)
AAV SM 100-10 (See SEQ ID NO: 41 in US20160017295)	AAV SM 100-10 (See SEQ ID NO: 33 in US20160017295)
AAV SM 100-3 (See SEQ ID NO: 40 in US20160017295)	AAV SM 100-3 (See SEQ ID NO: 32 in US20160017295)
AAV SM 10-1 (See SEQ ID NO: 38 in US20160017295)	AAV SM 10-1 (See SEQ ID NO: 30 in US20160017295)
AAV SM 10-2 (See SEQ ID NO: 10 in US20160017295)	AAV SM 10-2 (See SEQ ID NO: 22 in US20160017295)
AAV SM 10-8 (See SEQ ID NO: 39 in US20160017295)	AAV SM 10-8 (See SEQ ID NO: 31 in US20160017295)
AAV CBr-7.1 (See SEQ ID NO: 4 in WO2016065001)	AAV CBr-7.1 (See SEQ ID NO: 54 in WO2016065001)
AAV CBr-7.10 (See SEQ ID NO: 11 in WO2016065001)	AAV CBr-7.10 (See SEQ ID NO: 61 in WO2016065001)
AAV CBr-7.2 (See SEQ ID NO: 5 in WO2016065001)	AAV CBr-7.2 (See SEQ ID NO: 55 in WO2016065001)
AAV CBr-7.3 (See SEQ ID NO: 6 in WO2016065001)	AAV CBr-7.3 (See SEQ ID NO: 56 in WO2016065001)
AAV CBr-7.4 (See SEQ ID NO: 7 in WO2016065001)	AAV CBr-7.4 (See SEQ ID NO: 57 in WO2016065001)
AAV CBr-7.5 (See SEQ ID NO: 8 in WO2016065001)	AAV CHt-6.6 (See SEQ ID NO: 35 in WO2016065001)
AAV CHt-6.6 (See SEQ ID NO: 85 in WO2016065001)	AAV CHt-6.7 (See SEQ ID NO: 36 in WO2016065001)

AAV CHt-6.7 (See SEQ ID NO: 86 in WO2016065001)	AAV CHt-6.8 (See SEQ ID NO: 37 in WO2016065001)
AAV CHt-6.8 (See SEQ ID NO: 87 in WO2016065001)	AAV CHt-Pl (See SEQ ID NO: 29 in WO2016065001)
AAV CHt-Pl (See SEQ ID NO: 79 in WO2016065001)	AAV CHt-P2 (See SEQ ID NO: 1 in WO2016065001)
AAV CHt-P2 (See SEQ ID NO: 51 in WO2016065001)	AAV CHt-P5 (See SEQ ID NO: 2 in WO2016065001)
AAV CHt-P5 (See SEQ ID NO: 52 in WO2016065001)	AAV CHt-P6 (See SEQ ID NO: 30 in WO2016065001)
AAV CHt-P6 (See SEQ ID NO: 80 in WO2016065001)	AAV CHt-P8 (See SEQ ID NO: 31 in WO2016065001)
AAV CHt-P8 (See SEQ ID NO: 81 in WO2016065001)	AAV CHt-P9 (See SEQ ID NO: 3 in WO2016065001)
AAV CHt-P9 (See SEQ ID NO: 53 in WO2016065001)	AAV CKd-1 (See SEQ ID NO: 57 in US8734809)
AAV CKd-1 (See SEQ ID NO: 131 in US8734809)	AAV CKd-10 (See SEQ ID NO: 58 in US8734809)
AAV CKd-10 (See SEQ ID NO: 132 in US8734809)	AAV CKd-2 (See SEQ ID NO: 59 in US8734809)
AAV CKd-2 (See SEQ ID NO: 133 in US8734809)	AAV CKd-3 (See SEQ ID NO: 60 in US8734809)
AAV CKd-3 (See SEQ ID NO: 134 in US8734809)	AAV CKd-4 (See SEQ ID NO: 61 in US8734809)
AAV CKd-4 (See SEQ ID NO: 135 in US8734809)	AAV CKd-6 (See SEQ ID NO: 62 in US8734809)
AAV CKd-6 (See SEQ ID NO: 136 in US8734809)	AAV CKd-7 (See SEQ ID NO: 63 in US8734809)
AAV CKd-7 (See SEQ ID NO: 137 in US8734809)	AAV CKd-8 (See SEQ ID NO: 64 in US8734809)
AAV CKd-8 (See SEQ ID NO: 138 in US8734809)	AAV CKd-B 1 (See SEQ ID NO: 73 in US8734809)
AAV CKd-B 1 (See SEQ ID NO: 147 in US8734809)	AAV CKd-B2 (See SEQ ID NO: 74 in US8734809)
AAV CKd-B2 (See SEQ ID NO: 148 in US8734809)	AAV CKd-B3 (See SEQ ID NO: 75 in US8734809)
AAV CKd-B3 (See SEQ ID NO: in US8734809	AAV CKd-B3 (See SEQ ID NO: 149 in US8734809)

AAV CLv-1 (See SEQ ID NO: 65 in US8734809)	AAV CLv-1 (See SEQ ID NO: 139 in US8734809)
AAV CLvl-1 (See SEQ ID NO: 171 in US8734809)	AAV Civ 1-10 (See SEQ ID NO: 178 in US8734809)
AAV CLvl-2 (See SEQ ID NO: 172 in US8734809)	AAV CLv-12 (See SEQ ID NO: 66 in US8734809)
AAV CLv-12 (See SEQ ID NO: 140 in US8734809)	AAV CLvl-3 (See SEQ ID NO: 173 in US8734809)
AAV CLv-13 (See SEQ ID NO: 67 in US8734809)	AAV CLv-13 (See SEQ ID NO: 141 in US8734809)
AAV CLvl-4 (See SEQ ID NO: 174 in US8734809)	AAV Civ 1-7 (See SEQ ID NO: 175 in US8734809)
AAV Civ 1-8 (See SEQ ID NO: 176 in US8734809)	AAV Civ 1-9 (See SEQ ID NO: 177 in US8734809)
AAV CLv-2 (See SEQ ID NO: 68 in US8734809)	AAV CLv-2 (See SEQ ID NO: 142 in US8734809)
AAV CLv-3 (See SEQ ID NO: 69 in US8734809)	AAV CLv-3 (See SEQ ID NO: 143 in US8734809)
AAV CLv-4 (See SEQ ID NO: 70 in US8734809)	AAV CLv-4 (See SEQ ID NO: 144 in US8734809)
AAV CLv-6 (See SEQ ID NO: 71 in US8734809)	AAV CLv-6 (See SEQ ID NO: 145 in US8734809)
AAV CLv-8 (See SEQ ID NO: 72 in US8734809)	AAV CLv-8 (See SEQ ID NO: 146 in US8734809)
AAV CLv-Dl (See SEQ ID NO: 22 in US8734809)	AAV CLv-Dl (See SEQ ID NO: 96 in US8734809)
AAV CLv-D2 (See SEQ ID NO: 23 in US8734809)	AAV CLv-D2 (See SEQ ID NO: 97 in US8734809)
AAV CLv-D3 (See SEQ ID NO: 24 in US8734809)	AAV CLv-D3 (See SEQ ID NO: 98 in US8734809)
AAV CLv-D4 (See SEQ ID NO: 25 in US8734809)	AAV CLv-D4 (See SEQ ID NO: 99 in US8734809)
AAV CLv-D5 (See SEQ ID NO: 26 in US8734809)	AAV CLv-D5 (See SEQ ID NO: 100 in US8734809)
AAV CLv-D6 (See SEQ ID NO: 27 in US8734809)	AAV CLv-D6 (See SEQ ID NO: 101 in US8734809)
AAV CLv-D7 (See SEQ ID NO: 28 in US8734809)	AAV CLv-D7 (See SEQ ID NO: 102 in US8734809)

AAV CLv-D8 (See SEQ ID NO: 29 in US8734809)	AAV CLv-D8 (See SEQ ID NO: 103 in US8734809); AAV CLv-K1 762, see SEQ ID NO: 18 in WO2016065001)
AAV CLv-K1 (See SEQ ID NO: 68 in WO2016065001)	AAV CLv-K3 (See SEQ ID NO: 19 in WO2016065001)
AAV CLv-K3 (See SEQ ID NO: 69 in WO2016065001)	AAV CLv-K6 (See SEQ ID NO: 20 in WO2016065001)
AAV CLv-K6 (See SEQ ID NO: 70 in WO2016065001)	AAV CLv-L4 (See SEQ ID NO: 15 in WO2016065001)
AAV CLv-L4 (See SEQ ID NO: 65 in WO2016065001)	AAV CLv-L5 (See SEQ ID NO: 16 in WO2016065001)
AAV CLv-L5 (See SEQ ID NO: 66 in WO2016065001)	AAV CLv-L6 (See SEQ ID NO: 17 in WO2016065001)
AAV CLv-L6 (See SEQ ID NO: 67 in WO2016065001)	AAV CLv-M1 (See SEQ ID NO: 21 in WO2016065001)
AAV CLv-M1 (See SEQ ID NO: 71 in WO2016065001)	AAV CLv-M11 (See SEQ ID NO: 22 in WO2016065001)
AAV CLv-M1 1 (See SEQ ID NO: 72 in WO2016065001)	AAV CLv-M2 (See SEQ ID NO: 23 in WO2016065001)
AAV CLv-M2 (See SEQ ID NO: 73 in WO2016065001)	AAV CLv-M5 (See SEQ ID NO: 24 in WO2016065001)
AAV CLv-M5 (See SEQ ID NO: 74 in WO2016065001)	AAV CLv-M6 (See SEQ ID NO: 25 in WO2016065001)
AAV CLv-M6 (See SEQ ID NO: 75 in WO2016065001)	AAV CLv-M7 (See SEQ ID NO: 26 in WO2016065001)
AAV CLv-M7 (See SEQ ID NO: 76 in WO2016065001)	AAV CLv-M8 (See SEQ ID NO: 27 in WO2016065001)
AAV CLv-M8 (See SEQ ID NO: 77 in WO2016065001)	AAV CLv-M9 (See SEQ ID NO: 28 in WO2016065001)
AAV CLv-M9 (See SEQ ID NO: 78 in WO2016065001)	AAV CLv-R1 (See SEQ ID NO: 30 in US8734809)
AAV CLv-R1 (See SEQ ID NO: 104 in US8734809)	AAV CLv-R2 (See SEQ ID NO: 31 in US8734809)
AAV CLv-R2 (See SEQ ID NO: 105 in US8734809)	AAV CLv-R3 (See SEQ ID NO: 32 in US8734809)
AAV CLv-R3 (See SEQ ID NO: 106 in US8734809)	AAV CLv-R4 (See SEQ ID NO: 33 in US8734809)
AAV CLv-R4 (See SEQ ID NO: 107 in US8734809)	AAV CLv-R5 (See SEQ ID NO: 34 in US8734809)

AAV CLv-R5 (See SEQ ID NO: 108 in US8734809)	AAV CLv-R6 (See SEQ ID NO: 35 in US8734809)
AAV CLv-R6 (See SEQ ID NO: 109 in US8734809); AAV CLv-R7 802 (see SEQ ID NO: 36 in US8734809)	AAV CLv-R7 (See SEQ ID NO: 110 in US8734809)
AAV CLv-R8 (See SEQ ID NO: 37 in US8734809)	AAV CLv-R8 (See SEQ ID NO: 111 in US8734809)
AAV CLv-R9 (See SEQ ID NO: 38 in US8734809)	AAV CLv-R9 (See SEQ ID NO: 112 in US8734809)
AAV CSp-1 (See SEQ ID NO: 45 in US8734809)	AAV CSp-1 (See SEQ ID NO: 119 in US8734809)
AAV CSp-10 (See SEQ ID NO: 46 in US8734809)	AAV CSp-10 (See SEQ ID NO: 120 in US8734809)
AAV CSp-11 (See SEQ ID NO: 47 in US8734809)	AAV CSp-11 (See SEQ ID NO: 121 in US8734809)
AAV CSp-2 (See SEQ ID NO: 48 in US8734809)	AAV CSp-2 (See SEQ ID NO: 122 in US8734809)
AAV CSp-3 (See SEQ ID NO: 49 in US8734809)	AAV CSp-3 (See SEQ ID NO: 123 in US8734809)
AAV CSp-4 (See SEQ ID NO: 50 in US8734809)	AAV CSp-4 (See SEQ ID NO: 124 in US8734809)
AAV CSp-6 (See SEQ ID NO: 51 in US8734809)	AAV CSp-6 (See SEQ ID NO: 125 in US8734809)
AAV CSp-7 (See SEQ ID NO: 52 in US8734809)	AAV CSp-7 (See SEQ ID NO: 126 in US8734809)
AAV CSp-8 (See SEQ ID NO: 53 in US8734809)	AAV CSp-8 (See SEQ ID NO: 127 in US8734809)
AAV CSp-8.10 (See SEQ ID NO: 38 in WO2016065001)	AAV CSp-8.10 (See SEQ ID NO: 88 in WO2016065001)
AAV CSp-8.2 (See SEQ ID NO: 39 in WO2016065001)	AAV CSp-8.2 (See SEQ ID NO: 89 in WO2016065001)
AAV CSp-8.4 (See SEQ ID NO: 40 in WO2016065001)	AAV CSp-8.4 (See SEQ ID NO: 90 in WO2016065001)
AAV CSp-8.5 (See SEQ ID NO: 41 in WO2016065001)	AAV CSp-8.5 (See SEQ ID NO: 91 in WO2016065001)
AAV CSp-8.6 (See SEQ ID NO: 42 in WO2016065001)	AAV CSp-8.6 (See SEQ ID NO: 92 in WO2016065001)
AAV CSp-8.7 (See SEQ ID NO: 43 in WO2016065001)	AAV CSp-8.7 (See SEQ ID NO: 93 in WO2016065001)

AAV CSp-8.8 (See SEQ ID NO: 44 in WO2016065001)	AAV CSp-8.8 (See SEQ ID NO: 94 in WO2016065001)
AAV CSp-8.9 (See SEQ ID NO: 45 in WO2016065001)	AAV CSp-8.9 (See SEQ ID NO: 95 in WO2016065001)
AAV CSp-9 842 (See SEQ ID NO: 54 in US8734809)	AAV CSp-9 (See SEQ ID NO: 128 in US8734809)
AAV.hu.48R3 (See SEQ ID NO: 183 in US8734809)	AAV.VR-355 (See SEQ ID NO: 181 in US8734809)
AAV3B (See SEQ ID NO: 48 in WO2016065001)	AAV3B (See SEQ ID NO: 98 in WO2016065001)
AAV4 (See SEQ ID NO: 49 in WO2016065001)	AAV4 (See SEQ ID NO: 99 in WO2016065001)
AAV5 (See SEQ ID NO: 50 in WO2016065001)	AAV5 (See SEQ ID NO: 100 in WO2016065001)
AAVF1/HSC1 (See SEQ ID NO: 20 in WO2016049230)	AAVF1/HSC1 (See SEQ ID NO: 2 in WO2016049230)
AAVF11/HSC11 (See SEQ ID NO: 26 in WO2016049230)	AAVF11/HSC11 (See SEQ ID NO: 4 in WO2016049230)
AAVF12/HSC12 (See SEQ ID NO: 30 in WO2016049230)	AAVF12/HSC12 (See SEQ ID NO: 12 in WO2016049230)
AAVF13/HSC13 (See SEQ ID NO: 31 in WO2016049230)	AAVF13/HSC13 (See SEQ ID NO: 14 in WO2016049230)
AAVF14/HSC14 (See SEQ ID NO: 32 in WO2016049230)	AAVF14/HSC14 (See SEQ ID NO: 15 in WO2016049230)
AAVF15/HSC15 (See SEQ ID NO: 33 in WO2016049230)	AAVF15/HSC15 (See SEQ ID NO: 16 in WO2016049230)
AAVF16/HSC16 (See SEQ ID NO: 34 in WO2016049230)	AAVF16/HSC16 (See SEQ ID NO: 17 in WO2016049230)
AAVF17/HSC17 (See SEQ ID NO: 35 in WO2016049230)	AAVF17/HSC17 (See SEQ ID NO: 13 in WO2016049230)
AAVF2/HSC2 (See SEQ ID NO: 21 in WO2016049230)	AAVF2/HSC2 (See SEQ ID NO: 3 in WO2016049230)
AAVF3/HSC3 (See SEQ ID NO: 22 in WO2016049230)	AAVF3/HSC3 (See SEQ ID NO: 5 in WO2016049230)
AAVF4/HSC4 (See SEQ ID NO: 23 in WO2016049230)	AAVF4/HSC4 (See SEQ ID NO: 6 in WO2016049230)
AAVF5/HSC5 (See SEQ ID NO: 25 in WO2016049230)	AAVF5/HSC5 (See SEQ ID NO: 11 in WO2016049230)

AAVF6/HSC6 (See SEQ ID NO: 24 in WO2016049230)	AAVF6/HSC6 (See SEQ ID NO: 7 in WO2016049230)
AAVF7/HSC7 (See SEQ ID NO: 27 in WO2016049230)	AAVF7/HSC7 (See SEQ ID NO: 8 in WO2016049230)
AAVF8/HSC8 (See SEQ ID NO: 28 in WO2016049230)	AAVF8/HSC8 (See SEQ ID NO:9 in WO2016049230)
AAVF9/HSC9 (See SEQ ID NO: 10 in WO2016049230)	AAVF9/HSC9 882 (see SEQ ID NO: 29 in WO2016049230)

[00293] In one embodiment, the AAV vector (also referred to as a rAAV virion) as disclosed herein comprises a capsid protein from any of those disclosed in WO2019/241324, which is specifically incorporated herein in its entirety by reference. In some embodiments of the invention described herein, the rAAV vector comprises a liver specific capsid, e.g., a liver specific capsid selected from XL32 and XL32.1, as disclosed in WO2019/241324, which is incorporated herein in its entirety by reference. In some embodiments, the rAAV vector is a AAVXL32 or AAVXL32.1 as disclosed in WO2019/241324, which is incorporated herein in its entirety by reference.

[00294] Exemplary chimeric or variant capsid proteins that can be used as the AAV capsid in the rAAV vector described herein can be selected from Table 2 from U.S. provisional application 62,937,556, filed on November 19, 2019, which is specifically incorporated herein in its reference, or can be used with any combination with wild type capsid proteins and/or other chimeric or variant capsid proteins now known or later identified and each is incorporated herein. In some embodiments, the rAAV vector encompassed for use is a chimeric vector, e.g., as disclosed in 9,012,224 and US 7,892,809, which are incorporated herein in their entirety by reference.

[00295] In some embodiments, the rAAV vector is a haploid rAAV vector, as disclosed in US application US2018/0371496 and PCT/US18/22725, or polyploid rAAV vector, e.g., as disclosed in PCT/US2018/044632 filed on 7/31/2018 and in US application 16/151,110, each of which are incorporated herein in their entirety by reference. In some embodiments, the rAAV vector is a rAAV3 vector, as disclosed in 9,012,224 and WO 2017/106236 which are incorporated herein in their entirety by reference.

[00296] In a particular embodiment, the rAAV is a AAVXL32 or AAVXL32.1 AAV vector as disclosed in WO2019/241324, which is incorporated herein in its entirety by reference. In some embodiments, the rAAV vector comprises a capsid disclosed in WO2019241324A1, or International Patent application PCT/US2019/036676, which are incorporated herein in their entirety by reference. In some embodiments, the AAV vector is a AAV8 vector or a rational haploid comprising an AAV8 capsid protein. In some embodiments, the recombinant AAV vector is a chimeric AAV vector, haploid AAV vector, a hybrid AAV vector or polyploid AAV vector. In some embodiments, the recombinant AAV vector is a rational haploid vector, a mosaic AAV vector, a chemically modified

AAV vector, or a AAV vector from any AAV serotypes, for example, from any AAV serotype disclosed in Table 1 as disclosed in International Applications WO2020/102645, and WO2020/102667, each of which are incorporated herein in their entirety.

[00297] In an embodiment, an rAAV vector useful in the treatment of Pompe Disease as disclosed herein is an AAV3b capsid. AAV3b capsids encompassed for use are described in 2017/106236, and 9,012,224 and 7,892,809, and International application PCT/US19/61653, filed Nov 15, 2019, and International Applications WO2020/102645, and WO2020/102667, each of which are incorporated herein in their entirety. In addition, AAV3b capsids of the AAV vector for use according to the methods as disclosed herein are disclosed in International Patent Applications WO 2020/102645 and WO2021102107, which are incorporated herien in its entirity by reference herein.

[00298] In some embodiments, the AAV3b capsid comprises SEQ ID NO: 44 as disclosed in International Patent Applications WO 2020/102645 and WO2021102107. In an embodiment, the AAV capsid used in the treatment of Pompe Disease can be a modified AAV capsid that is derived in whole or in part from the AAV capsid set forth in SEQ ID NO: 44. In some embodiments, the amino acids from an AAV3b capsid as set forth in SEQ ID NO: 44 can be, or are substituted with amino acids from another capsid of a different AAV serotype, wherein the substituted and/or inserted amino acids can be from any AAV serotype, and can include either naturally occurring or partially or completely synthetic amino acids.

[00299] In another embodiment, an AAV capsid used in the treatment of Pompe Disease is an AAV3b265D capsid. In this particular embodiment, an AAV3b265D capsid comprises a modification in the amino acid sequence of the two-fold axis loop of an AAV3b capsid via replacement of amino acid G265 of the AAV3b capsid with D265. In some embodiments, an AAV3b265D capsid comprises SEQ ID NO: 46. However, the modified virus capsids of the invention are not limited to AAV capsids set forth in SEQ ID NO: 46 as set forth in International Patent Applications WO 2020/102645 and WO2021102107. In some embodiments, the amino acids from AAV3b265D as set forth in SEQ ID NO. 46 can be, or are substituted with amino acids from a capsid from an AAV of a different serotype, wherein the substituted and/or inserted amino acids can be from any AAV serotype, and can include either naturally occurring or partially or completely synthetic amino acids.

[00300] In another embodiment an rAAV vector useful in the treatment of Pompe Disease as disclosed herein is an AAV3b265D549A capsid. In this particular embodiment, an AAV3b265D549A capsid comprises a modification in the amino acid sequence of the two-fold axis loop of an AAV3b capsid via replacement of amino acid G265 of the AAV3b capsid with D265 and replacement of amino acid T549 of the AAV3b capsid with A549. In some embodiments, an AAV3b265D549A capsid comprises SEQ ID NO: 50 as disclosed herein International Patent Applications WO 2020/102645 and WO2021102107. However, the modified virus capsids of the invention are not limited to AAV capsids set forth in SEQ ID NO: 50. In some embodiments, the

amino acids from AAV3b265D549A as set forth in SEQ ID NO: 50 can be, or are substituted with amino acids from a capsid from an AAV of a different serotype, wherein the substituted and/or inserted amino acids can be from any AAV serotype, and can include either naturally occurring or partially or completely synthetic amino acids. In some embodiments, the amino acids from AAV3bSASTG (i.e., a AAV3b capsid comprising Q263A/T265 mutations) can be, or are substituted with amino acids from a capsid from an AAV of a different serotype, wherein the substituted and/or inserted amino acids can be from any AAV serotype, and can include either naturally occurring or partially or completely synthetic amino acids.

[00301] In another embodiment, an rAAV vector useful in the treatment of Pompe Disease as disclosed herein is an AAV3b549A capsid. In this particular embodiment, an AAV3b549A capsid comprises a modification in the amino acid sequence of the two-fold axis loop of an AAV3b capsid via replacement of amino acid T549 of the AAV3b capsid with A549. In some embodiments, an AAV3b549A capsid comprises SEQ ID NO: 52 as disclosed herein International Patent Applications WO 2020/102645 and WO2021102107. However, the modified virus capsids of the invention are not limited to AAV capsids set forth in SEQ ID NO: 52. In some embodiments, the amino acids from AAV3b549A as set forth in SEQ ID NO: 52 can be, or are substituted with amino acids from a capsid from an AAV of a different serotype, wherein the substituted and/or inserted amino acids can be from any AAV serotype, and can include either naturally occurring or partially or completely synthetic amino acids.

[00302] In another embodiment, an rAAV vector useful in the treatment of Pompe Disease as disclosed herein is an AAV3bQ263Y capsid. In this particular embodiment, an AAV3bQ263Y capsid comprises a modification in the amino acid sequence of the two-fold axis loop of an AAV3b capsid via replacement of amino acid Q263 of the AAV3b capsid with Y263. In some embodiments, an AAV3b549A capsid comprises SEQ ID NO: 54 as disclosed herein International Patent Applications WO 2020/102645 and WO2021102107. However, the modified virus capsids of the invention are not limited to AAV capsids set forth in SEQ ID NO: 54. In some embodiments, the amino acids from AAV3bQ263Y as set forth in SEQ ID NO: 54 can be, or are substituted with amino acids from a capsid from an AAV of a different serotype, wherein the substituted and/or inserted amino acids can be from any AAV serotype, and can include either naturally occurring or partially or completely synthetic amino acids.

[00303] In another embodiment, an rAAV vector useful in the treatment of Pompe Disease as disclosed herein is AAV3bSASTG serotype or comprises a AAV3bSASTG capsid. In this particular embodiment, an AAV3bSASTG capsid comprises a modification in the amino acid sequence to comprise a SASTG mutation, in particular, the AAV3b capsid was modified to resemble AAV2 Q263A/T265 subvariant by introducing these modifications at similar positions in the AAV3b capsid (as disclosed in Messina EL, et al., Adeno-associated viral vectors based on serotype 3b use components of the fibroblast growth factor receptor signaling complex for efficient transduction.

Hum. Gene Ther. 2012 Oct: 23(10):1031-4, Piacentino III, Valentino, et al. "X-linked inhibitor of apoptosis protein-mediated attenuation of apoptosis, using a novel cardiac-enhanced adeno-associated viral vector." Human gene therapy 23.6 (2012): 635-646.which are both incorporated herein in their entirety by reference). Accordingly, in some embodiments, an rAAV vector useful in the treatment of Pompe Disease as disclosed herein is AAV3bSASTG serotype or comprises a AAV3bSASTG capsid comprising a AAV3b Q263A/T265 capsid. In some embodiments, the amino acids from AAV3bSASTG can be, or are substituted with amino acids from a capsid from an AAV of a different serotype, wherein the substituted and/or inserted amino acids can be from any AAV serotype, and can include either naturally occurring or partially or completely synthetic amino acids.

[00304] One can target desired tissues using the appropriate capsids. For example, the central nervous system using AAV9 or a rhesus capsid or a rational haploid using at least one of a AAV9 or Rhesus viral protein. One can target the muscle using myo AAV, see, e.g., WO2019/2071323 and WO2022/020616, which are incorporated herein in their entirity by reference.

[00305] In order to facilitate their introduction into a cell, an rAAV vector genome useful in the invention are recombinant nucleic acid constructs that include (1) a heterologous sequence to be expressed (in one embodiment, a polynucleotide encoding a GAA polypeptide) and (2) viral sequence elements that facilitate integration and expression of the heterologous genes. The viral sequence elements may include those sequences of an AAV vector genome that are required in cis for replication and packaging (e.g., functional ITRs) of the DNA into an AAV capsid. In an embodiment, the heterologous gene encodes GAA, which is useful for correcting a GAA-deficiency in a patient suffering from Pompe Disease. In an embodiment, such an rAAV vector genome may also contain marker or reporter genes. In an embodiment, an rAAV vector genome can have one or more of the AAV3b wild-type (WT) cis genes replaced or deleted in whole or in part, but retain functional flanking ITR sequences.

III. Optimized rAAV Vector Genome

[00306] In some embodiments of the methods and compositions as disclosed herein, an optimized rAAV vector genome is created from any of the elements disclosed herein and in any combination, including nucleic acid sequences encoding a promoter, an ITR, a poly-A tail, elements capable of increasing or decreasing expression of a heterologous gene, and in one embodiment, a nucleic acid sequence that is codon optimized for expression of GAA protein *in vivo* (i.e., wildtype GAA or codon optimized GAA) and optionally, one or more element to reduce immunogenicity. Such an optimized rAAV vector genome can be used with any AAV capsid that has tropism for the tissue and cells in which the rAAV vector genome is to be transduced and expressed.

[00307] In some embodiments, rAAV genome lacks the AAV P5 promoter or, a fragment thereof, which is normally located upstream of the liver-specific promoter as disclosed herein. Normally, the P5 promoter controls expression of the AAV rep/cap proteins during AAV replication. In some

embodiments, this P5 promoter fragment is present in the rAAV vector as disclosed herein which contains predicted transcription factor binding sites, e.g., cyclic AMP-responsive element-binding protein 3 (CREB3), which can be activated by endoplasmic reticulum (ER)/Golgi stress (Sampieri 2019), activating transcription factor 2 (ATF2), which is also involved in stress response (Watson 2017), Nuclear Receptor Subfamily 1 Group I Member 2 (NR1I2) (also known as Pregnane X receptor [PXR]) is known to be enriched in liver, and is activated by pregnane steroids, rifampin and other molecules including dexamethasone (NR1I2_HGNC) (Xing 2020). Accordingly, in some embodiments, a fragment of the AAV P5 promoter in the rAAV genome is removed without affecting the intended performance of the GAA cassette. In some embodiments, the rAAV vector also comprises a RNA polymerase II termination sequence located between the polyA signal and the 3' ITR. An exemplary terminal sequence is SEQ ID NO: 45, or SEQ ID NO:465, the later of which introduces two termination codons and one restriction site (e.g., XhoI) replaces TAG, and is located immediately downstream of the last coding amino acids of hGAA, and immediately located upstream of the 3' UTR.

IV. Subjects amenable to Treatment

A. Pompe Disease

[00308] The recombinant AAV expressing GAA protein as disclosed herein can be used in methods to treat Pompe disease. Pompe disease is a rare genetic disorder caused by a deficiency in the enzyme acid alpha-glucosidase (GAA), which is needed to break down glycogen, a stored form of sugar used for energy. Pompe disease is also known as glycogen storage disease type II, GSD II, type II glycogen storage disease, glycogenosis type II, acid maltase deficiency, alpha-1,4-glucosidase deficiency, cardiomegalia glycogenic diffusa, and cardiac form of generalized glycogenosis. The build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly in the heart, skeletal muscles, liver, respiratory and nervous system.

[00309] Glycogen storage disease type II, also referred to as Pompe disease, is a rare disorder of metabolism inherited in an autosomal recessive manner, caused by deficiency of the lysosomal enzyme acid α-glucosidase (GAA). This disorder leads to the accumulation of lysosomal glycogen and destruction of skeletal, smooth and cardiac muscle. Pompe disease ranges in severity from a severe, infantile-onset myopathy accompanied by severe hypotonia and hypertrophic cardiomyopathy (infantile-onset Pompe disease [IOPD]) to a late-onset myopathy (LOPD). The defect in GAA can vary from complete to partial deficiency of GAA, which correlates with clinical severity. LOPD presents with proximal leg weakness and in some cases respiratory insufficiency without significant cardiac involvement and may progress to fatal respiratory failure.

[00310] Early onset (or the infantile form, IOPD) is the result of complete or near complete deficiency of GAA. Symptoms begin in the first months of life and progress rapidly, with feeding

problems, poor weight gain, muscle weakness, floppiness, and head lag. Respiratory difficulties are often complicated by lung infections. The heart is grossly enlarged. Many infants with Pompe disease also have enlarged tongues. If untreated with Lumizyme, most babies die from cardiac or respiratory complications before their first birthday.

[00311] Late onset (or juvenile/adult, LOPD) Pompe disease is the result of a partial deficiency of GAA. The onset can be as early as the first decade of childhood or as late as the sixth decade of adulthood and is therefore characterized as slowly progressive. The primary symptom is proximal muscle weakness progressing to respiratory weakness and death from respiratory failure after a course lasting several years. The heart is usually not involved.

[00312] The presenting clinical manifestations of Pompe disease can vary widely depending on the age of disease onset and residual GAA activity. Residual GAA activity correlates with both the amount and tissue distribution of glycogen accumulation as well as the severity of the disease. Infantile-onset Pompe disease (less than 1% of normal GAA activity) is the most severe form and is characterized by hypotonia, generalized muscle weakness, and hypertrophic cardiomyopathy, and massive glycogen accumulation in cardiac and other muscle tissues. Death usually occurs within one year of birth due to cardiorespiratory failure. Juvenile-onset (1-10% of normal GAA activity) and adult-onset (10-40% of normal GAA activity) Pompe disease are more clinically heterogeneous, with greater variation in age of onset, clinical presentation, and disease progression. Juvenile- and adult-onset Pompe disease are generally characterized by lack of severe cardiac involvement, later age of onset, and slower disease progression, but eventual respiratory or limb muscle involvement results in significant morbidity and mortality. While life expectancy can vary, death generally occurs due to respiratory failure.

[00313] In any embodiment of the methods as disclosed herein, a GAA enzyme suitable for treating Pompe disease includes a wild-type human GAA, or a fragment or sequence variant thereof which retains the ability to cleave α1-4 linkages in linear oligosaccharides. In some embodiments of the methods and compositions as disclosed herein, the GAA protein encoded by a GAA nucleic acid sequence, e.g., SEQ ID NO: 1-18 as disclosed herein, or a N-terminal truncation thereof as disclosed herein in Table 1. In some embodiments of the methods and compositions as disclosed herein, the GAA protein is encoded by a codon optimized GAA nucleic acid sequence, for example, for any one or more of: (1) enhanced expression *in vivo, (2)* to reduce CpG islands or (3) reduce the innate immune response. In some embodiments of the methods and compositions as disclosed herein, the GAA protein is encoded by a codon optimized GAA nucleic sequence, for example, any nucleic acid sequence selected from any of: SEQ ID NO: 1-18, or a nucleic acid sequence having at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% sequence identity to SEQ ID NOS: 1-18, which encode a GAA polypeptide, where amino acid at position 199 is R (199R); amino acid at position 233 is H (233H), and amino acid at position 780 is I (780I), as compared to the wild type GAA protein.

[00314] In some embodiments of the methods and compositions as disclosed herein, a rAAV vector as described herein transduces the liver of a subject and secretes the hGAA polypeptide into the blood, which perfuses patient tissues where the hGAA polypeptide, is taken up by cells and transported to the lysosome, where the GAA enzyme acts to eliminate material that has accumulated in the lysosomes due to the enzyme deficiency. For lysosomal enzyme replacement therapy to be effective, the therapeutic enzyme must be delivered to lysosomes in the appropriate cells in tissues where the storage defect is manifest.

[00315] In some embodiments, upon administration, the AAV vector selectively expresses and secretes GAA from transduced hepatocytes. The primary mechanism of action of a AAV vector expressing hGAA polypeptide as disclosed herein is to secrete continuous low levels of endogenous GAA from the liver into the systemic circulation in order to provide therapeutic exposure levels of GAA to tissue (e.g., the muscle, but not exclusively the muscle), resulting in glycogen removal and restoration of cellular architecture and function.

B. Increasing GAA Activity in A Subject with Pompe Disease

[00316] In any embodiment of the methods as disclosed herein, administration of a AAV vector expressing GAA is administration to a muscle, and can be by any suitable method including intravenous administration, intra-arterial administration, and/or intra-peritoneal administration. Exemplary modes of administration include oral, rectal, transmucosal, intranasal, inhalation *(e.g.,* via an aerosol), buccal *(e.g.,* sublingual), vaginal, intrathecal, intraocular, transdermal, *in utero* (or *in ovo),* parenteral *(e.g.,* intravenous, subcutaneous, intradermal, intramuscular [including administration to skeletal, diaphragm and/or cardiac muscle], intradermal, intrapleural, intracerebral, and intraarticular), topical *(e.g.,* to both skin and mucosal surfaces, including airway surfaces, and transdermal administration), intralymphatic, and the like, as well as direct tissue or organ injection *(e.g.,* to liver, skeletal muscle, cardiac muscle, diaphragm muscle or brain). The most suitable route in any given case will depend on the nature and severity of the condition being treated and/or prevented and on the nature of the particular vector that is being used.

[00317] In any embodiment of the methods as disclosed herein, administration of a AAV vector expressing GAA as disclosed herein is to skeletal muscle according to the present invention, and includes but is not limited to administration to skeletal muscle in the limbs (e.g., upper arm, lower arm, upper leg, and/or lower leg), back, neck, head (e.g., tongue), thorax, abdomen, pelvis/perineum, and/or digits. Suitable skeletal muscles that can be injected are disclosed in International Application WO2021102107, which is incorporated herein its entirety by reference.

[00318] In any embodiment of the methods as disclosed herein, the rAAV vectors and/or rAAV genome are administered to the skeletal muscle, liver, diaphragm, costal, and/or cardiac muscle cells of a subject. For example, a conventional syringe and needle can be used to inject a rAAV virion suspension into an animal. Parenteral administration of a the rAAV vectors and/or rAAV genome, by

injection can be performed, for example, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, for example, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain agents for a pharmaceutical formulation, such as suspending, stabilizing and/or dispersing agents. Alternatively, the rAAV vectors and/or rAAV genome as disclosed herein can be in powder form (e.g., lyophilized) for constitution with a suitable vehicle, for example, sterile pyrogen-free water, before use.

[00319] In particular embodiments, more than one administration *(e.g.,* two, three, four, five, six, seven, eight, nine, 10, etc., or more administrations) may be employed to achieve the desired level of GAA expression over a period of various intervals, *e.g.,* hourly, daily, weekly, monthly, yearly, *etc.* Dosing can be single dosage or cumulative (serial dosing), and can be readily determined by one skilled in the art. As disclosed herein, it is envisioned that treatment of Pompe Disease according to the methods as disclosed herein comprises a one-time administration of an effective dose of a pharmaceutical composition comprising a AAV vector encoding a GAA polypeptide.

[00320] However, in alternative embodiments, treatment of a subject with Pompe disease may comprise multiple administrations of a pharmaceutical composition comprising a AAV vector encoding a GAA polypeptide when the subject is not administered long-term ERT, where the multiple administrations can be carried out over a range of time periods, such as, e.g., once yearly, or every 6-months, or about every 2-years, or about every 3-years, or about every 4 years, or about every 5-years or longer than 5-year intervals. The timing of administration can vary from individual to individual, depending upon such factors as the severity of an individual's symptoms. For example, in some embodiments, an effective dose of a AAV vector encoding a GAA polypeptide as disclosed herein can be administered to an individual once every year, or once every two years, or every six months for an indefinite period of time, or until the individual no longer requires therapy. A person of ordinary skill in the art will recognize that the condition of the individual can be monitored throughout the course of treatment and that the effective amount of a AAV vector encoding a GAA polypeptide as disclosed herein that is administered can be adjusted accordingly.

[00321] Injectables comprising a AAV vector encoding a GAA polypeptide as disclosed herein can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Alternatively, one may administer a AAV vector encoding a GAA polypeptide as disclosed herein in a local rather than systemic manner, for example, in a depot or sustained-release formulation. Further, the virus vector and/or virus capsid can be delivered adhered to a surgically implantable matrix *(e.g.,* as described in U.S. Patent Publication No. US-2004-0013645-Al). In some embodiments, a AAV vector encoding a GAA polypeptide as disclosed herein can be administered to the lungs of a subject by any suitable means, optionally by administering an aerosol suspension of respirable particles comprised of the virus vectors and/or virus capsids, which the subject inhales. The respirable particles can be liquid or

solid. Aerosols of liquid particles comprising the virus vectors and/or virus capsids may be produced by any suitable means, such as with a pressure-driven aerosol nebulizer or an ultrasonic nebulizer, as is known to those of skill in the art. *See, e.g.,* U.S. Patent No. 4,501,729. Aerosols of solid particles comprising the virus vectors and/or capsids may likewise be produced with any solid particulate medicament aerosol generator, by techniques known in the pharmaceutical art.

[00322] In some embodiments, a AAV vector encoding a GAA polypeptide as disclosed herein can be formulated in a solvent, emulsion or other diluent in an amount sufficient to dissolve an rAAV vector disclosed herein. In other aspects of this embodiment, the rAAV vectors and/or rAAV genome encoding GAA polypeptide as disclosed herein can herein may be formulated in a solvent, emulsion or a diluent in an amount of, e.g., less than about 90% (v/v), less than about 80% (v/v), less than about 70% (v/v), less than about 65% (v/v), less than about 60% (v/v), less than about 55% (v/v), less than about 50% (v/v), less than about 45% (v/v), less than about 40% (v/v), less than about 35% (v/v), less than about 30% (v/v), less than about 25% (v/v), less than about 20% (v/v), less than about 15% (v/v), less than about 10% (v/v), less than about 5% (v/v), or less than about 1% (v/v). In other aspects, the rAAV vectors and/or rAAV genome encoding a GAA polypeptide as disclosed herein can disclosed herein may comprise a solvent, emulsion or other diluent in an amount in a range of, e.g., about 1% (v/v) to 90% (v/v), about 1% (v/v) to 70% (v/v), about 1% (v/v) to 60% (v/v), about 1% (v/v) to 50% (v/v), about 1% (v/v) to 40% (v/v), about 1% (v/v) to 30% (v/v), about 1% (v/v) to 20% (v/v), about 1% (v/v) to 10% (v/v), about 2% (v/v) to 50% (v/v), about 2% (v/v) to 40% (v/v), about 2% (v/v) to 30% (v/v), about 2% (v/v) to 20% (v/v), about 2% (v/v) to 10% (v/v), about 4% (v/v) to 50% (v/v), about 4% (v/v) to 40% (v/v), about 4% (v/v) to 30% (v/v), about 4% (v/v) to 20% (v/v), about 4% (v/v) to 10% (v/v), about 6% (v/v) to 50% (v/v), about 6% (v/v) to 40% (v/v), about 6% (v/v) to 30% (v/v), about 6% (v/v) to 20% (v/v), about 6% (v/v) to 10% (v/v), about 8% (v/v) to 50% (v/v), about 8% (v/v) to 40% (v/v), about 8% (v/v) to 30% (v/v), about 8% (v/v) to 20% (v/v), about 8% (v/v) to 15% (v/v), or about 8% (v/v) to 12% (v/v).

[00323] In any embodiment of the methods as disclosed herein, a AAV vector encoding a GAA polypeptide can be an AAV of any serotype, including but not limited to encapsulated by any AAV8 capsid, or any AAV3b capsid selected from: AAV3b capsid (SEQ ID NO: 452); AAV3b265D capsid (SEQ ID NO: 454), AAV3b ST (S663V+T492V) capsid (SEQ ID NO: 456), AAV3b265D549A capsid (SEQ ID NO: 458); AAV3b549A capsid (SEQ ID NO: 460); AAV3bQ263Y capsid (SEQ ID NO: 462) or AAV3bSASTG capsid (i.e., a AAV3b capsid comprising Q263A/T265 mutations).

[00324] To facilitate delivery of a AAV vector encoding a GAA polypeptide as disclosed herein, it can be mixed with a carrier or excipient. Carriers and excipients that might be used include saline (especially sterilized, pyrogen-free saline) saline buffers (for example, citrate buffer, phosphate buffer, acetate buffer, and bicarbonate buffer), amino acids, urea, alcohols, ascorbic acid, phospholipids, proteins (for example, serum albumin), EDTA, sodium chloride, liposomes, mannitol,

sorbitol, and glycerol. USP grade carriers and excipients are particularly useful for delivery of virions to human subjects.

[00325] In addition to the formulations described previously, a AAV vector encoding a GAA polypeptide as disclosed herein can also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by IM injection. Thus, for example, a rAAV vector and/or rAAV genome as disclosed herein may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives.

[00326] In any embodiment of the methods as disclosed herein, the method is directed to treating Pompe Disease that results from a deficiency of GAA in a subject, wherein a AAV vector encoding a GAA polypeptide as disclosed herein is administered to a patient suffering from Pompe Disease, and following administration, GAA is secreted from cells in the liver and there is uptake of the secreted GAA by cells in skeletal muscle tissue, cardiac muscle tissue, diaphragm muscle tissue or a combination thereof, wherein uptake of the secreted GAA results in a reduction in lysosomal glycogen stores in the tissue(s), including but not limited to muscle. In some embodiments, a AAV vector encoding a GAA polypeptide as disclosed herein is encapsulated in a capsid, e.g., encapsulated by any AAV3b capsid selected from: AAV3b capsid (SEQ ID NO: 452); AAV3b265D capsid (SEQ ID NO: 454), AAV3b ST (S663V+T492V) capsid (SEQ ID NO: 456), AAV3b265D549A capsid (SEQ ID NO: 458); AAV3b549A capsid (SEQ ID NO: 460); AAV3bQ263Y capsid (SEQ ID NO: 462) or AAV3bSASTG capsid (i.e., a AAV3b capsid comprising Q263A/T265 mutations).

[00327] In a particular embodiment, at least about $1.6x10^{12}$ to about $4.0x10^{12}$ vg/kg will be administered per dose in a pharmaceutically acceptable carrier. In a further embodiment, dosages of the virus vector and/or capsid to be administered to a subject depend upon the mode of administration, the severity and type of Pompe disease (i.e., LOPD or IOPD) to be treated and/or prevented, the individual subject's condition, age and gender, and the particular virus vector or capsid, the nucleic acid encoding GAA polypeptide to be delivered, and the like, and can be determined in a routine manner.

[00328] Exemplary doses for achieving therapeutic effects are titers of at least about between 1.0E9vg/kg and 5.0E13 vg/kg, e.g., 1.0E9vg/kg and 5.0E12 vg/kg; 5.0E9vg/kg and 5.0E12 vg/kg; 5.0E9vg/kg and 1.0E12 vg/kg; 5.0E9vg/kg and 5.0E11 vg/kg; 5.0E9vg/kg and 5.0E10 vg/kg; and 1.0E9vg/kg and 1.0E10 vg/kg.1.5 x 10^{11} vg/kg, or at least about $1.5x10^{12}$ vg/kg, or at least about 4.0 $x10^{12}$ vg/kg. It is encompassed that the dose for achieving therapeutic effects as disclosed herein may also be determined by the strength of the liver specific promoter (LSP) operatively linked to the nucleic acid encoding the GAA polypeptide, as well as specific signal sequence, and ability of the cell to cleave the signal sequence when secreted from the cell. In contrast, the dose of the AAV encoding the GAA polypeptide as disclosed herein can be lower than about $1.6x10^{12}$ when the liver specific promoter is stronger than the LPS (SEQ ID NO: 97) used in a AAV8-LSPhGAA vector, however, the

dose of AAV should be titrated and determined based on the level of GAA expressed in the cell, as determined by transduction efficiency of the AAV capsid and the LSP, and the ability of the cell to secrete the expressed GAA polypeptide in order to avoid GAA accumulation in the transfected cell and any associated cell toxicity.

[00329] In another aspect, disclosed herein is a method of treating Pompe Disease by administering a nucleic acid encoding a GAA to a cell, comprising contacting the cell with a rAAV vector and/or rAAV genome as disclosed herein, under conditions for the nucleic acid to be introduced into the cell and expressed to produce GAA. In some embodiments, the cell is a cell *in vivo*. In some embodiments, the cell is a mammalian cell *in vivo*.

C. Increasing Motoneuron Function In A Mammal

[00330] In any embodiment of the methods as disclosed herein, a AAV vector encoding a GAA polypeptide as disclosed herein is useful in methods to increase phrenic nerve activity in a mammal having Pompe disease and/or insufficient GAA levels. For example, a AAV vector encoding a GAA polypeptide as disclosed herein, e.g., a rAAV vector and/or rAAV genome encapsulated in a capsid, e.g., encapsulated by AAV8 or any AAV3b capsid selected from: AAV3b capsid (SEQ ID NO: 452); AAV3b265D capsid (SEQ ID NO: 454), AAV3b ST (S663V+T492V) capsid (SEQ ID NO: 456), AAV3b265D549A capsid (SEQ ID NO: 458); AAV3b549A capsid (SEQ ID NO: 460); AAV3bQ263Y capsid (SEQ ID NO: 462) or AAV3bSASTG capsid, can be administered to the central nervous system (e.g., neurons). In another embodiment, retrograde transport a AAV vector encoding a GAA polypeptide as disclosed herein from the diaphragm (or other muscle) to the phrenic nerve or other motor neurons can result in biochemical and physiological correction of Pompe disease. These same principles could be applied to other neurodegenerative disease.

[00331] In an embodiment, a rAAV capsid of the rAAV virion used to treat Pompe Disease is any of those listed in Table 1 as disclosed in International Applications WO2020/102645, and WO2020/102667, each of which are incorporated herein in their entirety, and includes any of AAV8 or AAV3, or AAV3b (including but not limited to AAV3b serotypes AAV3b265D, AAV3b265D549A, AAV3b549A, AAV3bQ263Y, AAV3bSASTG (i.e., a AAV3b capsid comprising Q263A/T265 mutations) serotypes) is capable of reducing any one or more of the symptoms of (i) the feeling of weakness in a patient's lower extremities, including, the legs, trunk and/or arms, (ii) a shortness of breath, a hard time exercising, lung infections, a big curve in the spine, trouble breathing while sleeping, an enlarged liver, an enlarged tongue and/or a stiff joint, (iii) in a patient suffering from Pompe Disease by, *e.g.*, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95% as compared to a patient not receiving the same treatment. In other aspects of this embodiment, an AAV GAA of any serotype is capable of reducing any one or more of the systems of (i) the feeling of weakness in a patient's

lower extremities, including, the legs, trunk and/or arms, ii) a shortness of breath, a hard time exercising, lung infections, a big curve in the spine, trouble breathing while sleeping, an enlarged liver, an enlarged tongue and/or a stiff joint, (iii) in a patient suffering from Pompe Disease by, *e.g.*, about 10% to about 100%, about 20% to about 100%, about 30% to about 100%, about 40% to about 100%, about 50% to about 100%, about 60% to about 100%, about 70% to about 100%, about 80% to about 100%, about 10% to about 90%, about 20% to about 90%, about 30% to about 90%, about 40% to about 90%, about 50% to about 90%, about 60% to about 90%, about 70% to about 90%, about 10% to about 80%, about 20% to about 80%, about 30% to about 80%, about 40% to about 80%, about 50% to about 80%, or about 60% to about 80%, about 10% to about 70%, about 20% to about 70%, about 30% to about 70%, about 40% to about 70%, or about 50% to about 70% as compared to a patient not receiving the same treatment.

[00332] In any embodiment of the methods and compositions as disclosed herein, at least one symptom associated with Pompe Disease, or at least one adverse side effect associated with Pompe Disease are reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%, and the severity of at least one symptom associated with Pompe Disease, or at least one adverse side effect is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%. In another embodiment, at least one symptom associated with Pompe Disease, or at least one adverse side effect associated with Pompe Disease is reduced by about 10% to about 100%, about 20% to about 100%, about 30% to about 100%, about 40% to about 100%, about 50% to about 100%, about 60% to about 100%, about 70% to about 100%, about 80% to about 100%, about 10% to about 90%, about 20% to about 90%, about 30% to about 90%, about 40% to about 90%, about 50% to about 90%, about 60% to about 90%, about 70% to about 90%, about 10% to about 80%, about 20% to about 80%, about 30% to about 80%, about 40% to about 80%, about 50% to about 80%, or about 60% to about 80%, about 10% to about 70%, about 20% to about 70%, about 30% to about 70%, about 40% to about 70%, or about 50% to about 70%.

V. Methods of Administration

[00333] Without wishing to be bound by theory, the only current treatment for Pompe disease is long-term administration of recombinant human GAA (rhGAA) ERT, which is typically administered on an every-other week regimen. Herein, the inventors have demonstrated that a subject with Pompe disease can take breaks from the normal ERT regimen for extended period of time (e.g., extended periods of ERT cessation) without a clinical set back if the subject is administered a specific dose of AAV vector expressing a GAA polypeptide as disclosed herein. In some embodiments, withdrawal of

the administration of long-term ERT begins at about the time of administration of the AAV vector to the subject (e.g., the day before, the day of, or the day after), or in some embodiments, withdrawal of the administration of long-term ERT can occur at about 26 weeks, or anywhere within about 24 to about 26 weeks after administration of the AAV vector.

[00334] In some embodiments, a subject administered a AAV vector expressing GAA as disclosed herein, can, after an initial period of withdrawal of the administration of long-term ERT for an extended period of time, be administered complementary ERT, where the complementary ERT is administered after about 6-months, or about 1 year, or longer than a year of cessation of the long-term ERT. Stated differently and without wishing to be bound by theory, the technology disclosed herein relates to a method whereby a subject with Pompe disease who is administered a AAV vector expressing GAA as disclosed herein, can have breaks or "holidays" from the normal long-term ERT administration. That is, according to the methods as disclosed herein, a subject administered an AAV vector expressing GAA as disclosed herein can have extended periods of time with the absence of administration of long-term ERT administration. In some embodiments, the methods as disclosed herein enable flexibility in normal ERT regimens, in that extended breaks or withdrawal of administration of long-term ERT does not result in a clinical decline – that is, a subject remains clinically stable despite not having ongoing long-term ERT.

[00335] In some embodiments, the methods as disclosed herein encompass re-administration of ERT (herein referred to as "complementary ERT") after an extended period of time of cessation of ERT administration, and enable flexibility in normal ERT regimen, as the continued production of GAA expressed by the AAV permits ERT flexibility. In some embodiments, the complementary ERT is pulse administration of ERT, as disclosed herein. In some embodiments, the complementary ERT is at less frequent intervals, or at a lower dose, or at irregular doses, or at irregular intervals as compared to the prior administration of long-term ERT.

[00336] Accordingly, the methods as disclosed herein provide significant advantages to subjects with Pompe disease, including but not limited to reducing or eliminating the rigorous and arduous weekly, or every-other week infusions of long-term rhGAA ERT treatment, which are significantly time-consuming and geographically limiting, and hinders a patient with Pompe disease from travelling for prolonged periods from areas where their ERT infusions are administered. Additionally, as disclosed herein, the absence of ERT administration also reduces any side effects due to anti-rhGAA antibodies against the ERT, and also circumvents the need for administration of immune suppressants normally co-administered with the ERT. As such, the methods to treat Pompe disease as disclosed here leads to greater flexibility in Pompe treatment and an improvement in quality of life and lifestyle of subjects with Pompe disease.

[00337] Accordingly, in one embodiment, the technology relates to a method of treating Pompe disease in a subject, comprising administering to the subject a pharmaceutical composition comprising a recombinant adeno-associated virus (AAV) vector comprising in its genome, a heterologous nucleic

acid sequence encoding an alpha-glucosidase (GAA) polypeptide in expressible form wherein the heterologous nucleic acid is operatively linked to a liver-specific promoter, in the absence of administration of long-term GAA enzyme replacement therapy (ERT) for an extended period of time (e.g., ERT administration can be withdrawn or stopped at about 24, or at about 26 weeks, or earlier than 24- or 26 weeks, after administration of the recombinant AAV). In some embodiments, the dosage of the recombinant AAV comprising nucleic acid encoding GAA polypeptide ranges from 1.0E11vg/kg and 5.0E13 vg/kg, and in some embodiments, the GAA is expressed to a level that the subject obtains a blood serum level of GAA expressed by the AAV at a pharmaceutical activity range from 160 to ≤ 2,260 nmol/mL/hr, 165 to ≤ 2,260nmol/ml/hr, 175 to ≤ 2,260, 180 to ≤ 2,260, 185 to ≤ 2,260, 189 to ≤ 2,260 of at least within two weeks of administration. In some embodiments, the dosage of the AAV expressing a GAA polypeptide ranges from 11.0E11vg/kg and 5.0E13 vg/kg, and in some embodiments, is no more than $4.0E^{12}$ vg/kg, and in some embodiments, the GAA is expressed to a level that the subject obtains a blood serum level of GAA expressed by the AAV at a pharmaceutical activity range from 189 to ≤ 2,260 nmol/mL/hr of at least within two weeks of administration. In some embodiments, the dosage of the AAV expressing GAA is no more than $4.0E^{12}$ vg/kg, and in some embodiments, the GAA is expressed to a level that the subject obtains a blood serum level of GAA expressed by the AAV at a pharmaceutical activity range from 189 to ≤ 2,260 nmol/mL/hr of at least within two weeks of administration.

[00338] In some embodiments, the dosage of AAV expressing GAA is no more than $5.0E^{11}$vg/kg. In some embodiments, the dosages range from $1.0E^{9}$ vg/kg to $5.0E^{11}$vg/kg.

[00339] In some embodiments, the dosage of AAV expressing GAA is no more than 5.0E13 vg/kg. In some embodiments, the dosages range from 1.0E9vg/kg or 5.0E13 vg/kg.

[00340] In particular, the technology described herein relates to the discovery that a single infusion of a rAAV vector expressing human acid alpha-glucosidase (GAA) can be a stand-alone replacement for repeated infusions of enzyme replacement therapy (ERT) with recombinant human GAA protein (rhGAA). The inventors demonstrate that a one-time administration of AAV expressing GAA leads to long-term transduction of a normal GAA gene into hepatocytes and continuous constitutive expression of GAA in the systemic circulation. Accordingly, the inventors demonstrate herein that administration of a composition comprising AAV expressing hGAA can replace the biweekly exogenous administration of ERT that subjects with Pompe disease normally receive. That is, the inventors have demonstrated herein that subjects with Pompe that are administered a AAV expressing hGAA as disclosed herein can have long term cessation of ERT.

[00341] In particular, described herein is a method of treating Pompe in a subject in need thereof by administering the subject a composition comprising a AAV vector expressing the α-glucosidase (GAA) protein, where the subject is not being concurrently administered a GAA enzyme replacement therapy. In some embodiments, the technology relates to a method of administering a AAV expressing GAA where the subject can be withdrawn from a GAA enzyme replacement therapy

(ERT) for an extended period of time, e.g., at least 3 months, at least 4 months, at least 5 months, at least 1 year, at least 1½ years and points in between 6 months or longer. In some embodiments, the subject is withdrawn from ERT on the day of, or shortly before administration of a AAV expressing GAA, and is clinically stable with respect to at least one or more, as disclosed herein. In some embodiments, the subject is withdrawn from ERT at any time between 1-2 days before or after administration, and about 6-months after administration of a AAV expressing GAA, and is clinically stable with respect to at least one or more Pompe symptoms for at least 6 months, as disclosed herein.

[00342] Additionally, the inventors have also discovered that Pompe patients administered a AAV expressing GAA according to the methods and dose ranges as disclosed herein, there is minimal immune response to the GAA protein expressed by the AAV. According, in some embodiments, there is minimal, or no need for immune modulation or administration of immune suppressants at the time of, or before, or after the administration of the AAV to the subject, and therefore normal immune suppressants protocols which are typically administered when a subject is administered a viral vector, or undergoing gene therapy are not required.

[00343] Accordingly, in all embodiments herein, the method to treat Pompe comprises, or consists essentially of, or consists of, administering an AAV vector expressing GAA as disclosed herein, in the absence of administration of ERT for Pompe, and also in the absence of immune modulation. In some embodiments, the subject has late onset Pompe Disease (LOPD) or infantile-onset Pompe disease.

[00344] In all aspects disclosed herein, the AAV , that comprise a nucleotide sequence containing inverted terminal repeats (ITRs), a promoter, a heterologous gene, a poly-A tail and potentially other regulator elements for use to treat a Pompe disease, e.g., late onset Pompe disease (LOPD), wherein the heterologous gene is GAA, and wherein the vector, e.g., rAAV can be administered to a patient in a therapeutically effective dose that is delivered to the appropriate tissue and/ or organ for expression of the heterologous GAA gene and treatment of the disease, e.g., Pompe disease.

[00345] In some embodiments, a subject administered a AAV vector expressing GAA as disclosed herein, can, after an initial period of withdrawal of the administration of long-term ERT for an extended period of time, be administered complementary ERT, where the complementary ERT is administered after about 6-months, or about 1 year, or longer than a year of cessation of the long-term ERT. Stated differently and without wishing to be bound by theory, the technology disclosed herein relates to a method whereby a subject with Pompe disease who is administered a AAV vector expressing GAA as disclosed herein, can have breaks or "holidays" from the normal long-term ERT administration. That is, according to the methods as disclosed herein, a subject administered an AAV vector expressing GAA as disclosed herein can have extended periods of time with the absence of administration of long-term ERT administration. In some embodiments, the methods as disclosed herein enable flexibility in normal ERT regimens, in that extended breaks or withdrawal of administration of long-term ERT does not result in a clinical decline – that is, a subject remains clinically stable despite not having ongoing long-term ERT.

[00346] In some embodiments, the methods as disclosed herein encompass re-administration of ERT (herein referred to as "complementary ERT") after an extended period of time of cessation of ERT administration, and enable flexibility in normal ERT regimen, as the continued production of GAA expressed by the AAV permits ERT flexibility. In some embodiments, the complementary ERT is pulse administration of ERT, as disclosed herein. In some embodiments, the complementary ERT is at less frequent intervals, or at a lower dose, or at irregular doses, or at irregular intervals as compared to the prior administration of long-term ERT.

[00347] Accordingly, the methods as disclosed herein provide significant advantages to subjects with Pompe disease, including but not limited to reducing or eliminating the rigorous and arduous weekly, or every-other week infusions of long-term rhGAA ERT treatment, which are significantly time-consuming and geographically limiting, and hinders a patient with Pompe disease from travelling for prolonged periods from areas where their ERT infusions are administered. Additionally, as disclosed herein, the absence of ERT administration also reduces any side effects due to anti-rhGAA antibodies against the ERT, and also circumvents the need for administration of immune suppressants normally co-administered with the ERT. As such, the methods to treat Pompe disease as disclosed here leads to greater flexibility in Pompe treatment and an improvement in quality of life and lifestyle of subjects with Pompe disease.

[00348] Accordingly, in one embodiment, the technology relates to a method of treating Pompe disease in a subject, comprising administering to the subject a pharmaceutical composition comprising a recombinant adeno-associated virus (AAV) vector comprising in its genome, a heterologous nucleic acid sequence encoding an alpha-glucosidase (GAA) polypeptide in expressible form wherein the heterologous nucleic acid is operatively linked to a liver-specific promoter, in the absence of administration of long-term GAA enzyme replacement therapy (ERT) for an extended period of time (e.g., ERT administration can be withdrawn or stopped at about 24, or at about 26 weeks, or earlier than 24- or 26 weeks, after administration of the recombinant AAV). In some embodiments, the dosage of the recombinant AAV comprising nucleic acid encoding GAA polypeptide ranges from 1.0E9 vg/kg to 5.0E13 vg/kg, and in some embodiments, the GAA is expressed to a level that the subject obtains a blood serum level of GAA expressed by the AAV at a pharmaceutical activity range from 160 to ≤ 2,260 nmol/mL/hr, 165 to ≤ 2,260nmol/ml/hr, 175 to ≤ 2,260, 180 to ≤ 2,260, 185 to ≤ 2,260, 189 to ≤ 2,260 of at least within two weeks of administration. In some embodiments, the dosage of the AAV expressing GAA is in the range of 1.0E9vg/kg and 5.0E13 vg/kg, and in some embodiments, the GAA is expressed to a level that the subject obtains a blood serum level of GAA expressed by the AAV at a pharmaceutical activity range from 189 to ≤ 2,260 nmol/mL/hr of at least within two weeks of administration. In some embodiments, the dosage of the AAV expressing GAA is in the range of 1.0E9vg/kg and 5.0E13 vg/kg, and in some embodiments, the GAA is expressed to a level that the subject obtains a blood serum level of GAA expressed by the AAV at a pharmaceutical activity range from 189 to ≤ 2,260 nmol/mL/hr of at least within two weeks of administration.

[00349] In particular, the technology described herein relates to the discovery that a single infusion of a rAAV vector expressing human acid alpha-glucosidase (GAA) can be a stand-alone replacement for repeated infusions of enzyme replacement therapy (ERT) with recombinant human GAA protein (rhGAA). The inventors demonstrate that a one-time administration of AAV expressing GAA leads to long-term transduction of a normal GAA gene into hepatocytes and continuous constitutive expression of GAA in the systemic circulation. Accordingly, the inventors demonstrate herein that administration of a composition comprising AAV expressing hGAA can replace the biweekly exogenous administration of ERT that subjects with Pompe disease normally receive. That is, the inventors have demonstrated herein that subjects with Pompe that are administered a AAV expressing hGAA as disclosed herein can have long term cessation of ERT.

[00350] In particular, described herein is a method of treating Pompe in a subject in need thereof by administering the subject a composition comprising a AAV vector expressing the α-glucosidase (GAA) protein, where the subject is not being concurrently administered a GAA enzyme replacement therapy. In some embodiments, the technology relates to a method of administering a AAV expressing GAA where the subject can be withdrawn from a GAA enzyme replacement therapy (ERT) for an extended period of time, e.g., at least 3 months, at least 4 months, at least 5 months, at least 1 year, at least 1½ years and points in between 6 months or longer. In some embodiments, the subject is withdrawn from ERT on the day of, or shortly before administration of a AAV expressing GAA, and is clinically stable with respect to at least one or more, as disclosed herein. In some embodiments, the subject is withdrawn from ERT at any time between 1-2 days before or after administration, and about 6-months after administration of a AAV expressing GAA, and is clinically stable with respect to at least one or more Pompe symptoms for at least 6 months, as disclosed herein.

[00351] Additionally, the inventors have also discovered that Pompe patients administered a AAV expressing GAA according to the methods and dose ranges as disclosed herein, there is minimal immune response to the GAA protein expressed by the AAV. According, in some embodiments, there is minimal, or no need for immune modulation or administration of immune suppressants at the time of, or before, or after the administration of the AAV to the subject, and therefore normal immune suppressants protocols which are typically administered when a subject is administered a viral vector, or undergoing gene therapy are not required.

[00352] Accordingly, in all embodiments herein, the method to treat Pompe comprises, or consists essentially of, or consists of, administering an AAV vector expressing GAA as disclosed herein, in the absence of administration of ERT for Pompe, and also in the absence of immune modulation. In some embodiments, the subject has late onset Pompe Disease (LOPD) or infantile-onset Pompe disease.

[00353] The disclosure herein relates, in general, to a method to treat a subject with Pompe Disease, comprising administering to the subject with Pompe disease a pharmaceutical composition comprising, or consisting essentially of, a recombinant adenovirus associated (AAV) vector comprising in its genome, a heterologous nucleic acid sequence encoding a polypeptide comprising an

alpha-glucosidase (GAA) polypeptide, wherein the heterologous nucleic acid is operatively linked to a liver-specific promoter, and wherein the subject is not administered a GAA enzyme replacement therapy (ERT) for an extended period of time, or can have extended breaks from ERT. In one embodiment, ERT is continued, but at least one of: dosage or frequency is reduced.

[00354] Without wishing to be bound by theory, the inventors have discovered a method to treat Pompe disease with AAV-mediated delivery of GAA to the subject, where the rAAV expresses GAA to a steady state shortly after administration, such that the subject could be withdrawn from ERT as early as, or at, or around the time of the rAAV administration, e.g., ERT can be withdrawn the day before administration, the same day of administration, or the day after administration, or within a week, or within 2-weeks of administration. As disclosed herein, a steady state of GAA expression by the rAAV as disclosed herein is a serum level of GAA at a pharmacological activity range from 189 to ≤ 2,260 nmol/mL/hr.

[00355] In some embodiments, the method to treat Pompe disease with rAAV expressing GAA as disclosed herein comprises administration of a therapeutically effective amount of a rAAV to result in a serum level of expressed hGAA within a pharmacological activity range of between 189 to 410 nmol/mL/hr, or 410 to ≤ 2,260 nmol/mL/hr.

[00356] In some embodiments, the method to treat Pompe disease with rAAV expressing GAA as disclosed herein comprises administration of a rAAV to result in a serum level of expressed hGAA within a range of 189 to ≤ 2,260 nmol/mL/hr, and where the subject achieves clinical stability of one or more symptoms of Pompe disease. Clinical stability includes a steady state in any one or more of the parameters: the 6MWT (6-minute walk test), FVC (Forced vital capacity). In some embodiments, clinical stability refers to a stable level in either motor function (as determined by the 6MWT) and/or pulmonary function (as determined by the FVC) in two consecutive assessments no less than 3-months apart. In some embodiments, a clinical stable level of motor function as determined by the 6MWT is ≤ 12% decline, or less than a 43-meter decrease from baseline in two consecutive assessments no less than 3-months apart. Stated differently, a clinical stable level of motor function as determined by the 6MWT position is within a 0-12% decline from a baseline level in two consecutive assessments no less than 3-months apart.

[00357] In some embodiments, a clinical stable level of pulmonary function as determined by the FVC % predicted in an upright position is ≤ 15% decrease from baseline in two consecutive assessments no less than 3-months apart. Stated differently, a clinical stable level of pulmonary function as determined by the % FVC predicted in an upright position is between 1-14% from a baseline in two consecutive assessments no less than 3-months apart.

[00358] In some embodiments, the baseline level of the 6MWT or FVC is the level measured at or before administration of the rAAV expressing GAA. In some embodiments, the baseline level of the 6MWT or FVC is the level measured at or before administration of the rAAV expressing GAA when the subject is concurrently administered GAA ERT. In some embodiments, the baseline level of the

6MWT or FVC is the level measured at or before administration of the rAAV expressing GAA when the subject is withdrawn from GAA ERT. In some embodiments, the baseline level of the 6MWT or, FVC is the level before withdrawing GAA ERT, e.g, at about 24 to about 26 weeks. In some embodiments, clinical stability is maintained between before ERT withdrawl and after ERT withdrawl of Pompe patients where the patients have received single administration of AAV comprising nucleic acid encoding GAA administrated at the the time of ERT administration, before ERT administration, or, after ERT administration. Clinical stability is maintained indicate that 6MWT and or, FVC are within the ranges from baseline as described herein.

[00359] In some embodiments, the method to treat Pompe disease with rAAV expressing GAA as disclosed herein comprises administration of an amount of rAAV to result in a reduction of glycogen levels in one or more tissues to within a normal range, where the normal range is the glycogen levels in the comparative tissue of a subject without Pompe disease.

A. AAV-hGAA Dosages

[00360] In some embodiments, the methods disclosed herein relate to human subjects can be administered a rAAV expressing GAA as disclosed herein at a dose in the range of 1.0E11vg/kg and 5.0E13 vg/kg. In some embodiments, ERT withdrawal can occur at the time of the administration of the rAAV expressing GAA, or occurring at about 24 or 26 weeks after recombinant AAV administration. In some embodiments, there can be a therapeutic correction of disease pathophysiology with administration of the rAAV expressing GAA as disclosed herein, even in the absence of ERT, and also protection against immune response to the expressed hGAA e.g, as measured by the antibodies against the expressed hGAA, therefore demonstrating that subjects with Pompe disease that are administered a AAV expressing hGAA as disclosed herein can have long term cessation of ERT, which is further discussed, e.g., in International Patent Application No. PCT/US2023/013713, which is incorporated herein by reference in its entirety.

[00361] In some embodiments the dose of the a rAAV vector or rAAV genome to be administered to the subject according to the method to treat Pompe Disease as disclosed herein depends upon the mode of administration, the promoter used, the signal peptide used, the severity of the Pompe disease or other condition to be treated and/or prevented, the individual subject's condition, the particular virus vector or capsid, the liver-specific promoter being used and the nucleic acid to be delivered, including but not limited to, nucleic acid encoding the signal peptide attached to the 5' of the nucleic acid encoding expressible GAA polypeptide, and the like, and can be determined in a routine manner.

[00362] In some embodiments, the therapeutically effective amount of the rAAV vector expressing GAA is an amount that results in a serum GAA concentration at steady state similar to the GAA pharmacological activity achieved by long tern GAA ERT (e.g within 5%, 10%, 20% of such levels). For example, a target GAA serum concentration at steady state ranging from about 160 to $\leq$ 2,260 nmol/mL/hr, from about 189 to $\leq$ 2,260 nmol/mL/hr, or rangin from 410 to $\leq$ 2,260 nmol/mL/hr. In

some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to achieve a target GAA serum concentration at steady state that confers pharmacological activity ranges from 189 to ≤ 2,260 nmol/mL/hr. In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to increase the tissue GAA levels in the subject to >0.30 μmol 4MU/min/gram of tissue, where the normal range of tissue GAA content in a subject without Pompe disease is 0.36 ±/0.13 μmol 4MU/min/gram of tissue. In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to increase the tissue GAA levels in the subject to between 0.25 to 0.4 μmol 4MU/min/gram of tissue. In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to result in a normal tissue GAA content of about 0.36 μmol 4MU/min/gram of tissue, e.g.. about 0.25, or about 0.26, or about 0.27, or about 0.28, or about 0.29, or about 0.30, or about 0.31, or about 0.32, or about 0.33, or about 0.34, or about 0.35, or about 0.36, or about 0.37, or about 0.38, or about 0.39, or about 0.40 μmol 4MU/min/gram of tissue.

[00363] In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to increase the tissue GAA levels in the subject to between 0.1-0.5 μmol 4MU/min/gram of tissue. In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to result in a normal tissue GAA content of about greater than 0.36 μmol 4MU/min/gram of tissue. In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to increase tissue GAA content or levels in the subject within the range 0.2-0.4 μmol 4MU/min/gram of tissue. In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to increase tissue GAA content in the subject to within 40%, or within 30%, or within 20%, or within 10%, or within 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the normal muscle tissue GAA content of 0.36 ± 0.13 (μmol 4MU/min/gram of tissue), where the GAA content of normal muscle tissue is a reference level of GAA in a subject without Pompe Disease. In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to increase tissue GAA content in the subject greater than 0.1 mol 4MU/min/gram of tissue, where the normal range GAA content in subjects with Pompe disease is 0.05 ± 0.04 (μmol 4MU/min/gram of tissue). In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to increase tissue GAA content in the subject more than 2-fold, or 3-fold, or 4-fold, or 5-fold, or 6-fold, or 7-fold, or 8-fold, or 9-fold, or 10-fold, or more than 10-fold of the level of GAA tissue content in the subject with Pompe. In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to increase tissue GAA content in the subject to about 50%, or, about 40%, or about 30%, or about 20%, or about 10%, or about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2% or about 1% of the level of GAA tissue content in the subject with Pompe. In some embodiments, the GAA activity in muscle is at least 1.5 fold, at least 2 fold, at least 3 fold, at least 5 fold, at least 8 fold,

or at least 10 fold than the level prior to AAV administration. In some embodiments, the GAA activity in muscle is at least 1.5 fold, at least 2 fold, at least 3 fold, at least 5 fold, at least 8 fold, or at least 10 fold than the level after the long term ERT was withdrawn for at least about 24 weeks.

[00364] In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to reduce the tissue glycogen levels in the subject within the range 0.25 % wet tissue weight to about 1.5 % wet tissue weight. In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to reduce the muscle tissue glycogen levels in the subject to within 40%, or within 30%, or within 20%, or within 10%, or within 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the normal muscle tissue glycogen content of 0.99% ± 0.74 (% wet tissue weight), which is the normal muscle tissue glycogen content (measured as % wet tissue weight), of a subject that does not have Pompe disease.

[00365] In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount of GAA to exhibit an improvement in the therapeutic index of 3- to 5-fold.

[00366] In some embodiments, the dose of the rAAV vector expressing GAA is a therapeutically effective amount to result in the subject having clinically stable levels of hGAA at 10-weeks, or at least 20 weeks, or 30 weeks post AAV administration.

[00367] In an embodiment, as used herein, without limitation, the term "effective amount" is synonymous with "therapeutically effective amount", "effective dose", or "therapeutically effective dose." In an embodiment, the effectiveness of a therapeutic compound disclosed herein to treat Pompe Disease can be determined, without limitation, by observing an improvement in an individual based upon one or more clinical symptoms, and/or physiological indicators associated with Pompe Disease. In an embodiment, an improvement in the symptoms associated with Pompe Disease can be indicated by a reduced need for a concurrent therapy.

[00368] In some embodiments, exemplary doses for achieving therapeutic effects of a rAAV vector expressing hGAA as disclosed herein is within the range of $1.0E^{9}$ vg/kg to $5.0E^{11}$vg/kg. In some embodiments, the dose administerered to a subject is at least about $1.0E^{9}$ vg/kg, at least about $1.0E^{10}$ vg/kg, at least about 1.0E11 vg/kg, at least about 1.0E12vg/kg, about 1.1E12 vg/kg, about 1.2E12 vg/kg, about 1.3E12 vg/kg, about 1.4E12 vg/kg, about 1.5E12 vg/kg, about 1.6E12 vg/kg, about 1.7E12 vg/kg, about 1.8E12 vg/kg, about 1.9E12 vg/kg, about 2.0E12 vg/kg, about 3.0E12 vg/kg, about 4.0E12 vg/kg, about 5.0E12 vg/kg, about 6.0E12 vg/kg, about 7.0E12 vg/kg, about 8.0E12 vg/kg, about 9.0E12 vg/kg, about 1.0E13 vg/kg, about 1.2E13 vg/kg, about 1.2E13 vg/kg, about 1.2E13 vg/kg, about 1.3E13 vg/kg, about 1.4E13 vg/kg, about 1.5E13 vg/kg, about 1.6E13 vg/kg, about 1.7E13 vg/kg, about 1.8E13 vg/kg, about 1.9E13 vg/kg, about 2.0E13 vg/kg, about 3.0E13 vg/kg, about 4.0E13 vg/kg, about 5.0E13 vg/kg, about 6.0E13 vg/kg, about 7E13 vg/kg, about 8E13 vg/kg, about 9E13 vg/kg, or about 10E14 vg/kg. In some embodiments the rAAV administration is accompanied with immunomodulators, e.g, prednisone, methotrexate or, a combination thereof. In

some embodiments the rAAV of the invention is packaged within AAV XL 32 or AAV XL 32.1 capsid.

[00369] In preferred embodiments, exemplary doses for achieving therapeutic effects according to the methods as disclosed herein are titers of at between 1.2E12 and 4.0E12 vg/kg, for example, least about 1.0E12 vg/kg, about 1.1E12 vg/kg, about 1.2E12 vg/kg, about 1.3E12 vg/kg, about 1.4E12 vg/kg, about 1.5E12 vg/kg, about 1.6E12 vg/kg, about 1.7E12 vg/kg, about 1.8E12 vg/kg, about 1.9E12 vg/kg, about 2.0E12 vg/kg, about 2.1E12 vg/kg, about 2.2E12 vg/kg, about 2.3E12 vg/kg, about 2.4E12 vg/kg, about 2.5E12 vg/kg, about 2.6E12 vg/kg, about 2.7E12 vg/kg, about 2.8E12 vg/kg, about 2.9E12 vg/kg, about 3.0E12 vg/kg, about 3.1E12 vg/kg, about 3.2E12 vg/kg, about 3.3E12 vg/kg, about 3.4E12 vg/kg, about 3.5E12 vg/kg, about 3.6E12 vg/kg, about 3.7E12 vg/kg, about 3.8E12 vg/kg, about 3.9E12 vg/kg, about 4.0E12 vg/kg.

[00370] In preferred embodiments, exemplary doses for achieving therapeutic effects according to the methods as disclosed herein are titers of at between 1.0E11vg/kg and 5.0E13 vg/kg, for example, 1.0E11vg/kg, 1.1E11vg/kg, 1.2E11vg/kg, 1.3E11vg/kg, 1.4E11vg/kg, 1.5E11vg/kg, 1.6E11vg/kg, 1.7E11vg/kg, 1.8E11vg/kg, 1.9E11vg/kg, about 1.0E12vg/kg, about 1.1E12 vg/kg, about 1.2E12 vg/kg, about 1.3E12 vg/kg, about 1.4E12 vg/kg, about 1.5E12 vg/kg, about 1.6E12 vg/kg, about 1.7E12 vg/kg, about 1.8E12 vg/kg, about 1.9E12 vg/kg, about 2.0E12 vg/kg, about 3.0E12 vg/kg, about 4.0E12 vg/kg, about 5.0E12 vg/kg, about 6.0E12 vg/kg, about 7.0E12 vg/kg, about 8.0E12 vg/kg, about 9.0E12 vg/kg, about 1.0E13 vg/kg, about 1.2E13 vg/kg, about 1.2E13 vg/kg, about 1.2E13 vg/kg, about 1.3E13 vg/kg, about 1.4E13 vg/kg, about 1.5E13 vg/kg, about 1.6E13 vg/kg, about 1.7E13 vg/kg, about 1.8E13 vg/kg, about 1.9E13 vg/kg, about 2.0E13 vg/kg, about 3.0E13 vg/kg, about 4.0E13 vg/kg, about 5.0E13 vg/kg.

[00371]

[00372] In some embodiments, a rAAV vector expressing hGAA as disclosed herein useful for the methods to treat Pompe Diseases, exemplary doses for achieving therapeutic effects are titers of at least about 1.0E12 to 4.0E12 vg/kg, or about 1.2E12 to 3.0E12 vg/kg, or about 1.2E12 to 2.5E12 vg/kg, or about 2.5E12 to 4.0E12 vg/kg.

[00373] In some embodiments, the dosage may be modified by a person of ordinary skill in the art, e.g., the dose administered can be lower than 1.0E12 vg/kg, or lower than about 5.0E11 vg/kg where a stronger promoter than the LSP of SEQ ID NO: 97 is operatively linked to the nucleic acid encoding GAA. In contrast, in alternative embodiments, the dosage may be modified by a person of ordinary skill in the art, e.g., the dose of the rAAV vector administered can be higher than about 1.6E12 vg/kg, or higher than about 5.0E12 vg/kg when a weaker liver-specific promoter than the LSP of SEQ ID NO: 97 used in the AAV8-LSPhGAA vector is operatively linked to the nucleic acid encoding GAA. Exemplary doses for achieving therapeutic effects are titers of at least about $1.0E^{5}$, $1.0E^{6}$, $1.0E^{7}$, $1.0E^{8}$, $1.0E^{9}$, $1.0E^{10}$, $1.0E^{11}$, $1.0E^{12}$ vg/kg, optionally about $1.0E^{10}$ to about $1.0E^{12}$ transducing units (vg/kg),

and optionally does not exceed about $4.0E^{12}$ vg/kg or optionally is about $3.0E^{12}$ transducing units (vg/kg).

[00374] In one embodiment, no percentage of the administered dose of rAAV vector expressing hGAA as disclosed herein is retained in the liver following administration, e.g., at least 1, 2, 3, 4 weeks or more following administration.

[00375] In one embodiment, less than 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% of the administered dose of rAAV vector expressing hGAA as disclosed herein is retained in the liver following administration, e.g., at least 1, 2, 3, 4 weeks or more following administration.

[00376] In one embodiment, less than $1.0E^{9}$ vg/kg to $5.0E^{11}$vg/kg of the administered rAAV vector expressing hGAA as disclosed herein is retained in the liver following administration, e.g., at least 1, 2, 3, 4 weeks or more following administration.

[00377] In one embodiment, less than $1.0E^{9}$ vg/kg, $1.0E^{10}$ vg/kg, 1.0E11 vg/kg, 1.0E12vg/kg, 1.1E12 vg/kg, 1.2E12 vg/kg, 1.3E12 vg/kg, 1.4E12 vg/kg, 1.5E12 vg/kg, 1.6E12 vg/kg, 1.7E12 vg/kg, 1.8E12 vg/kg, 1.9E12 vg/kg, 2.0E12 vg/kg, 3.0E12 vg/kg, 4.0E12 vg/kg, 5.0E12 vg/kg, 6.0E12 vg/kg, 7.0E12 vg/kg, 8.0E12 vg/kg, 9.0E12 vg/kg, 1.0E13 vg/kg, 1.2E13 vg/kg, 1.2E13 vg/kg, 1.2E13 vg/kg, 1.3E13 vg/kg, 1.4E13 vg/kg, 1.5E13 vg/kg, 1.6E13 vg/kg, 1.7E13 vg/kg, 1.8E13 vg/kg, 1.9E13 vg/kg, 2.0E13 vg/kg, 3.0E13 vg/kg, 4.0E13 vg/kg, or 5.0E13 vg/kg of the administered rAAV vector expressing hGAA as disclosed herein is retained in the liver following administration, e.g., at least 1, 2, 3, 4 weeks or more following administration.

[00378] In a further embodiment, administration of rAAV vector or rAAV genome according to the methods as disclosed herein to treat a subject with Pompe disease can result in production of a GAA protein with a circulatory half-life of 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, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, one month, two months, three months, four months or more.

[00379] In some embodiments, the methods for treatment of Pompe as disclosed herein relate to a single dose of a rAAV expressing hGAA is used to treat a subject in a single administration. However, in some embodiments, the dose of rAAV to be administered can be given to the subject in multiple administrations, e.g., a dose of rAAV can be divided into sub-doses and administered in multiple administrations.

[00380] In some embodiments, it is envisioned that the methods for treatment of Pompe as disclosed herein can comprise multiple administrations of a single dose of a rAAV expressing hGAA, that is,

the subject can be treated with a booster administration (i.e., a second, third, fourth, etc.) of a rAAV expressing hGAA after a defined period of time after the initial or first administration. The dose of a booster administration (i.e., 2nd, 3rd, 4th, or 5th etc.) can be the same dose (amount) of rAAV-hGAA administered in the first administration, or can be a higher dose, or a lower dose, depending on the factors above, including, but not limited to, a therapeutically effective dose to achieve any one or more of (i) serum GAA levels indicating steady state of GAA expression, (ii) reduced glycogen levels and/or, maintained glycogen levels within normal range in the muscle, and (iii) one or more Pompe symptoms, including muscle function and/or pulmonary function within clinically stable levels. As disclosed herein, a steady state of GAA expression by the rAAV as disclosed herein is a serum level of GAA at a pharmacological activity range from 165 to≤ 2260 nmol/ml/hr or, from 189 to ≤ 2,260 nmol/mL/hr. Stability of one or more symptoms of Pompe disease can be determined by the clinical stability parameters as disclosed herein, and includes a steady state in the 6MWT (6-minute walk test) and/or FVC (Forced vital capacity) in two consecutive assessments no less than 3-months apart as disclosed herein. In some embodiments, a clinical stable level of motor function as determined by the 6MWT is ≤ 12% decline, or less than a 43-meter decrease from baseline in two consecutive assessments no less than 3-months apart. In some embodiments, a clinical stable level of pulmonary function as determined by the FVC % predicted in an upright position is ≤ 15% decrease from baseline in two consecutive assessments no less than 3-months apart.

[00381] In an embodiment, the time period of between administration of a first dose, and a subsequent dose (i.e., a booster dose) of a rAAV vector according to the methods for treatment of Pompe as disclosed herein is selected from any of the following: about 4 months, about 6 months, about 7 months, about 8 months, about 9 months, about 12 months, about 18 months, about 24 months, or about 3 years, about 4 years, about 5 years, or more than 5 years

[00382] In another embodiment, administration of a rAAV vector or rAAV genome as disclosed herein for the treatment of Pompe Disease results in an increase in weight by, e.g., at least 0.5 pounds, at least 1 pound, at least 1.5 pounds, at least 2 pounds, at least 2.5 pounds, at least 3 pounds, at least 3.5 pounds, at least 4 pounds, at least 4.5 pounds, at least 5 pounds, at least 5.5 pounds, at least 6 pounds, at least 6.5 pounds, at least 7 pounds, at least 7.5 pounds, at least 8 pounds, at least 8.5 pounds, at least 9 pounds, at least 9.5 pounds, at least 10 pounds, at least 10.5 pounds, at least 11 pounds, at least 11.5 pounds, at least 12 pounds, at least 12.5 pounds, at least 13 pounds, at least 13.5 pounds, at least 14 pounds, at least 14.5 pounds, at least 15 pounds, at least 20 pounds, at least 25 pounds, at least 30 pounds, at least 50 pounds.

[00383] In another embodiment, an AAV GAA of any serotype, as disclosed herein for the treatment of Pompe Disease results in an increase in weight by, e.g., from 0.5 pounds to 50 pounds, from 0.5 pounds to 30 pounds, from 0.5 pounds to 25 pounds, from 0.5 pounds to 20 pounds, from 0.5 pounds to 15 pounds, from 0.5 pounds to ten pounds, from 0.5 pounds to 7.5 pounds, from 0.5 pounds to 5

pounds, from 1 pound to 15 pounds, from 1 pound to 10 pounds, from 1 pound to 7.5 pounds, form 1 pound to 5 pounds, from 2 pounds to ten pounds, from 2 pounds to 7.5 pounds.

B. Withdrawal of long-term ERT

[00384] Treatment of Pompe disease is normally by administration of long-term enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (rhGAA) and has previously reported to prolong survival of both LOPD and IOPD patients through improvement in pulmonary and muscle function. However, Schoser *et al*, report that after a period of stabilization, both these parameters continue to decline over time (see Schoser et al., 2017 Neurol, 264: 621-30). Additionally, ERT with recombinant GAA protein has numerous disadvantages, including but not limited to, short-half life of the administerted recombinant GAA in the blood, lack of efficient skeletal muscle updake, potential for high titer antibody response and even some patients failing to respond to ERT, and rigorous administration of a recombinant GAA infusion every 2 weeks, that can take between 5-8 hours. Moreover, while disease progression is slowed compared with untreated subjects, the benefits of ERT may not be long-lasting, and many patients die or remain weak despite treatment compliance (Tarnopolsky et al. 2016 Can J Neurol Sci, 43: 472-85).

[00385] The waning efficacy in subjects receiving recombinant GAA protein ERT is partially explained by an immune response to ERT where high, sustained anti-GAA antibody titers (HSAT) are formed. Subjects with HSAT demonstrated greatly increased mortality, in comparison with patients who formed no or only low titer antibodies (Banugaria et al. 2011). Furthermore, the ability to prevent antibody formation in subjects at risk for HSAT with immunosuppression, which significantly prolonged survival, confirmed the clinical relevance of HSAT (Mendelsohn et al. 2009; Banugaria et al. 2013; Kazi et al. 2017).

[00386] Subjects with Pompe's disease are considered as cross-reactive immunologic material (CRIM) positive if they have residual GAA enzyme activity and CRIM negative if no residual GAA activity is detected. Based on pooled clinical studies data, 28% of Pompe's disease cases are infantile-onset, of which about 85% are classic infantile-onset and three quarters of those are CRIM positive (Kemper, Comeau, and Green 2013). Determination of CRIM status in newly diagnosed IOPD patients is important since it allows for the institution of preventive immunomodulatory measures before beginning ERT, thus offsetting the worst damaging effects of HSAT. CRIM-negative Pompe disease subjects produced HSAT and demonstrated markedly reduced efficacy from ERT with rhGAA (Amalfitano et al. 2001). In the first pilot study of ERT in Pompe disease using Chinese hamster ovary cell-derived rhGAA, the two subjects who were CRIM-negative produced higher titers of anti-GAA antibodies than the third subject who was CRIM-positive. This corresponded with a markedly reduced efficacy of ERT in the CRIM-negative subjects. The relevance of antibody formation to efficacy of therapy in Pompe disease has been emphasized by the poor response of CRIM-negative subjects to ERT, which correlated with the onset of HSAT (Kishnani et al. 2010).

[00387] While no LOPD subjects are CRIM negative, some mount high antibody responses to rhGAA capable of interfering with optimal efficacy of ERT (Patel et al. 2012; de Vries et al. 2017; "LUMIZYME Prescribing Information" 2014). In addition, all Pompe subjects mount some level of anti-GAA antibody response with unknown effects on ERT efficacy.

[00388] In some embodiments, the rAAV vectors expressing a GAA polypeptide as disclosed herein can be used in methods to treat subjects with Pompe disease, and comprises administering a AAV expressing hGAA as disclosed herein that enables the subject to have an extended period of cessation of the administration of long-term ERT. In particular, rAAV vectors expressing a GAA polypeptide as disclosed herein can be administered to a subject with Pompe disease that enables them to have the ability to reduce, or eliminate the clinical need for long-term hGAA ERT administration for an extended period of time.

[00389] Accordingly, another aspect of the technology disclosed herein relates to a method to treat Pompe Disease by administrating to the subject with Pompe disease a composition comprising a rAAV vector expressing a GAA polypeptide as disclosed herein, where in some embodiments, the methods enable subjects with Pompe disease to withdraw from, or stop long-term administration of recombinant human GAA (rhGAA) ERT, which is normally administered on a weekly or every-other week regimen. In some embodiments, the methods disclosed herein enable a subject with Pompe disease to take breaks from the normal ERT regimen for extended period of time (e.g., extended periods of ERT cessation) if the subject is administered a specific dose of AAV vector expressing a GAA polypeptide as disclosed herein. In some embodiments, withdrawal of the administration of long-term ERT begins at about the time of administration of the AAV vector to the subject (e.g., the day before, the day of, or the day after), or in some embodiments, withdrawal of the administration of long-term ERT can occur at about 24 weeks, or anywhere within about 24 weeks to about 26 weeks after administration of the AAV vector.

[00390] As disclosed herein, "long-term ERT" refer to the standard-of-care (SOC) treatment for a subject with Pompe disease, including IOPD and LOPD, and is normally a regimen of intravenous administration of recombinant human alglucisudease alfa protein (rhGAA) to the subject on a regular and frequent basis, e.g., every week or every 2 weeks, without any breaks in the regimen, and where the administered rhGAA protein provides an exogenous source of GAA. MYOZYME® (alglucosidase alfa) which was first US approved product (2006) for the treatment of Pompe disease and LUMIZYME® (alglucosidase alfa) which was approved in 2010 are exemplary current standard-of-care (SOC) treatments for infantile-onset and late-onset Pompe patients. The normal long-term ERT administration regimen is intravenously administration of Alglucosidase alfa every 2 weeks as an infusion at a dose of 20 mg/Kg (LUMIZYME Prescribing Information 2014).

[00391] As disclosed herein, in some embodiments, the methods as disclosed herein by administering a AAV expressing hGAA as disclosed herein enable the withdrawal or cessation of administration of long-term ERT for an extended period of time. In some embodiments, the extended period of time is

at least about 3-months, or at least about 6-months, or at least about 1 year, or longer than 1 year.

[00392] As disclosed herein, "extended period" of time, as referred to in reference to time period that administration of long-term ERT is stopped, refers to a time period that is longer than 1 month, and in some embodiments is a time period longer than if up to 5 administrations of ERT are missed.

[00393] Accordingly, in some embodiments, the methods to treat a subject with Pompe Disease with a AAV expressing hGAA as disclosed herein comprises administering to the subject a pharmaceutical composition comprising a AAV expressing GAA and where the subject is not administered long-term GAA enzyme replacement therapy (ERT) for an extended period of time. In some embodiments, the cessation or withdrawal of administration of long-term ERT occurs anywhere between 1-2 days of administration and at least 24 weeks after the administration of the AAV-GAA vector. That is, in some embodiments, the subject being treated can stop the administration of ERT on the day of, or the day before or after administration of AAV-GAA. In some embodiments, the subject being treated according to the methods as disclosed herein can stop ERT after about 1 week, or about 2 weeks, or about 3 weeks, or about 1 month, or about 2 months, or about 3 months, or about 4 months, or about 5 months, or about 6 months after the administration of the AAV-GAA.

[00394] The exact timeframe for stopping ERT, or for ERT cessation, by each subject according to the methods as disclosed herein can be determined by an ordinary skilled practitioner, but without wishing to be limited by theory, encompassed herein is a method to treat a subject with Pompe disease by administering a AAV expressing hGAA as disclosed herein, where ERT is stopped at time point that the serum GAA levels achieved from expression by the AAV-hGAA is near or about a serum level of within a pharmacological activity range of at least 165 nmol/ml/hr or, of at least 189 nmol/ml/hr, for example, between 189 to $\leq$ 2,260 nmol/mL/hr. In some embodiments, encompassed herein is a method where ERT is stopped at time point that the serum GAA levels achieved from expression by the AAV-hGAA is within 50%, or within 60%, or within 70% or within 80% of a serum level of within a pharmacological activity range of between 189 nmol/mL/hr. In some embodiments, encompassed herein is a method to treat Pompe disease by administering a AAV expressing a hGAA polypeptide as disclosed herein, where ERT is stopped at time point that the serum GAA levels achieved from expression by the AAV-hGAA is within 50%, or within 60%, or within 70% or within 80% of a serum level of within a pharmacological activity range of between 165 to about 2000 nmol/mL/hr.

[00395] In some embodiments, encompassed herein is a method to treat Pompe disease by administering a AAV expressing a hGAA polypeptide as disclosed herein, where ERT is stopped at time point that the serum GAA levels achieved from a normal ERT regimen are replaced with a GAA serum level achieved from expression by the AAV-hGAA. For example, as the serum GAA levels due to the recombinant hGAA from the last ERT administration declines, there is a concurrent increase in serum GAA levels achieved from expression by the AAV-hGAA, so that ERT withdrawal or cessation does not result in a decline in clinical stability of one or more symptoms of Pompe disease

in the subject, as measured by the 6MWT or FVC according to the methods as disclosed herein. For illustration purposes only, in some embodiments, ERT withdrawal or cessation occurs when the administered AAV-hGAA results in the expressed GAA to achieve a serum GAA level for clinical stability of one or more symptoms of Pompe disease in the subject, for example, a clinical stable level of motor function as determined by the 6MWT is ≤ 12% decline, or less than a 43-meter decrease from baseline in two consecutive assessments no less than 3-months apart, or a clinical stable level of pulmonary function as determined by the FVC % in an upright position is ≤ 15% decrease from baseline in two consecutive assessments no less than 3-months apart, therefore making superfluous the recombinant hGAA from the last ERT administration.

[00396] In some embodiments, the method to treat Pompe disease by administering a AAV expressing a hGAA polypeptide as disclosed herein enables long term cessation of ERT for a period of about 1 year, or about 15 months, or about 18 months, or about 24 months, or about 30 months or more than 30 months while maintaining clinical stable with one or more symptoms of Pompe disease, as measured by 6MWT and/or % FVC, as disclosed herein.

[00397] Accordingly, the rAAV vectors encoding a GAA polypeptide as disclosed herein and the methods as disclosed herein provide significant advantages to subjects with Pompe disease, including but not limited to reducing or eliminating the rigorous and arduous weekly, or every-other week infusions of long-term rhGAA ERT treatment, which are significantly time-consuming and geographically limiting, and hinders a patient with Pompe disease from travelling for prolonged periods from areas where their ERT infusions are administered. Additionally, as disclosed herein, the absence of ERT administration also reduces any side effects due to anti-rhGAA antibodies against the ERT, and also circumvents the need for administration of immune suppressants normally co-administered with the ERT. As such, the methods to treat Pompe disease by administering a AAV expressing a hGAA polypeptide as disclosed herein leads to greater flexibility in Pompe treatment and an improvement in quality of life and lifestyle of subjects with Pompe disease.

C. Administration of Complementary ERT

[00398] In some embodiments, the method to treat Pompe disease by administering a AAV expressing a hGAA polypeptide as disclosed herein enables a subject to have breaks or "holidays" from the normal regimen of administration long-term ERT. That is, according to the methods as disclosed herein, a subject who is administered an AAV vector expressing GAA as disclosed herein can take extended periods of time in the absence of administration of long-term ERT. Moreover, in some embodiments, a subject administered a AAV vector expressing GAA as disclosed herein, can, after an initial period of withdrawal of the administration of long-term ERT for an extended period of time, be administered complementary ERT, where the complementary ERT is administered after about 6-months, or about 1 year, or longer than a year of cessation of the long-term ERT. Accordingly, the methods to treat Pompe disease by administering a AAV expressing a hGAA

polypeptide as disclosed herein enable flexibility in normal long-term ERT administration regimens, allowing both extended breaks or absence of administration of long-term ERT which does not result in a clinical decline – that is, a subject remains clinically stable despite not having ongoing long-term ERT administration for an extended period of time.

[00399] In some embodiments, the methods to treat Pompe disease by administering a AAV expressing a hGAA polypeptide as disclosed herein encompass re-administration of ERT (herein referred to as "complementary ERT") after an extended period of time of cessation of ERT administration, and enable flexibility in normal ERT regimen, as the continued production of GAA expressed by the AAV permits include ERT flexibility. In some embodiments, the complementary ERT is pulse administration of ERT, as disclosed herein. In some embodiments, the complementary ERT is at less frequent intervals, or at a lower dose, or at irregular doses, or at irregular intervals as compared to the prior administration of long-term ERT.

[00400] In some embodiments, the methods to treat Pompe disease by administering a AAV expressing a hGAA polypeptide as disclosed herein encompass recommencement of ERT (herein referred to as "complementary ERT") after an extended period of at least 6 months to about 1 year of absence of long-term ERT administration. In some embodiments, complementary ERT can be for a short-period of time, and can be followed by a second extended period of ERT administration cessation. In some embodiments, complementary ERT can be for a period of anywhere between 3 months to about 2 years, for example, about 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10months, 11 months, or for about 1 year.

[00401] In some embodiments, the methods to treat Pompe disease by administering a AAV expressing a hGAA polypeptide as disclosed herein encompasses administering a rAAV expressing GAA according to as subject with Pompe, wherein administration of long-term ERT continues after administration of the recombinant AAV. However, the ERT is at a lower dose and/or frequency than before the administration of the recombinant AAV vector. For example, after administration of the AAV vector, long-term ERT can be administered every 3 weeks, once a month, bimonthly, once every 3 months, every 4 months, every 5 months, every 6 months for at least 24 weeks after administration of the AAV-GAA. Dosage of the long-term ERT can be reduced in one embodiment. In one method, a pulse administration regimen of long-term ERT after administration of the AAV vector can be used so that an irregular dosing schedule and/or amount can be used. As discussed herein, in some embodiments, administration of long-term ERT can be withdrawn at 24 weeks, or earlier as disclosed herein.

[00402] In some embodiments, due to continued expression of GAA by the administered AAV vector, the methods disclosed herein enable flexibility of administration of both long-term ERT or complementary ERT, such that if a subject plans to miss, or inadvertently or accidently misses one or more ERT administrations of a long-term ERT or complementary ERT regimen, the subject will maintain clinical stability. Currently, if ERT is missed, a much larger amount of ERT is needed to

return to the same clinical level.

[00403] In some embodiments, the complementary ERT is at less frequent administration intervals, or at a lower dose, or at irregular doses, or at irregular administration intervals as compared to the prior administration of long-term ERT. For example, in some embodiments, the dose of rhGAA administered in a complementary ERT is less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 2%, or less than 1% of the normal dose of the rhGAA administered in a long-term ERT regimen.

[00404] In some embodiments, the complementary ERT is administered as pulse administration. In alternative embodiments, as a subject administered the rAAV vector compositions as disclosed herein can take breaks or interruptions from the regular dosing regimen of the long-term ERT administration or complementary ERT, where the long-term ERT or complementary ERT are administered by pulse administration. For example, in some embodiments, the administration of the long-term ERT or complementary ERT can be administered by pulsed administration. In certain embodiments, a subject administered the compositions can have pulsed administration of the long-term ERT or complementary ERT.

[00405] In certain embodiments, pulsed administration of the complementary ERT is suitable provided the subject has been administered the AAV vector composition as disclosed herein at a sufficient dose for continuous expression of GAA to maintain clinical stability and/or maintain a serum GAA level at or above 189 n mol/hr* (e.g., during the entire duration of the ERT break or "ERT holiday" where the regularly scheduled ERT is not administered). In certain embodiments, the methods disclosed herein allows a subject to undergo pulsed administration of complementary ERT for the lifetime of the subject.

[00406] In some embodiments, the regimen of administration of the complementary ERT can have intermittent breaks, where the administration of ERT is halted (e.g., the duration of the break or "ERT holiday" where the regimen of administration of ERT is halted).

[00407] In some embodiments, the methods encompass administration of complementary ERT by pulsed administration, where the pulsed administration of complementary ERT occurs least once a month, at least every other month, or at least every 6 months, or at least every year, or every other year. As the methods disclosed herein comprise administering a AAV vector at a sufficient dose for continuous expression of GAA in the subject and to maintain a serum GAA level at or above 189 n mol/hr*, if complementary ERT is administered, pulsed administration can substantially reduce the amount of ERT administered to the patient per dose or per total treatment regimen with an increased effectiveness, and allows for increased flexibility in a ERT administration regimen. This represents a significant saving in time, effort and expense and, more importantly, improved quality of life for Pompe patients, as well as a lower ERT dose which can lessens any side effects, including anti-GAA antibodies to the administered rhGAA protein.

[00408] In some embodiments, administration of complementary ERT is a pulsed administration. In certain embodiments, a pulsed administration comprises administering complementary ERT for about 8 weeks, followed by not administering complementary ERT for about 4 weeks. In some embodiments, the pulsed administration comprises administering complementary ERT for about 6 weeks (i.e., 6 weekly infusions, or 3 infusions every 2 weeks), followed by not administering a complementary ERT for about 2 weeks. In certain embodiments, the pulsed administration comprises administering complementary ERT for about 4 weeks, followed by not administering complementary ERT for about 2 weeks. In some embodiments, the pulsed administration comprises administering complementary ERT for about 2 weeks, followed by not administering complementary ERT for about 2 weeks.

D. Absence of long-term immune suppression

[00409] In another aspect, the technology relates to methods to treat Pompe disease by administering a AAV expressing a hGAA polypeptide as disclosed herein, where the administration of a composition comprising a AAV-GAA vector is administered to the subject without ongoing immune suppression. That is, in some embodiments, immune suppression is not administered to the subject long term.

[00410] In some embodiments, an immune suppressant or immune modulator is administered to the subject intermittently, or for a transient period, e.g., as an immune prophylaxis to the subject to prevent or reduce any immune response to the administered AAV vector, therefore allowing, if necessary, a subsequent or booster administration of the AAV vector expressing GAA according to the methods as disclosed herein.

[00411] In some embodiments, an immune modulator is administered for an initial period at, or around the time the AAV vector expressing GAA as disclosed herein is administered to the subject. For example, an immune modulator is administered starting at about 24hrs before AAV vector expressing GAA is administered to the subject. In some embodiments, an immune modulator is administered starting at about 24hrs before AAV administration and is administered for at least 1 day, or at least 2 days, or at least 3 days or at least 4 days, or at least 5 days, or at least 6 days, or for about 1 week, or for longer than 1 week after administration of the AAV vector expressing GAA. In some embodiments, an immune modulator is administered starting at, or about 24hrs before AAV administration and is administered for no more than 1 day, or 2 days, 3 days, or 4 days, or 5 days, or 6 days, or for 1 week, or for 2 weeks, or for 3 weeks or for 1 month after administration of the AAV vector expressing GAA.

[00412] In some embodiments, an immune modulator is administered to the subject at tapering lower doses, e.g., at a first dose for a first period of time, at a second lower dose for a second period of time, and third dose that is lower than the second dose – for a third period of time, and so forth until no immune response to the AAV or GAA is produced. For example, in some embodiments, the first dose

of an immune modulator is started at, or about 24hrs before AAV administration and is administered for at least 1 day, or at least 2 days, or at least 3 days or at least 4 days, or at least 5 days, or at least 6 days, or for about 1 week, or about 2 weeks, or about 3 weeks, or about 4 weeks, after which the immune modulator is reduced to a third dose (which is lower than the second dose) for a third period of time (e.g., for at least 1 day, or at least 2 days, or at least 3 days or at least 4 days, or at least 5 days, or at least 6 days, or for about 1 week).

[00413] For exemplary purposes only, in some embodiments, the methods to treat Pompe Disease as disclosed herein comprise administering prednisone as an immune suppressant, i.e., immune prophylaxis, at a first dose of 60 milligrams (given orally) starting 24 hours prior to AAV vector administration. In some embodiments, prednisone is continued at 60 mg/day po through the completion of week four after vector administration, after which, at the beginning of week 5 the prednisone dose is tapered to a second dose level of 55 mg/day po and maintained for 7 days. In some embodiments, at the Beginning of week 6 the dose is tapered to a third dose level of 50 mg/day po and maintained for 7 days etc., so that the dose of the immune suppressant (i.e., prednisone) is tapered on a weekly basis by 5 mg/day, after an initial immune suppressant dose for 4 weeks.

[00414] The use of prednisone is exemplified herein as an immune suppressant for immune prophylaxis according to the methods as disclosed herein. However, it is envisioned that prednisone can be readily substituted with a different immune modulator and administration regimen known by a person of ordinary skill in the art.

[00415] In some embodiments, normal immune prophylaxis for preventing immune reactivity to the expressed GAA is stopped, or withdrawn on day 1, or shortly before or after administration of the rAAV expressing GAA according to the methods as disclosed herein.

(i) Immune Modulation and Immunosuppression:

[00416] As disclosed herein, in some embodiments, the methods to treat Pompe disease by administering a AAV expressing a hGAA polypeptide as disclosed herein to the subject without ongoing immune suppression. That is, in some embodiments, immune suppression is not administered to the subject long term, and is only administered for a short and pre-defined period, including an initial period (with an initial dose) and a tapering period (with incremental tapering doses) after the administration of the AAV vector expressing GAA to the subject. Accordingly, in some embodiments, the immune suppression is administered for between 4 weeks to up to about 15 weeks after the administration of the AAV vector expressing GAA to the subject, and can be administered in an initial and tapering doses as disclosed herein.

[00417] Accordingly, in some embodiments, the methods and compositions using the AAV vectors and AAV genomes as described herein, for treating Pompe, further comprises administering an immune modulator for an initial period followed by a tapering period. In some embodiments, the

immune modulator can be administered at the time of rAAV vector administration, before rAAV vector administration or, after the rAAV vector administration.

[00418] In any embodiment of the methods and compositions as disclosed herein, a subject being administered a rAAV vector or rAAV genome as disclosed herein is also administered an immunosuppressive agent. Various methods are known to result in the immunosuppression of an immune response of a patient being administered AAV. Methods known in the art include administering to the patient an immunosuppressive agent, such as a proteasome inhibitor. One such proteasome inhibitor known in the art, for instance as disclosed in U.S. Patent No. 9,169,492 and U.S. Patent Application No. 15/796,137, both of which are incorporated herein by reference, is bortezomib. In another embodiment, an immunosuppressive agent can be an antibody, including polyclonal, monoclonal, scfv or other antibody derived molecule that is capable of suppressing the immune response, for instance, through the elimination or suppression of antibody producing cells. In a further embodiment, the immunosuppressive element can be a short hairpin RNA (shRNA). In such an embodiment, the coding region of the shRNA is included in the rAAV cassette and is generally located downstream, 3' of the poly-A tail. The shRNA can be targeted to reduce or eliminate expression of immunostimulatory agents, such as cytokines, growth factors (including transforming growth factors β1 and β2, TNF and others that are publicly known).

[00419] In some embodiments, the immune modulator is an immunoglobulin degrading enzyme such as IdeS, IdeZ, IdeS/Z, Endo S, or, their functional variant. Non-limiting examples of references of such immunoglobulin degrading enzymes and their uses as described in US 7,666,582, US 8,133,483, US 20180037962, US 20180023070, US 20170209550, US 8,889,128, WO2010/057626, US 9,707,279, US 8,323,908, US 20190345533, US 20190262434, and WO2020/016318, each of which are incorporated in their entirety by reference.

[00420] In some embodiments, the immune modulator or immunosuppressive agent is a proteasome inhibitor. In certain aspects, the proteasome inhibitor is Bortezomib. In some aspects of the embodiment, the immune modulator comprises bortezomib and anti CD20 antibody, Rituximab. In other aspects of the embodiment, the immune modulator comprises bortezomib, Rituximab, methotrexate, and intravenous gamma globulin. Non-limiting examples of such references, disclosing proteasome inhibitors and their combination with Rituximab, methotrexate and intravenous gamma globulin, as described in US 10,028,993, US 9,592,247, and, US 8,809,282, each of which are incorporated in their entirety by reference. One such proteasome inhibitor known in the art, for instance as disclosed in U.S. Patent No. 9,169,492 and U.S. Patent Application No. 15/796,137, both of which are incorporated herein by reference, is bortezomib.

[00421] In another embodiment, an immunosuppressive agent can be an antibody, including polyclonal, monoclonal, scfv or other antibody derived molecule that is capable of suppressing the immune response, for instance, through the elimination or suppression of antibody producing cells. In a further embodiment, the immunosuppressive element can be a short hairpin RNA (shRNA). In such

an embodiment, the coding region of the shRNA is included in the rAAV cassette and is generally located downstream, 3' of the poly-A tail. The shRNA can be targeted to reduce or eliminate expression of immunostimulatory agents, such as cytokines, growth factors (including transforming growth factors β1 and β2, TNF and others that are publicly known).

[00422] In alternative embodiments, the immune modulator is an inhibitor of the NF-kB pathway. In certain aspects of the embodiment, the immune modulator is Rapamycin or, a functional variant. Non-limiting examples of references disclosing rapamycin and its use described in US 10,071,114, US 20160067228, US 20160074531, US 20160074532, US 20190076458, US 10,046,064, are incorporated in their entirety. In other aspects of the embodiment, the immune modulator is synthetic nanocarriers comprising an immunosuppressant. Non limiting examples of references of immunosuppresants, immunosuppressants coupled to synthetic nanocarriers, synthetic nanocarriers comprising rapamycin, and/or, toloregenic synthetic nanocarriers, their doses, administration and use as described in US20150320728, US 20180193482, US 20190142974, US 20150328333, US20160243253, US 10,039,822, US 20190076522, US 20160022650, US 10,441,651, US 10,420,835, US 20150320870, US 2014035636, US 10,434,088, US 10,335,395, US 20200069659, US 10,357,483, US 20140335186, US 10,668,053, US 10,357,482, US 20160128986, US 20160128987, US 20200038462, US 20200038463, each of which are incorporated in their entirety by reference.

[00423] In some embodiments, the immune modulator is synthetic nanocarriers comprising rapamycin (ImmTOR™ nanoparticles) (Kishimoto, et al., 2016, Nat Nanotechnol, 11(10): 890-899; Maldonado, et al., 2015, PNAS, 112(2): E156-165), as disclosed in US20200038463, US Patent 9,006,254 each of which is incorporated herein in its entirety. In some embodiments, the immune modulator is an engineered cell, e.g., an immune cell that has been modified using SQZ technology as disclosed in WO2017192786, which is incorporated herein in its entirety by reference.

[00424] In some embodiments, the immune modulator is selected from the group consisting of poly-ICLC, 1018 ISS, aluminum salts, Amplivax, AS15, BCG, CP-870,893, CpG7909, CyaA, dSLIM, GM-CSF, IC30, IC31, Imiquimod, ImuFact IMP321, IS Patch, ISS, ISCOMATRIX, Juvlmmune, LipoVac, MF59, monophosphoryl lipid A, Montanide IMS 1312, Montanide ISA 206, Montanide ISA 50V, Montanide ISA-51, OK-432, OM-174, OM-197-MP-EC, ONTAK, PEPTEL, vector system, PLGA microparticles, resiquimod, SRL172, Virosomes and other Virus-like particles, YF-17D, VEGF trap, R848, beta-glucan, Pam3Cys, and Aquila's QS21 stimulon. In another further embodiment, the immunomodulator or adjuvant is poly-ICLC.

[00425] In some embodiments, the immune modulator is a small molecule that inhibit the innate immune response in cells, such as chloroquine (a TLR signaling inhibitor) and 2-aminopurine (a PKR inhibitor), can also be administered in combination with the composition comprising at least one rAAV as disclosed herein. Some non-limiting examples of commercially available TLR-signaling inhibitors include BX795, chloroquine, CLI-095, OxPAPC, polymyxin B, and rapamycin (all

available for purchase from INVIVOGEN™). In addition, inhibitors of pattern recognition receptors (PRR) (which are involved in innate immunity signaling) such as 2-aminopurine, BX795, chloroquine, and H-89, can also be used in the compositions and methods comprising at least one rAAV vector as disclosed herein for in vivo protein expression as disclosed herein.

[00426] In some embodiments, a rAAV vector can also encode a negative regulators of innate immunity such as NLRX1. Accordingly, in some embodiments, a rAAV vector can also optionally encode one or more, or any combination of NLRX1, NS1, NS3/4A, or A46R. Additionally, in some embodiments, a composition comprising at least one rAAV vector as disclosed herein can also comprise a synthetic, modified-RNA encoding inhibitors of the innate immune system to avoid the innate immune response generated by the tissue or the subject.

[00427] In some embodiments, an immune modulator for use in the administration methods as disclosed herein is an immunosuppressive agent. As used herein, the term "immunosuppressive drug or agent" is intended to include pharmaceutical agents which inhibit or interfere with normal immune function. Examples of immunosuppressive agents suitable with the methods disclosed herein include agents that inhibit T-cell/B- cell costimulation pathways, such as agents that interfere with the coupling of T-cells and B-cells via the CTLA4 and B7 pathways, as disclosed in U.S. Patent Pub. No 2002/0182211. In one embodiment, an immunosuppressive agent is cyclosporine A. Other examples include myophenylate mofetil, rapamicin, and anti- thymocyte globulin. In one embodiment, the immunosuppressive drug is administered in a composition comprising at least one rAAV vector as disclosed herein, or can be administered in a separate composition but simultaneously with, or before or after administration of a composition comprising at least one rAAV vector according to the methods of administration as disclosed herein. An immunosuppressive drug is administered in a formulation which is compatible with the route of administration and is administered to a subject at a dosage sufficient to achieve the desired therapeutic effect. In some embodiments, the immunosuppressive drug is administered transiently for a sufficient time to induce tolerance to the rAAV vector as disclosed herein.

[00428] Various methods are known to result in the immunosuppression of an immune response of a patient being administered AAV. Methods known in the art include administering to the patient an immunosuppressive agent, such as a proteasome inhibitor. One such proteasome inhibitor known in the art, for instance as disclosed in U.S. Patent No. 9,169,492 and U.S. Patent Application No. 15/796,137, both of which are incorporated herein by reference, is bortezomib. In some embodiments, an immunosuppressive agent can be an antibody, including polyclonal, monoclonal, scfv or other antibody derived molecule that is capable of suppressing the immune response, for instance, through the elimination or suppression of antibody producing cells. In a further embodiment, the immunosuppressive element can be a short hairpin RNA (shRNA). In such an embodiment, the coding region of the shRNA is included in the rAAV cassette and is generally located downstream, 3' of the poly-A tail. The shRNA can be targeted to reduce or eliminate

expression of immunostimulatory agents, such as cytokines, growth factors (including transforming growth factors β1 and β2, TNF and others that are publicly known).

[00429] The use of such immune modulating agents facilitates the ability to for one to use multiple dosing (e.g., multiple administration) over numerous months and/or years. This permits using multiple agents as discussed below, e.g., a rAAV vector encoding multiple genes, or multiple administrations to the subject.

[00430] In some aspects of the invention, the recombinant AAV comprising a nucleic acid encoding human GAA is produced by the triple transfection method that uses close ended linear duplexed DNA molecules that lack bacterial backbone sequences, for example, as described in PCT/US2021/013689, published as WO/2021/146591, which is incorporated herein by reference in its entirety. In some embodiments, the rAAV of the invention is manufactured using plasmid DNA as starting material. In several embodiments, the rAAV of the invention is manufactured using close ended linear duplexed DNA as starting material. Non- limiting examples of close ended linear duplex nucleic acids include doggy bone DNA (dbDNA) or dumbbell-shaped DNA. The close ended linear duplex nucleic acids may be generated within cells or using in vitro cell free system. Cell free *in vitro* synthesis of dumbbell-shaped DNA and doggy bone DNA are described in U.S. Patent No. 6,451,563; Efficient production of superior dumbbell-shaped DNA minimal vectors for small hairpin RNA expression-Nucleic Acids Res. 2015 Oct 15; 43(18): e120; High-Purity Preparation of a Large DNA Dumbbell-Antisense & nucleic acid drug development 11:149–153 (2001);US 9,109,250; U.S. Patent No. 9,499,847; U.S. Patent No. 10,501,782; and WO 2018033730 A1; all of which are herein incorporated by reference in their entireties. DNA from cell free *in vitro* synthesis is devoid of any prokaryotic DNA modifications (e.g., is substantially free of bacterial DNA).

[00431] One example of an *in vitro* process for producing a closed linear DNA (e.g., containing the ITRs described herein) comprises (a) contacting a DNA template flanked on either side by a protelomerase target sequence with at least one DNA polymerase in the presence of one or more primers under conditions promoting amplification of said template; and (b) contacting amplified DNA produced in (a) with at least one protelomerase under conditions promoting formation of a closed linear expression cassette DNA. The closed linear DNA may be a closed DNA expression cassette DNA product that may comprise, consist or consist essentially of a eukaryotic promoter operably linked to a coding sequence of interest and optionally, a eukaryotic transcription termination sequence. The closed linear expression cassette DNA product may additionally lack one or more bacterial or vector sequences, typically selected from the group consisting of: (i) bacterial origins of replication; (ii) bacterial selection markers (typically antibiotic resistance genes) and (iii) unmethylated CpG motifs.

E. Pharmaceutical Compositions

[00432] The rAAV vectors as disclosed herein for use in the methods of administration as disclosed herein can be formulated in a pharmaceutical composition with a pharmaceutically acceptable excipient, i.e., one or more pharmaceutically acceptable carrier substances and/or additives, e.g., buffers, carriers, excipients, stabilizers, etc. The pharmaceutical composition may be provided in the form of a kit. Pharmaceutical compositions comprising the rAAV vectors as disclosed herein for use in the methods of administration as disclosed herein and uses thereof are known in the art.

[00433] Accordingly, a further aspect of the invention provides a pharmaceutical composition comprising a rAAV vector as disclosed herein for use in the methods of administration as disclosed herein. Relative amounts of the active ingredient (e.g., a rAAV vectors aa disclosed herein), 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 percent and 99 percent (w/w) of the active ingredient. By way of example, the composition may comprise between 0.1 percent and 100 percent, e.g., between.5 and 50 percent, between 1-30 percent, between 5- 80 percent, at least 80 percent (w/w) active ingredient.

[00434] The pharmaceutical compositions 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 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 of the invention. In some embodiments, a pharmaceutically acceptable excipient may be at least 95 percent, at least 96 percent, at least 97 percent, at least 98 percent, at least 99 percent, or 100 percent 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. 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, 21 st Edition, A. R. Gennaro, Lippincott, Williams and 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.

Compositions/formulations

[00435] The rAAV vectors as disclosed herein can be formulated in a composition. For example, the rAAV vectors as disclosed herein can be formulated in a pharmaceutical composition with a pharmaceutically acceptable excipient, i.e., one or more pharmaceutically acceptable carrier substances and/or additives, e.g., buffers, carriers, excipients, stabilisers, etc. The composition, e.g., the pharmaceutical composition may be provided in the form of a kit. It is noted the terms "composition" and "formulation" are used interchangeably here.

[00436] Accordingly, in one aspect, provided herein is a composition comprising the recombinant AAV vector particles described herein. Generally, the composition comprises the recombinant AAV vector particles described herein at a concentration from about $1e^{9}$ vg/ml to about $1e^{15}$vg/ml. In some embodiments, the composition comprises the recombinant AAV vector particles described herein at a concentration from about $1e^{10}$vg/ml to about $1e^{14}$ vg/ml. In some embodiments, the composition comprises the recombinant AAV vector particles described herein at a concentration from about $1e^{12}$vg/ml to about $1e^{14}$ vg/ml. In some embodiments, the composition comprises the recombinant AAV vector particles described herein at a concentration from about $1e^{12}$vg/ml to about $1e^{15}$ vg/ml. For example, the composition comprises the recombinant AAV vector particles described herein at a concentration from about $3e^{9}$vg/ml to about $3e^{13}$ vg/ml, from about $2.5e^{10}$vg/ml to about $1e^{14}$ vg/ml, from about $3e^{10}$vg/ml to about $1e^{13}$ vg/ml, or from $1e^{11}$vg/ml to about $5e^{12}$ vg/ml.

[00437] In some embodiments, the composition comprises the recombinant AAV vector particles described herein at a concentration of about $1e^{11}$vg/ml, or about $1.5e^{12}$ vg/ml, or about $2e^{11}$ vg/ml, or about $2.5e^{12}$ vg/ml, or about $3e^{12}$ vg/ml, or about $3.5e^{12}$ vg/ml, or about $4e^{12}$ vg/ml, or about $4.5e^{12}$ vg/ml, or about $5e^{12}$ vg/ml, or about $5.5e^{12}$ vg/ml, or about $6e^{12}$ vg/ml, or about $6.5e^{12}$ vg/ml, or about $7e^{12}$ vg/ml, or about $7.5e^{12}$ vg/ml, or about $8e^{12}$ vg/ml, or about $8.5e^{12}$ vg/ml, or about $9e^{12}$ vg/ml, or about $9.5e^{13}$ vg/ml, or about $1e^{13}$vg/ml, or about $1.5e^{13}$vg/ml, or about $2e^{13}$vg/ml, or about $2.5e^{13}$vg/ml, or about $3e^{13}$vg/ml, or about $3.5e^{13}$vg/ml, or about $4e^{13}$ vg/ml, or about $4.5e^{13}$ vg/ml, or about $5e^{13}$ vg/ml, or about $5.5e^{13}$ vg/ml, or about $6e^{13}$ vg/ml, or about $6.5e^{13}$ vg/ml, or about $7e^{13}$vg/ml, or about $7.5e^{13}$vg/ml, or about $8e^{13}$vg/ml, or about $8.5e^{13}$vg/ml, or about $9e^{13}$vg/ml, or about $9.5e^{13}$ vg/ml, or about $1e^{14}$ vg/ml.

[00438] The pharmaceutical composition comprises the population of purified recombinant adeno-associated virus (rAAV) described herein. The pharmaceutical composition comprising the rAAV, comprises a buffer of pH about 6.5 to about 8.0. In some embodiments, the pH is about 6.5 to about 7.5. For example, the pH is from about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4 or about 7.5. In some preferred embodiments, the pH is less than about 7.5. For example, the pH is less than about 7.4, less than about 7.3, less than about 7.2, less than about 7.1, less than about 7.0, less than about 6.9, less than about 6.8, less than about 6.7, or less

than about 6.6. In some embodiments, the pharmaceutical composition comprises one or, more excipients, comprising one or, more multivalent ions and/or, salts thereof. In some embodiments, the multivalent ions can be selected or, optionally selected from the group consisting of citrate, sulfate, magnesium and phosphate. In some embodiments, the pharmaceutical composition comprises one or, more excipients, comprising one or, more ions selected or, optionally selected from the group consisting of, sodium, potassium, chroride, ammonium, carbonate, nitrate, chlorate, chlorite, and calcium. In some embodiments, the pharmaceutical composition comprising the rAAV, further comprises a non-ionic surfactant. In some embodiments, the non-ionic surfactant is selected from the group consisting of polyoxyethylene fatty alcohol ethers, polyoxyethylene alkyl phenyl ethers, polyoxyethylene-polyoxypropylene block copolymers, alkylglucosides, alkyl phenol ethoxylates, preferably polysorbates, polyoxyethylene alkyl phenyl ethers, and any combinations thereof. In some embodiments, non-ionic surfactant is selected from the group consisting of TWEEN 60 nonionic detergent, PPG-PEG-PPG Pluronic 10R5, Polyoxyethylene (18) tridecyl ether, Polyoxyethylene (12) tridecyl ether, MERPOL SH surfactant, MERPOL OJ surfactant, MERPOL HCS surfactant, Poloxamer P188, Poloxamer P407, Poloxamer P338 IGEPAL CO-720, IGEPAL CO-630, IGEPAL CA-720, Brij S20, BrijSl0, Brij 010, Brij Cl0, BRIJ 020, ECOSURF EH-9 ,ECOSURF EH-14, TERGITOL 15-S-7, PF-68, ECOSURF SA-15, TERGITOL15-S-9, TERGITOL 15-S-12, TERGITOL L-64, TERGITOLNP-7, TERGITOL NP-8, TERGITOL NP-9, TERGITOL NP-9.5,TERGITOL NP-10, TERGITOL NP-11, TERGITOL NP-12, TERGITOLNP-13, polysorbate 20, and any combinations thereof. In some embodiments, the pharmaceutical composition further comprises polyol, or, sugar, or similar. See, e.g., International Patent No. WO2022/159679, which is incorporated herein by reference in its entirety.

[00439] In some embodiments, the composition comprises a buffer. It is noted that any physiological buffer can be used. Non-limiting examples of buffers include, but are not limited to, PBS, Tris.HCl, phosphate, citric acid, histidine, tromethamine, succinic acid, malic acid, α-ketoglutaric acid, carbonate (bicarbonate-carbonic acid buffer), and protein buffers. In some embodiments, the buffer is PBS. In some embodiments, the buffer comprises Tris. In some embodiments, buffer is Tris.HCl. In some embodiments, the buffer is histidine buffer.

[00440] Generally, the buffer has a salt concentration of from about 50 mM to about 750 mM. For example, the buffer has a salt concentration from about 75 mM to about 700 mM, from about 100 mM to about 650 mM, from about 120 mM to about 600 mM, or from about 140 mM to about 550 mM. In some embodiments, the buffer has a salt concentration from about 150mM to about 400mM. In some embodiments, the buffer has a salt concentration of about 150 mM, about 175 mM, about 200 mM, about 225 mM, about 250 mM, about 275 mM, about 300 mM, about 325 mM, about 350 mM, about 375 mM, about 400 mM, about 425 mM, about 450 mM, or about 475 mM. In some preferred embodiments, the buffer has a salt concentration of about 150 mM, about 200 mM or about 365 mM.

[00441] In some embodiments, the ionic strength of the composition is at least about 100 mM. For example, the ionic strength of the composition is from about 125 mM to about 750 mM, or from about 150 mM to about 500 mM, or from about 175 mM to about 700 mM, from about 200mM to about 600 mM, or from about 225 mM to about 550 mM, or from about 250 mM to about 500 mM, or from about 275 mM to about 450 mM, or from about 300 mM to about 400 mM. In some embodiments, the ionic strength of the composition is at least about 125 mM, at least about 150 mM, at least about 175 mM, at least about 200 mM, at least about 225 mM, at least about 250 mM, at least about 275 mM, at least about 300 mM, at least about 325 mM, at least about 350 mM, at least about 375 mM, at least about 400 mM, at least about 425 mM, at least about 450 mM, at least about 475 mM or at least about 500 mM. In some embodiments, the ionic strength of the composition is less than 100mM, for example about 95mM, about 90mM, about 85mM, about 80mM, about 75mM, about 70mM, about 65mM, about 60mM, about 55mM, about 50mM, or, even less.

[00442] The osmolarity of the composition is maintained at near isotonic levels. For example, the osmolarity of the composition can be from about 100 mOsm to about 600 mOsm, such as from about 125 mOsm to about 500 mOsm, or, from about 130 mOsm to about 350 mOsm, or, from about 140 mOsm to about 400 mOsm, or, from about 140 mOsm to about 350 mOsm, or from about 200 mOsm to about 400 mOsm, or from about 500 mOsm to about 600 mOsm, or from about 200 mOsm to about 600 mOsm, or from about 300 mOsm to about 600 mOsm, or from about 200 mOsm to about 500 mOsm, or from about 300 mOsm to about 400 mOsm, or from about 150 mOsm to about 350 mOsm, or from about 175 mOsm to about 300 mOsm, or from about 300 mOsm to about 375 mOsm, or from about 200 mOsm to about 350 mOsm, or from about 225 mOsm to about 325 mOs, or from about 525 mOsm to about 590 mOsm. In some embodiments, the composition comprises an isotonic solution.

[00443] Generally, the composition has a pH of about 6.5 to about 8.0. For example, the composition has a pH of about 6.5 to about 7.5. In some embodiments, the composition has a pH of from about 7 to about 8. For example, the composition has a pH of from about 7.3 to about 7.9. In some other non-limiting example, the composition has a pH of from about 7.4 to about 7.8 or from about 7.4 to about 7.7. In some embodiments, the composition has a pH of from about 7.3 to about 7.6, e.g., from about 7.3 to about 7.55. In some preferred embodiments, the composition has a pH less than about 7.5. For example, the composition has a pH about 7.4 or lower, about 7.3 or lower, about 7.2 or lower, about 7.1 or lower, about 7.0 or lower, about 6.9 or lower, about 6.8 or lower, about 6.7 or lower, about 6.6 or lower, or about 6.5 or lower.

[00444] The composition can comprise one or more ions and/or salts thereof. Exemplary ions include, but are not limited to sodium, potassium, chloride, magnesium ammonium, carbonate, nitrate, chlorate, chlorite, and calcium. The ions can be provided as a salt, such as a halide (F, Cl, Br, I) salt of sodium, potassium, magnesium, and/or calcium, non-limiting examples of which include NaCl, KCl, $MgCl_2$, $CaCl_2$, and combinations thereof. Additional exemplary salts that can be used include, but are not limited to, carboxylic acid salts, such as acetates, propionates, pyrrol idonecarboxylates (or

pidolates) or sorbates; poly hydroxylated carboxylic acid salts, such as gluconates, heptagluconates, ketogluconates, lactate gluconates, ascorbates or pantothenates; mono- or polycarboxyl hydroxy acid salts, such as citrates or lactates; amino acid salts, such as aspartates or glutamates; and fulvate salts. The salts are individually included at a concentration of from about 500 μM to about 500 mM.

[00445] In some embodiments, the composition comprises one or more multivalent ions and/or salts thereof. Exemplary multivalent ions include, but are not limited to, calcium, citrate, sulfate, magnesium, and phosphate. Multivalent ions and/or salts thereof can be individually included in the composition at a concentration of from about 500 μM to about 500 mM, for example, at a concentration of about 500 μM, about 750 μM, about 1 mM, about 1.3 mM, about 1.5 mM, about 1.7 mM, about 2.3 mM, about 2.5 mM, about 2.7 mM, about 3.3 mM, about 3.5 mM, about 3.7 mM, about 4.3 mM, about 4.5 mM, about 4.7 mM, about 5 mM, about 10 mM, about 25 mM, about 50 mM, about 75 mM, about 80mM, about 85mM, about 90mM, about 95mM, about 100 mM, about 125 mM, about 150 mM, about 175 mM, about 200 mM, about 225 mM, about 250 mM, about 275 mM, about 300 mM, about 325 mM, about 350 mM, about 375 mM, about 400 mM, about 425 mM, about 450 mM, about 475 mM, or about 500 mM. Non limiting examples of salts are NaCl, KCl, $CaCl_2$, $CaSO_4$, $MgSO_4$, Na_3PO_4, $CaCO_3$, $NaNO_3$, $Al_2(SO4)_3$.

[00446] In some embodiments, the composition comprises NaCl. When present, NaCl can be at a concentration from about 100 mM to about 500 mM, or from about 125 mM to about 450 mM, or from about 100 mM to about 200 mM, or from about 150 mM to about 200 mM. For example, the composition can comprise NaCl at a concentration from about 150 mM to about 425 mM, from about 175 mM to about 400 mM, or from about 175 mM to about 375 mM, or from about 200 mM to about 375 mM.

[00447] In some embodiments, the composition comprises KCl. When present, KCl can be at a concentration from about 1 mM to about 10 mM. For example, the composition can comprise KCl at a concentration from about 1.5 mM to about 7.5 mM.

[00448] In some embodiments, the composition comprises $CaCl_2$. When present, $CaCl_2$ can be at a concentration from about 0.1 mM to about 2 mM. For example, the composition can comprise $CaCl_2$ at a concentration from about 0.5 mM to about 1.5 mM. In some embodiments, the composition comprises $CaCl_2$ at a concentration from about 0.75 mM to about 1.25 mM.

[00449] In some embodiments, the composition comprises $MgCl_2$. When present, $MgCl_2$ can be at a concentration from about 0.1 mM to about 1.5 mM. For example, the composition can comprise $MgCl_2$ at a concentration from about 0.25 mM to about 1 mM or from about 0.25 mM to about 0.75 mM.

[00450] In some embodiments, the composition comprises $MgSO_4$. When present, $MgSO_4$ can be at a concentration from about 5 mM to about 150 mM. For example, the composition can comprise $MgSO_4$ at a concentration from about 10 mM to about 120 mM, or from about 10 mM to about 50

mM, or from about 15 mM to about 45 mM, or about 75 mM to about 125 mM, or from about 80 mM to about 100 mM, or from about 85 mM to about 95 mM, or from about 15 mM to about 100 mM.

[00451] In some embodiments, the composition comprises phosphate, e.g., mono basic or dibasic phosphate or a salt thereof. When present, the phosphate, e.g., mono basic or dibasic phosphate or a salt thereof can be at a concentration from about 5 mM to about 30 mM. For example, the composition can comprise phosphate, e.g., mono basic or dibasic phosphate or a salt thereof at a concentration from about 7.5 mM to about 25 mM. In some embodiments, the composition comprises phosphate, e.g., mono basic or dibasic phosphate or a salt thereof at a concentration from about 10 mM to about 20 mM.

[00452] In some embodiments, the composition comprises a mono basic phosphate or a salt thereof at a concentration from about 0.25 mM to about 3 mM. For example, the composition comprises a mono basic phosphate or a salt thereof at a concentration from about 0.5 mM to about 2.75 mM, or from about 0.75 mM to about 2.5 mM or from about 1 mM to about 2.25 mM. In some embodiments, the mono basic phosphate or salt thereof is potassium phosphate monobasic.

[00453] In some embodiments, the composition comprises a dibasic phosphate or a salt thereof at a concentration from about 5 mM to about 15 mM. For example, the composition comprises a dibasic phosphate or a salt thereof at a concentration from about 7.5 mM to about 12.5 mM or from about 8 mM to about 10 mM. In some embodiments, the dibasic phosphate or a salt thereof is sodium phosphate dibasic. In some embodiments, the composition is substantially free of dibasic phosphate, e.g., sodium phosphate dibasic.

[00454] In some embodiments, the composition comprises Tris (e.g., Tris.HCl) or a salt thereof at a concentration from about 1 mM to about 50 mM. For example, the composition comprises Tris (e.g., Tris.HCl) or a salt thereof at a concentration of from about 5 mM to about 40 mM, or from about 7.5 mM to about 35 mM, or from about 10 mM to about 30 mM or from about 15 mM to about 25 mM.

[00455] In some embodiments, the composition comprises histidine or a salt thereof at a concentration from about 1 mM to about 50 mM. For example, the composition comprises histidine or a salt thereof at a concentration of from about 5 mM to about 40 mM, or from about 7.5 mM to about 35 mM, or from about 10 mM to about 30 mM or from about 15 mM to about 25 mM.

[00456] The composition can also comprise a bulking agent. Exemplary bulking agents include, but are not limited to sugars, polyols and (PVP K24). Exemplary polyols include, but are not limited to, polyhydroxy hydrocarbons, monosaccharides, disaccharides, and trisaccharides. Some exemplary polyols include but are not limited to, sorbitol, mannitol, glycerol, propylene glycol, polyethylene glycol, dulcitol, sucrose, lactose, maltose, trehalose and dextran. In some embodiments, polyol is sorbitol, sucrose or mannitol. In some embodiments, the bulking agent is sorbitol. In some embodiments, the bulking agent is sucrose. In some embodiments, the bulking agent is mannitol. In some embodiments, the bulking agent is trehalose, e.g., trehalose dehydrate. In some embodiments, the bulking agent is a dextran, e.g., Dextran T40 and/or Dextran T10.

[00457] When present, the bulking agent can be present at a concentration of from about 0.5 % (w/v) to about 10% (w/v). For example, the composition can comprise a bulking agent, e.g., a polyol or providone (PVP K24) at a concentration from about from about 1 % (w/v) to about 7.5% (w/v), e.g., from about 1%(w/v) to about 4% (w/v) or from about 4%(w/v) to about 6% (w/v).

[00458] In some embodiments, the composition comprises glycerol, sorbitol, sucrose, or mannitol at a concentration from about 1% (w/v) to about 10% (w/v). In some embodiments, the composition comprises glycerol, sorbitol, sucrose, or mannitol at a concentration from about 1%(w/v) to about 10%(w/v). In some embodiments, the composition comprises sorbitol at concentration from about 3%(w/v) to about 6% (w/v). In some embodiments, the composition comprises sorbitol at concentration of about 1% (w/v), about 2% (w/v), about 3% (w/v), about 4% (w/v), about 5% (w/v), about 6% (w/v), about 7% (w/v), about 8% (w/v), about 9% (w/v), or about 10% (w/v). In some embodiments, the composition comprises sucrose at concentration from about 3%(w/v) to about 6% (w/v). In some embodiments, the composition comprises sucrose at concentration of about 1% (w/v), about 2% (w/v), about 3% (w/v), about 4% (w/v), about 5% (w/v), about 6% (w/v), about 7% (w/v), about 8% (w/v), about 9% (w/v), or about 10% (w/v). In some embodiments, the composition comprises mannitol at concentration from about 3%(w/v) to about 6% (w/v). In some embodiments, the composition comprises mannitol at concentration of about 1% (w/v), about 2% (w/v), about 3% (w/v), about 4% (w/v), about 5% (w/v), about 6% (w/v), about 7% (w/v), about 8% (w/v), about 9% (w/v), or about 10% (w/v).

[00459] The composition can also comprise a non-ionic surfactant. The non-ionic surfactant can be selected from the group consisting of polyoxyethylene fatty alcohol ethers, polyoxyethylene alkyl phenyl ethers, polyoxyethylene-polyoxypropylene block copolymers, alkylglucosides, alkyl phenol ethoxylates, preferably polysorbates, polyoxyethylene alkyl phenyl ethers, and any combinations thereof. Non-limiting examples of suitable non-ionic surfactants include polyoxyethylene (12) isooctylphenyl ether (e.g., IGEPAL® CA-270 polyoxyethylene (12) isooctylphenyl ether), polyoxyethylenesorbitan monooleate (e.g., TWEEN® 80 polyoxyethylenesorbitan monooleate), polyethylene glycol octadecyl ether (e.g., Brij® S20 polyethylene glycol octadecyl ether), seed oil surfactant (e.g., EcosurfTM SA-15 seed oil surfactant), poloxamer 188 (a copolymer of polyoxyethylene and polyoxypropylene), nonylphenol ethoxylate (e.g., TergitolTM NP-10 nonylphenol ethoxylate), and combinaitons thereof. In some embodiments, the non-ionic surfactant is selected from the group consisting of TWEEN 60 nonionic detergent, PPG-PEG-PPG Pluronic 10R5, Pluronic F-68 (PF 68), Polyoxyethylene (18) tridecyl ether, Polyoxyethylene (12) tridecyl ether, MERPOL SH surfactant, MERPOL OJ surfactant, MERPOL HCS surfactant, Poloxamer P188, Poloxamer P407, Poloxamer P 338, IGEPAL CO-720, IGEPAL CO-630, IGEPAL CA-720, Brij S20, BrijSl0, Brij 010, Brij Cl0, BRIJ 020, ECOSURF EH-9 ,ECOSURF EH-14, TERGITOL 15-S-7, ECOSURF SA-15, TERGITOL15-S-9, TERGITOL 15-S-12, TERGITOL L-64, TERGITOLNP-7, TERGITOL NP-8, TERGITOL NP-9, TERGITOL NP-9.5,TERGITOL NP-10, TERGITOL NP-11,

TERGITOL NP-12, TERGITOLNP-13, polysorbate 20, and any combinations thereof. In some embodiments, the non-ionic surfactant is Poloxamer P 188, Poloxamer P407, Pluronic F-68, Ecosurf SA-15, Brij S20, Tergitol NP-10, IGEPAL CA 720 or Tween 80. In some embodiments, the composition is substantially free of a non-ionic surfactant. In some embodiments, the non-ionic surfactant is not a polysorbate, e.g., Tween 80 (also referred to as polysorbate 80 or PS80).

[00460] When present, the non-ionic surfactant can be present at a concentration from about 0.0001% (w/v) to about 0.01% (w/v). For example, the composition can comprise a non-ionic surfactant at a concentration from about 0.0005% (w/v) to about 0.0015% (w/v). In some embodiments, the composition can comprise a non-ionic surfactant at a concentration of about 0.0001% (w/v), about 0.0002% (w/v), about 0.0003% (w/v), about 0.0004% (w/v), about 0.0005% (w/v), about 0.0006% (w/v), about 0.0007% (w/v), about 0.0008% (w/v), about 0.0009% (w/v), about 0.001% (w/v), about 0.002% (w/v), about 0.003% (w/v), about 0.004% (w/v), about 0.005% (w/v), about 0.006% (w/v), about 0.007% (w/v), about 0.008% (w/v), about 0.009% (w/v), or about 0.01%. (w/v). In some preferred embodiments, the composition comprises a non-ionic surfactant at a concentration of about 0.0005% (w/v) or about 0.001% (w/v).

[00461] In some embodiments, the composition comprises, in addition to the rAAV, a buffer (e.g., PBS, Tris.HCl, phosphate, citric acid, histidine, tromethamine, succinic acid, malic acid, α-ketoglutaric acid, carbonate buffer), a bulking agent (e.g., a polyol such as sorbitol, mannitol, glycerol, propylene glycol, polyethylene glycol, dulcitol, sucrose, lactose, maltose, trehalose and dextran) and a non-ionic surfactant (e.g., Poloxamer P 188, Poloxamer P407, Pluronic F-68, Ecosurf SA-15, Brij S20, Tergitol NP-10, IGEPAL CA 720 or Tween 80).

[00462] In some embodiments, the composition comprises, in addition to the rAAV, a buffer (e.g., PBS, Tris.HCl, phosphate, citric acid, histidine, tromethamine, succinic acid, malic acid, α-ketoglutaric acid, carbonate buffer), a bulking agent (e.g., a polyol such as sorbitol, mannitol, glycerol, propylene glycol, polyethylene glycol, dulcitol, sucrose, lactose, maltose, trehalose and dextran), a non-ionic surfactant (e.g., Poloxamer P 188, Poloxamer P407, Pluronic F-68, Ecosurf SA-15, Brij S20, Tergitol NP-10, IGEPAL CA 720 or Tween 80), and a multivalent ion (e.g., a multivalent ion selected from the group consisting of calcium, citrate, sulfate, and magnesium).

[00463] In some embodiments, the composition comprises, in addition to the rAAV, a buffer (e.g., PBS, Tris.HCl, phosphate, citric acid, histidine, tromethamine, succinic acid, malic acid, α-ketoglutaric acid, carbonate buffer), a bulking agent (e.g., a polyol such as sorbitol, mannitol, glycerol, propylene glycol, polyethylene glycol, dulcitol, sucrose, lactose, maltose, trehalose and dextran), and a multivalent ion (e.g., a multivalent ion selected from the group consisting of calcium, citrate, sulfate, and magnesium).

[00464] It is noted that any one of the specific buffers or group of buffers listed in the description of the compositions can be used with any one of the specific bulking agents or group of bulking agents listed in the description of the compositions and with any of the specific non-ionic surfactants or group of surfactants listed in the description of the compositions and with any of the specific multivalent ions and multivalent ion group listed in the description of the compositions. Similarly, any one of the specific bulking agents or group of bulking agents listed in the description of the compositions can be used with any one of the specific buffers or group of buffers listed in the description of the compositions and with any of the specific non-ionic surfactants or group of surfactants listed in the description of the compositions and with any of the specific multivalent ions and multivalent ion group listed in the description of the compositions. Likewise, any of the specific non-ionic surfactants or group of surfactants listed in the description of the compositions can be used with any one of the specific buffers or group of buffers listed in the description of the compositions and with any one of the specific bulking agents or group of bulking agents listed in the description of the compositions and with any of the specific multivalent ions and multivalent ion group listed in the description of the compositions. As well, any of the specific multivalent ions and multivalent ion group listed in the description of the compositions can be used with any one of the specific buffers or group of buffers listed in the description of the compositions and with any one of the specific bulking agents or group of bulking agents listed in the description of the compositions and with any of the specific non-ionic surfactants or group of surfactants listed in the description of the compositions. In other words, all individual specific combinations of buffers, buffer group, bulking agents, bulking agent groups, non-ionic surfactants, non-ionic surfactant groups, multivalent ions and multivalent ion groups listed in the description of the compositions are specifically contemplated and claimed.

Exemplary compositions

[00465] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 10 mM Phosphate pH 7.4, about 200 mM NaCl, about 5 mM KCl, about 1% (w/v) mannitol, and about 0.0005% (w/v) IGEPAL CA 720.

[00466] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 20 mM Phosphate pH 7.4, about 300 mM NaCl, about 3 mM KCl, about 3 % (w/v) mannitol, and about 0.001% (w/v) Brij S20.

[00467] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 20 mM Phosphate pH 7.4, about 300 mM NaCl, about 3 mM KCl, about 3 % (w/v) sorbitol, and about 0.001% (w/v) Ecosurf SA-15.

[00468] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 10 mM Phosphate pH 7.4, about 350 mM NaCl, about 2.7 mM KCl, about 5 % (w/v) sorbitol, and about 0.001% (w/v) poloxamer 188.

[00469] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 10mM Phosphate pH 6.95-7.2, about 137mM NaCl, about 2.7mM KCl, about 0.9mM $CaCl_2$, about 0.5mM $MgCl_2$, and about 0.001% (w/v) Pluronic F-68.

[00470] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 10mM Phosphate pH 7.3, about 180 mM NaCl, about 2.7 mM KCl, about 5 % (w/v) sorbitol, and about 0.001% (w/v) Poloxamer 188.

[00471] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 15 mM Phosphate pH 7.4, about 375 mM NaCl, about 3.5 mM KCl, about 5 % (w/v) sorbitol, and about 0.0005% (w/v) Tergitol NP-10.

[00472] In some embodiments, the c composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 15 mM Phosphate pH 7.4, about 375 mM NaCl, about 3.5 mM KCl, about 3 % (w/v) glycerol, and about 0.0005% (w/v) Tween 80.

[00473] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 10mM Phosphate pH 7.6, about 137 mM NaCl, about 2.7 mM KCl, about 5% (w/v) sorbitol, and about 0.01% Pluronic F-68.

[00474] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 10mM Phosphate pH 7.4, about 137 mM NaCl, about 2.7 mM KCl, about 5% (w/v) sorbitol, about 0.01% Pluronic F-68, and about 20 mM $MgSO_4$.

[00475] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 10mM Phosphate pH 7.6, about 137 mM NaCl, about 2.7 mM KCl, about 5% (w/v) mannitol, and about 0.01% Pluronic F-68.

[00476] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 10mM Phosphate pH 7.3, about 137 mM NaCl, about 2.7 mM KCl, about 5% (w/v) mannitol, about 0.01% Pluronic F-68, and about 20 mM $MgSO_4$.

[00477] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 10mM Phosphate pH 7.4, about 137 mM NaCl, about 2.7 mM KCl, about 5% (w/v) sorbitol, and about 20 mM $MgSO_4$.

[00478] In some embodiments, the composition, e.g., the pharmaceutical composition comprises, in addition to the rAAV, about 10mM Phosphate pH 7.4, about 137 mM NaCl, about 2.7 mM KCl, about 5% (w/v) mannitol, and about 20 mM $MgSO_4$.

[00479] In some embodiments, the composition, e.g., the pharmaceutical composition comprises recombinant AAV vector (rAAV), in 10 mM Phosphate pH 7.4, 200 mM NaCl, 5 mM KCl, 1% (w/v) mannitol, 0.0005% (w/v) IGEPAL CA 720 to a fill volume of 5ml. In some embodiments, the fill volume is 1ml, 2ml, 3ml, 4 ml, 5ml, 6 ml, 7 ml, 8 ml, 9 ml, or, 10 ml.

[00480] In some embodiments, the composition, e.g., the pharmaceutical composition comprises recombinant AAV vector (rAAV), in 20 mM Phosphate pH 7.4, 300 mM NaCl, 3 mM KCl, 3 % (w/v)

mannitol, 0.001% (w/v) Brij S20 to a fill volume of 5ml. In some embodiments, the fill volume is 1ml, 2ml, 3ml, 4 ml, 5ml, 6 ml, 7 ml, 8 ml, 9 ml, or, 10 ml.

[00481] In some embodiments, the composition, e.g., the pharmaceutical composition comprises recombinant AAV vector (rAAV), in 20 mM Phosphate pH 7.4, 300 mM NaCl, 3 mM KCl, 3 % (w/v) sorbitol, 0.001% (w/v) Ecosurf SA-15 to a fill volume of 5ml. In some embodiments, the fill volume is 1ml, 2ml, 3ml, 4 ml, 5ml, 6 ml, 7 ml, 8 ml, 9 ml, or, 10 ml.

[00482] In some embodiments, the composition, e.g., the pharmaceutical composition comprises recombinant AAV vector (rAAV), in 10 mM Phosphate pH 7.4, 350 mM NaCl, 2.7 mM KCl, 5 % (w/v) sorbitol, 0.001% (w/v) poloxamer 188 to a fill volume of 5ml. In some embodiments, the fill volume is 1ml, 2ml, 3ml, 4 ml, 5ml, 6 ml, 7 ml, 8 ml, 9 ml, or, 10 ml.

[00483] In some embodiments, the composition, e.g., the pharmaceutical composition comprises recombinant AAV vector (rAAV), in 15 mM Phosphate pH 7.4, 375 mM NaCl, 3.5 mM KCl, 5 % (w/v) sorbitol, 0.0005% (w/v) Tergitol NP-10 to a fill volume of 5ml. In some embodiments, the fill volume is 1ml, 2ml, 3ml, 4 ml, 5ml, 6 ml, 7 ml, 8 ml, 9 ml, or, 10 ml.

[00484] In some embodiments, the composition, e.g., the pharmaceutical composition comprises recombinant AAV vector (rAAV), in 15 mM Phosphate pH 7.4, 375 mM NaCl, 3.5 mM KCl, 3 % (w/v) glycerol, 0.0005% (w/v) Tween 80 to a fill volume of 5ml. In some embodiments, the fill volume is 1ml, 2ml, 3ml, 4 ml, 5ml, 6 ml, 7 ml, 8 ml, 9 ml, or, 10 ml.

[00485] Additional exemplary compositions/compositions comprising rAAV are described in PCT/US2022/0137279, the content of which is incorporated herein by reference in its entirety.

[00486] All compositions stored between -60°C to about -80°C

[00487] The rAAV vectors as disclosed herein for use in the methods of administration as disclosed herein 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 some embodiments, the delivery of one treatment (e.g., gene therapy vectors) is still occurring when the delivery of the second (e.g., one or more therapeutic) begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery." In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, e.g., an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be

observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered. The composition described herein and the at least one additional therapy can be administered simultaneously, in the same or in separate compositions, or sequentially. For sequential administration, the gene therapy vectors described herein can be administered first, and the one or more therapeutic can be administered second, or the order of administration can be reversed. The gene therapy vectors and the one or more therapeutic can be administered during periods of active disorder, or during a period of remission or less active disease. The gene therapy vectors can be administered before another treatment, concurrently with the treatment, post-treatment, or during remission of the disorder.

[00488] When administered in combination, the rAAV vectors as disclosed herein for use in the methods of administration as disclosed herein and the one or more therapeutic (e.g., second or third therapeutic), or all, can be administered in an amount or dose that is higher, lower or the same as the amount or dosage of each used individually, e.g., as a monotherapy. In certain embodiments, the administered amount or dosage of a rAAV vector as disclosed herein for use in the methods of administration as disclosed herein and the one or more therapeutic (e.g., second or third agent), or all, is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50%) than the amount or dosage of each used individually. In other embodiments, the amount or dosage of the rAAV vector as disclosed herein for use in the methods of administration as disclosed herein and the one or more therapeutic (e.g., second or third agent), or all, that results in a desired effect (e.g., treatment of a cardiovascular disease or heart disease) is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50% lower) than the amount or dosage of each individually required to achieve the same therapeutic effect.

[00489] In some embodiments, the methods of administration of a rAAV vector as disclosed herein can deliver a rAVV vector disclosed herein alone, or in combination with an additional agent, for example, an immune modulator as disclosed herein.

[00490] In some embodiments, the AAV vectors expressing GAA as disclosed herein are not administered concurrently with, or in combination with ERT. In alternative embodiments, the AAV vectors expressing GAA as disclosed herein are administered in combination with ERT for a maximum period of 24 weeks or shorter than 24 weeks after administration of the AAV expressing ERT. In some embodiments, the AAV vectors expressing GAA as disclosed herein are administered in combination with an immune modulator for an initial period and, optionally a tapering period after administration of the AAV expressing ERT.

VI. Definitions

[00491] The following terms are used in the description herein and the appended claims:

[00492] The terms "a," "an," "the" and similar references used in the context of describing the present invention (especially in the context of the following claims) are to be construed to cover both the

singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Further, ordinal indicators – such as "first," "second," "third," etc. – for identified elements are used to distinguish between the elements, and do not indicate or imply a required or limited number of such elements, and do not indicate a particular position or order of such elements unless otherwise specifically stated. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the present invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the present specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[00493] Furthermore, the term "about," as used herein when referring to a measurable value such as an amount of the length of a polynucleotide or polypeptide sequence, dose, time, temperature, and the like, is meant to encompass variations of± 20%, ± 10%, ± 5%, ± 1%, ± 0.5%, or even± 0.1% of the specified amount.

[00494] Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

[00495] As used herein, the transitional phrase "consisting essentially of' means that the scope of a claim is to be interpreted to encompass the specified materials or steps recited in the claim, "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *See, In re Herz,* 537 F.2d 549, 551-52, 190 USPQ 461,463 (CCPA 1976) (emphasis in the original); *see also* MPEP § 2111.03. Thus, the term "consisting essentially of' when used in a claim of this invention is not intended to be interpreted to be equivalent to "comprising." Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination.

[00496] Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted.

[00497] To illustrate further, if, for example, the specification indicates that a particular amino acid can be selected from A, G, I, Land/or V, this language also indicates that the amino acid can be selected from any subset of these amino acid(s) for example A, G, I or L; A, G, I or V; A or G; only L; etc. as if each such subcombination is expressly set forth herein. Moreover, such language also indicates that one or more of the specified amino acids can be disclaimed (e.g., by negative proviso). For example, in particular embodiments the amino acid is not A, G or I; is not A; is not G or V; etc. as if each such possible disclaimer is expressly set forth herein.

[00498] The term "parvovirus" as used herein encompasses the family Parvoviridae, including autonomously replicating parvoviruses and dependoviruses. The autonomous parvoviruses include members of the genera Parvovirus, Erythrovirus, Densovirus, Iteravirus, and Contravirus. Exemplary

autonomous parvoviruses include, but are not limited to, minute virus of mouse, bovine parvovirus, canine parvovirus, chicken parvovirus, feline panleukopenia virus, feline parvovirus, goose parvovirus, H1 parvovirus, Muscovy duck parvovirus, B19 virus, and any other autonomous parvovirus now known or later discovered. Other autonomous parvoviruses are known to those skilled in the art. See, e.g., BERNARD N. FIELDS et al., VIROLOGY, volume 2, chapter 69 (4th ed., Lippincott-Raven Publishers).

[00499] As used herein, the term "adeno-associated virus" (AAV), includes but is not limited to, AAV type 1, AAV type 2, AAV type 3 (including types 3A and 3B), AAV type 4, AAV type 5, AAV type 6, AAV type 7, AAV type 8, AAV type 9, AAV type 10, AAV type 11, avian AAV, bovine AAV, canine AAV, equine AAV, ovine AAV, and any other AAV now known or later discovered. *See, e.g.,* BERNARD N. FIELDS *et al.,* VIROLOGY, volume 2, chapter 69 (4th ed., Lippincott-Raven Publishers). A number of relatively new AAV serotypes and clades have been identified *(see, e.g.,* Gao et al., (2004) *J. Virology* 78:6381-6388; Moris et al., (2004) *Virology* 33-:375- 383); and also Table 1 as disclosed in U.S. Provisional Application 62,937,556, filed on November 19, 2019 and Table 1 in International Applications WO2020/102645, and WO2020/102667, each of which is incorporated herein in their entirety.

[00500] The genomic sequences of various serotypes of AAV and the autonomous parvoviruses, as well as the sequences of the native inverted terminal repeats (ITRs), Rep proteins, and capsid subunits are known in the art. Such sequences may be found in the literature or in public databases such as GenBank. *See, e.g.,* GenBank Accession Numbers NC_002077, NC_001401, NC_001729, NC_001863, NC_001829, NC_001862, NC_000883, NC_001701, NC_001510, NC_006152, NC_006261, AF063497, U89790, AF043303, AF028705, AF028704, J02275, J01901, J02275, X01457, AF288061, AH009962, AY028226, AY028223, NC_001358, NC_001540, AF513851, AF513852, AY530579; the disclosures of which are incorporated by reference herein for teaching parvovirus and AAV nucleic acid and amino acid sequences. *See also, e.g.,* Srivistava et al., (1983) *J Virology* 45:555; Chiarini et al., (1998) *J. Virology* 71:6823; Chiarini *et al.,* (1999) *J. Virology* 73:1309; Bantel-Schaal et al., (1999) *J. Virology* 73:939; Xiao et al., (1999) *J. Virology* 73:3994; Muramatsu et al., (1996) *Virology* 221:208; Shade et al., (1986) *J. Viral.* 58:921; Gao et al., (2002) *Proc. Nat. Acad. Sci. USA* 99:11854; Morris et al., (2004) *Virology* 33-:375- 383; international patent publications WO 00/28061, WO 99/61601, WO 98/11244; and U.S. Patent No. 6,156,303; the disclosures of which are incorporated by reference herein for teaching parvovirus and AAV nucleic acid and amino acid sequences. *See also* Table 1 and Table 5 disclosed in 62,937,556, filed on November 19, 2019 or Table 1 as disclosed in International Applications WO2020/102645, and WO2020/102667, each of which is incorporated herein in their entirety. The capsid structures of autonomous parvoviruses and AAV are described in more detail in BERNARD N. FIELDS *et al.,* VIROLOGY, volume 2, chapters 69 & 70 (4th ed., Lippincott-Raven Publishers). *See also,* description of the crystal structure of AAV2 (Xie et al., (2002) *Proc. Nat. Acad. Sci.* 99:10405-10),

AAV4 (Padron et al., (2005) *J. Viral.* 79: 5047-58), AAV5 (Walters et al., (2004) *J. Viral.* 78: 3361-71) and CPV (Xie et al., (1996) *J. Mal. Biol.* 6:497-520 and Tsao et al., (1991) *Science* 251: 1456-64).

[00501] The term "tropism" as used herein refers to preferential entry of the virus into certain cells or tissues, optionally followed by expression *(e.g.,* transcription and, optionally, translation) of a sequence(s) carried by the viral genome in the cell, *e.g.,* for a recombinant virus, expression of a heterologous nucleic acid(s) of interest.

[00502] As used here, "systemic tropism" and "systemic transduction" (and equivalent terms) indicate that the virus capsid or virus vector of the invention exhibits tropism for and/or transduces tissues throughout the body *(e.g.,* brain, lung, skeletal muscle, heart, liver, kidney and/or pancreas).

[00503] As used herein, "selective tropism" or "specific tropism" means delivery of virus vectors to and/or specific transduction of certain target cells and/or certain tissues.

[00504] Unless indicated otherwise, “efficient transduction” or “efficient tropism,” or similar terms, can be determined by reference to a suitable control (e.g., at least about 50%, 60%, 70%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 500% or more of the transduction or tropism, respectively, of the control). In particular embodiments, the virus vector efficiently transduces or has efficient tropism for liver cells and muscle cells. Suitable controls will depend on a variety of factors including the desired tropism and/or transduction profile.

[00505] Similarly, it can be determined if a virus “does not efficiently transduce” or “does not have efficient tropism” for a target tissue, or similar terms, by reference to a suitable control. In particular embodiments, the virus vector does not efficiently transduce (i.e., has does not have efficient tropism) for kidney, gonads and/or germ cells. In particular embodiments, transduction (e.g., undesirable transduction) of tissue(s) (e.g., kidney) is 20% or less, 10% or less, 5% or less, 1% or less, 0.1% or less of the level of transduction of the desired target tissue(s) (e.g., liver, skeletal muscle, diaphragm muscle, cardiac muscle and/or cells of the central nervous system).

[00506] As used herein, the term "polypeptide" encompasses both peptides and proteins, unless indicated otherwise.

[00507] A "polynucleotide" is a sequence of nucleotide bases, and may be RNA, DNA or DNA-RNA hybrid sequences (including both naturally occurring and non-naturally occurring nucleotides), but in representative embodiments are either single or double stranded DNA sequences.

[00508] The terms "heterologous nucleotide sequence" and "heterologous nucleic acid molecule" are used interchangeably herein and refer to a nucleic acid sequence that is not naturally occurring in the virus. Generally, the heterologous nucleic acid molecule or heterologous nucleotide sequence comprises an open reading frame that encodes a polypeptide and/or nontranslated RNA of interest (e.g., for delivery to a cell and/or subject).

[00509] A “chimeric nucleic acid” comprises two or more nucleic acid sequences covalently linked together to encode a fusion polypeptide. The nucleic acids may be DNA, RNA, or a hybrid thereof.

[00510] The term "fusion polypeptide" comprises two or more polypeptides covalently linked together, typically by peptide bonding.

[00511] As used herein, an "isolated" polynucleotide (e.g., an "isolated DNA" or an "isolated RNA") means a polynucleotide at least partially separated from at least some of the other components of the naturally occurring organism or virus, for example; the cell or viral structural components or other polypeptides or nucleic acids commonly found associated with the polynucleotide. In representative embodiments an "isolated" nucleotide is enriched by at least about 10-fold, 100'-fold, 1000-fold, 10,000-fold or more as compared with the starting material.

[00512] Likewise, an "isolated" polypeptide means a polypeptide that is at least partially separated from at least some of the other components of the naturally occurring organism or virus, for example, the cell or viral structural components or other polypeptides or nucleic acids commonly found associated with the polypeptide. In representative embodiments an "isolated" polypeptide is enriched by at least about 10-fold, 100-fold, 1000-fold, 10,000-fold or more as compared with the starting material.

[00513] An "isolated cell" refers to a cell that is separated from other components with which it is normally associated in its natural state. For example, an isolated cell can be a cell in culture medium and/or a cell in a pharmaceutically acceptable carrier of this invention. Thus, an isolated cell can be delivered to and/or introduced into a subject. In some embodiments, an isolated cell can be a cell that is removed from a subject and manipulated as described herein *ex vivo* and then returned to the subject.

[00514] A population of virions can be generated by any of the methods described herein. In one embodiment, the population is at least 101 virions. In one embodiment, the population is at least 102 virions, at least 103, virions, at least 104 virions, at least 105 virions, at least 106 virions, at least 107 virions, at least 108 virions, at least 109 virions, at least 1010 virions, at least 1011 virions, at least 1012 virions, at least 1013 virions, at least 1014 virions, at least 1015 virions, at least 1016 virions, or at least 1017 virions. A population of virions can be heterogeneous or can be homogeneous (e.g., substantially homogeneous or completely homogeneous).

[00515] A "substantially homogeneous population" as the term is used herein, refers to a population of virions that are mostly identical, with few to no contaminant virions (those that are not identical) therein. A substantially homogeneous population is at least 90% of identical virions (e.g., the desired virion), and can be at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, at least 99.9% of identical virions.

[00516] A population of virions that is completely homogeneous contains only identical virions.

[00517] As used herein, by "isolate" or "purify" (or grammatical equivalents) a virus vector or virus particle or population of virus particles, it is meant that the virus vector or virus particle or population of virus particles is at least partially separated from at least some of the other components in the starting material. In representative embodiments an "isolated" or "purified" virus vector or virus

particle or population of virus particles is enriched by at least about 10-fold, 100-fold, 1000-fold, 10,000-fold or more as compared with the starting material.

[00518] Unless indicated otherwise, "efficient transduction" or "efficient tropism," or similar terms, can be determined by reference to a suitable control *(e.g.,* at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 500% or more of the transduction or tropism, respectively, of the control). In particular embodiments, the virus vector efficiently transduces or has efficient tropism for neuronal cells and cardiomyocytes. Suitable controls will depend on a variety of factors including the desired tropism and/or transduction profile.

[00519] A "therapeutic polypeptide" is a polypeptide that can alleviate, reduce, prevent, delay and/or stabilize symptoms that result from an absence or defect in a protein in a cell or subject and/or is a polypeptide that otherwise confers a benefit to a subject, *e.g.,* enzyme replacement to reduce or eliminate symptoms of a disease, or improvement in transplant survivability or induction of an immune response.

[00520] The terms "heterologous nucleotide sequence" and "heterologous nucleic acid molecule" are used interchangeably herein and refer to a nucleic acid sequence that is not naturally occurring in the virus. Generally, the heterologous nucleic acid molecule or heterologous nucleotide sequence comprises an open reading frame that encodes a polypeptide and/or nontranslated RNA of interest *(e.g.,* for delivery to a cell and/or subject), for example the GAA polypeptide.

[00521] As used herein, the terms "virus vector," "vector" or "gene delivery vector" refer to a virus *(e.g.,* AAV) particle that functions as a nucleic acid delivery vehicle, and which comprises the vector genome *(e.g.,* viral DNA [vDNA]) packaged within a virion. Alternatively, in some contexts, the term "vector" may be used to refer to the vector genome/vDNA alone.

[00522] An "rAAV vector genome" or "rAAV genome" is an AAV genome *(i.e.,* vDNA) that comprises one or more heterologous nucleic acid sequences. rAAV vectors generally require only the inverted terminal repeat(s) (TR(s)) in *cis* to generate virus. All other viral sequences are dispensable and may be supplied in *trans* (Muzyczka, (1992) *Curr. Topics Microbial. Immunol.* 158:97). Typically, the rAAV vector genome will only retain the one or more TR sequence so as to maximize the size of the transgene that can be efficiently packaged by the vector. The structural and non-structural protein coding sequences may be provided in *trans (e.g.,* from a vector, such as a plasmid, or by stably integrating the sequences into a packaging cell). In embodiments of the invention the rAAV vector genome comprises at least one ITR sequence (e.g., AAV TR sequence), optionally two ITRs *(e.g.,* two AAV TRs), which typically will be at the 5' and 3' ends of the vector genome and flank the heterologous nucleic acid, but need not be contiguous thereto. The TRs can be the same or different from each other.

[00523] The term "terminal repeat" or "TR" includes any viral terminal repeat or synthetic sequence that forms a hairpin structure and functions as an inverted terminal repeat *(i.e.,* an ITR that mediates

the desired functions such as replication, virus packaging, integration and/or provirus rescue, and the like). The TR can be an AAV TR or a non-AAV TR. For example, a non-AAV TR sequence such as those of other parvoviruses (e.g., canine parvovirus (CPV), mouse parvovirus (MVM), human parvovirus B-19) or any other suitable virus sequence *(e.g.,* the SV40 hairpin that serves as the origin of SV40 replication) can be used as a TR, which can further be modified by truncation, substitution, deletion, insertion and/or addition. Further, the TR can be partially or completely synthetic, such as the "double-D sequence" as described in United States Patent No. 5,478,745 to Samulski *et al.*

[00524] An "AAV terminal repeat" or "AAV TR," including an "AAV inverted terminal repeat" or "AAV ITR" may be from any AAV, including but not limited to serotypes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 or any other AAV now known or later discovered. An AAV terminal repeat need not have the native terminal repeat sequence *(e.g.,* a native AAV TR or AAV ITR sequence may be altered by insertion, deletion, truncation and/or missense mutations), as long as the terminal repeat mediates the desired functions, *e.g.,* replication, virus packaging, integration, and/or provirus rescue, and the like.

[00525] AAV proteins VP1, VP2 and VP3 are capsid proteins that interact together to form an AAV capsid of an icosahedral symmetry. VP1.5 is an AAV capsid protein described in US Publication No. 2014/0037585.

[00526] The virus vectors of the invention can further be "targeted" virus vectors *(e.g.,* having a directed tropism) and/or a "hybrid" parvovirus *(i.e.,* in which the viral TRs and viral capsid are from different parvoviruses) as described in international patent publication WO 00/28004 and Chao et al., (2000) *Molecular Therapy* 2:619.

[00527] The virus vectors of the invention can further be duplexed parvovirus particles as described in international patent publication WO O1/92551 (the disclosure of which is incorporated herein by reference in its entirety). Thus, in some embodiments, double stranded (duplex) genomes can be packaged into the virus capsids of the invention.

[00528] Further, the viral capsid or genomic elements can contain other modifications, including insertions, deletions and/or substitutions.

[00529] A "chimeric' capsid protein as used herein means an AAV capsid protein (e.g., any one or more of VP1, VP2 or VP3) that has been modified by substitutions in one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) amino acid residues in the amino acid sequence of the capsid protein relative to wild type, as well as insertions and/or deletions of one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) amino acid residues in the amino acid sequence relative to wild type. In some embodiments, complete or partial domains, functional regions, epitopes, etc., from one AAV serotype can replace the corresponding wild type domain, functional region, epitope, etc. of a different AAV serotype, in any combination, to produce a chimeric capsid protein of this invention. Production of a chimeric capsid protein can be carried out according to protocols well known in the art and a significant number of chimeric capsid proteins are described in the literature as well as herein that can be included in the capsid of this invention.

[00530] As used herein, the term "haploid AAV" shall mean that AAV as described in International Application WO2018/170310, or US Application US2018/037149, which are incorporated herein in their entirety by reference. In some embodiments, a population of virions is a haploid AAV population where a virion particle can be constructed wherein at least one viral protein from the group consisting of AAV capsid proteins, VP1, VP2 and VP3, is different from at least one of the other viral proteins, required to form the virion particle capable of encapsulating an AAV genome. For each viral protein present (VP1, VP2, and/or VP3), that protein is the same type (e.g., all AAV2 VP1). In one instance, at least one of the viral proteins is a chimeric viral protein and at least one of the other two viral proteins is not a chimeric. In one embodiment VP1 and VP2 are chimeric and only VP3 is non-chimeric. For example, only the viral particle composed of VP1/VP2 from the chimeric AAV2/8 (the N-terminus of AAV2 and the C-terminus of AAV8) paired with only VP3 from AAV2; or only the chimeric VP1/VP2 28m-2P3 (the N-terminal from AAV8 and the C-terminal from AAV2 without mutation of VP3 start codon) paired with only VP3 from AAV2. In another embodiment only VP3 is chimeric and VP1 and VP2 are non-chimeric. In another embodiment at least one of the viral proteins is from a completely different serotype. For example, only the chimeric VP1/VP2 28m-2P3 paired with VP3 from only AAV3. In another example, no chimeric is present.

[00531] The term a "hybrid" AAV vector or parvovirus refers to a rAAV vector where the viral TRs or ITRs and viral capsid are from different parvoviruses. Hybrid vectors are described in international patent publication WO 00/28004 and Chao et al., (2000) Molecular Therapy 2:619. For example, a hybrid AAV vector typically comprises the adenovirus 5' and 3' cis ITR sequences sufficient for adenovirus replication and packaging (i.e., the adenovirus terminal repeats and PAC sequence).

[00532] The term "polyploid AAV" refers to a AAV vector which is composed of capsids from two or more AAV serotypes, e.g., and can take advantages from individual serotypes for higher transduction but not in certain embodiments eliminate the tropism from the parents.

[00533] The term "GAA" or "GAA polypeptide," as used herein, encompasses mature (~76 or ~67 kDa) and precursor (e.g., ~110 kDa) GAA as well as modified (e.g., truncated or mutated by insertion(s), deletion(s) and/or substitution(s)) GAA proteins or fragments thereof that retain biological function (i.e., have at least one biological activity of the native GAA protein, e.g., can hydrolyze glycogen, as defined above) and GAA variants (e.g., GAA II as described by Kunita et al., (1997) Biochemica et Biophysica Acta 1362:269; GAA polymorphisms and SNPs are described by Hirschhorn, R. and Reuser, A. J. (2001) in The Metabolic and Molecular Basis for Inherited Disease (Scriver, C. R., Beaudet. A. L., Sly, W. S. & Valle, D. Eds.), pp. 3389-3419, McGraw-Hill, New York, see pages 3403-3405; each incorporated herein by reference in its entirety). Any GAA coding sequence known in the art may be used, for example, see the coding sequences of FIGS. 8 and 9; GenBank Accession number NM_00152 and Hoefsloot et al., (1988) EMBO J. 7:1697 and Van Hove et al., (1996) Proc. Natl. Acad. Sci. USA 93:65 (human), GenBank Accession number NM_008064 (mouse), and Kunita et al., (1997) Biochemica et Biophysics Acta 1362:269 (quail); the disclosures of

which are incorporated herein by reference for their teachings of GAA coding and noncoding sequences. The term "GAA", or, "hGAA" or, "rhGAA" is used interchangeably to refer to nucleic acid encoding human GAA or, to human GAA polypeptide.

[00534] The term "targeting peptide" is also referred to as a "targeting sequence" as used herein is intended to refer to a peptide that targets a particular subcellular compartment, for example, a mammalian lysosome. A targeting peptide encompassed for use herein is a lysosome targeting peptide that is mannose-6-phosphate-independent. An exemplary targeting sequence is an IGF2 targeting peptide as disclosed herein.

[00535] The term "signal sequence" is used interchangeably herein with the term "secretory signal sequence" or "leader sequence" or "signal peptide" or variations thereof, and intended to refer to amino acid sequences that function to enhance (as defined above) secretion of an operably linked polypeptide, (e.g., a GAA peptide) from the cell as compared with the level of secretion seen with the native polypeptide. As defined above, by "enhanced" secretion, it is meant that the relative proportion of GAA polypeptide synthesized by the cell that is secreted from the cell is increased; it is not necessary that the absolute amount of secreted protein is also increased. In particular embodiments of the invention, essentially all (i.e., at least 95%, 97%, 98%, 99% or more) of the GAA-polypeptide is secreted. It is not necessary, however, that essentially all or even most of the GAA polypeptide is secreted, as long as the level of secretion is enhanced as compared with the native GAA polypeptide. Exemplary leader sequences include, but are not limited to the innate GAA signal sequence (also referred to as endogenous GAA signal sequence), AAT sequence, IL2(1-3), IL2 leader sequence (IL2 wt), a modified IL2 leader sequence (IL2 mut), fibronectin (FN1, also referred to as FBN), or IgG leader sequence or functional variants thereof, as disclosed herein.

[00536] As used herein, the term "amino acid" encompasses any naturally occurring amino acid, modified forms thereof, and synthetic amino acids. Naturally occurring, levorotatory (L-) amino acids are disclosed in Table 2 of US Publication 2018/0371496, which is incorporated herein in its entirety. Alternatively, the amino acid can be a modified amino acid residue (nonlimiting examples are shown in Table 4 of US Publication of US Publication 2018/0371496) and/or can be an amino acid that is modified by post-translation modification (e.g., acetylation, amidation, formylation, hydroxylation, methylation, phosphorylation or sulfatation). Further, the non-naturally occurring amino acid can be an "unnatural" amino acid as described by Wang et al., Annu Rev Biophys Biomol Struct. 35:225-49 (2006). These unnatural amino acids can advantageously be used to chemically link molecules of interest to the AAV capsid protein.

[00537] To illustrate further, if, for example, the specification indicates that a particular amino acid can be selected from A, G, I, L and/or V, this language also indicates that the amino acid can be selected from any subset of these amino acid(s) for example A, G, I or L; A, G, I or V; A or G; only L; etc. as if each such subcombination is expressly set forth herein. Moreover, such language also indicates that one or more of the specified amino acids can be disclaimed (e.g., by negative proviso).

For example, in particular embodiments the amino acid is not A, G or I; is not A; is not G or V; etc. as if each such possible disclaimer is expressly set forth herein.

[00538] As used herein, the phrase "promoter" refers to a region of DNA that generally is located upstream of a nucleic acid sequence to be transcribed that is needed for transcription to occur, i.e. which initiates transcription. Promoters permit the proper activation or repression of transcription of a coding sequence under their control. A promoter typically contains specific sequences that are recognized and bound by plurality of TFs. TFs bind to the promoter sequences and result in the recruitment of RNA polymerase, an enzyme that synthesizes RNA from the coding region of the gene. A great many promoters are known in the art.

[00539] The term "synthetic promoter" as used herein relates to a promoter that does not occur in nature. Parts of the synthetic promoter may be naturally occurring (e.g. the minimal promoter), but the synthetic promoter as a complete entity is not naturally occurring.

[00540] As used herein, "minimal promoter" (also known as the "core promoter") refers to a short DNA segment which is inactive or largely inactive by itself, but can mediate transcription when combined with other transcription regulatory elements. Minimum promoter sequence can be derived from various different sources, including prokaryotic and eukaryotic genes. Examples of minimal promoters are discussed above, and include the dopamine beta-hydroxylase gene minimum promoter, cytomegalovirus (CMV) immediate early gene minimum promoter (CMV-MP), and the herpes thymidine kinase minimal promoter (MinTK). A minimal promoter typically comprises the transcription start site (TSS) and elements directly upstream, a binding site for RNA polymerase II, and general transcription factor binding sites (often a TATA box).

[00541] As used herein, "proximal promoter" relates to the minimal promoter plus the proximal sequence upstream of the gene that tends to contain primary regulatory elements. It often extends approximately 250 base pairs upstream of the TSS, and includes specific TFBS. The proximal promoter can be a naturally occurring liver-specific proximal promoter. However, the proximal promoter can be synthetic.

[00542] A "functional variant" of a promoter or other nucleic acid sequence in the context of the present invention is a variant of a reference sequence that retains the ability to function in the same way as the reference sequence, e.g. as a liver-specific promoter. Alternative terms for such functional variants include "biological equivalents" or "equivalents".

[00543] The terms "liver-specific" or "liver-specific expression" when in reference to a promoter refers to the ability of promoter to enhance or drive expression of a gene in the liver (or in liver-derived cells) in a preferential or predominant manner as compared to other tissues (e.g. spleen, muscle, heart, lung, and brain). Expression of the gene can be in the form of mRNA or protein. In some embodiments, liver-specific expression is such that there is negligible expression in other (i.e. non-liver) tissues or cells, i.e. expression is highly liver-specific. In some embodiments, while a liver-

specific promoter drives expression preferentially in the liver, it can also drive expression of the gene in another tissue of interest at a lower level, e.g., muscle.

[00544] The skilled person can thus easily determine whether any variant of the liver-specific promoter recited above remains functional (i.e. it is a functional variant as defined above). For example, any given promoter to be assessed can be operably linked to a minimal promoter (e.g. positioned upstream of CMV-MP) and the ability of the promoter to drive liver-specific expression of a gene (typically a reporter gene) is measured. Similarly, the ability of a promoter to drive liver-specific expression can be readily assessed by the skilled person (e.g. as described in the examples below). Expression levels of a gene driven by a variant of a reference promoter can be compared to the expression levels driven by the reference sequence. In some embodiments, where liver-specific expression levels driven by a variant promoter are at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% of the expression levels driven by the reference promoter, it can be said that the variant remains functional. Suitable nucleic acid constructs and reporter assays to assess liver-specific expression enhancement can easily be constructed, and the examples set out below give suitable methodologies.

[00545] Liver-specificity can be identified wherein the expression of a gene (e.g. a therapeutic or reporter gene) occurs preferentially or predominantly in liver-derived cells. Preferential or predominant expression can be defined, for example, where the level of expression is significantly greater in liver-derived cells than in other types of cells (i.e. non-liver-derived cells). For example, expression in liver-derived cells is suitably at least 5-fold higher than non-liver cells, preferably at least 10-fold higher than non-liver cells, and it may be 50-fold higher or more in some cases. For convenience, liver-specific expression can suitably be demonstrated via a comparison of expression levels in a hepatic cell line (e.g. liver-derived cell line such as Huh7 and/or HepG2 cells) or liver primary cells, compared with expression levels in a kidney-derived cell line (e.g. HEK-293), a cervical tissue-derived cell line (e.g. HeLa) and/or a lung-derived cell line (e.g. A549).

[00546] The synthetic liver-specific promoters of the present invention are preferably suitable for promoting expression in the liver of a subject, e.g., driving liver-specific expression of a transgene, preferably a therapeutic transgene.

[00547] Preferred synthetic liver-specific promoters of the present invention are suitable for promoting liver-specific transgene expression and have an activity in liver cells which is at least 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350% or 400% of the activity of the TBG promoter (see, e.g., SEQ ID NO: 435 as disclosed in International Application WO2021102107).

[00548] The synthetic liver-specific promoters of the present invention are preferably suitable for promoting liver-specific expression at a level at least 1.5-fold greater than a CMV-IE promoter (see, e.g., SEQ ID NO: 433 as disclosed in International Application WO2021102107) in liver-derived

cells, preferably at least 2-fold greater than a CMV promoter in liver-derived cells (e.g. HEK-293, HeLa, and/or A549 cells).

[00549] The terms "identity" and "identical" and the like refer to the sequence similarity between two polymeric molecules, e.g., between two nucleic acid molecules, such as between two DNA molecules. Sequence alignments and determination of sequence identity can be done, e.g., using the Basic Local Alignment Search Tool (BLAST) originally described by Altschul et al. 1990 (J Mol Biol 215: 403-10), such as the "Blast 2 sequences" algorithm described by Tatusova and Madden 1999 (FEMS Microbiol Lett 174: 247-250).

[00550] The term "synthetic" as used herein means a nucleic acid molecule that does not occur in nature. Synthetic nucleic acid expression constructs of the present invention are produced artificially, typically by recombinant technologies. Such synthetic nucleic acids may contain naturally occurring sequences (e.g. promoter, enhancer, intron, and other such regulatory sequences), but these are present in a non-naturally occurring context. For example, a synthetic gene (or portion of a gene) typically contains one or more nucleic acid sequences that are not contiguous in nature (chimeric sequences), and/or may encompass substitutions, insertions, and deletions and combinations thereof.

[00551] A "spacer sequence" or "spacer" as used herein is a nucleic acid sequence that separates two functional nucleic acid sequences. It can have essentially any sequence, provided it does not prevent the functional nucleic acid sequence (e.g. cis-regulatory element) from functioning as desired (e.g. this could happen if it includes a silencer sequence, prevents binding of the desired transcription factor, or suchlike). Typically, it is non-functional, as in it is present only to space adjacent functional nucleic acid sequences from one another.

[00552] The term "pharmaceutically acceptable" as used herein is consistent with the art and means compatible with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

[00553] By the terms "treat," "treating" or "treatment of' (and grammatical variations thereof) it is meant that the severity of the subject's condition is reduced, at least partially improved or stabilized and/or that some alleviation, mitigation, decrease or stabilization in at least one clinical symptom is achieved and/or there is a delay in the progression of the disease or disorder.

[00554] The terms "prevent," "preventing" and "prevention" (and grammatical variations thereof) refer to prevention and/or delay of the onset of a disease, disorder and/or a clinical symptom(s) in a subject and/or a reduction in the severity of the onset of the disease, disorder and/or clinical symptom(s) relative to what would occur in the absence of the methods of the invention. The prevention can be complete, *e.g.,* the total absence of the disease, disorder and/or clinical symptom(s). The prevention can also be partial, such that the occurrence of the disease, disorder and/or clinical symptom(s) in the subject and/or the severity of onset is substantially less than what would occur in the absence of the present invention.

[00555] A "treatment effective" amount as used herein is an amount that is sufficient to provide some

improvement or benefit to the subject. Alternatively stated, a "treatment effective" amount is an amount that will provide some alleviation, mitigation, decrease or stabilization in at least one clinical symptom in the subject. Those skilled in the art will appreciate that the therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject.

[00556] A "prevention effective" amount as used herein is an amount that is sufficient to prevent and/or delay the onset of a disease, disorder and/or clinical symptoms in a subject and/or to reduce and/or delay the severity of the onset of a disease, disorder and/or clinical symptoms in a subject relative to what would occur in the absence of the methods of the invention. Those skilled in the art will appreciate that the level of prevention need not be complete, as long as some preventative benefit is provided to the subject.

[00557] The phrase a "therapeutically effective amount" and like phrases mean a dose or plasma concentration in a subject that provides the desired specific pharmacological effect, e.g. to express a therapeutic gene in the liver, and secretion into the plasma. It is emphasized that a therapeutically effective amount may not always be effective in treating the conditions described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art. The therapeutically effective amount may vary based on the route of administration and dosage form, the age and weight of the subject, and/or the disease or condition being treated.

[00558] The terms "individual," "subject," and "patient" are used interchangeably, and refer to any individual subject with a disease or condition in need of treatment. For the purposes of the present disclosure, the subject may be a primate, preferably a human, or another mammal, such as a dog, cat, horse, pig, goat, or bovine, and the like.

[00559] Additional patents incorporated for reference herein that are related to, disclose or describe an AAV or an aspect of an AAV, including the DNA vector that includes the gene of interest to be expressed are: U.S. Patent Nos. 6,491,907; 7,229,823; 7,790,154; 7,201898; 7,071,172; 7,892,809; 7,867,484; 8,889,641; 9,169,494; 9,169,492; 9,441,206; 9,409,953; and, 9,447,433; 9,592,247; and, 9,737,618.

[00560] The invention provided herein can further be described in any of the following numbered paragraphs:

1. A recombinant adenovirus associated (rAAV) vector comprising in its genome:

a. 5' and 3' AAV inverted terminal repeats (ITR) sequences, and

b. located between the 5' and 3' ITRs, a heterologous nucleic acid sequence encoding all or a portion of an endogenous GAA signal peptide, a heterologous signal peptide and an alpha-glucosidase (GAA) polypeptide,

wherein the GAA polypeptide comprises amino acid residues 28-952 of SEQ ID NO: 1, 57-952 of SEQ ID NO:1, or comprises a N-terminal GAA polypeptide fragment comprising amino acids 28, 28-29, 28-30, 28-31, 28-32, or 28-33 of SEQ ID NO: 1 and a deletion of any number of amino acids from the next about 5 amino acids to

about 40 amino acids after the N terminal GAA polypeptide fragment of SEQ ID NO: 1, and wherein the heterologous signal peptide can be inserted immediately after the N-terminal GAA polypeptide fragment and before the remaining amino acids of the GAA polypeptide, wherein the heterologous signal peptide is optionally fused at position 57 of the remaining amino acids of the GAA polypeptide, and where the GAA polypeptide can extend to amino acid 952 of SEQ ID NO: 1, or a functional fragment thereof, and

wherein the nucleic acid sequence encoding the GAA polypeptide can be codon optimized, and wherein the heterologous nucleic acid is operatively linked to a liver-specific promoter and a poly A sequence.

2. The recombinant AAV vector of paragraph 1, where the codon optimized nucleic acid sequence encoding the GAA polypeptide is selected from the group consisting of SEQ ID NO: 1-18, or functional fragment thereofs.
3. The recombinant AAV vector of any of the preceding paragraphs, which comprises the nucleic acid sequence of SEQ ID NO: 23, or a functional variant thereof.
4. The recombinant AAV vector of any of the preceding paragraphs, wherein the heterologous nucleic acid sequence encodes a GAA protein comprising a signal peptide fused to the GAA polypeptide, wherein the signal peptide is an endogenous GAA signal peptide, or a heterologous signal peptide, or a combination thereof.
5. The recombinant AAV vector of any of the preceding paragraphs, wherein the nucleic acid encoding SEQ ID NO: 3 is wildtype.
6. The recombinant AAV vector of any of the preceding paragraphs, further comprising at least one of a UTR, or a reverse RNA polII terminator sequence.
7. The recombinant AAV vector of any of the preceding paragraphs, wherein the AAV genome comprises, in the 5' to 3' direction:

a. a 5' ITR,
b. a liver-specific promoter sequence,
c. an 5' UTR sequence,
d. a nucleic acid encoding a portion or all of the endogenous GAA signal peptide,
e. a nucleic acid encoding a heterologous signal peptide or the N-terminal GAA polypeptide fragment,
f. a nucleic acid encoding an alpha-glucosidase (GAA) polypeptide, wherein the GAA polypeptide is functionally active,
g. a poly A sequence, and
h. a reverse RNA pol II terminator sequence.

8. The recombinant AAV vector of any of the preceding paragraphs, wherein the UTR is 5' or 3'.

9. The recombinant AAV vector of any of the preceding paragraphs, wherein nucleic acid encoding the signal peptide encodes a signal sequence is selected from any of: an endogenous GAA signal peptide, a fibronectin signal peptide (FN1), a IL-2 wt signal peptide, modified IL-2 signal peptide, IL2(1-3) signal peptide, IgG signal peptide, a AAT signal peptide, a A2M signal peptide, or a PZP signal peptide, or an active fragment thereof having signal peptide activity.
10. The recombinant AAV vector of any of the preceding paragraphs, wherein the nucleic acid sequence encodes a GAA polypeptide having the amino acid sequence of SEQ ID NO: 1, or a polypeptide having at least 80% sequence identity to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).
11. The recombinant AAV vector of any of the preceding paragraphs, wherein the nucleic acid sequence encoding the GAA polypeptide is SEQ ID NO: 3, or a nucleic acid sequence having at least 80%, or at least 85%, or at least 90% sequence identity to SEQ ID NO: 3 that encodes a GAA polypeptide having at least 80% sequence identity to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).
12. The recombinant AAV vector of any of the preceding paragraphs, wherein the 5' UTR sequence comprises SEQ ID NO: 41, or a nucleic acid having at least 80% sequence identity to SEQ ID NO: 41.
13. The recombinant AAV vector of any of the preceding paragraphs, wherein the 5' UTR sequence comprises SEQ ID NO: 40, or a nucleic acid having at least 80% sequence identity to SEQ ID NO: 40.
14. The recombinant AAV vector of any of the preceding paragraphs, further comprising an intron sequence located 5' of the nucleic acid sequence encoding the signal peptide, and 3' of the promoter.
15. The recombinant AAV vector of any of the preceding paragraphs, wherein the intron sequence is selected from the group consisting of: MVM sequence, a HBB2 sequence, an CMVIE intron sequence, or a UBC intron sequence or a SV40 sequence.
16. The recombinant AAV vector of any of the preceding paragraphs, wherein the GAA polypeptide is a N-terminal truncated GAA polypeptide selected from any disclosed in Table 1.
17. The recombinant AAV vector of any of the preceding paragraphs, further comprising at least one polyA sequence located 3' of the nucleic acid encoding the GAA gene and 5' of the 3' ITR sequence.

18. The recombinant AAV vector of any of the preceding paragraphs, wherein the heterologous nucleic acid sequence further comprises a 3' UTR sequence, wherein the 3' UTR sequence is located 3' of the nucleic acid encoding the GAA polypeptide and 5' of the 3' ITR sequence, or is located between the nucleic acid encoding the GAA polypeptide and the poly A sequence, or RNA pol II terminator sequence.
19. The recombinant AAV vector of any of the preceding paragraphs, wherein the heterologous nucleic acid sequence further comprises a 3' intron sequence, wherein the 3' intron sequence is located 3' of the nucleic acid encoding the GAA polypeptide and 5' of the 3' ITR sequence, or is located between the nucleic acid encoding the GAA polypeptide and the poly A sequence or RNA polII terminator sequence.
20. The recombinant AAV vector of any of the preceding paragraphs, wherein the ITR comprises an insertion, deletion or substitution.
21. The recombinant AAV vector of any of the preceding paragraphs, wherein one or more CpG islands in the ITR are removed.
22. The recombinant AAV vector of any of the preceding paragraphs, wherein

a. the nucleic acid encoding the signal peptide is selected from any of the group consisting of:

AAT signal peptide (e.g., SEQ ID NO: 67), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 67;

a fibronectin signal peptide (FN1) (e.g., SEQ ID NO: 73-75), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 73-75;

an endogenous GAA signal peptide (SEQ ID NO: 51), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 51;

an hIGF2 signal peptide (e.g., SEQ ID NO: 72), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 72;

a IgG1 (201) signal peptide (SEQ ID NO: 54), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 54;

wtIL2 leader peptide (SEQ ID NO: 55), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 55;

mutant IL2 leader peptide (SEQ ID NO: 56) or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 56; and

b. the nucleic acid encoding the GAA polypeptide is selected from any of the group consisting of: SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 or a nucleic acid sequence having at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% sequence identity to SEQ ID NOS: 1-18.

23. The recombinant AAV vector of any of the preceding paragraphs, wherein the nucleic acid encoding the GAA polypeptide is selected from SEQ ID NO: 3, or a nucleic acid sequence having at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 3 which encodes a GAA polypeptide at least 85% sequence identity to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).

24. The recombinant AAV vector of any of the preceding paragraphs, wherein the nucleic acid encoding the GAA polypeptide encodes a GAA polypeptide beginning at any of amino acid residues 35, 40, 50, 57, 60, 68, 69, 70, 72, 74, 779, 790, 791, 792, 793, or 796 of SEQ ID NO: 1 or a sequence 80% identical to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).

25. The recombinant AAV vector of any of the preceding paragraphs, wherein the GAA polypeptide has an endogenous GAA signal peptide attached, or a heterologous signal peptide attached to the N-terminal of the GAA polypeptide, wherein the endogenous signal peptide has the amino acid sequence of SEQ ID NO: 59 or a sequence at least 80% sequence identity to SEQ ID NO: 59, and the heterologous signal peptide is selected from the group consisting of: SEQ ID NO: 60 (201 IgG signal peptide), or an IL2 wild type signal peptide (SEQ ID NO: 61), modified IL2 signal peptide (SEQ ID NO: 62), A2M signal peptide (SEQ ID NO: 63), or PZP signal peptide (SEQ ID NO: 64), or artificial signal peptide (SEQ ID NO: 65), or cathpetsin L signal peptide (SEQ ID NO: 66) or signal peptides at least 90% sequence identity to SEQ ID NOS: 60-66.

26. The recombinant AAV vector of any of the preceding paragraphs, wherein the liver specific promoter is selected from any of: SEQ ID NOS: 86, 88, 91-96, 146-150 or 439-441, or a liver specific promoter having at least 80% sequence identity to SEQ ID NOs: 86, 88, 91-96, 146-150 or 439-441.
27. The recombinant AAV vector of any of the preceding paragraphs, wherein the liver specific promoter is selected from any of: SEQ ID NOS: 98 or 99, or a liver specific promoter having at least 80% sequence identity to SEQ ID NOs: 98 or 99.
28. The recombinant AAV vector of any of the preceding paragraphs, wherein the liver specific promoter is SEQ ID NOS: 97, or a liver specific promoter having at least 80% sequence identity to SEQ ID NO: 97.
29. The recombinant AAV vector of any of the preceding paragraphs, wherein the recombinant vector is manufactured from the plasmid of SEQ ID NO: 27.
30. The recombinant AAV vector of any of the preceding paragraphs, wherein the nucleic acid comprises SEQ ID NO: 25, or a functional fragment thereof.
31. The recombinant AAV vector of any of the preceding paragraphs, wherein the recombinant AAV vector is a chimeric AAV vector, haploid AAV vector, a hybrid AAV vector or polyploid AAV vector.
32. The recombinant AAV vector of any of the preceding paragraphs, wherein the recombinant AAV vector is a rational haploid vector, a mosaic AAV vector, a chemically modified AAV vector, or a AAV vector from any AAV serotypes.
33. The recombinant AAV vector of any of the preceding paragraphs, wherein the recombinant AAV vector is selected from the group consisting of: a AAVXL32 vector, a AAVXL32.1 vector, a AAV8 vector, or a haploid AAV8 vector comprising at least one AAV8 capsid protein.
34. The recombinant AAV vector of any of the preceding paragraphs, wherein the serotype is AAV3b.
35. The recombinant AAV vector of any of the preceding paragraphs, wherein the AAV3b serotype comprises one or mutations in a capsid protein selected from any of: 265D, 549A, Q263Y.
36. The recombinant AAV vector of any of the preceding paragraphs, wherein the AAV3b serotype is selected from any of: AAV3b265D, AAV3b265D549A, AAV3b549A or AAV3bQ263Y, or AAV3bSASTG.
37. The recombinant AAV vector of any of the preceding paragraphs, wherein the poly A sequence is a full length HGF poly A sequence.
38. The recombinant AAV vector of any of the preceding paragraphs, wherein poly A sequence is selected from SEQ ID NO: 42, 43 or 44, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 42-44.

39. The recombinant AAV vector of any of the preceding paragraphs, wherein the reverse RNA pol II terminator sequence is SEQ ID NO: 45, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 45.
40. A pharmaceutical composition comprising the recombinant AAV vector of any one of the previous paragraphs in a pharmaceutically acceptable carrier.
41. A method to treat a subject with Pompe Disease, or a glycogen storage disease type II (GSD II, Acid Maltase Deficiency) or having a deficiency in alpha-glucosidase (GAA) polypeptide, comprising administering any of the recombinant AAV vector, or the rAAV genome or the nucleic acid sequence of any one of the previous paragraphs to the subject.
42. The method of paragraph 38, wherein the AAV vector manufactured from the plasmid of SEQ ID NO: 27.
43. The method of any of the preceding paragraphs, where the recombinant AAV vector comprises the nucleic acid sequence of SEQ ID NO: 3, or a functional fragment thereof.
44. The method of any of the preceding paragraphs, where the recombinant AAV vector comprises the nucleic acid sequence of SEQ ID NO: 23, or a functional variant thereof.
45. The method of any of the preceding paragraphs, wherein GAA polypeptide is secreted from the subject's liver and there is uptake of the secreted GAA by skeletal muscle tissue, cardiac muscle tissue, diaphragm muscle tissue or a combination thereof, wherein uptake of the secreted GAA results in a reduction in lysosomal glycogen stores in the tissue(s).
46. The method of any of the preceding paragraphs, wherein the administering to the subject is selected from any of: intramuscular, sub-cutaneous, intraspinal, intracisternal, intrathecal, intravenous administration.
47. The method of any of the preceding paragraphs, where the recombinant AAV vector is a chimeric AAV vector, haploid AAV vector, a hybrid AAV vector or polyploid AAV vector.
48. The method of any of the preceding paragraphs, where the recombinant AAV vector is a rational haploid vector, a mosaic AAV vector, a chemically modified AAV vector, or a AAV vector from any AAV serotypes.
49. The method of any of the preceding paragraphs, where the recombinant AAV vector is a AAVXL32 vector or a AAVXL32.1 vector or a AAV8 vector, or a haploid AAV8 vector comprising at least one AAV8 capsid protein.
50. The method of any of the preceding paragraphs, where the recombinant AAV vector is a AAV8 vector.

51. The method of any of the preceding paragraphs, where the recombinant AAV vector is administered at a dosage range of between 1.0E11vg/kg and 5.0E13 vg/kg.
52. The method of any of the preceding paragraphs, further comprising receiving GAA protein enzyme replacement therapy, and withdrawing GAA protein enzyme replacement therapy (ERT) on the same day, a day after or, any time between day 1 and 26 weeks after administration of the recombinant AAV vector.
53. A nucleic acid construct comprising SEQ ID NO: 3, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 3.
54. The nucleic acid of paragraph 50, wherein the expression of the nucleic acid sequence of SEQ ID NO: 3 or a nucleic acid having 80% sequence identity thereto encodes a GAA polypeptide having at least 80% sequence identity to SEQ ID NO: 1 and wherein there is R at position 199, a H at position 223 and I at position 780.
55. A nucleic acid construct comprising SEQ ID NO: 23, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NO: 23.
56. The nucleic acid construct of paragraph 52, comprising SEQ ID NO: 3 or SEQ ID NO: 25, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 3 or 25.
57. The nucleic acid of any of the preceding paragraphs, wherein the expression of the nucleic acid sequence of SEQ ID NO: 3 or a nucleic acid having 80% sequence identity thereto encodes a GAA polypeptide having at least 80% sequence identity to SEQ ID NO: 1 and wherein there is R at position 199, a H at position 223 and I at position 780.
58. A recombinant AAV comprising the nucleic acid construct of any of the preceding paragraphs.
59. The recombinant AAV vector of any of the preceding paragraphs, wherein the AAV lacks at least 1 amino acids of the GAA N terminus.
60. The recombinant AAV vector of any of the preceding paragraphs, wherein the AAV lacks at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 or mor amino acids of the GAA N terminus.
61. The recombinant AAV vector of any of the preceding paragraphs, wherein the heterologous signal peptide is inserted immediately after the endogenous GAA signal peptide or a potion thereof.

EXAMPLES

EXAMPLE 1: generating rAAV vectors

[00561] The rAAV genomes were packed into capsids to generate rAAV vectors using a rAAV

producing cell line. Solely for proof of principal of rAAV vector construction, the capsids used were AAV3b capsids.

[00562] Making rAAV in the rAAV producing cell line: triple transfection technique was used to make rAAV in a suspension rAAV producer cell line, which can be scaled up for making clinical grade vector. Alternatively, different plasmids can be used, e.g., 1) pXX680 – ad helper and 2) pXR3 the Rep and Cap 3) and the Transgene plasmid (ITR—transgene-ITR).

[00563] The rAAV genomes generated in Example 1 are used to generate rAVV vectors using a rAAV producing cell line, according to the methods as described in US patent 9,441,206, which is incorporated herein in its entirety by reference. In particular, rAAV vectors or rAAV virions are produced using a method comprising: (a) providing a rAAV producing cell line an AAV expression system; (b) culturing the cells under conditions in which AAV particles are produced; and (c) optionally isolating the AAV particles. Ratios of triple transfection of the plasmid and transfection cocktail volumes can be optimized, with varying plasmid ratios of XX680, AAV rep/cap helper and TR plasmid to determine the optimal plasmid ratio for rAAV vector production.

[00564] In some instances, the cells are cultured in suspension under conditions in which AAV particles are produced. In another embodiment, the cells are cultured in animal component-free conditions. The animal component-free medium can be any animal component-free medium (e.g., serum-free medium) compatible with the rAAV producer cell line. Examples include, without limitation, SFM4Transfx-293 (Hyclone), Ex-Cell 293 (JRH Biosciences), LC-SFM (Invitrogen), and Pro293-S (Lonza). Conditions sufficient for the replication and packaging of the AAV particles can be, e.g., the presence of AAV sequences sufficient for replication of an rAAV genome described herein and encapsidation into AAV capsids (e.g., AAV rep sequences and AAV cap sequences) and helper sequences from adenovirus and/or herpesvirus.

[00565] Bacterial DNA sequences from the plasmid backbone can be packaged into AAV capsids during manufacturing of the recombinant AAV vectors leading to activations of the innate immune system through its interaction with TLR9 (Akira, 2006; Chadeuf, 2005; Wright, 2014). Various technologies can be used to eliminate plasmid backbone sequences in recombinant AAV preparations, for example minicircles which have limited scalability (Schnodt, 2016). Another method to avoid bacterial DNA sequence in the plasmid backbone is to use closed ended linear duplex DNA, which includes a range of DNA replication technology, including but not limited to doggy bone DNA (dbDNA™) for specifically manufacturing of recombinant AAV vectors. Using closed ended linear duplex DNA, such as dbDNA™ eliminates the bacterial backbone and has been used to produce vaccines and lentivirus (Walters et al, 2014; Scott et al, 2015; Karda et al, 2019) and was shown to be unable to trigger TLR9 responses by DNA vaccine developers.

[00566] Accordingly, in alternative embodiments, generation of rAAV vectors for use in the methods and compositions as disclosed herein can be performed using closed ended linear duplex DNA, including but not limited to Doggybone technology (dbDNA™), as disclosed in US Application

2018/0037943 and Karbowniczek et al., Bioinsights, 2017, which is incorporated herein in its entirety by reference. In brief, a plasmid for AAV production using a closed ended linear duplex DNA technology can comprise the ITRs, promoter and gene of interest, e.g., GAA as disclosed herein, is flanked by a 56bp palindromic protelomerase recognition sequence. The plasmid is denatured, and in the presence of a Phi29 DNA polymerase, and appropriate primers, Phi29 initiates rolling circle amplification (RCA), creating a double stranded cancatameric repeats of the original construct. When protelomerase is added, binding of the palindromic protelomerase recognition sequences occurs and cleavage-joining reaction occurs to result in a monomeric double stranded (ds) linear covalently closed DNA construct. Addition of common restriction enzymes remove the undesired DNA plasmid backbone sequence and digestion with exonuclease activity, resulting in dbDNA which can be size fractionated to isolate the dbDNA sequence encoding the ITRs, promoter and gene of interest. An exemplary plasmid for generation of rAAV vectors using closed ended linear duplex DNA such as dbDNA™ technology, comprises in the following 5' to 3' direction: 5'-protelomerase RS, 5'ITR, LSP promoter, GAA (e.g., wild-type or codon optimized), 3'UTR, hGH poly(A), 3' ITR, 3'-protelomerase RS (sense strand), where the sense strand is linked to the complementary antisense strand for a stranded (ds) linear covalently closed DNA construct. The use of closed ended linear duplex DNA, e.g., doggy bone DNA (dbDNA™) as a starting material for the manufacturing of an AAV vector for use in the methods and composition as disclosed herein eliminates the bacterial backbone used to propagate the plasmid containing AAV vector with an inability for the product to trigger Toll-like receptor 9 (TLR9) responses. An exemplary dbDNA plasmid for use in the manufacturing of a rAAV vector for use in the methods and compositions as disclosed herein is SEQ ID NO: 37. In some embodiments, the 4780bp fragment of 347-5126bp of SEQ ID NO: 37 (i.e., the ITR-to-ITR sequence of SEQ ID NO: 37) can be replaced by any ITR-to-ITR sequence as disclosed herein, e.g., a ITR-to-ITR sequence selected from any of: SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 31-35 as disclosed herein. Use of closed ended linear duplex DNA technology for manufacturing further reduce the risk for liver enzyme elevations observed at a dose of 1.6E13 vg/kg in patients with Pompe disease.

Example 2: Comparison of the M3 construct and Actus 101

[00567] Study Objective: The primary objective of this study presented herein in this example is to evaluate a series of gene therapy vector variants for tissue biodistribution and expression of human acid glucosidase alpha (GAA) in a mouse model of Pompe Disease. The following vectors ACTUS 101 (lot AB20200915), M3 dbp (lot AB20200914) and M3 db (lot AB20201117) were included in this study.

[00568] Background: ACTUS-101 (AAV2/8-LSPhGAA) (SEQ ID NO:451) is an infectious non-replicating recombinant adeno-associated viral vector (AAV) serotype 8, pseudotyped with AAV2

inverted terminal repeats (ITR), expressing human GAA under the control of a liver specific promoter (LSP). The GAA has an amino acid composition that is the same as in the FDA approved Enzyme Replacement Therapy Myozyme/Lumizyme for the treatment of Pompe Disease.

[00569] The Original ACTUS-101 transgene cassette was designed without codon optimization. Several design iterations have been made since the original design and have characterized these in a series of in vivo studies in wild type mice and in GAA knockout (KO) mice.

[00570] An additional change includes the use of synthetic doggy bone DNA (dbDNA™) as a starting material for the manufacturing of the gene therapy vector, eliminating the bacterial backbone and thus minimizing the ability of the product to trigger Toll-like receptor 9 (TLR9) responses.

[00571] The M3 vector (SEQ ID NO: 37) in this study uses the same AAV8 capsid as in ACTUS-101 and is made using the doggy bone precursor plasmid (dbp) for lot AB20200914 and doggy bone DNA (db) for lot AB20201117.

[00572] Table 5: Study design:

Mouse strain	**GAA -/- mice, JAX strain 004154, B6;129-Gaa<tm1Rabn>/J**
Sex	Male
Age	5-7 weeks
Mice per vector	N=5
Doses per vector	3e10 vg/mouse (LOW); 3e11 vg/mouse dose 2 (HIGH)
Injection Volume	150 ul
Route of Administration	tail vein injection
Necropsy	28 days post-injection
Number of vectors	3
Post-harvest analysis	GAA expression in sera, GAA activity in sera, GAA uptake by target tissues, GAA activity in target tissues, glycogen reduction in target tissues

Table 6: Treatment groups:

Group	**Vector**	**Number of mice**	
		3e10*	3e11*
1	SALINE	5	N/A
2	ACTUS 101	5	5
3	M3 dbp	5	5
4	M3 db	5	5

*Vector doses in vector genomes/mouse

[00573] Postharvest analysis: GAA expression in sera over time by western blotting and semi-quantitative densitometry; GAA expression in liver by western blotting and semi-quantitative densitometry GAA uptake by select tissues (heart and diaphragm) by western blotting and semi-quantitative densitometry, GAA enzymatic activity in sera over time by 4MU assay; GAA enzymatic activity in liver by 4MU assay; GAA uptake by select tissues (heart, diaphragm and quad) by 4MU assays; glycogen content in select tissues (heart, diaphragm and quad).

[00574] Materials and Methods

[00575] Cloning and vector quantification: All vectors were made using methods as described in Example 1. The constructs were packaged in the AAV8 viral capsid and titered by digital droplet PCR (ddPCR) method using primers directed at vector ITRs.

[00576] Tissue preservation: Fresh tissue and sera specimens were immediately frozen and stored at -80°C until use for molecular biology analyses.

[00577] Analysis of GAA protein levels in tissues by Western Blot and Densitometry: Tissues were homogenized in T-PER buffer (ThermoFisher 78510) with Halt Protease Inhibitor Cocktail (Thermo 78430) in TissueLyser and protein was quantified by BCA assay. Samples were heated at 95 degrees C for 5 minutes and 50µg protein was loaded onto Novex Wedge Well 4-12% Tris/Glycine gel (Invitrogen LC2675), run at 225V for 40 minutes using Tris Glycine Running buffer (ThermoFisher) and transferred onto iBlot2 NC Mini Stacks (Thermo IB23002) using the P0 program (20 V 1 min, 23V 4 min, 25V 2 min). Membranes were washed in PBST and stained with Ponceau S stain (Sigma P7170) for 5 minutes followed by washing 3X with distilled water.

[00578] Membranes were imaged on iBright imager (FL15000) using the Ponceau S setting and destained using 0.1M NaOH for 30 sec followed by rinsing the membrane with water for 2-3 minutes. Blocking was done in Superblock (TBS) blocking solution (ThermoFisher 37536) for 1 hour at room temperature. Acid-α-glucosidase (GAA) protein detection was obtained after incubation overnight at 4°C with a rabbit anti-GAA antibody (AbCam 137068) diluted 1:8000 in PBS 0.05% tween 20, followed by a goat anti-rabbit HRP conjugated antibody (Abcam ab205718) diluted 1:10000. The HRP enzyme activity was detected by Clarity Enhanced Chemiluminescence (ECL) Western Blotting Substrate (BioRad 1705061). The images were acquired by iBright imaging system, densitometry was performed on iBright software v. 4.0.1 and results were expressed as relative calculation (ratio) of the intensity of GAA antibody detected band per total protein by Ponceau S staining. For liver samples, rhGAA was run as a standard curve for absolute quantification.

[00579] Measurement of GAA secretable protein levels in blood by Western Blot (WB) and Densitometry: Fresh blood samples obtained from submandibular bleed were centrifuged and serum collected. 1.5 ul serum was diluted in 18.5 ul T- PER buffer (ThermoFisher 78510) and 20 ul 2X sample buffer (Sigma S3401) and heated at 95 degrees C for 5 minutes. Samples (40µl) were run onto Novex Wedge Well 4-12% Tris/Glycine gel (Invitrogen LC2675) at 225V for 40 minutes using Tris

Glycine Running buffer (ThermoFisher) and transferred onto iBlot2 NC Mini Stacks (Thermo IB23002) using the P0 program (20 V 1 min, 23V 4 min, 25V 2 min). Membranes were washed in PBST and stained with Ponceau S stain (Sigma P7170) for 5 minutes followed by washing 3X with distilled water. Membranes were imaged on iBright imager (FL15000) using the Ponceau S setting and destained using 0.1M NaOH for 30 sec followed by rinsing the membrane with water for 2-3 minutes. Blocking was done in Superblock (TBS) blocking solution (ThermoFisher 37536) for 1 hour at room temperature. Acid-α-glucosidase (GAA) protein detection was obtained after incubation overnight at 4°C with a rabbit anti-GAA antibody (AbCam 137068) diluted 1:8000 in PBS 0.05% tween 20, followed by a goat anti-rabbit HRP conjugated antibody (Abcam ab205718) diluted 1:10000. The HRP enzyme activity was detected by Clarity Enhanced Chemiluminescence (ECL) Western Blotting Substrate (BioRad 1705061). The images were acquired by the image analyzer iBright imaging system, densitometry was performed on iBright software v. 4.0.1 and results were given by relative calculation (ratio) of the intensity of GAA antibody detected band per total protein by Ponceau S staining.

[00580] GAA activity measurement in tissues: GAA activity was measured on frozen tissues following homogenization and sonication of tissue samples in distilled water. Depending upon the tissue size, 10-50 mg tissue was weighed and homogenized, the homogenates were sonicated at 4 degree C 3 times for 15 seconds, then centrifuged for 3 min at 15000 RPM. For serum GAA, 10 ul was analyzed, with or without 80 μM acarbose. The reaction was set up with 10ul of supernatant and 20 ul of substrate - 4MUα-D-glucoside, in a 96 wells plate (VWR62402-970). The reaction mixture was incubated at 37 degrees C for one hour and was stopped by adding 130ul of Sodium Carbonate buffer pH10.5. A standard curve (0- 1000 pmol/ ul of 4MU) was used to measure released fluorescent 4MU from individual reaction mixture, using TECAN GENios microplate reader at 465 nm (Emission) and 360 nm (excitation). The protein concentrations of the clarified supernatants were quantified via the Bradford assay (Bio-Rad Laboratories, Cat No. 500-0006). GAA activity was measured in the tissue homogenates by conversion of the artificial substrate 4-methylumbelliferyl (4-MU) α-D-glucoside to the fluorescent product umbelliferone at acidic pH 4.3 as described [1]. To calculate the GAA activity, released 4MU concentration was divided by the sample protein concentration and activity was reported as nmol/hour/mg protein. QA and QC samples were run on the same plate for experimental assay controls.

[00581] GAA activity measurement in serum: Fresh blood samples obtained from submandibular bleed were centrifuged and serum collected. 10 ul of serum was treated 2ul of 800 μM acarbose. The reaction was set up with 10ul of supernatant and 20 ul of substrate - 4MUα-D-glucoside, in a 96 wells plate (VWR62402-970). The reaction mixture was incubated at 37 degrees C for one hour and was stopped by adding 130ul of Sodium Carbonate buffer pH10.5. A standard curve of rhGAA (R&D Systems, Cat. No 8329-GH) Standards, 2,000 ng/mL to 25 ng/mL was used. Released fluorescent 4MU from individual reaction mixture was measured using BioTek FLx800 Reader, Excitation filter

= 360/40 and Emission filter = 460/40. GAA activity was determined by interpolation to the standard curve with a 4-parameter curve fit model and activity was reported as ng/ml.

[00582] Glycogen content: Glycogen content of tissues was measured indirectly as the glucose released after total digestion by amyloglucosidase of the tissue homogenates using the Aspergillus niger assay system and the glucose reagent (Infinity Glucose; TR15421, Thermo Scientific, VA, USA) in a standardized reaction using the Aspergillus niger assay system. The same tissue homogenates used above were used to measure total glycogen content in each tissue. The reaction was set up with 20ul of supernatant and 55ul distilled water. Samples were boiled for 3 min and immediately cooled on ice for 10 min. 25 ul of amyloglucosidase (1:50 in 0.1M potassium acetate pH5.5) was added to each reaction tube. A reaction control tube without any amyloglucosidase (homogenate + water) was also set up for each reaction tube. Both sample tube and control sample reaction tubes were incubated at 37 degrees C for 90 minutes and reaction, was stopped by boiling the tubes for 3min followed by centrifugation for 3 min at 15000 RPM. The glucose released from each reaction tube was determined by adding 30 ul of supernatant into 1ml of Infinity glucose reagent (TR15421) and measuring on spectrophotometer at 340nm (Shimadzu UV-1700).

[00583] Observations: As observed in FIGs 1A-1D, expression of GAA in cardiac serum was not significantly higher when driven from the M3 construct as compared to Actus 101 over a 4 week period of time. In fact, GAA expression from the M3 construct was reduced at week 4 (Fig. 1D) as compared to week 3 (Fig 1C), whereas GAA expression from Actus 101 was sustained for at least 4 weeks. Similarly, as observed in FIGs 2A2-D, the activity of GAA in cardiac serum was not significantly higher from the M3 construct (high or low dose) as compared to Actus 101 over a 4 week period of time. Further, data presented herein showed that the M3 construct was similarly unable to increase GAA levels and activity in target tissues, such as the heart, diaphragm, quadriceps muscle and liver, following administration as compared to Actus 101 (see, e.g., FIGs 3A-4D).

[00584] Additionally, as shown in FIGs 5A-5D, a reduction in glycogen did not track in a dose dependent manner in mice following administration of the M3 construct. A significant dose dependent reduction of glycogen reduction was observed in the heart, diaphragm, quadriceps muscle and liver in mice administration Actus 101, however, this trend was not observed following administration of the M3 construct.

[00585] Accordingly, the data presented herein in this Example indicates that the M3 construct fails to perform better than Actus 101 with regards to increasing GAA protein levels and activity that can be sustained over a long period of time (e.g., more than 4 weeks) and that was capable of inducing glycogen clearance in the cell.

[00586] Further, additional variants based on the Actus 101 construct were developed and tested for their ability to promote glycogen clearance in the cell. Such constructs include pP110 and pP113. As shown in FIG. 41, pP110 exhibited a superior ability to promote glycogen clearance from the heart as

compared to Actus 101 and pP113—a marked reduction of glyocen levels are observed in the heart following administration of pP110. A greater reduction of glycogen was observed when the pP110 was administered at a dose of 3E11 as compared to an administration of 3E10, confirming that this effect is dosage dependent.

Example 3: Comparison of the M4 construct and Actus 101

[00587] Study Objective: The primary objective of this study presented herein in this example is to evaluate a series of gene therapy vector variants for tissue biodistribution and expression of human acid glucosidase alpha (GAA) in a mouse model of Pompe Disease. The following vectors ACTUS 101 (lot AB20210329) and M4 dbp (lot AB20210412) were included in this study.

[00588] Background: ACTUS-101 (AAV2/8-LSPhGAA) is an infectious non-replicating recombinant adeno-associated viral vector (AAV) serotype 8, pseudotyped with AAV2 inverted terminal repeats (ITR), expressing human GAA under the control of a liver specific promoter (LSP). The GAA has an amino acid composition that is the same as in the FDA approved Enzyme Replacement Therapy Myozyme/Lumizyme for the treatment of Pompe Disease

[00589] This study compares Modification 4 (M4) vector to ACTUS-101. The specific elements that were removed include all Cytosine-phosphate-Guanine (CpG) dinucleotides found within the protein coding sequence, and a remnant fragment of the AAV P5 promoter located upstream of the LSP promoter. M4 also includes an RNA polymerase II termination sequence between the poly(A) signal and the 3'ITR to prevent the potential formation of the double stranded RNA.

[00590] An additional change includes the use of synthetic doggy bone DNA (dbDNA™) as a starting material for the manufacturing of the gene therapy vector, eliminating the bacterial backbone and thus minimizing the ability of the product to trigger Toll-like receptor 9 (TLR9) responses.

[00591] The M4 vector in this study uses the same AAV8 capsid as in ACTUS-101 and is made using the doggy bone precursor plasmid (dbp).

Table 7: Study design:

Mouse strain	**GAA -/- mice, JAX strain 004154, B6;129-Gaa<tm1Rabn>/J**
Sex	Male
Age	7-12 weeks
Mice per vector	N=4-8
Doses per vector	3e10 vg/mouse Low 3e11 vg/mouse High
Injection Volume	150 ul
Route of Administration	tail vein injection

Necropsy	21 days post-injection (3-week sacrifice) and 56 days post-injection (8-week sacrifice)
Number of vectors	2
Post-harvest analysis	GAA expression in sera, GAA activity in sera, GAA uptake by target tissues, GAA activity in target tissues, glycogen reduction in target tissues

Table 8: Treatment groups:

Group	Vector	Number of mice
		3e11*
1	SALINE	4
2	ACTUS 101	4
3	M4 dbp	4
4	M4 dbp	4

*Vector doses in vector genomes/mouse

[00592] Postharvest analysis: GAA expression in sera over time by western blotting and semi-quantitative densitometry; GAA uptake by target organs (heart, diaphragm) by western blotting and semi-quantitative densitometry, GAA enzymatic activity in sera over time by 4MU assay; GAA enzymatic activity in liver by 4MU assay; GAA uptake by select tissues (heart, diaphragm) by 4MU assays; glycogen content in select tissues (heart, diaphragm).

[00593] Materials and Methods

[00594] Cloning and vector quantification: All vectors were made using methods as described in Example 1. The constructs were packaged in the AAV8 viral capsid and titered by digital droplet PCR (ddPCR) method using primers directed at vector ITRs.

[00595] Tissue preservation: Fresh tissue and sera specimens were immediately frozen and stored at -80°C until use for molecular biology analyses.

[00596] Analysis of GAA protein levels in tissues by Western Blot and Densitometry: Tissues were homogenized in T-PER buffer (ThermoFisher 78510) with Halt Protease Inhibitor Cocktail (Thermo 78430) in TissueLyser and protein was quantified by BCA assay. Samples were diluted in T-PER buffer (ThermoFisher 78510) and 2X sample buffer (Sigma S3401), heated at 95 degrees C for 5 minutes and 50µg protein was loaded onto Novex Wedge Well 4-12% Tris/Glycine gel (Invitrogen LC2675), run at 225V for 40 minutes using Tris Glycine Running buffer (ThermoFisher) and transferred onto iBlot2 NC Mini Stacks (Thermo IB23002) using the P0 program (20 V 1 min, 23V 4 min, 25V 2 min). Membranes were washed in PBST and stained with Ponceau S stain (Sigma P7170) for 5 minutes followed by washing 3X with distilled water. Membranes were imaged on iBright imager (FL15000) using the Ponceau S setting and destained using 0.1M NaOH for 30 sec followed

by rinsing the membrane with water for 2-3 minutes. Blocking was done in Superblock (TBS) blocking solution (ThermoFisher 37536) for 1 hour at room temperature. Acid-α-glucosidase (GAA) protein detection was obtained after incubation overnight at 4°C with a rabbit anti-GAA antibody (AbCam 137068) diluted 1:8000 in PBS 0.05% tween 20, followed by a goat anti-rabbit HRP conjugated antibody (Abcam ab205718) diluted 1:10000. The HRP enzyme activity was detected by Clarity Enhanced Chemiluminescence (ECL) Western Blotting Substrate (BioRad 1705061). The images were acquired by iBright imaging system, densitometry was performed on iBright software v. 4.0.1 and results were expressed as relative calculation (ratio) of the intensity of GAA antibody detected band per total protein by Ponceau S staining. For liver samples, rhGAA was run as a standard curve for absolute quantification.

[00597] Measurement of GAA secretable protein levels in blood by Western Blot (WB) and Densitometry: Fresh blood samples obtained from submandibular bleed were centrifuged and serum collected. 1.5 ul serum was diluted in 18.5 ul T- PER buffer (ThermoFisher 78510) and 20 ul 2X sample buffer (Sigma S3401) and heated at 95 degrees C for 5 minutes. Samples (40µl) were run onto Novex Wedge Well 4-12% Tris/Glycine gel (Invitrogen LC2675) at 225V for 40 minutes using Tris Glycine Running buffer (ThermoFisher) and transferred onto iBlot2 NC Mini Stacks (Thermo IB23002) using the P0 program (20 V 1 min, 23V 4 min, 25V 2 min). Membranes were washed in PBST and stained with Ponceau S stain (Sigma P7170) for 5 minutes followed by washing 3X with distilled water. Membranes were imaged on iBright imager (FL15000) using the Ponceau S setting and destained using 0.1M NaOH for 30 sec followed by rinsing the membrane with water for 2-3 minutes. Blocking was done in Superblock (TBS) blocking solution (ThermoFisher 37536) for 1 hour at room temperature. Acid-α-glucosidase (GAA) protein detection was obtained after incubation overnight at 4°C with a rabbit anti-GAA antibody (AbCam 137068) diluted 1:8000 in PBS 0.05% tween 20, followed by a goat anti-rabbit HRP conjugated antibody (Abcam ab205718) diluted 1:10000. The HRP enzyme activity was detected by Clarity Enhanced Chemiluminescence (ECL) Western Blotting Substrate (BioRad 1705061). The images were acquired by the image analyzer iBright imaging system, densitometry was performed on iBright software v. 4.0.1 and results were given by relative calculation (ratio) of the intensity of GAA antibody detected band per total protein by Ponceau S staining.

[00598] GAA activity measurement in tissues: GAA activity was measured on frozen tissues following homogenization and sonication of tissue samples in distilled water. Depending upon the tissue size, 10-50 mg tissue was weighed and homogenized, the homogenates were sonicated at 4 degree C 3 times for 15 seconds, then centrifuged for 3 min at 15000 RPM. For serum GAA, 10 ul was analyzed, with or without 80 µM acarbose. The reaction was set up with 10ul of supernatant and 20 ul of substrate - 4MUα-D-glucoside, in a 96 wells plate (VWR62402-970). The reaction mixture was incubated at 37 degrees C for one hour and was stopped by adding 130ul of Sodium Carbonate buffer pH10.5. A standard curve (0- 1000 pmol/ ul of 4MU) was used to measure released fluorescent

4MU from individual reaction mixture, using TECAN GENios microplate reader at 465 nm (Emission) and 360 nm (excitation). The protein concentrations of the clarified supernatants were quantified via the Bradford assay (Bio-Rad Laboratories, Cat No. 500-0006). GAA activity was measured in the tissue homogenates by conversion of the artificial substrate 4-methylumbelliferyl (4-MU) α-D-glucoside to the fluorescent product umbelliferone at acidic pH 4.3 as described [1]. To calculate the GAA activity, released 4MU concentration was divided by the sample protein concentration and activity was reported as nmol/hour/mg protein. QA and QC samples were run on the same plate for experimental assay controls.

[00599] GAA activity measurement in serum: Fresh blood samples obtained from submandibular bleed were centrifuged and serum collected. 10 ul of serum was treated 2ul of 800 μM acarbose. The reaction was set up with 10ul of supernatant and 20 ul of substrate - 4MUα-D-glucoside, in a 96 wells plate (VWR62402-970). The reaction mixture was incubated at 37 degrees C for one hour and was stopped by adding 130ul of Sodium Carbonate buffer pH10.5. A standard curve of rhGAA (R&D Systems, Cat. No 8329-GH) Standards, 2,000 ng/mL to 25 ng/mL was used. Released fluorescent 4MU from individual reaction mixture was measured using BioTek FLx800 Reader, Excitation filter = 360/40 and Emission filter = 460/40. GAA activity was determined by interpolation to the standard curve with a 4-parameter curve fit model and activity was reported as ng/ml.

[00600] GAA activity measurement in serum- alternative method: GAA, 10 ul was analyzed, with or without 80 μM acarbose. The reaction was set up with 10ul of supernatant and 20 ul of substrate - 4MUα-D-glucoside, in a 96 wells plate (VWR62402-970). The reaction mixture was incubated at 37 degrees C for one hour and was stopped by adding 130ul of Sodium Carbonate buffer pH10.5. A standard curve (0- 1000 pmol/ ul of 4MU) was used to measure released fluorescent 4MU from individual reaction mixture, using TECAN GENios microplate reader at 465 nm (Emission) and 360 nm (excitation). The protein concentrations of the clarified supernatants were quantified via the Bradford assay (Bio-Rad Laboratories, Cat No. 500-0006). GAA activity was measured in the tissue homogenates by conversion of the artificial substrate 4-methylumbelliferyl (4-MU) α-D-glucoside to the fluorescent product umbelliferone at acidic pH 4.3 as described [1]. To calculate the GAA activity, released 4MU concentration was divided by the sample protein concentration and activity was reported as nmol/hour/mg protein. A QA and QC samples were run on the same plate for experimental assay controls.

[00601] Glycogen content: Glycogen content of tissues was measured indirectly as the glucose released after total digestion by amyloglucosidase of the tissue homogenates using the Aspergillus niger assay system and the glucose reagent (Infinity Glucose; TR15421, Thermo Scientific, VA, USA) in a standardized reaction using the Aspergillus niger assay system. The same tissue homogenates used above were used to measure total glycogen content in each tissue. The reaction was set up with 20ul of supernatant and 55ul distilled water. Samples were boiled for 3 min and immediately cooled on ice for 10 min. 25 ul of amyloglucosidase (1:50 in 0.1M potassium acetate

pH5.5) was added to each reaction tube. A reaction control tube without any amyloglucosidase (homogenate + water) was also set up for each reaction tube. Both sample tube and control sample reaction tubes were incubated at 37 degrees C for 90 minutes and reaction, was stopped by boiling the tubes for 3min followed by centrifugation for 3 min at 15000 RPM. The glucose released from each reaction tube was determined by adding 30 ul of supernatant into 1ml of Infinity glucose reagent (TR15421) and measuring on spectrophotometer at 340nm (Shimadzu UV-1700).

[00602] Observations:

[00603] Expression of GAA protein levels in serum was markedly higher in mice that were administered the M4 construct as compared to those administered Actus 101. This was observed at 3 weeks and 8 weeks post administration (FIGs 6A-6C and 10A-10H, respectively). This increased level of GAA protein following administration of M4 translated to a marked increase in GAA activity present in the serum in mice; increased GAA activity was observed at 3 weeks and 8 weeks post administration (FIGs 7A-7C and 11A-11H, respectively). Similar results were additionally observed in numerous target tissues. Increased GAA protein levels and GAA activity were observed in the heart, diaphragm and liver at 3 weeks post administration and up to 8 weeks post administration (see FIGs 8A-8C, 12A-12C and 13A-13C, respectively).

[00604] Finally, as shown in FIGs 14A-14C, a significant dose dependent reduction in glycogen was observed following administration of low and high doses of the M4 construct as compared to Actus 101. This dose dependent reduction was observed in various target tissues, including the heart, diaphragm and liver 8 weeks post administration with either a high or low dose of the M4 construct.

[00605] Accordingly, the data presented herein in this Example indicates that the M4 construct out performs Actus 101 with regards to increasing GAA protein levels and activity that can be sustained over a long period of time (e.g., more than 8 weeks) and that was capable of inducing glycogen clearance in the cell.

Example 4: Comparison of the various M4 constructs

[00606] Numerous M4 constructs having different codon-optimized GAA sequences have been developed and tested for their ability to induce superior levels of GAA protein and activity, as well as their ability to promote glycogen clearance in the cell. Four M4 constructs, i.e., Seq12 (SEQ ID NO: 30), Seq99 (SEQ ID NO: 29), Seq3 (SEQ ID NO:28), and Seq100 (SEQ ID NO: 27), which comprise codon optimized nucleic acid sequences: SEQ ID NO:7 (Seq12), SEQ ID NO:13, (Seq99), SEQ ID NO: 3 (Seq100) and SEQ ID NO: 4 (Seq3), respectively, which encode a GAA polypeptide of SEQ ID NO: 1, were selected for further study, as being identified as being best in class, and data provided herein this example shows the comparison of these constructs.

[00607] All vectors were made at AskBio RTP using proprietary Pro10 cell production system, e.g., as described in US patent 9,441,206, the contents of which are incorporated herein by reference in its

entirety. The constructs were packaged in the AAV8 viral capsid and titered by digital droplet PCR (ddPCR) method using primers directed at vector ITRs.

[00608] All assays and analysis were performed as described herein in Example 2.

[00609] Observations: As shown in FIG 22, expression of GAA in serum driven from the Seq100 construct was markedly higher at days 7, 14 and 21 post administration as compared to the Actus 101 and the other M4 constructs (i.e., Seq12, Seq99, and Seq3). It was further noted that not all M4 constructs were capable of driving sustainable GAA levels in a similar manner; Seq12, Seq99, Seq3 fail to drive high expression of GAA that was sustained for at least 21 days post administration. Seq100 was additionally found to drive high expression of GAA protein in the liver 21 days post administration, whereas other M4 constructs fail to do so (see FIG. 23). Similarly, increased GAA RNA copy numbers were markedly increased following Seq100 administration as compared to Actus 101 or the other M4 constructs. Accordingly, the data presented herein indicate that Seq100 was a superior M4 construct with regards to driving sustainable, high levels of GAA protein as compared to the other M4 constructs tested.

[00610] To further assess Seq100's capability to drive high levels of GAA protein expression in target tissues, GAA protein levels and activity, as well as glycogen clearance from the cell was assessed. As shown in Fig. 25, GAA protein levels were markedly higher than Actus or other M4 constructs 21 days post administration in the liver, heart and diaphragm. Increased GAA activity levels were similarly observed in the liver, heart and diaphragm in Seq100-administered mice as compared to Actus or other M4 constructs 21 days post administration (see, e.g., FIG 26A). Finally, a significant reduction of glycogen was observed in the liver, heart and diaphragm in Seq100-administered mice as compared to Actus or other M4 constructs 21 days post administration (see, e.g., FIG 26B). Accordingly, the data presented herein indicate that Seq100 (comprising codon optimized nucleic acid sequence of SEQ ID NO: 3) was a superior M4 construct with regards to driving sustainable high levels of GAA protein and activity in target tissues (e.g., liver, heart, and diaphragm) as compared to the other M4 constructs tested.

[00611] The data presented herein in this example show that a specific M4 construct, Seq100, was surprisingly, and unexpectedly superior as compared to the other M4 constructs exemplified herein (i.e., Seq12, Seq99, and Seq3). This indicates that the results presented herein were not due to the presence of a codon optimized GAA sequence, but rather, was due to the specific codon optimized sequence included in the Seq100 construct, which is SEQ ID NO: 3.

[00612] Further, as shown herein in FIG. 42, the M4 variants p065 and p072 showed a greater reduction in glyocogen present in the heart as compared to M4 following administration. This result was found to be dosage dependent; a greater reduction in glyocogen in the heart was observed at a dose of 3E11 as compared to 3E10 for both p065 and p072.

Example 5: Constructs encoding a GAA-signal peptide, a heterologous signal peptide, and a GAA polypeptide

[00613] Numerous constructs comprising a GAA-signal peptide, or a fragment thereof, a heterologous signal peptide, and a GAA polypeptide were generated. Exemplary constructs generated are described in Table 10 herein. In particular, SEQ ID NO: 463 and 464 are exemplary plasmids (pP112 and pP113, respectively) where pP112 , (see, e.g., Fig. 29) is a plasmid comprising in the 5' to 3' direction: [ITR]-LSP-[1-27aa GAA-SP]-[201lp]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO: 1]-[3'UTR]-[hGH polyA]-ITR2, and pP113 (see, e.g., Fig. 29) is a plasmid comprising in a 5' to 3' direction: [ITR]-LSP-[1-24aa GAA-SP]-met-[201lp]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO: 1]-[3'UTR]-[hGH polyA]-ITR2. The nucleic acid encoding the N-terminal truncated GAA polypeptide in pP112 and pP113 can be readily substituted for any nucleic acid sequence encoding a GAA polypeptide, including codon optimized nucleic acid sequences: SEQ ID NO:7 (Seq12), SEQ ID NO:13, (Seq99), SEQ ID NO: 3 (Seq100) and SEQ ID NO: 4 (Seq3), as well as 5' deletions thereof, such that the nucleic acid sequences encode for a N-terminal truncated GAA polypeptide beginning at amino acid residues selected from any of: 28, 35, 40, 50, 57, 57, 68, 69, 70, 72, 74, 89, 779, 790, 791, 792, 793 or 796. Similarly, the 201lp (having an amino acid sequence of: MEFGLSWVFLVALLKGVQCE (SEQ ID NO: 60) encoded by nucleic acid sequence SEQ ID NO: 54) is an exemplary heterologous signal peptide included in plasmids pP112 and pP113, and can be readily substituted for other heterologous leader peptide disclosed herein, e.g., any of: wtIL2 lp: MYRMQLLSCIALSLALVTNS (SEQ ID NO: 61) encoded by nucleic acid sequence SEQ ID NO: 55, or mutIL2 lp: MYRMQLL***LLI***ALSLALVTNS (SEQ ID NO: 62) encoded by nucleic acid sequence SEQ ID NO: 56, A2M signal peptide MGKNKLLHPSLVLLLLVLLPTDA (SEQ ID NO: 63) encoded by nucleic acid sequence SEQ ID NO: 57, PZP signal peptide MRKDRLLHLCLVLLLILLSASDSNS (SEQ ID NO: 64) encoded by nucleic acid sequence SEQ ID NO: 58.

[00614] rAAV vectors were generated using the Pro10 cell production system, e.g., as described in US patent 9,441,206, the contents of which are incorporated herein by reference in its entirety. The constructs were packaged in the AAV8 viral capsid and tittered by digital droplet PCR (ddPCR) method using primers directed at vector ITRs. All assays and analysis were performed as described herein in Example 3.

[00615] Analysis and Observations: pP112 and pP113 were used to generate infectious non-replicating recombinant adeno-associated viral vector (AAV) serotype 8, pseudotyped with AAV2 inverted terminal repeats (ITR), expressing human GAA under the control of a liver specific promoter (LSP), where there is a GAA-signal peptide (or 1-24 amino acid portion of the GAA-signal peptide and a heterologous 201lp signal peptide to promote expression of the GAA polypeptide, and where the GAA polypeptide is a N-terminal truncated protein beginning at amino acid 57 of SEQ ID NO:1.

[00616] Male GAA knock-out mice were injected with the generated AAV via a tail vein injection; 5 male mice were included in each group (i.e., control (saline), pP112, pP113). AAV was administered at a dose of $1x10^6$ in a total volume of 150ul. Weekly bleeds were performed on the mice for 4 weeks. Each mouse was then sacrificed at 4 weeks, and serum and target tissue was removed for anaylsis.

[00617] Expression of GAA in serum was assessed 4 weeks post administration of rAAV generated from pP112 and pP113 plasmids. After 4 weeks, the animals were sacrificed and tissue was harvested. GAA expression was assessed in sera over time by western blotting (Figure 30) and semi-quantitative densitometry (Figure 31). GAA uptake by the liver was also assessed by western blotting (Figure 35A) and semi-quantitative densitometry (Figure 35B). GAA enzymatic activity in sera, and heart over time was assessed by 4MU assay (Figures 32 and 33). Glycogen content was also assessed in the heart (Figure 34), as described in Example 3.

[00618] rAAV encoding GAA polypeptide comprising both a N-terminal endogenous GAA signal peptide or a fragment thereof, and a heterologous 201lp signal peptide promoted GAA expression in the serum (Figures 30 and 31), and increased GAA activity in the serum and target tissues (e.g., heart) (Figures 32 and 33). A reduction of glycogen levels in the heart as compared a rAAV encoding a GAA polypeptide comprising only a N-terminal heterologous signal peptide was also observed (Figure 34). Finally, a reduction in GAA retention in the liver was noted 4 weeks following administration of the rAAV (Figures 35A and 35B).

Example 6: Constructs encoding a GAA-signal peptide, a heterologous signal peptide, and a GAA polypeptide

[00619] pP112 and pP113 are used to generate infectious non-replicating recombinant adeno-associated viral vector (AAV) serotype 8, pseudotyped with AAV2 inverted terminal repeats (ITR), expressing human GAA under the control of a liver specific promoter (LSP), where there is a GAA-signal peptide (or 1-24 amino acid portion of the GAA-signal peptide and a heterologous 201lp signal peptide to promote expression of the GAA polypeptide, and where the GAA polypeptide is a N-terminal truncated protein beginning at amino acid 57 of SEQ ID NO:1, as described in Example 5.

[00620] Male GAA knock-out mice are injected with the generated AAV via a tail vein injection; 5 male mice are included in each group (i.e., control (saline), pP112, pP113), as described in Example 5. AAV is administered at a dose of $1x10^6$ in a total volume of 150ul. Weekly bleeds are performed on the mice for 12 weeks. Each mouse is then sacrificed at 12 weeks, and serum and target tissue is removed for anaylsis.

[00621] Expression of GAA in serum is assessed 12-weeks after administration of rAAV generated from pP112 and pP113 plasmids. After 12 weeks, the animals are sacrificed and tissue harvested, and GAA expression in sera over time by western blotting and semi-quantitative densitometry is assessed, as well as GAA uptake by target organs (heart, diaphragm) by western blotting and semi-quantitative densitometry. GAA enzymatic activity in sera over time is assessed by 4MU assay; and GAA

enzymatic activity in liver is assessed by 4MU assay; GAA uptake by select tissues (heart, diaphragm) is assessed by 4MU assays; glycogen content in select tissues (heart, diaphragm) is also assessed, as described in Example 3.

[00622] rAAV encoding GAA polypeptide comprising both a N-terminal endogenous GAA signal peptide or a fragment thereof, and a heterologous 201lp signal peptide promotes GAA expression in the serum, and increases GAA activity in the serum and target tissues (e.g., heart). A reduction of glycogen levels in the heart as compared a rAAV encoding a GAA polypeptide comprising only a N-terminal heterologous signal peptide is also observed. Finally, a reduction in GAA retention in the liver is noted 12 weeks following administration of the rAAV with p113 compared to p112.

Example 7: Constructs encoding a GAA-signal peptide, a heterologous signal peptide, and a GAA polypeptide

[00623] Numerous constructs comprising a GAA-signal peptide, or a fragment thereof, a heterologous signal peptide, and a GAA polypeptide, are modified to include an optimized liver-specific promoter. Exemplary constructs that are modified are described in Table 10 herein. For example, the liver-specific promoter (LSP) described in SEQ ID NO: 463 and 464 is swapped with the SP0412 promoter (SEQ ID NO: 91) to enhance the expression of the construct in the liver. For example, such modified exemplary plasmids sequences would include a plasmid comprising in the 5' to 3' direction: [ITR]-SP0412-[1-27aa GAA-SP]-[201lp]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO: 1]-[3'UTR]-[hGH polyA]-ITR2 (i.e., a modified pP112), and a plasmid comprising in a 5' to 3' direction: [ITR]-SP0412-[1-24aa GAA-SP]-met-[201lp]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO: 1]-[3'UTR]-[hGH polyA]-ITR2 (i.e., a modified pP113). The nucleic acid encoding the N-terminal truncated GAA polypeptide in pP112 and pP113 can be readily substituted for any nucleic acid sequence encoding a GAA polypeptide, including codon optimized nucleic acid sequences: SEQ ID NO:7 (Seq12), SEQ ID NO:13, (Seq99), SEQ ID NO: 3 (Seq100) and SEQ ID NO: 4 (Seq3), as well as 5' deletions thereof, such that the nucleic acid sequences encode for a N-terminal truncated GAA polypeptide beginning at amino acid residues selected from any of: 28, 35, 40, 50, 57, 57, 68, 69, 70, 72, 74, 89, 779, 790, 791, 792, 793 or 796. Similarly, the 201lp (having an amino acid sequence of: MEFGLSWVFLVALLKGVQCE (SEQ ID NO: 60) encoded by nucleic acid sequence SEQ ID NO: 54) is an exemplary heterologous signal peptide included in plasmids pP112 and pP113, and can be readily substituted for other heterologous leader peptide disclosed herein, e.g., any of: wtIL2 lp: MYRMQLLSCIALSLALVTNS (SEQ ID NO: 61) encoded by nucleic acid sequence SEQ ID NO: 55, or mutIL2 lp: MYRMQLL***LLI***ALSLALVTNS (SEQ ID NO: 62) encoded by nucleic acid sequence SEQ ID NO: 56, A2M signal peptide MGKNKLLHPSLVLLLLVLLPTDA (SEQ ID NO: 63) encoded by nucleic acid sequence SEQ ID NO: 57, PZP signal peptide MRKDRLLHLCLVLLLILLSASDSNS (SEQ ID NO: 64) encoded by nucleic acid sequence SEQ ID NO: 58.

[00624] Modified plasmids described in this Example are used to generate infectious non-replicating recombinant adeno-associated viral vector (AAV) serotype 8, pseudotyped with AAV2 inverted terminal repeats (ITR), expressing human GAA under the control of the SP0412 promoter, where there is a GAA-signal peptide (or 1-24 amino acid portion of the GAA-signal peptide and a heterologous 201lp signal peptide to promote expression of the GAA polypeptide, and where the GAA polypeptide is a N-terminal truncated protein beginning at amino acid 57 of SEQ ID NO:1, as described in Example 5.

[00625] Male GAA knock-out mice are injected with the generated AAV via a tail vein injection as descibred in Example 5. Expression of GAA in serum is assessed 4 weeks after administration of rAAV generated from modified plasmids. After 4 weeks, the animals are sacrificed and tissue harvested, and GAA expression in sera over time by western blotting and semi-quantitative densitometry is assessed, as well as GAA uptake by target organs (heart, diaphragm) by western blotting and semi-quantitative densitometry. GAA enzymatic activity in sera over time is assessed by 4MU assay; and GAA enzymatic activity in liver is assessed by 4MU assay; GAA uptake by select tissues (heart, diaphragm) is assessed by 4MU assays; glycogen content in select tissues (heart, diaphragm) is also assessed, as described in Example 3.

[00626] rAAV encoding GAA polypeptide comprising both a N-terminal endogenous GAA signal peptide or a fragment thereof, and a heterologous 201lp signal peptide promotes GAA expression in the serum, and increases GAA activity in the serum and target tissues (e.g., heart). A reduction of glycogen levels in the heart as compared a rAAV encoding a GAA polypeptide comprising only a N-terminal heterologous signal peptide is also observed. Finally, a reduction in GAA retention in the liver is noted 4 weeks following administration of the rAAV with modified p113 compared to p112.

Example 8: Constructs encoding a 5'UTR with intron, GAA-signal peptide, a heterologous signal peptide, and a GAA polypeptide

[00627] Numerous constructs comprising a fragment of the GAA-signal peptide, a heterologous signal peptide, and a GAA polypeptide are modified to include a 5'UTR+intron sequence upstream of the GAA sequence. In particular, constructs P072 and P092 (see, e.g., Table 10) are modified to include three changes, generating mod-P072 and mod-P092, respectively.

[00628] First, the 5'UTR of P072 and P092 is replaced with a 5'UTR comprising an intron sequence. Second, the 3'UTR of P072 and P092 is removed. And third, a bi-directional polyA sequence is added immediately following the hGH polyA sequence of P072 and P092. Accordingly, mod-P072 is a construct comprising in the 5' to 3' direction: [ITR]-LSP-[5'UTR+intron]-[1-24aa GAA-SP]-[Signal Peptide]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO: 1]-[hGH polyA]-[Bi-directional polyA]-[ITR2]. Mod-P092 is a construct comprising in the 5' to 3' direction: [ITR]-LSP-[5'UTR+intron]-[1-27aa GAA-SP]-[Signal Peptide]-[GAA polypeptide starting at amino acid 57 of SEQ ID NO: 1]-[hGH polyA]-[Bi-directional polyA]-[ITR2] (FIG. 37)

[00629] Further, the Actus construct is modified to remove residual wtAAV DNA sequences immediately 5' and 3' to the ITRs, generating the mod-Actus construct. Such removal of residual wtAAV DNA avoids homologous recombination between the Rep and Cap plasmid used in generating rcAAV. mod-P072 and mod-P092 constructs are also modified to remove the residual wtAAV DNA immediately 5' and 3' to the ITRs. (FIG. 37)

[00630] Modified plasmids described in this Example, i.e., mod-Actus, mod-P072 and mod-P092, are used to generate infectious non-replicating recombinant adeno-associated viral vector (AAV) serotype 8, pseudotyped with AAV2 inverted terminal repeats (ITR), expressing human GAA under the control of the LSP promoter, where there is a GAA-signal peptide (or a 1-24 amino acid or a 1-27 amino acid portion of the GAA-signal peptide) and a heterologous signal peptide to promote expression of the GAA polypeptide, and where the GAA polypeptide is a N-terminal truncated protein beginning at amino acid 57 of SEQ ID NO:1, as described in Example 5.

[00631] The generated AAV viruses are used to infect Huh7 cells to assess their efficacy. 6-well culture dishes comprising a population of seeded Huh7 cells are infected at an MOI of $1E^6$ vg/cell. 48 hours post infection, cell lysates and cell supernatants are obtained from the culture. GAA enzymatic activity is measured in the cell lysate (i.e., nmol/hr/mg protein) and supernatant (i.e., nmol/hr/ml). AAV viruses generated from the mod-Actus construct display the highest GAA enzymatic activity in the cell, and AAV viruses generated from the mod-P072 construct yield the highest level of GAA secretion into the supernatant (FIGs 38A and 38B).

[00632] To assess the efficacy of the AAVs *in vivo*, male and female wild-type mice (C57BL/6J) are injected with the generated AAV via a tail vein injection. Each virus is administered at a low dose ($3E^{10}$), mid-level dose ($6E^{10}$), and high dose ($3E^{11}$) per mouse in a 150µl total volume. GAA expression levels and activity are assessed in sera weekly for 4 weeks following administration. After 4 weeks, the animals are sacrificed and tissue harvested, and GAA expression in sera over time by western blotting and semi-quantitative densitometry is assessed, as well as GAA uptake by target organs (heart, quadriceps muscle) by western blotting and semi-quantitative densitometry. GAA enzymatic activity in sera over time is assessed by 4MU assay; GAA enzymatic activity in liver is assessed by 4MU assay; and GAA uptake by select tissues (heart, quadriceps muscle) is assessed by 4MU assays.

[00633] Consistent with the *in vitro* data, rAAVs expressing the 1-24 amino acid portion of the GAA-signal peptide, a 5'UTR+intron, and a bi-directional polyA (i.e., generated by the mod-P072 construct) exhibit the highest level of GAA in the serum of male and female mice (FIG. 39A-39C).

[00634] To assess what tissues express the modified rAAVs described herein in this example, liver, heart, and quadriceps tissue are assessed for GAA levels following administration. rAAVs expressing the full length GAA signal peptide (i.e., generated by the mod-Actus construct) exhibit the highest expression level of GAA in the liver *in vivo* at a high dose (FIG. 40A), whereas rAAVs expressing the 1-24 amino acid portion of the GAA-signal peptide, a 5'UTR+intron, and a bi-directional polyA (i.e.,

generated by the mod-P072 construct) exhibits the highest level of GAA uptake in the heart and quadriceps muscle at a high dose (FIG. 40B and 40C).

[00635] Further mod-Actus AAV exhibits the highest expression level of GAA in the liver at low and mid-level doses, as compared to mod-P072 and mod-P092 AAVs, indicating that GAA is retained in the liver at a higher rate. Mod-P072 AAV exhibits a higher GAA activity in the heart, as compared to mod-Actus and mod-P092, indicating that mod-P072 AAV has a greater uptake in the heart. Mod-Actus and mod-P072 AAVs exhibit a higher GAA activity in the quadriceps muscle as, compared to mod-P092.

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[00636] While the present inventions have been described and illustrated in conjunction with a number of specific embodiments, those skilled in the art will appreciate that variations and modifications may be made without departing from the principles of the inventions as herein illustrated, as described and claimed. The present inventions may be embodied in other specific forms without departing from their spirit or essential characteristics. The described embodiments are considered in all respects to be illustrative and not restrictive.

[00637] In closing, regarding the exemplary embodiments of the present invention as shown and described herein, it will be appreciated that a genomic construct, comprising an AAV (adeno-associated virus) viral virion is disclosed and configured for delivery of AAV vectors. Because the principles of the invention may be practiced in a number of configurations beyond those shown and described, it is to be understood that the invention is not in any way limited by the exemplary embodiments, but is generally directed to a genomic construct, comprising an AAV (adeno-associated virus) viral virion apparatus and is able to take numerous forms to do so without departing from the spirit and scope of the invention.

[00638] Certain embodiments of the present invention are described herein, including the best mode known to the inventor(s) for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor(s) expect skilled artisans to employ such variations as appropriate, and the inventor(s) intend for the present invention to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described embodiments in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[00639] Groupings of alternative embodiments, elements, or steps of the present invention are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other group members disclosed herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[00640] Unless otherwise indicated, all numbers expressing a characteristic, item, quantity, parameter, property, term, and so forth used in the present specification and claims are to be understood as being modified in all instances by the term "about." As used herein, the term "about" means that the characteristic, item, quantity, parameter, property, or term so qualified encompasses a range of plus or

minus ten percent above and below the value of the stated characteristic, item, quantity, parameter, property, or term. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical indication should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and values setting forth the broad scope of the invention are approximations, the numerical ranges and values set forth in the specific examples are reported as precisely as possible. Any numerical range or value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Recitation of numerical ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate numerical value falling within the range. Unless otherwise indicated herein, each individual value of a numerical range is incorporated into the present specification as if it were individually recited herein. Similarly, as used herein, unless indicated to the contrary, the term "substantially" is a term of degree intended to indicate an approximation of the characteristic, item, quantity, parameter, property, or term so qualified, encompassing a range that can be understood and construed by those of ordinary skill in the art.

[00641] Use of the terms "may" or "can" in reference to an embodiment or aspect of an embodiment also carries with it the alternative meaning of "may not" or "cannot." As such, if the present specification discloses that an embodiment or an aspect of an embodiment may be or can be included as part of the inventive subject matter, then the negative limitation or exclusionary proviso is also explicitly meant, meaning that an embodiment or an aspect of an embodiment may not be or cannot be included as part of the inventive subject matter. In a similar manner, use of the term "optionally" in reference to an embodiment or aspect of an embodiment means that such embodiment or aspect of the embodiment may be included as part of the inventive subject matter or may not be included as part of the inventive subject matter. Whether such a negative limitation or exclusionary proviso applies will be based on whether the negative limitation or exclusionary proviso is recited in the claimed subject matter.

[00642] When used in the claims, whether as filed or added per amendment, the open-ended transitional term "comprising" (along with equivalent open-ended transitional phrases thereof such as "including," "containing" and "having") encompasses all the expressly recited elements, limitations, steps and/or features alone or in combination with un-recited subject matter; the named elements, limitations and/or features are essential, but other unnamed elements, limitations and/or features may be added and still form a construct within the scope of the claim. Specific embodiments disclosed herein may be further limited in the claims using the closed-ended transitional phrases "consisting of" or "consisting essentially of" in lieu of or as an amendment for "comprising." When used in the claims, whether as filed or added per amendment, the closed-ended transitional phrase "consisting of"

excludes any element, limitation, step, or feature not expressly recited in the claims. The closed-ended transitional phrase "consisting essentially of" limits the scope of a claim to the expressly recited elements, limitations, steps and/or features and any other elements, limitations, steps and/or features that do not materially affect the basic and novel characteristic(s) of the claimed subject matter. Thus, the meaning of the open-ended transitional phrase "comprising" is being defined as encompassing all the specifically recited elements, limitations, steps and/or features as well as any optional, additional unspecified ones. The meaning of the closed-ended transitional phrase "consisting of" is being defined as only including those elements, limitations, steps and/or features specifically recited in the claim, whereas the meaning of the closed-ended transitional phrase "consisting essentially of" is being defined as only including those elements, limitations, steps and/or features specifically recited in the claim and those elements, limitations, steps and/or features that do not materially affect the basic and novel characteristic(s) of the claimed subject matter. Therefore, the open-ended transitional phrase "comprising" (along with equivalent open-ended transitional phrases thereof) includes within its meaning, as a limiting case, claimed subject matter specified by the closed-ended transitional phrases "consisting of" or "consisting essentially of." As such, embodiments described herein or so claimed with the phrase "comprising" are expressly or inherently unambiguously described, enabled and supported herein for the phrases "consisting essentially of" and "consisting of."

[00643] While aspects of the invention have been described with reference to at least one exemplary embodiment, it is to be clearly understood by those skilled in the art that the invention is not limited thereto. Rather, the scope of the invention is to be interpreted only in conjunction with the appended claims and it is made clear, here, that the inventor(s) believe that the claimed subject matter is the invention.

[00644] The references disclosed in the specification and Examples, including but not limited to patents and patent applications, and international patent applications are all incorporated herein in their entirety by reference.

[00645] All patents, patent publications, and other publications referenced and identified in the present specification are individually and expressly incorporated herein by reference in their entirety for the purpose of describing and disclosing, for example, the compositions and methodologies described in such publications that might be used in connection with the present invention. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

SEQUENCES

Table 9:

SEQ ID NO:	SEQUENCE
1	>GAA polypeptide | ACTUS101 MGVRHPPCSHRLLAVCALVSLATAALLGHILLHDFLLVPRELSGSSPVLEETHPAHQQGASRPGPRDAQAHPGRPRAVPTQCDVPPNSRFDCAPDKAITQEQCEARGCCYIPAKQGLQGAQMGQPWCFFPPSYPSYKLENLSSSE MGYTATLTRTTPTFFPKDILTLRLDVMMETENRLHFTIKDPANRRYEVPLETPRVHSRAPSPLYSVEFSEEPFGVIVHRQLDGRVLLNTTVAPLFFADQFLQLSTSLPSQYITGLAEHLSPLMLSTSWTRITLWNRDLAPTPGAN LYGSHPFYLALEDGGSAHGVFLLNSNAMDVVLQPSPALSWRSTGGILDVYIFLGPEPKSVVQQYLDVVGYPFMPPYWGLGFHLCRWGYSSTAITRQVVENMTRAHFPLDVQWNDLDYMDSRRDFTFNKDGFRDFPAMVQELHQGG RRYMMIVDPAISSSGPAGSYRPYDEGLRRGVFITNETGQPLIGKVWPGSTAFPDFTNPTALAWWEDMVAEFHDQVPFDCMWIDMNEPSNFTRGSEDGCPNNELENPPYVPGVVGGTLQAATICASSHQFLSTHYNLHNLYGLTEA TASHRALVKARGTRPFVISRSTFAGHGRYAGHWTGDVWSWEQLASSVPEILQFNLLGVPLVGADVCGFLGNTSEELCVRWTQLGAFYPFMRNHNSLLSLPQEPYSFSEPAQQAMRKALTLRYALLPHLYTLFHQAHVAGETVAR PLFLEFPKDSSTWTVDHQLLWGEALLITPVLQAGKAEVTGYFPLGTWYDLQTVPIEALGSLPPPPAAPREPAIHSEGQWVTLPAPLDTINVHLRAGYIIPLQGPGLTTTESRQQPMALAVALTKGGEARGELFWDDGESLEVLER GAYTQVIFLARNNTIVNELVRVTSEGAGLQLQKVTVLGVATAPQQVLSNGVPVSNFTYSPDTKVLDICVSLLMGEQFLVSWC*.
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4	> coGAA GAA nucleic acid
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5	> coGAA GAA nucleic acid
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6	> coGAA GAA nucleic acid ATGGGGGTGAGGCACCCCCCCTGTTCTCACAGGCTGCTGGCTGTGTGCCCTGGCTACTGCTGCCCTCGTCGGCCACATCCTGCTGGTGCCCAGGGACGTGTCTGGCTCTAGCCCAGTGC TGGAGGAAACCCATCCTGCCCACCAGCAGGGGCCAGCAGGCCTGGCCTCAGGATGCCCAGGCTCATCCTGGGAGCCCAGGCTGTGCCCACCCAGTGTGATGTGCCTCCCAACTCTAGATTGACTGTGCCCTGACAAGGC CATCACTCAGGAGCAGTGTGAGGCCAGGGGTGCTGCTACATCCCTGCCAAGCAGGGGCTGCAGGGGCCCAGATGGCCCACCTTGGTGCTTCTTCCCTCCCCAGCTACCCTCTTACAAGCTGGAGAACCTGAGCAGCTCTGAG ATGGGGTACACTGCTACCCTGACTAGGACCACCCCCACCTTCTCCCTAAGGATATCCTGACCCTGAGACTCAGAACAAGCCTGCACTTCACTATTAAGGACCCTGCTAACAGGAGGTATGAGGTGC CCCTGGAGACCCCCAGGGTGCACAGCAGGGCCCCCAGCCCCCTTGTGGCTGATGTTCTGCCACAGGCAGCTGGCATGCCACCACTGTGGCTCCTCGTTCTTTGC TGACCAGTTCCTGCAGCTGAGCACTAGCCTGCCCAGCCAGTCATGCTGAGCACTAGCATGCCACTGGAACAGGGACCTGGCCCCCACTCCTGGGGCTAAT CTGTATGGCAGCCACCCTTTTACCTGGCCCTGGAGGATGGGGGGTCTGCCCATGGGGTGTTCCTGCTGAACTCTAATGCCATGGATGTGTGGCTGAGTGGAGGACACTGGGGGCATCCTGGATG TGTACATCTTCCTGGGCCCTGAGCCCAAGTATCTGTGGTATGTGGGCTATCCCTTTATGCCCCCCTAITGGGCCTGGGGTTCACCTGTGCAGGTGGGGGTATTCTTCTACTGCCATCACCAGGCAGGT GGTGGAGAAATGACCAGGGCCCACTTCCCCCTGGATGTGCAGTGGAATGACCTGGACATATATGGACAGCAGGAGGCACTTCACTTTCAACAAGATGGTTCAGGACTTCCCTGCTATGGTGCAGGAGCTGCACCAGGGGGGG AGCAGGTACATATGATCATTGTGATCCTGCCCATCTCTAGCTCTGGCCCTCGCTGGCAGCTACAGCCCATATCGATGACCCTCGAGCAGGCGGCGCTGTTCATCACCAATGACATCAATGTGCATCTGAGGCTGGCTA GCACTGCTTTCCCTCGATTTCACCAACCCCACTGCTCTGGCTGGTGGAGGAGCATGGTGGCTGAGTTTCATGATCAGTGCCTTTTGATGGGATTGTGGTCGTTCGCCTCGCCTACTGCATCAGAGGCTCTGAGGATGG CTGTCCCAATAATGAGCTGGAGAACCCCCCCTATGTGCCTCGGGTGGTGGGGGCACCCTGCAGCGTGCTACCATCTGCTAGCTCTCATCAGTTCCTGCAGCACTCACTACAACCTGCACAACCTGTATGGCGTGACTGAGGCT ATTGCCAGCCATAGGCCCTGTGAAGGCCAGAGGCACCTTTGCTGCCATGCCACTGGACTGGGAATGTGTGGAGCAGCTGGGACATGCTGGCCTCTTCTGTGC CTGAGATCCTGCAGTTCAACCTGCTGGGGGTGCCCCTGGTGGAGGCTGTGTGTGAGGTGGACTCACGTCGGGGCTTTTTATCCCTTCATGAGGAACCACAATAGCCT GCTGTCTCTGCCCCAGGAGCCCTATTCTTCTCTGAGCCTGCCCAGCAGGCCATGAGGAAGGCCCTGACTCTGAGGTATGCCTGCTGCCCCACCTGTTACACACCTGTTCCACCAGGCCCATGTGGCCAGG CCCCTGTTTCTGGAGTTCCCTAAGGACAGCTCTACCTGGATCACCAGCTGCTGTGGGGGAGGCCCTGCTGATCACTCCAGTCCTGCAGGCTGGCAAAGCTGAGGTGACTGGCTACTTCCCCCTGGGCACCTGGTATG ACCTGCAGACTGTGTCCCATTGAGGCTCTGGGCAGCCTGCCCCCCCCCCCTGCTGCTCCTAGGAGCCTGCCATTCACTCTGAGGCCAGTGGCTCTACCATCTGTGACTGTGCTGCTGCTGGCTGCTATCCTGGCTA CATCATCCCCCTGCAGGGGCCTGGCCTGACCACCACTGAGAGCAGCCAGCCCATGGCCTGGCTGTGGCCCTGACTAAGGGGGGGGAGGCTAGGGGGGGAGCTGTTCTACTGCAGCTGCTGGAAGTGCTGGAGAGG GCGGCTTACACCCACGTCATTTCCTCGCCACAGAACAACACTATTGTCAATGAGCTGGTGAGGTCGACCTCTGCCCGCCCTCGCCCTGCACCTGCACAACGCTGACTCTGCTGGGGTGGCCACTGCCCCCCAGCAGGTGCTGAGCA ATGGGGTGCCTGTGAGCAACTTTACCTACTCCCCTGATACCAAGGTGCTGCATCTGTGTGTCTCTGCTGATGGGCGAACAGTTTCTGGTGCTCTTGGTGCTGA
7	> coGAA GAA nucleic acid ATGGGGGTGAGGCACCCCCCCTGCTCTCACAGGCTGCTGGCTGTGTGCCCTGGCTACTGCTGCCCTCGTCGGCCACATCCTGCTGGTGCCCAGGGAGCTGTCTGGCAGCTCTCCTGTGC TGGAGGAAACTCATCCTGCCCATCAGCAGGGGCCCTCAGGCCCAGGCCCATCCTGGCAGCCCCAGACGCTGTGATGTGCCCCCCAACCCAGTGTGATGTTGCCCCTGATAAGGC CATCACCCAGGAGCAGTGTGAGGCCAGGGGGCTGCTGCTACATCCCTGCCAAGCAGGGCTGCAGGGGCCCAGATGGCCCACCTTGGTGCTTCTTCCCTCCCCAGCTACCCTCTTACAAGCTGGAGAACCTGAGCAGCTCTGAG ATGGGCTATACTGCCACCCTGACCAGGACATCCTGACTCTGAGACTGGATGTGATGGAGACTCAGAACAGGCTGCACATTCACCATCAAGGAGGTATGAGGTGC CTCTGGAGACTCCTAGAGTGCACAGCAGGGCTCCCTCTCCCCTGTACTCTGTGAGAGTTCTCTGAGGAGCCCTTTGGGGTGATTGTGCACACACAGCTGGATGGCAGGGTGCTGCTGAACACCACTGCTGCTGCTATCCTGGCTA TGACCAGTTCCTGCAGCTGTCTACCTCTGCCCAGCCAGTACATTACTGGGCTGGCTGAACATCTGTCCCCTGATGCTGACCAGGATCACTCTGTGGAACAGGAGACCTGGCCCCCACTCCTGGGGCTAAT CTGTATGGGAGCCACCCATTCTACCTGGCCCTGGAGGATGGGGGCTCTGCCCATGGGGTGTTCCTGCTGAACTCTAATGCCATGGATGTGTGGCTGAGTGGAGGACACTGGGGGCATCCTGGATG TGTACATTTTCCTGGGCCCTGAGCCCAAGTACCTGTGGTGCAGCAGTACCTGGATGGTGCTGGGCCTGCTGGCCTTCACCTGTGCAGGTGGGGGTATTCTACTGCCATCACCAGGCAGGT GGTGGAGAACATGACCAGGGCCCACTTCCCCCTGGATGTGCAGTGGAATGATCTGGACATATATGGACAGCAGGAGGCACTTCACTTTCAACAAGATGGTTCAGGACTTCCCTGCTATGGTGCAGGAGCTGCACCAGGGGGGG GCACTGCTTTCCCTCGATTTCACCAACCCCACTGCTCTGGCTGGTGGAGGAGCATGGTGGCTGAGTTTCATGATCAGTGCCTTTTGATGGGATTGTGGTCGTTCGCCTCGCCTACTGCATCAGAGGCTCTGAGGATGG CTGTCCCAATAATGAGCTGGAGAACCCCCCCTATGTGCCTCGGGTGGTGGGGGCACCCTGCAGCGTGCTACCATCTGCTAGCTCTCATCAGTTCCTGCAGCACTCACTACAACCTGCACAACCTGTATGGCGTGACTGAGGCT ATTGCCAGCCATAGGCCCTGTGAAGGCCAGAGGCACCTTTGCTGCCATGCCACTGGACTGGGAATGTGTGGAGCAGCTGGGACATGCTGGCCTCTTCTGTGC CTGAGATCCTGCAGTTCAACCTGCTGGGGGTGCCCCTGGTGGAGGCTGTGTGTGAGGTGGACTCACGTCGGGGCTTTTTATCCCTTCATGAGGAACCACAATAGCCT GCTGTCTCTGCCCCAGGAGCCCTATTCTTCTCTGAGCCTGCCCAGCAGGCCATGAGGAAGGCCCTGACTCTGAGGTATGCCTGCTGCCCCACCTGTTACACACCTGTTCCACCAGGCCCATGTGGCCAGG CCCCTGTTTCTGGAGTTCCCTAAGGACAGCTCTACCTGGATCACCAGCTGCTGTGGGGGAGGCCCTGCTGATCACTCCAGTCCTGCAGGCTGGCAAAGCTGAGGTGACTGGCTACTTCCCCCTGGGCACCTGGTATG ACCTGCAGACTGTGTCCCATTGAGGCTCTGGGCAGCCTGCCCCCCCCCCCTGCTGCTCCTAGGAGCCTGCCATTCACTCTGAGGCCAGTGGCTCTACCATCTGTGACTGTGCTGCTGCTGGCTGCTATCCTGGCTA CATCATCCCCCTGCAGGGGCCTGGCCTGACCACCACTGAGAGCAGCCAGCCCATGGCCTGGCTGTGGCCCTGACTAAGGGGGGGGAGGCTAGGGGGGGAGCTGTTCTACTGCAGCTGCTGGAAGTGCTGGAGAGG GCGGCTTACACCCACGTCATTTCCTCGCCACAGAACAACACTATTGTCAATGAGCTGGTGAGGTCGACCTCTGCCCGCCCTCGCCCTGCACCTGCACAACGCTGACTCTGCTGGGGTGGCCACTGCCCCCCAGCAGGTGCTGAGCA ATGGGGTGCCTGTGAGCAACTTTACCTACTCCCCTGATACCAAGGTGCTGCATCTGTGTGTCTCTGCTGATGGGCGAACAGTTTCTGGTGCTCTTGGTGCTGA
8	> coGAA GAA nucleic acid ATGGGGGTGAGGCACCCTCCCTGCAGCCACAGGCTGCTGGCTGTGTGCTCTGGGTGAGCCTGGCCACATTCTGCTGGTGCCCAGGGAACTGTCTGGCAGCTCTCCTGTGC TGGAGGAGACCCATCCTGCCCACCAGCAGGGGCCAGCAGGCCTGGCCCTAGGGATGCTCAGGCCCAGGGCTGTGCCCACCCAACAGCAGGTTTGATGTGCCCCTGACAAGGC CATCACCCAGGAGCAGTGTGAGGCCAGGGGCCTGCTGCTACATCCCTGCCAAGCAGGGCTGCAGGGGCCCAGATGGCCCACCTTGGTGCTTCTTCCCTCCCCAGCTATCCCCTCTTACAAGCTGGAGAACCTGAGCAGCTCTGAG ATGGGCTACACTGCCACCCTGACCAGGACATCCTGACTCTGAGACTGGATGTGATGGAGACTCAGAACAGGCTGCACATTCACCATCAAGGAGGTATGAGGTGC CTCTGGAGACTCCTAGAGTGCACAGCAGGGCTCCCTCTCCCCTGTACTCTGTGAGAGTTCTCTGAGGAGCCCTTTGGGGTGATTGTGCACACACAGCTGGATGGCAGGGTGCTGCTGAACACCACTGCTGCTGCTATCCTGGCTA TGACCAGTTCCTGCAGCTGTCTACCTCTGCCCAGCCAGTACATTACTGGGCTGGCTGAACATCTGTCCCCTGATGCTGACCAGGATCACTCTGTGGAACAGGAGACCTGGCCCCCACTCCTGGGGCTAAT CTGTATGGGAGCCACCCATTCTACCTGGCCCTGGAGGATGGGGGCTCTGCCCATGGGGTGTTCCTGCTGAACTCTAATGCCATGGATGTGTGGCTGAGTGGAGGACACTGGGGGCATCCTGGATG TGTACATTTTCCTGGGCCCTGAGCCCAAGTACCTGTGGTGCAGCAGTACCTGGATGGTGCTGGGCCTGCTGGCCTTCACCTGTGCAGGTGGGGGTATTCTACTGCCATCACCAGGCAGGT GGTGGAGAACATGACCAGGGCCCACTTCCCCCTGGATGTGCAGTGGAATGATCTGGACATATATGGACAGCAGGAGGCACTTCACTTTCAACAAGATGGTTCAGGACTTCCCTGCTATGGTGCAGGAGCTGCACCAGGGGGGG GCACTGCTTTCCCTCGATTTCACCAACCCCACTGCTCTGGCTGGTGGAGGAGCATGGTGGCTGAGTTTCATGATCAGTGCCTTTTGATGGGATTGTGGTCGTTCGCCTCGCCTACTGCATCAGAGGCTCTGAGGATGG CTGTCCCAATAATGAGCTGGAGAACCCCCCCTATGTGCCTCGGGTGGTGGGGGCACCCTGCAGCGTGCTACCATCTGCTAGCTCTCATCAGTTCCTGCAGCACTCACTACAACCTGCACAACCTGTATGGCGTGACTGAGGCT ATTGCCAGCCATAGGCCCTGTGAAGGCCAGAGGCACCTTTGCTGCCATGCCACTGGACTGGGAATGTGTGGAGCAGCTGGGACATGCTGGCCTCTTCTGTGC CTGAGATCCTGCAGTTCAACCTGCTGGGGGTGCCCCTGGTGGAGGCTGTGTGTGAGGTGGACTCACGTCGGGGCTTTTTATCCCTTCATGAGGAACCACAATAGCCT GCTGTCTCTGCCCCAGGAGCCCTATTCTTCTCTGAGCCTGCCCAGCAGGCCATGAGGAAGGCCCTGACTCTGAGGTATGCCTGCTGCCCCACCTGTTACACACCTGTTCCACCAGGCCCATGTGGCCAGG CCCCTGTTTCTGGAGTTCCCTAAGGACAGCTCTACCTGGATCACCAGCTGCTGTGGGGGAGGCCCTGCTGATCACTCCAGTCCTGCAGGCTGGCAAAGCTGAGGTGACTGGCTACTTCCCCCTGGGCACCTGGTATG ACCTGCAGACTGTGTCCCATTGAGGCTCTGGGCAGCCTGCCCCCCCCCCCTGCTGCTCCTAGGAGCCTGCCATTCACTCTGAGGCCAGTGGCTCTACCATCTGTGACTGTGCTGCTGCTGGCTGCTATCCTGGCTA CATCATCCCCCTGCAGGGGCCTGGCCTGACCACCACTGAGAGCAGCCAGCCCATGGCCTGGCTGTGGCCCTGACTAAGGGGGGGGAGGCTAGGGGGGGAGCTGTTCTACTGCAGCTGCTGGAAGTGCTGGAGAGG GCGGCTTACACCCACGTCATTTCCTCGCCACAGAACAACACTATTGTCAATGAGCTGGTGAGGTCGACCTCTGCCCGCCCTCGCCCTGCACCTGCACAACGCTGACTCTGCTGGGGTGGCCACTGCCCCCCAGCAGGTGCTGAGCA ATGGGGTGCCTGTGAGCAACTTTACCTACTCCCCTGATACCAAGGTGCTGCATCTGTGTGTCTCTGCTGATGGGCGAACAGTTTCTGGTGCTCTTGGTGCTGA

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9 > coGAA GAA nucleic acid

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10 > coGAA GAA nucleic acid

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TGTACATCTTCCTGGGCCTGACCCTAAGTCTGTGGTGCAGCACATACCTGGATGTGGTGGCTATCCCTTCATGCCCCCCTACTGCGGCCTGGCCTTCACCTCTGCAGTGGGGCTATAGCAGCACTGCCATCACCAGCAGGT
GGTGGAGAATATGACTAGGGCCCATTTCCCCTGGATGTGCAGTGGAATGACCTGGATTACATGGACAGAGGAGGACTTCACCTTCAATAAGATGGCTTTAGGACTTTCCTGCCATGGTGCAGGAGCTGCATCAGGGGGG
AGGAGGTATATGATGATTGTGGATCCTGCCCTCGTGGCCCTGCTGGCAGCTATAGGCCCTATGATGGCCCTATGAGGCCCTGAGAGGGGGTGTTCATTACCAATGACATGGCCACTGGCCTGAGCCTGGCCTGGCCT
CTACTGCCTTTCCTCGACTTCACTAACCCCACTGCCCTGGCCTGAGTTCCATGACCAGCTGCCCTTTGATGCCATGTGGATTGACATGAATGAGCCCTCTAACTTCATCAGGGGCTCTGAGGATGG
CTGCCCCCAATAATGAGCTGGAGAACCCCCCCTATGTGCCTGGGGTGCCCACCATCTGTGCCAGCAGCCACCCATTATAATCTGCACAACCCTGTAATGGCCTGACTGAGGCC
ATTGCCAGCCATAGGGCCCTGGTGAAGGCTACTAGGGCCATCGGCACGTATATGCTGCCACTGACATCGTGGGATGTGTGGAGCAGCTGGCCAGCTCTGTGC

	CTGAGATTCTGCAGTTTAACCTGCTGGGGGTGCCCCTGGTGGGGGCTGATGTGTGTGGCTTCCTGGGGAACACCTCTGAGGAGCTGTGTGTGAGGTGGACCCAGCTGGGGGCTTTTTACCCCTTTATGAGGAACCATAATAGCCT GCTGAGCCTGCCTCAGGAGCCCTACAGCTTCTCTGAGCCTGCCCAGCAGGCCATGAGGAAGGCCCTGACCCTGAGGTATGCCCTCCTGCCCCATCTCTACACCCTCTTTCACCAGGCCCATGTGGCTGGGGAGACTGTGGCCAGA CCCCTGTTCCTGGAGTTCCCAAAGGACTCTTCTACCTGGACTGTGGACCACCAGCTGCTGTGGGGGGAGGCCCTGCTGATTACCCCTGTGCTGCAGGCTGGGAAGGCTGAGGTGACTGGGTATTTCCCCCTGGGCACCTGGTATG ACCTGCAGACTGTGCCAATTGAGGCTCTGGGCAGCCTGCCTCCCCCCCCTGCTGCTCCTAGGGAGCCTGCCATTCACTCTGAGGGCCAGTGGGTGACCCTGCCAGCCCCTCTGGACACTATCAATGTGCACCTGAGGGCTGGCTA CATCATCCCCCTGCAGGGGCCTGGCCTGACTACCACTGAGAGCAGGCAGCAGCCTATGGCTCTGGCTGTGGCCCTGACCAAGGGGGGGGAGGCCAGGGGGGAGCTGTTCTGGGATGATGGGGAGTCTCTGGAGGTGCTGGAGAGG GGGGCCTACACCCAGGTGATCTTCCTGGCCAGGAATAATACCATTGTGAATGAGCTGGTGAGAGTGACTTCTGAGGGGGCTGGCCTGCAGCTGCAGAAGGTGACTGTGCTGGGGGTGGCCACTGCCCCCCAGCAGGTCCTGTCTA ATGGGGTGCCTGTGTCTAACTTTACCTACAGCCCTGACACCAAGGTGCTGGACATCTGTGTGAGCCTGCTGATGGGGGAGCAGTTCCTGGTGAGCTGGTGTTGA
11	> coGAA GAA nucleic acid ATGGGGGTGAGGCACCCCCCTTGCTCTCACAGGCTGCTGGCTGTCTGTGCCCTGGTGAGCCTGGCCACTGCTGCTCTGCTGGGGCACATCCTGCTGCATGATTTTCTGCTGGTGCCCAGGGAGCTGTCTGGGAGCTCTCCAGTGC TGGAGGAGACCCACCCTGCCCACCAGCAGGGGGCCAGCAGACCTGGGCCCAGGGATGCTCAGGCTCACCCTGGCAGGCCCAGGGCTGTGCCCACTCAGTGTGATGTGCCCCCCAACAGCAGGTTTGACTGTGCCCCTGACAAGGC CATCACCCAGGAGCAGTGTGAGGCTAGGGGCTGCTGTTACATCCCTGCCAAGCAGGGCCTGCAGGGGGCCCAGATGGGCCAGCCCTGGTGCTTCTTCCCCCCCAGCTACCCCAGCTACAAGCTGGAGAACCTGTCTAGCTCTGAG ATGGGCTATACTGCTACCCTGACTAGGACCACCCCTACTTTCTTCCCCAAGGACATCCTGACCCTGAGGCTGGATGTGATGATGGAGACTGAGAATAGGCTGCATTTCACCATCAAGGACCCTGCTAACAGGAGGTATGAAGTGC CCCTGGAGACCCCCAGGGTGCATAGCAGGGCCCCCTCTCCTCTGTACTCTGTGGAGTTCTCTGAAGAGCCCTTTGGGGTGATTGTGCATAGGCAGCTGGATGGCAGGGTGCTGCTGAACACTACTGTGGCCCCCCTGTTTTTGC TGACCAGTTCCTGCAGCTGAGCACCAGCCTGCCCAGCCAGTACATCACTGGCCTGGCTGAGCACCTGAGCCCACTGATGCTGAGCACCAGCTGGACTAGGATTACCCTGTGGAACAGGGACCTGGCCCCCACTCCTGGGGCCAAC CTGTATGGCAGCCACCCCTTCTACCTGGCCCTGGAGGATGGGGGCTCTGCCCATGGGGTGTTCCTGCTGAACAGCAATGCCATGGATGTGGTGCTGCAGCCCTCTCCTGCCCTGTCTTGGAGGAGCACTGGGGGGATTCTGGATG TGTACATCTTTCTGGGGCCTGAGCCCAAGTCTGTGGTGCAGCAGTACCTGGATGTGGTGGGGTACCCCTTTATGCCTCCCTATTGGGGCCTGGGGTTCCATCTGTGCAGGTGGGGGTACTCTAGCACTGCTATCACCAGGCAGGT GGTGGAGAACATGACCAGGGCCCATTTCCCCCTGGATGTGCAGTGGAATGACCTGGATTACATGGACTCTAGAAGGGACTTCACCTTCAACAAGGATGGCTTCAGGGATTTCCCTGCTATGGTGCAGGAGCTGCATCAGGGGGGC AGGAGGTACATGATGATTGTGGATCCTGCCATCAGCAGCTCTGGGCCTGCTGGGAGCTATAGGCCTTATGATGAGGGCCTGAGGAGGGGGGTGTTTATTACCAATGAGACTGGCCAGCCCCTGATTGGCAAGGTGTGGCCAGGCA GCACTGCCTTCCCTGACTTCACTAACCCTACTGCTCTGGCCTGGTGGGAGGACATGGTGGCTGAATTTCATGACCAGGTGCCCTTTGATGGGATGTGGATTGACATGAATGAGCCTTCTAATTTCATCAGGGGCTCTGAGGATGG GTGCCCCAACAATGAGCTGGAGAACCCCCCCTATGTGCCTGGGGTGGTGGGGGGCACCCTGCAGGCTGCCACTATCTGTGCTAGCAGCCATCAGTTCCTGAGCACTCACTACAATCTGCACAACCTGTATGGCCTGACTGAGGCC ATTGCCAGCCATAGGGCCCTGGTGAAGGCTAGGGGCACTAGGCCCTTTGTGATCAGCAGGAGCACCTTTGCTGGCCATGGGAGGTATGCTGGCCACTGGACTGGGGATGTGTGGAGCAGCTGGGAGCAGCTGGCCAGCTCTGTGC CTGAGATCCTGCAGTTCAACCTGCTGGGGGTGCCCCTGGTGGGGGCTGATGTGTGTGGCTTCCTGGGGAACACCTCTGAAGAGCTGTGTGTGAGGTGGACCCAGCTGGGGGCCTTCTACCCCTTCATGAGGAATCACAACAGCCT GCTGAGCCTGCCTCAGGAGCCCTACTCTTTCTCTGAGCCTGCCCAGCAGGCCATGAGGAAGGCTCTGACCCTGAGGTATGCCCTGCTGCCTCACCTGTACACCCTGTTTCATCAGGCCCATGTGGCTGGGGAGACTGTGGCCAGG CCCCTGTTCCTGGAGTTCCCCAAGGATAGCAGCACCTGGACTGTGGACCACCAGCTGCTGTGGGGGGAAGCCCTGCTGATCACCCCTGTGCTGCAGGCTGGCAAGGCTGAGGTGACTGGCTACTTCCCCCTGGGCACCTGGTATG ACCTGCAGACTGTGCCCATTGAGGCCCTGGGCTCTCTGCCCCCTCCCCCTGCTGCCCCCAGGGAGCCTGCCATCCACTCTGAGGGCCAGTGGGTGACTCTGCCTGCCCCTCTGGATACCATTAATGTGCACCTGAGGGCTGGGTA CATCATCCCTCTGCAGGGCCCTGGCCTGACTACCACTGAGAGCAGGCAGCAGCCTATGGCCCTGGCTGTGGCTCTGACCAAGGGGGGGGAGGCCAGGGGGGAGCTGTTCTGGGATGATGGGGAGAGCCTGGAGGTGCTGGAGAGG GGGGCTTATACCCAGGTGATCTTCCTGGCCAGGAACAACACCATTGTGAATGAGCTGGTGAGGGTGACCTCTGAGGGGGCTGGCCTGCAGCTGCAGAAGGTGACTGTGCTGGGGGTGGCCACTGCCCCTCAGCAGGTGCTGAGCA ATGGGGTGCCTGTGAGCAATTTCACTTACAGCCCTGACACCAAGGTGCTGGATATTTGTGTGAGCCTGCTGATGGGGGAGCAGTTCCTGGTGTCTTGGTGCTAA
12	> coGAA GAA nucleic acid ATGGGGGTGAGGCATCCCCCCTGCAGCCATAGGCTGCTGGCTGTGTGTGCCCTGGTGAGCCTGGCTACTGCTGCCCTGCTGGGGCACATCCTGCTGCATGACTTCCTGCTGGTGCCCAGGGAACTGTCTGGCAGCAGCCCTGTGC TGGAGGAGACTCATCCTGCTCACCAGCAGGGGGCCTCCAGGCCTGGCCCCAGGGATGCCCAGGCTCACCCTGGCAGGCCCAGGGCTGTGCCCACTCAGTGTGATGTGCCCCCCAACAGCAGGTTTGACTGTGCCCCTGACAAGGC CATCACTCAGGAGCAGTGTGAGGCCAGGGGCTGCTGCTATATCCCTGCCAAGCAGGGGCTGCAGGGGGCCCAGATGGGGCAGCCTTGGTGCTTTTTCCCCCCCAGCTACCCCAGCTACAAGCTGGAGAACCTGTCTAGCTCTGAG ATGGGCTATACTGCCACTCTGACCAGGACCACCCCCACCTTCTTCCCCAAAGACATTCTGACCCTGAGGCTGGATGTGATGATGGAGACTGAGAATAGGCTGCACTTCACCATCAAGGACCCTGCTAACAGGAGGTATGAGGTGC CCCTGGAGACTCCTAGGGTGCACAGCAGGGCCCCCAGCCCCCTGTATTCTGTGGAGTTCTCTGAGGAGCCCTTTGGGGTGATTGTGCATAGGCAGCTGGATGGGAGGGTGCTGCTGAACACTACTGTGGCTCCCCTGTTCTTTGC TGACCAGTTCCTGCAGCTGAGCACCAGCCTGCCCTCTCAGTACATCACTGGCCTGGCTGAGCACCTGAGCCCCCTGATGCTGAGCACCAGCTGGACCAGGATCACTCTGTGGAACAGAGACCTGGCCCCCACCCCTGGGGCCAAC CTGTATGGCAGCCATCCCTTCTACCTGGCTCTGGAGGATGGGGGTCTGCCCATGGGGTGTTTCTGCTGAACAGCAATGCCATGGATGTGGTGCTGCAGCCCAGCCCTGCCCTGAGCTGGAGGAGCACTGGGGGCATCCTGGATG TGTACATTTTCCTGGGCCCTGAACCCAAGTCTGTGGTGCAGCAGTACCTGGATGTGGTGGGGTATCCCTTCATGCCTCCTTACTGGGGCCTGGGCTTCCATCTGTGCAGGTGGGGCTACAGCAGCACTGCTATCACCAGGCAGGT GGTGGAGAACATGACCAGGGCCCATTTCCCCCTGGATGTGCAGTGGAATGATCTGGACTACATGGACTCTAGGAGGGACTTCACTTTCAACAAGGATGGCTTCAGAGATTTCCCTGCCATGGTGCAGGAGCTGCACCAGGGGGGC AGAAGGTACATGATGATTGTGGACCCTGCCATCTCTAGCTCTGGCCCTGCTGGGAGCTACAGGCCCTATGATGAGGGGCTGAGGAGGGGGGTGTTTATCACCAATGAGACTGGCCAGCCCCTGATTGGCAAGGTGTGGCCTGGCA GCACTGCCTTCCCTGACTTCACCAATCCCACTGCCCTGGCCTGGTGGGAGGATATGGTGGCTGAGTTCCATGACCAGGTGCCCTTTGATGGGATGTGGATTGACATGAATGAGCCCAGCAACTTTATCAGGGGCTCTGAGGATGG CTGCCCCAACAATGAACTGGAAAACCCCCCCTATGTGCCTGGGGTGGTGGGGGGCACTCTGCAGGCTGCCACTATCTGTGCCAGCAGCCACCAGTTCCTGAGCACCCACTACAACCTGCACAATCTGTATGGCCTGACTGAGGCC ATTGCCAGCCACAGGGCCCTGGTGAAGGCTAGGGGCACCAGGCCCTTTGTGATCAGCAGGAGCACCTTTGCTGGCCATGGCAGGTATGCTGGCCACTGGACTGGGGATGTGTGGAGCTCTTGGGAGCAGCTGGCCAGCTCTGTGC CTGAGATCCTGCAGTTCAACCTGCTGGGGGTGCCCCTGGTGGGGGCTGATGTGTGTGGCTTTCTGGGCAATACTTCTGAGGAGCTGTGTGTGAGGTGGACCCAGCTGGGGGCCTTTTACCCCTTCATGAGGAACCACAACTCTCT GCTGAGCCTGCCCCAGGAACCCTATAGCTTTTCTGAGCCTGCCCAGCAGGCCATGAGGAAGGCCCTGACTCTGAGGTATGCTCTGCTGCCCCACCTGTACACCCTGTTCCACCAGGCCCATGTGGCTGGGGAGACTGTGGCCAGG CCCCTGTTCCTGGAGTTCCCCAAGGACAGCAGCACTTGGACTGTGGACCACCAGCTGCTGTGGGGGGAGGCTCTGCTGATCACTCCTGTGCTGCAGGCTGGCAAGGCTGAGGTGACTGGCTACTTCCCCCTGGGGACTTGGTATG ACCTGCAGACTGTGCCTATTGAGGCCCTGGGGAGCCTGCCTCCCCCCCCTGCTGCTCCCAGGGAGCCTGCCATCCACTCTGAGGGGCAGTGGGTGACTCTGCCTGCTCCCCTGGACACTATCAATGTGCACCTGAGGGCTGGGTA CATCATCCCCCTGCAGGGCCCTGGGCTGACCACCACTGAGTCTAGGCAGCAGCCCATGGCTCTGGCTGTGGCTCTGACCAAGGGGGGGGAGGCCAGGGGGGAGCTGTTCTGGGATGATGGGGAGAGCCTGGAGGTGCTGGAGAGG GGGGCCTACACCCAGGTGATCTTCCTGGCTAGAAACAACACCATTGTGAATGAGCTGGTGAGGGTGACTTCTGAGGGGGCTGGGCTGCAGCTGCAGAAGGTGACTGTGCTGGGGGTGGCTACTGCCCCACAGCAGGTGCTGTCTA ATGGGGTGCCAGTGTCTAACTTCACCTATAGCCCTGATACTAAGGTGCTGGACATCTGTGTGTCTCTGCTGATGGGGGAGCAGTTCCTGGTGTCTTGGTGCTGA

13	> coGAA GAA nucleic acid ATGGGGGTGAGGCATCCTCCCTCGCAGCCATAGGCTGCTGGCTGTGTCGCCTGGTCTGCTCGTCGGCTACTGCTGCTCCTGCGGCCACATCCTGCTGCTGGTGCCTAGGGACGTCTGTGGCAGCAGCCCTGTCC TGGAGGAGACCACCTGCCCATCAGCAGGGGCCTCTAGACCTGGCCCAGGGATGCCCAGGCCATCCTGGGAGCCCGAGGCTGTGCCCACCCAGTGTGATGTGCCTCCCAACAGCAGGTTTGACTGTGCTCGACAAAGC CATCACCCAGGAGCAGTGTGAACGCCAGGGGCTGTTGTTACATTCCTGCCCAAGCAGGGCCTGCAGGGGCCCAGCGATGGCCCACGCCTGGTGCTTCTTCCCCCCTAGCTACCCAGCTACAAGCTGGAGAATCTGAGCAGCTCTGAA ATGGGCTACACTGCCACACCTGACTAGGACCACCCCCACCTTCTCCCTAAGGATATCCTGACCCTGAGGCTGGATGTGATGATGGAGACTCAGAACAAGCTCCACTTCACCATCAAGGATCCTGCCCAACAGGAGGTATGAGGTGC CCCTGGAGACCCCCAGGGTGCACAGCAGGCTCCCCTCCCCTGTATTCTCTGTGAGGAGCCCTTTGGGCTGATTGTCGCACAGGCAGCTGGCATCCCCTGTCACTACTGTGGCTCCCCTGTTCTTTGC TGATCAGTTCCTGCAGCTGAGCCATCACTGGCTGGCTGAGCACCTGACATCGTCGAGCCACGATCACCCTGTGGAACAGGGACCTGGCTCCCACCCCTGGGGCCAAT CTGTATGGCAGCCACCCCTTCTACCTGGCCTCGCCCATGGGGTGTTCCTGCTGAACTCTAATGCCATGGATGTGGTGCTGACAGCCCAGCCCTGCCTGAGCTGGAGGACACTGGGGGCATCCTGCATG TGTACATCTTCCTGGGCCCTGAGCCCAAGTATCTGGTATGTGGGGTACCCTTTCATGCCCCCCTACTGGGGCCTGGGCCTTCCACCTGTGCAGGTGGGGGTACAGCAGCACTGCCATCACCAGGCAGGT GGTGGAGAATATGACCAGGGCCCACTTCCCCCTGGATGTGCAGTGGAATGATCTGAGGAGGCACTTCACCTTCAAGAAGATGGCTTCCAGGACTTTCCTCGCCATGGTGCAGGAGCTGCACCAGGGGGGC AGCAGGTACATGATCATTGTGGACCCAGCCATCTCTAGCTCTGGCCCAGCTGCAGCCCTACAGCCCTGAGCAGGCGGCTGTTCATCACTAATGACAGACTGCCCACGCCCTGATTGCCAAGTGTGCCCTGGGA GTGCCCTAACAATGAGCTGGAGAACCCCCCTTATGTGCTCGGGTGGTGGGGGCACCCTGCAGCTGCCCACCATCTGTCCAGCACCACCATGCTTCCTGTCTACCCACTACAACCTGCGACAATCTGTATGGCGTCAGGATG ATTGCCAGCCACAGGCCCTGGTGAAGCTATGGGGACCAGGAGCACCTTTGCTGGCATGGCATATGTCGCCATTGGACTGGGATGTGTGGTCTAGCTGGCATCGCTCTGTGC CTGAGATCCTGCAGTTCAATCTGCTGGGGGTGCCCCTGGTGGGGTTCCTGGGCAATACCTCTGAGGACCTGTGTGTGAGGTGGACCCACCTGCTGCCTCACCTGTGCTGGGGAGACTGTGTGGCCAGG GCTGAGCCTGCCTCAGGAGCCCTATTCTTTTTCTGAGCCTGCCAGCAGGCTATGAGGAAGGCCCTGACTCTGAGGTATGCCTGCTCACCTGTTCCACCAGGCCCATGTGCCAGTGGCTGGGGAGACTGTGGCCAGG CCCCTGTTCCTGGAGTTCCCCAAGGATAGCTCTACCTGGACCATCAGCTGCTGTGGGGGAGGCCCTGCTGATCACCCCTGTGCTGCAGCCTGAGTGACTGGCTACTTTCCCTCTGGCACCTGGTATG ATCTGCAGACTGTGTGCCCATTGAAGCCCTGGCAGCCTGCCTCCCCCTGCTGCCCCTAGGAGCCTGCCATCCACTCTGAGGGCCAGTGGGTGCCTACAGGTGGGATCCTGGATG CATCATTCCCCTGCAGGGCCCTGGGCTGACCACCACTGAGAGCAGGCAGCCCATGGCTCTGGCTGTGGCCCTGACCAAGGGGGGGGGAGCCAGGGGGAGCCTGTGGATGGTGCTGGAGAGG GCGGCCTACACCCACGTCGATCTTCCTCGCCCAGCAGAATAATACCATTGTCGAATGCAGCTCGTGAGGCGCCCTCGCCCTGCACGTCACTCTGCTGGGGGTGGCTACTGCTCCTCAGCAGGTGCTCTCTA ATGGGGTGCCTGTGAGCAACTTCACTTACAGCCCTGACACTAAGGTGCTGATGAGCCGTGTGATGGGGCAGCAGTTCCTGGTGTCTTGGTGCTGA
14	> coGAA GAA nucleic acid ATGGGAGTGAGGCACCCCCCCTGCTCCCATAGACTCCTGGCTGTCTGTGCCCTGGTGTCCTTGGCAACAGCTGCACTCCTGGGGCACATCCTACTCCATGATTTCCTGCTGGTTCCCAGAGAGCTGAGTGGCTCCTCCCCAGTCC TGGAGGAGATCACCCCAGCTCACCAGCAGGAGCCCAGACATCCCTGGCAGACCCCAGAGCAGTGCCCACACAGTGTGATGTCCCCCCCCAACACAGCAGATTTGATTGTTGCCCCTGACAAGGC CATAACCCAGGAGCAGTGTGAAGCCCAGGGCCTGCAGAGGGCCCAGCGATGGCCCACGCCCTGGTGCTTCTTCCCCCCTAGCTACCCAGCTACAAGCTGGAGAATCTGAGCAGCTCTGAA ATGGGCTACACAGCCACCCTGACCCAAGGACATCCTGACCCTGAGGATGTGCTGCTCATCACCATCAAAGATCCAGCTAACAGGAGATATGAGGTGC CCTTAGAGACCCCTAGAGTCCACAGCAGAGCACCTTCCCCACTCTACTGTGGAGTTCTCTGAGGAGCCCTTTGGGTGATTGTGCACACACAGCTGGATGGCAGAGTGCTGCTCCCTGTTCTTTGC TGACCAGTTCCTTCAGCTGTCCACCTCTGCCCTCTCAGTATATCACAGGCCTGGCTGAGCACCTCAGCCATGGCATCACCCTGTGGAACAGGGGATGTGTGGTCTAGCTGGCATCGCTCTGTGC CTCTATGGGTCTCACCCTTTCTACCTAGCTCTGGAGGATGGAGGGTCTGCACATGGGGTGTTCCTCGTCAACCCTGCCCAGCCCAGCCCTGCCTGAGCTGGAGGACACTGGGGGCATCCTGGATG TCTACATCTTCCTAGGCCCAGAGCCCAAGTCTGTGGTGCAGCATGTCCTTCATGCCTCCATACTGGGGCCTGGGCCTTCCACCTGTCAGCTATCACTAGACAGGT GGTGGAGAACATGACCAGGGCCCACTTCCCCCTGGATGTCCAGTGGAATGATCTAGACTACATGGACTTCCACCTTCAAGAAGATGGCTTCCAGGACTTCCTCGCCATGGTGCAGGAGCTGCACCAGGGAGGA AGAAGATACATGATCATTGTGGATCCTGCCATCAGCAGCTCTGGCCCTATGATGAGGGTCTGAGAAGGGGGTTTTCATCACCAATGAGACAGGCCAGCCTCTGATTGGAAGTGTGGCCAGGGT CCACTGCCTTCCCAGACTTCACCAACCCCACAGCCCTGGCCTGGTGGGAGGACATGGTGGCCTTCCATCACCCCAGTGCTCCAGGCTTCCCAACTTCATAAGAGGCCTCTGAGGATGG CTGCCCCCAACAATGAGCTAGAGAACCCACCCTATGTGCCTGGGGTGATGTTCCTCGTCAACCCTGCCCAGCCCAGCCCTGCCTGAGCTGGAGGACACTGGGGGCATCCTGGATG ATTGCCTCCCACAGGCCTGGTGAAGCCATAGGGGACCAAGAGCACCTTTGCTGGCCATGGCATATGTCGCCATTGGACAGGGGATGTGTGGAGCTAGCCTCCTCTGTGC CAGAAATCCTGCAGTTTAACCTGCTGGGGGTGCCTCTGGTTGGCTTCCTGGGCAACACCTCAGAGGACCTGTGTGTGAGATGGACCCACCTGCTGCCTCACCTGTGCTGGGGAGACTGTGTGGCCAGA GCTCAGTCTGCCCCAGGAGCCTTACAGCTTCTGAGCCTGCCAGCAGGCCATGAGGAAGGCCCTCACCTCCCCCCACCTTCTACACACTGTTCCACCAGGCCCATGTAGCAGGGGAGACAGTGGCCAGA CCCCTCTTCCTGGAGTTCCCCAAGGACTCTACAGCACCTGGACCACACCAGCTCCTGTGGGGGAGGCCCTGCTCATCACCCCAGTGCTCCAGGCTTCCCAACTTCATAAGAGGCCTCTGGGCACATGGTATG ACCTGCAGACAGTGCCAATAGAGGCCTTGGCAGCCTCCCACGTGCAGCCCATCCACTCTGAGGGCAGTGGGTGCCTACAGGTGGGATCCTGGATGTGCAGTGGAATGATCTGAGGAGGCACTTCACCTTCAAGAAGATGGCTTCCAGGACTTCCTCGCCATGGTGCAGGAGCTGCACCAGGGAGGA CATCATCCCCCTGCAGGGCCCTGGCCTGACCACCACTGAGAGCAGGCAGCCCATGGCTCTGGCTGTGGCCCTGACCAAGGGGGGGGGAGCCAGGGGGAGCCTGTGGATGGTGCTGGAGAGG GGGGCCTACACCCACGTCGATCTTCCTCGCCCAGCAGAATAATACCATTGTCGAATGCAGCTCGTGAGGCGCCCTCGCCCTGCACGTCACTCTGCTGGGGGTGGCTACTGCTCCTCAGCAGGTGCTCTCTA ATGGGGTGCCTGTGAGCAACTTCACTTACAGCCCTGACACTAAGGTGCTGATGAGCCGTGTGATGGGGCAGCAGTTCCTGGTGTCTTGGTGCTGA
15	> coGAA GAA nucleic acid ATGGGTGTTAGGCATCCACCATGTTCTCATAGGCTTTTAGCTGTGTGTTGGTATATCACTGGCAACTGCTGCACTTTTAGGTCATATTCTACTAGTACCAAGGGAGTTATCTGGTTCTTCTCCACGTTT TGGAGGAGACTCATCCTGCTCATCAGCAGGGTGCATCAAGGCCAGGTCCTAGAGATGCACAGGCATCCAACACAGTGTGATGTTGATTGTCGCCACCAAATTCAAGGTTTGATTGTCTCCTGATAAAGC TATAACACAGGAACAGTGTGAGGCTAGGGGATGTTGTTATATACCAGCTAAACAAGGTCTTGGTGTTTTTTCCTCCTTCATATCCTTCATATAAATTGGAAAATCTGAGTTCATCTGAG ATGGGTTATACTGCAACATTGACTAGAACTACACCAACATTTTTCCTAAAGATTAGATTGTGATGATTGGAAACTCAAAATAGACTTCATTTACAATTAAAGATCCAGCTAATAGAGGTATGAGGTTC CATTAGAGACACCTAGGGTGCATTCTAGAGCTCCTTGTATAGTGTTGAGTTTAGTGAGGAACCATTTGGTGTTATAGTGCATACACAGCTGGATGGTAGATTCTTCTTAATACAACAGTGGCTCCTCTATTTTTGC TGATCAATTTTTGCAATTGAGTACTTCTTTGCCATCTCAGTATAATAACTGGTTTAGCAGAACATTTGAGTCCTTTCATACATCTTGCTGCACAACGCATAACAATTATGGAATAGGATCTTGCTCCTACACCTGGTGCCAAAT

	CTGTATGGTTCTCACTCCATTTATCTTGCTTTAGAGGATGGTGGAAGTGCTCATGGTGTGTTTTTGTTGAATTCTAATGCTATGGATGTAGTGCTTCAACCATCACCAGCTCTTAGTTGGAGATCAACAGGTGGAAATACTGGATG
	TATATATATTTTTAGGTCCAGAACCTAAATCTGTGGTGCAGCAATATTTAGATGTAGTGTGGCTTACGCCACCTTATTCCGGTCTTGCATTTCATCTTTCTAGTGGGGTTATTCTTCAACTGCAATTACAAGACACAGGT
	AGTGGAGAATATGACTAGAGCTCATTTTCCACTGGATGTGGAATGATTTAGATTATAGGATTCTAGGAGGGATTTTACTTTTAATAAAGATGGTTTTAGAGATTTCCTGCAATGGTGGCAGGAACTTCATCAGGGTGGT
	AGAAGGTATATGATGATTGTGGATACCTGCTATATCAAGTTCTGGTCCCTGCAGAAGTTATAGGCCTTATGATGGTATAGTGGATAGATATGAATGACACTGGTCAGCCTCTGATTGGAAAAGTGTGGCCTGGATCAACAGCTTTCCTGATTTTACAAATCCTACTGCTTTAGCTGGCAGAATTTCATGATCAGCTGCCTTTTGATGTGATATGAATGAACCATCTAATTTTATAAGAGGATCTGAGGATGG
	TTGTCCTAATAATGAACTGGAGAATCCTCCATATGTTCCTGGTGTAGTGGGTGGAACATTGCAGGCTGCAACTATCATGCATCACATCAGTTTCTAAGTACTCATTATAATCTTCATAATTTGTATGGTTTGACAGAAGCA
	ATAGCATCTCATAGAGCAATTGTGATTTCAAGGTCTACATTTGCAGACATGGTACATATGCTGGACATTGGACACAGCAGATGTGTGGAGTCATGAGGAGCAGCTAGCAAGTAGTGTGC
	CAGAAATATTGCAGTTTAATCTGTTAGGAGTTCCACTTGTGGGTGCTGATGTTTGTGGTGAGATGGACTCAGCTTGGTGCTTTTTATCCATTTATAGAGAAATCATAATAGTCT
	ACTTTCTCTTCCACAGGAACCATATAGTTTTCTGAGCCTGCTCAGCAAGCAATGAGGAAAGCACTTACTCTGAGGTAATGCTCTTCTGCCACATCTTTATACACTTTTCATACAGGCACATGTAGCCTGGAGACACGTGGCAAGG
	CCACTATTTTGGAATTCCTAAAGATTCAAGTAACATGGACAGTGGATCATCAGTTGTTGTGGGGTGAAGCTTTACTATTACACCAGTCTCGCAAGCAGGTAAAGCAGAGGTGACAGGTTATTTCCACTGGGTACTTGGTATG
	ATCTGCAGACAGTGCCAATAGAAGCTCTGGGTAGTTTGCCACCTCCACCTGCTCCTAGAGAACCTGCTATACATAGTCAGCGTCAGTCAGCGTAACACTACCAGCACCATTCGAGGCTCGATA
	TATAATACCTTTGCAAGGTCCTGGTTTAACAACTACAGAGTCCTAGGCAGCCAATGGCACTTGCTGTGGCACTGACAAAAGGTGGAGAAGCAAGGGGTGAGCTATTTTGGGATGATGAATCTCTTGAAGTGTTAGAAAGG
	GGTGCATATACTCACGTAATTTTTTTGGCTAGGAATAAATACATCTGAAGTGAATGAGCTGGTAAGATTAACATCTGCAGAAAGTAACTGTCGCTAGGAGTAGCTACTGCACCACACAGCAGGTATTGTCTA
	ATGGAGTACCTGTGTCTAATTTTACTATAGTCCAGATACAAAAGTGTTAGATATTTGTGTCTTTGCTGATGGGAGCAGTCATTCTTGTGTCATGGTGT
16	> coGAA GAA nucleic acid
	ATGGGGAGTTAGGCATCCTCCATGTTCTCATAGGCTGTTGGCAGTATGTGCTCTTGTGTCACTGGCTACATGCTGCTCATGATTTTTACTTGTGCCTAGGGAGCTGTCTGGATCTTCTCCTGTAC
	TAGAGGAGACACATCCTGCTCATCAGCAAGGTGCATCAAGGCCAGGACCAAGAGATGCTCAGGCTCATCCTGGAAGGCCTAGAGCAGTGCCTCAATTCAAGATTTGATGTGCACCTGATAAAGC
	TATAACACAAGAACAGTGTGAGGCTAGGGGTTGTTATATTCCTGCAAAACAAGGGTTGCAAGGGGCACAGATGGCAACCTTGGTTGTTCTTCCCACCATCTTATCCTAGTTATAAATTGGAGAATTTGTCTTCAAGTGAA
	ATGGGGTATACAGCTACATTGACAAGAACAACTCCAACATTTTTTCCAAAGGATATTCTTACTTTGAGGCTAGATTGTGGAGACACAGAATAGCTTGCATTTTACTATAAAGATCCAGCTAATAGAAGATATGAGGTTC
	CTTTAGAGACTCCAAGGGTGCATTCTAGAGCTCCTTCTCCTTTGTATAGTGTGGAGTTTCAGAGGAACCATTTGGTGTTATTGTTCATACACAGCTGGATGGTAGGGTGCTGTTGAATACTACAGTAGCTCCTCTGTTTTTGC
	TGATCAGTTTTTACAGTTGTCAACTAGTCTTCCAAGTCAGTATATTACAGGTTTGGCAGAGCATCTATCTCCATTGATCGTCTACAAGTTGCCAGCACCTCTTGATACAATTAATGTGCATTTGAGAGCTGGTTA
	TTGTATGGATCACATCCATTTTATATTTGGCATTGGAAGATGGAGGGTCTGCTCATGGAGTTTTTTTATTGAATAGTATGCTATGGAATGGGTTTTTATTGGTTTGTCATCTTGTATGTCAGAGGCTATTGTTAGACAGAGGCA
	TTTATATATTTTTTAGGGCCTGAACCTAAGTCTGTGGTGCAGCAATATTTAGATGTAGTTGGATATCCTTTTATGCCCTCCTTATTGGGGACTTGGTTTTCATCTTTGTAGATGGGGTTTATAGTTCTACTGCAATAACAAGGCAGGT
	GGTGGAGAATATGACAAGAGCACATTTTCCACTTGATGTGCAATGGAATGATTTAGATTATAGGATTCTAGAAGAGATTTTACTTTTTAATAAGCATGCGTTTCTAGTTGGAGCAATCTGCATTCAGGGTGGA
	AGAAGGTATATGATGATTGTGGATACCAGCTATTTCTAGTCTGGTCCTGCTGGTCTTATAGGCCATATGATGAGAGGCGTGTTTATTACAAATGAAACAGGCCACCTCTAATTGGGAAGTGTGGCCTGGGA
	GTACTGCTTTTCCAGATTTTACAAATCCAACAGCACTTGCAGTGGGAGGATATGGTGGGCAGAGTTTCATGATCAAGTTCCTTTTGATGGGATCGTGGATAGATATGAATGAGTTCCTATTATAATCTACATAAATTTGTATGGTTTGACAGAGGCA
	TTGTCCAAATAATGAGTTGGAGAATCCACCTTATGTGCCAGGTGTAGTGGGTGGAACACTGCAGGCAGCAACTATTTGTGCATCATTATAATCTACATAAATTTGTATGGTTTGACAGAGGCA
	ATAGCTTCTCATAGGGCTTGGTGAAGGCTAGAGGTACAAGACCTTTTGTGATTTCTAGAAGTACTTTCGCAGGGCATGGTACATTGCAGCACATTGCATCATGTGGATCTTCTTGGGAGCAACTCTGCATTCACTGTAC
	CTGAGATATTGCAGTTTAATTTGCTAGGAGTGCCACTTGTGGTGGTTCCTGGGTAATACTAGTGAGAGCTGTGTGTGAGATGGACACAGCTAGGTGCTTTTTATCCATTTATAGAGGAATCATAATAGTCTCT
	GCTGTCACTGCCACAAGAACCATATTCATTTCTGAACCTGCACAGCAAGCTATGAGAAAGGCATTGACTCTTAGATATGCACTGTTCACTCATCTATATACACTGTTCATCAGGCTCATGTAGCAGGTGAAACAGTGGCAAGG
	CCACTTTTCCTGGAGTTCCCAAAGGATTCTTCTACTTGGACAGTGGATCATCAGCTATTGTGGGGTGAGGCATTATTGATTACTCCTGTGCTTCAAGCTGGAAAAGCAGAGGTGACAGGATATTTCCCTTTAGGATG
	ATCTGCAGACTGTGCCTATAGAGGCACTGGGTTCATTGCCACCTGCTGCACTAGGGATCAGTGGTGTTTTTTCACCAAGTATTCAAACTGGAAAATCTGAGTAGTAGTGAA
	TATTATACCTCTGCAGGGTCCTGGGTTGACTACTACTGAATCAAGACAGCCATGGCATCTGGCAGTGGCATCTAGAGGAGCCAGCTCTGCAGCTCCACAGCAAGTTTTAAGTA
	ATGGAGTACCTGTGTCTAATTTTACTATAGTCCAGATACAAAAGTGTTGATGGGTCGAGCAATTTCTAGTGAGTTGGTCT
17	> coGAA GAA nucleic acid
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19	> coGAA GAA nucleic acid w/o signal peptide
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20	> coGAA GAA nucleic acid w/o signal peptide
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		GCTGGCTACA TCATCCCCCT GCAGGGCCCT GGCCTGACTA CCACTGAGTC TAGGCAGCAG CCCATGGCCC TGGCTGTGGC TCTGACCAAG GGGGGGGAGG CCAGGGGGGA GCTGTTCTGG GATGATGGGG AGTCTCTGGA GGTGCTGGAG AGGGGGGCCT ACACCCAGGT GATCTTCCTG GCTAGGAATA ACACCATTGT CAATGACCTG CTGAGGGTGA CCTCTGAGGG GGCTGGCCTG CAGCTGCAGA AGGTGACTGT GCTGGGGGTG GCTACTGCCC CCCAGCAGGT GCTGAGCAAT GGGGTGCCTG TGAGCAACTT CACCTATAGC CCTGACACCA AGGTGCTGGA CATCTGTGTG AGCCTGCTGA TGGGGGAGCA GTTCCTGGTG AGCTGGTGCT AA
	22	> coGAA GAA nucleic acid w/ hFN1 signal peptide ATGCTTAGGGGTCCGGGGCCCGGGCTGCTGCTGCTGGCCGTCCAGTGCCTGGGGACAGCGGTGCCCTCCACGGGAGCCTCGAAGAGCAAGAGG GGCCATATCCTGCTGCATGACTTCCTGCTGGTGCCTAGGGAGCTGTCTGGCAGCAGCCCTGTGCTGGAAGAGACCCACCCTGCTCACCAGCAGGGGGCC AGCAGGCCAGGCCCCAGGGATGCCCAGGCCCACCCTGGCAGACCCAGGGCTGTGCCCACCCAGTGTGATGTGCCTCCCAACAGCAGATTTGACTGTGCCCCTGATAAGGCCATTACTCAG GAACAGTGTGAGGCCAGGGGCTGCTGCTATATCCCTGCCAAGCAGGGCCTGCAGGGGGCCCAGATGGGGCAGCCCTGGTGCTTCTTCCCCCCCAGCTACCCCTCTTATAAGCTGGAGAAT CTGAGCAGCTCTGAAATGGGCTACACTGCCACTCTGACCAGGACTACCCCCACCTTCTTCCCCAAGGATATTCTGACTCTGAGGCTGGATGTGATGATGGAGACTGAGAACAGGCTGCAC TTCACCATCAAGGACCCTGCCAACAGGAGGTATGAGGTGCCCCTGGAAACTCCCAGGGTGCACTCTAGGGCCCCCAGCCCCCTGTATTCTGTGGAGTTCTCTGAGGAGCCTTTTGGGGTC ATTGTCCACAGGCAGCTGGATGGCAGGGTGCTGCTGAATACTACTGTGGCCCCTCTGTTCTTTGCTGACCAGTTCCTGCAGCTGAGCACCAGCCTGCCTTCTCAGTACATTACTGGCCTG GCTGAGCATCTGAGCCCCCTGATGCTGAGCACCTCTTGGACCAGAATCACCCTGTGGAACAGGGACCTGGCTCCCACTCCTGGGGCCAACCTGTATGGCAGCCACCCCTTCTACCTGGCC CTGGAGGATGGGGGCTCTGCCCATGGGGTGTTCCTGCTGAACAGCAATGCCATGGATGTGGTGCTGCAGCCCTCTCCTGCCCTGTCTTGGAGATCTACTGGGGGCATCCTGGATGTGTAT ATCTTCCTGGGGCCTGAGCCCAAGTCTGTGGTGCAGCAGTACCTGGATGTGGTGGGCTACCCCTTCATGCCCCCCTACTGGGGCCTGGGCTTCCACCTGTGCAGGTGGGGCTACTCTTCT ACTGCTATCACCAGGCAGGTGGTGGAGAACATGACCAGGGCTCACTTCCCTCTGGATGTGCAGTGGAATGACCTGGACTACATGGACTCTAGGAGAGACTTCACTTTTAATAAGGATGGG TTCAGGGACTTTCCTGCCATGGTGCAGGAGCTGCATCAGGGGGGCAGGAGATATATGATGATTGTGGACCCTGCTATTTCTAGCTCTGGCCCTGCTGGCAGCTATAGGCCCTATGATGAG GGGCTGAGGAGGGGGGTGTTCATCACTAATGAGACTGGCCAGCCCCTGATTGGCAAGGTGTGGCCTGGCTCTACTGCCTTCCCTGATTTCACCAACCCCACTGCCCTGGCCTGGTGGGAG GATATGGTGGCTGAGTTTCATGACCAGGTGCCCTTTGATGGCATGTGGATTGACATGAATGAGCCCAGCAACTTTATCAGGGGCTCTGAAGATGGCTGCCCCAACAATGAGCTGGAGAAC CCCCCCTATGTGCCTGGGGTGGTGGGGGGCACCCTGCAGGCTGCCACCATCTGTGCCAGCAGCCACCAGTTCCTGAGCACCCACTATAACCTGCACAACCTGTATGGCCTGACTGAGGCC ATTGCCTCTCACAGGGCCCTGGTGAAGGCTAGGGGGACTAGGCCCTTTGTGATCAGCAGGTCTACTTTTGCTGGCCATGGCAGGTATGCTGGGCACTGGACTGGGGATGTGTGGTCTAGC TGGGAGCAGCTGGCCAGCTCTGTGCCTGAGATCCTGCAGTTTAATCTGCTGGGGGTGCCCCTGGTGGGGGCTGATGTGTGTGGCTTCCTGGGCAATACCTCTGAGGAGCTGTGTGTGAGG TGGACTCAGCTGGGGGCTTTCTACCCCTTCATGAGAAACCACAACTCTCTGCTGAGCCTGCCCCAGGAGCCCTATTCTTTTTCTGAGCCTGCCCAGCAGGCTATGAGGAAGGCCCTGACT CTGAGGTATGCCCTGCTGCCCCACCTGTATACCCTGTTCCATCAGGCCCATGTGGCTGGGGAGACTGTGGCCAGACCTCTGTTCCTGGAGTTCCCCAAGGATAGCTCTACTTGGACTGTG GACCACCAGCTGCTGTGGGGGGAGGCTCTGCTGATCACCCCTGTGCTGCAGGCTGGGAAGGCTGAGGTGACTGGCTATTTCCCCCTGGGCACCTGGTATGATCTGCAGACTGTGCCCATT GAGGCCCTGGGCTCTCTGCCCCCTCCCCCTGCTGCCCCCAGGGAGCCTGCCATCCACTCTGAGGGCCAGTGGGTGACCCTGCCTGCCCCTCTGGACACTATCAATGTGCACCTGAGGGCT GGCTACATCATCCCCCTGCAGGGCCCTGGCCTGACTACCACTGAGTCTAGGCAGCAGCCCATGGCCCTGGCTGTGGCTCTGACCAAGGGGGGGGAGGCCAGGGGGGAGCTGTTCTGGGAT GATGGGGAGTCTCTGGAGGTGCTGGAGAGGGGGGCCTACACCCAGGTGATCTTCCTGGCTAGGAATAACACCATTGTCAATGAGCTGGTGAGGGTGACCTCTGAGGGGGCTGGCCTGCAG CTGCAGAAGGTGACTGTGCTGGGGGTGGCTACTGCCCCCCAGCAGGTGCTGAGCAATGGGGTGCCTGTGAGCAACTTCACCTATAGCCCTGACACCAAGGTGCTGGACATCTGTGTGAGC CTGCTGATGGGGGAGCAGTTCCTGGTGAGCTGGTGCTAA
	23	> ITR-to-ITR construct with coGAA nucleic acid >[L-ITR]-[ACTUS101-LSP]-[5'UTR]-[coGAA (w/sp)]-[3'UTR]-[PolIII_terminator]-[hGHpolyA]-[PolII_terminator-rev][R-ITR] CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTTGTAGTTAATGATTA ACCCGCCATGCTACTTATCTACGGCGCGCCACGCGTTCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCGAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTTACT AGTTCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCGAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTTACTAGTTCTAGAGCGGCCGCCAGTGTGCTGGAATTC GGCTTTTTTAGGGCTGGAAGCTACCTTTGACATCATTTCCTCTGCGAATGCATGTATAATTTCTACAGAACCTATTAGAAAGGATCACCCAGCCTCTGCTTTTGTACAACTTTCCCTTAAAAAACTGCCAATCCCACTGCTGTTT GGCCCAATAGTGAGAACTTTTTCCTGCTGCCTCTTGGTGCTTTTGCCTATGGCCCCTATTCTGCCTGCTGAAGACACTCTTGCCAGCATGGACTTAAACCCCTCCAGCTCTGACAATCCTCTTTCTCTTTTGTTTTACATGAAGG GTCTGGCAGCCAAAGCAATCACTCAAAGTTCAAACCTTATCATTTTTTGCTTTGTTCCTCTTGGCCTTGGTTTTGTACATCAGCTTTGAAAATACCATCCCAGGGTTAATGCTGGGGTTAATTTATAACTGAGAGTGCTCTAGTT CTGCAATACAGGACATGCTATAAAAATGGAAAGATGTTGCTTTCTGAGAGATCAGGTGGATTCTTGGGCATTTGCTTAAGCTTGGTACCGCCACCATGGGGGTGAGGCACCCTCCCTGTTCTCACAGGCTGCTGGCTGTGTGTGC TCTGGTGTCTCTGGCCACTGCTGCCCTGCTGGGCCATATCCTGCTGCATGACTTCCTGCTGGTGCCTAGGGAGCTGTCTGGCAGCAGCCCTGTGCTGGAAGAGACCCACCCTGCTCACCAGCAGGGGGCCAGCAGGCCAGGCCCC AGGGATGCCCAGGCCCACCCTGGCAGACCCAGGGCTGTGCCCACCCAGTGTGATGTGCCTCCCAACAGCAGATTTGACTGTGCCCCTGATAAGGCCATTACTCAGGAACAGTGTGAGGCCAGGGGCTGCTGCTATATCCCTGCCA AGCAGGGCCTGCAGGGGGCCCAGATGGGGCAGCCCTGGTGCTTCTTCCCCCCCAGCTACCCCTCTTATAAGCTGGAGAATCTGAGCAGCTCTGAAATGGGCTACACTGCCACTCTGACCAGGACTACCCCCACCTTCTTCCCCAA GGATATTCTGACTCTGAGGCTGGATGTGATGATGGAGACTGAGAACAGGCTGCACTTCACCATCAAGGACCCTGCCAACAGGAGGTATGAGGTGCCCCTGGAAACTCCCAGGGTGCACTCTAGGGCCCCCAGCCCCCTGTATTCT GTGGAGTTCTCTGAGGAGCCTTTTGGGGTCATTGTCCACAGGCAGCTGGATGGCAGGGTGCTGCTGAATACTACTGTGGCCCCTCTGTTCTTTGCTGACCAGTTCCTGCAGCTGAGCACCAGCCTGCCTTCTCAGTACATTACTG GCCTGGCTGAGCATCTGAGCCCCCTGATGCTGAGCACCTCTTGGACCAGAATCACCCTGTGGAACAGGGACCTGGCTCCCACTCCTGGGGCCAACCTGTATGGCAGCCACCCCTTCTACCTGGCCCTGGAGGATGGGGGCTCTGC CCATGGGGTGTTCCTGCTGAACAGCAATGCCATGGATGTGGTGCTGCAGCCCTCTCCTGCCCTGTCTTGGAGATCTACTGGGGGCATCCTGGATGTGTATATCTTCCTGGGGCCTGAGCCCAAGTCTGTGGTGCAGCAGTACCTG GATGTGGTGGGCTACCCCTTCATGCCCCCCTACTGGGGCCTGGGCTTCCACCTGTGCAGGTGGGGCTACTCTTCTACTGCTATCACCAGGCAGGTGGTGGAGAACATGACCAGGGCTCACTTCCCTCTGGATGTGCAGTGGAATG ACCTGGACTACATGGACTCTAGGAGAGACTTCACTTTTAATAAGGATGGGTTCAGGGACTTTCCTGCCATGGTGCAGGAGCTGCATCAGGGGGGCAGGAGATATATGATGATTGTGGACCCTGCTATTTCTAGCTCTGGCCCTGC TGGCAGCTATAGGCCCTATGATGAGGGGCTGAGGAGGGGGGTGTTCATCACTAATGAGACTGGCCAGCCCCTGATTGGCAAGGTGTGGCCTGGCTCTACTGCCTTCCCTGATTTCACCAACCCCACTGCCCTGGCCTGGTGGGAG

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	GGGGCACCCTCGACGGCTGCCACCATCTGTGCCCAGCAGCCACCACTATAACCTGCACACAACCTGTATCGCCTCACTCAGCCCATTCCCTCTCACAGGCCCTGGTGAAGGCTAGGGGACTAGGCGCCTTTGT
	GATCAGCAGGTCTACTTTGCTGCCATGGCAGGTATGCTGGGCACTGGACATGGGGATGTGGTCTAGCTGGGAGCAGCTGCCCAGCTGTCAATCCTGCAGTTTAATCTGCTGGGGGTGCCCCTGGTGGGGCTGAT
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	CTATGAGGAAGGCCCTGACTCTGAGGTATGCCCTGCTGTTCCATCAGCCCCATGTGGCTGGGGAGACATGTGGCCAGACCCTGTTCCTGGAGTTCCCCAAGGATAGCTCTACTTGGACTGTGGACCA
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	GCTGCCCCCAGGAGCCTGCCATCCACTCTGAGGGCCAGTGGGTGACCCTGCCTCCTGAGGGCTGGCTACATCATCCCCCTGCAGGCCCTGGCCTGACTACCACTGAGTCTAGGCAGC
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	CCTTCCCTGTCCTTCTGATTTTAAAAAAAGAGAAATGTTCTGGCACCTGCACTTGCCTAGTTTTGTTTTTGTTTCGTTTTGTTTGATGGAGAGCGTATGTTGTTTTAAACGCGGCCGCGTAGATAA
	GTAGCATGGCGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGC
	GAGCGAGCGCGCAG
24	> ITR-to-ITR construct with coGAA GAA nucleic acid >[L-ITR]-[ACTUS101-LSP]-[5'UTR]-[coGAA w/sp)]-[3'UTR]-[PolIII terminator]-[hGHpolyA]-[PolII terminator-rev][R-ITR] CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCG
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	GGCTTTTTTAGGGCTGGAAGCTACCTTTGACATCATTTCCTCTGCGAATGCATGTATAATTTCTACAGAACCTATTAGAAAGGATCACCCAGCCTCTGCTTTTGTTGAAAAATGCCAATCCCACTGCTGTTT
	GGCCCAATAGTGAGAAGTTTTCCTGCTGCCTCTTGGTGCTTTTGCCTATGGGCCCCTATTCTGCCTGCTGAAGACACTCTTGCCACGCATGCACTTAAACCCCTCCAGCTCTCAGTTTCTTCTTTTGTTTTACATGAAGG
	GTCTGGCATTAATTTTTGTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCTAGTT
	CTGCAATACAGGACATGCTATAAAATGGAAAGATGTTGCTTCTGAGAGATCAGGTGGATTCTTGGGCATTTGCTTAAGCTTGGTACCGCCACCATGGCGGAGTCAGACATCCTCCTTGTTCTCATAGACTGCTGGCTGTGTGTGC
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	GACTGGCTGTCAGCATCTGTCTCATCAATTGTCGTTCTACACATTATAATCTGCATAATCTGTATGACTCACGAGAGGCTATTGCTTCTCATAGAGCTCTGGTGAAGGCTAGAGGAACAAGACTTTTGT
	GATTTCTAGATCTACATTTGCTCGTGAAGATATGCTGGACATTGGACACAGGAGATGTAGTCTTCTTGGGACGACTACTCTTCTCGCCTGAGATTCAGTTTAATCTGCTGGTGGGAGTGAT
	GTGTGTGGATTTCTGGGAAATACATCTGAGGAGCTGTGTGAGATGGCACACAGCTGGGAGCTTTTTATCCTTTTATCGAGAAATCATAATTTCTCTGCTGCTCTGCCTGAGGCTTATTCTTTTTCTGAGCCTGCTCAGCAGG
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	GCTGCTCCTAGAGAGCCTGCTATTCATTCTGAGGGACAGTGGGTGACACTGCCTGCTCCTCTGGAATACAATTAATGTCGAGACTGGATATATTATTCCTCTGCAGGGACTGGACTGACAACAACAGAGTCTAGACAGC
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	AGCGAGCGAGCGCGCAG
25	> coGAA GAA nucleic acid plus BGH polyA
	ATGGGGGTGAGGCACCCTCCCTGTTCTCACAGGCTGCTGGCTGTGTGCTCTGGTGTCCTGGCCCATATCCTGCTGGTGGCCTAGGGAGCTGTCTGGCAGCAGCCCTGTGC
	TGGAAGAGACCCACCTGCTCACCAGCAGGGGCCAGGCCCACCCTGGCAGACCCAGGCTGTGCCCACCCAGTGTGATGCTGCCTCCCAACAGACGATTTGACTGTGCCCCTGATAAGGC
	CATTACTCAGGAACAGTGTGAGGCCAGGGGCTGCTGCTATATCCCTGCCAAGCAGGGGCCCAGGGGGCCCAGATGGGGCAGCCCTGGTGCTCTTCCCCCCCAGCTACCCCTCTTATAAGCTGGAGAATCTGAGCAGCTCTGAA
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	CCCACCTTGGCCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTCTGATTTTAAAAAA
26	> coGAA GAA nucleic acid plus BGH polyA and RevPolIII
	ATGGGAGTGAGGCACATCCTCCTTGTTCTCATAGACTGCTGGCTGTGTGCTCTGGTGTCTCTGGCTACACGCTGCTCTGCTGGGACATATTCTCGCTGCATGATTTCTCGCTAGTGCCTAGAGAGCTGTCTGGCAGCAGCCCTGTGCT
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	AGAGCTCTGGTGAAGGCTAGAGGAACAAGACCTTTTGTGATTTCTAGATCTACATTGTGCTGGACATGGAAGATGTATGGTCTTCTTGTGGCAGCAGCTAGCTTCTTCTGTGCCTGAGATTCTGCA
	GTTTAATCTGCTAGGAGTGCCCTGGTGGGACTGATGTGTGTGAGGTGGACTCAGCTGGGGGCTTTCTACCCTTCATGAGAAACCACAACTCTCTGCTGAGCCTGCCCCAGGAGCCCTATTCTTTTCTGAGCCTGCCCAGCAGGCTATGAGGAAGGCCCTGACTCTGAGTATGCCCTGCTGCCCCACCTGTATACCCTGTTCCATCAGGCCCATGTGGCCAGA
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	TTTCCTAAGGATTCTTCTACATGGACAGTTGATCATCAGCTGCTGTGGGGAGAGGCTCTGCTGATTACACCTGTGCTCCAGGCTGAGGTCGACAGGATATTTCCTCTGGGAACATGGTATGATCTGCAGACAGTGCC
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	ATTTTTCTGGCTAGAAATAATACAATTGTGAATGAGCTGGTGAGAGTGACATCTGAGGGAGCTGGACTGCAGCTGCAGAAGGTGACAGTGCTGGGAGTGGCTACAGCTCCTCAGCAGGTGCTGTCTAATGGAGTGCCTGTGTCTAA TTTTACATATTCTCCTGATACAAAGGTGCTGGATATTTGTGTGTCTCTGCTGATGGGAGAGCAGTTTCTGGTGTCTTGCTGTTAATGATTTAAATCTCGAGCCGGGCGGAGTGTGTTAGTCTCTCCAGAGGGAGGCTGGTTCCCCA GGGAAGCAGAGCCTGTGTGCGGGCAGCAGCTGTGTGCGGGCCTGGGGGTTGTTAAGTGCAATTATTTTTAATAAAAGGGGCATTTGGAAAAAAAAAAAAAAAGGTAGCAGTCGACAGATGAATTCTGCAGATCTGTGGCTTCTAGCT GCCCGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATTATGGGGTGGA GGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAG CCTCCCGAGTTGTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATT GCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTCTGATTTTAAAAAAAAGAGAAATGTTCTGGCACCTGCACTTGCACTGGGGACAGCCTATTTTGCTAGTTTGTTTTGTTTCGTTTTGTTTTGATGGAGAGCGTA TGTT
27	> coGAA plasmid construct TCTAGAGCTAGCATATGGATCCATCGATTTAGGGATAACAGGGTAATTATCAGCACACAATTGCCCATTATACGCGCGTATAATGGACTATTGTGTGCTGATATCTGTACACTTAAGGGCTAGATCTTAGCTTACGTCACTAGAG GGTCCACGTTTAGTTTTTAAGATCCATTGATCTCCTAAACGCTGCAAGATTCGCAACCTGGTATACTTAGCCTAGGCGCTAGGTCCTAGTGCAGCGGGACTTTTTTTCTAAAGTCGTTGAGAGGAGGAGTCGTCAGACCAGATAG CTTTGATGTCCTGATCGGAAGGATCGTTGGCCCCCCTGCAGGCAGCTGTTAATTAACTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGC GCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTTGTAGTTAATGATTAACCCGCCATGCTACTTATCTACGGCGCGCCACGCGTTCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCGAGCA TTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTTACTAGTTCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCGAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCT CAGGAGCACAAACATTCCTTACTAGTTCTAGAGCGGCCGCCAGTGTGCTGGAATTCGGCTTTTTTAGGGCTGGAAGCTACCTTTGACATCATTTCCTCTGCGAATGCATGTATAATTTCTACAGAACCTATTAGAAAGGATCACC 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28	> coGAA plasmid construct
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29	> coGAA plasmid construct
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	TGGATGTGGTACATCTTCCTGGGCCCTGAGCCCAAGTCTGTGGTCGGGTGACCTTTCACTGAGCGGCCTGGCCTTCCCACCTGTGCAGCGACACTGCCATCACCAG
	GCAGGTGTTGCAGAAATATGACAGGGCCCACTTCCCCCTGGATGTGCAGTGGAATGATCTGGACTTACATGGATGTCATTGCAGGCACTTCACCTTCAACAAGGATGGCTTCGTCGATTGGCACAGCAG
	GGGGGCAGGAGGTACATGATTGTGGACCCAGCTACAGGCCCTGAGAGGCCGAGGGGGGTGTTCATCACTAATGAGACTGGCCAGCCCCTGATTGGCAAGGTGTGGC
	CTGGGAGCACTGCCTTCCCTGACTTCACCAACCCCACTGCCCTGGTGGGAGATATGGTGGCTGAGTTCCATCACCAGGTTGCCCTTGAACATTATTAGGGCTCTGA
	GGATGGGTGCCTAACAATGAGCTGGAGAACCCCCTTATGTGCTGGGGTGGTGGGGGCACCTGCCACCTATCCTGTCTACCCACTACAACCTGCAAATCTGTATGGGCTGACT
	GAGGCTATTGCCAGCCACAGGGCCCTGGTGAAGGCTAGGGGACCAGGCCTTTGTGATCAGCAGACACCTTTGCTGGCCATTGGACTGGGGATGTGTGGTCTAGCTGGGAGCAGCTGGCCAGCTT
	CTGTGCCTGAGATCCTGCAGTTCAATCTGCTGGGGTGCCCCTGGTGGGGGCTGATGTGTGTGGTTCCTGGGCAATACCTCTGCAGCAGCTCTGTCGCTCACCTGTTCCACCAGGCCCATGTGGCTGGGGAGACTGTG
	CAGCCTGCTGAGCCTGCCTCAGGAGCCCTATTCTTTTCTGAGCCTGCCCAGCAGGCTATGAGGAAGGCCCTGACTCTGAGGTATGCCCTCGCTTCCACACCTGTTCCACCAGGCCCATGTGGCTGGGGAGACTGTG

	GCCAGGCCCCTGTTCCTGGAGTTCCCCAAGGATAGCTCTACCTGGACTGTGGACCATCAGCTGCTGTGGGGGAGGCCCTGCTGATCACCCCTGTGCTGCAGGCTGGCAAGGCTGAGGTGACTGGCTACTTTCCTCTGGGCACCT GGTATGATCTGCAGACTGTGCCCATTGAAGCCCTGGGCAGCCTGCCTCCTCCCCCTGCTGCCCCTAGGGAGCCTGCCATCCACTCTGAGGGCCAGTGGGTGACCCTGCCAGCCCCTCTGGACACCATCAATGTGCATCTGAGGGC TGGCTACATCATTCCCCTGCAGGGCCCTGGGCTGACCACCACTGAGAGCAGGCAGCAGCCCATGGCTCTGGCTGTGGCCCTGACCAAGGGGGGGGAGGCCAGGGGGGAGCTGTTCTGGGATGATGGGGAGAGCCTGGAGGTGCTG GAGAGGGGGGCCTACACCCAGGTGATCTTCCTGGCCAGGAATAATACCATTGTGAATGAGCTGGTGAGGGTGACTTCTGAGGGGGCTGGCCTGCAGCTGCAGAAGGTGACTGTGCTGGGGGTGGCTACTGCTCCTCAGCAGGTGC TGTCTAATGGGGTGCCTGTGAGCAACTTCACTTACAGCCCTGACACTAAGGTGCTGGACATTTGTGTGAGCCTGCTGATGGGGGAGCAGTTCCTGGTGTCTTGGTGCTGATTTAAATCTCGAGCCGGGCGGAGTGTGTTAGTCTC TCCAGAGGGAGGCTGGTTCCCCAGGGAAGCAGAGCCTGTGTGCGGGCAGCAGCTGTGTGCGGGCCTGGGGGTTGTTAAGTGCAATTATTTTTAATAAAAGGGGCATTTGGAAAAAAAAAAAAAAAGGTAGCAGTCGACAGATGAAT TCTGCAGATCTGTGGCTTCTAGCTGCCCGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTG TCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCTCCT GGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGT GATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTCTGATTTTAAAAAAAAGAGAAATGTTCTGGCACCTGCACTTGCACTGGGGACAGCCTATTTTGCTAGTTTGTTTT GTTTCGTTTTGTTTTGATGGAGAGCGTATGTTGTTTAAACGCGGCCGCGTAGATAAGTAGCATGGCGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGG CCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGTTAATTAAGGCGCCCTAGGCCGACCCTTAGACTCTGTACTCAGTTCTATAAACGAGCCATTGGATACGAGATCCG TAGATTGATAAGGGACACGGAATATCCCCGGACGCAATAGACACCGGTGGACAGCTTGGTATCCTGAGCACAGTCGCGCGTCCGAATCTAGCTCTACTTTAGAGGCCCCGGATTCTGATGGTCGTAGACCGCAGAACCGATTGGG GGGATGAGATCTACTAGTTATCAGCACACAATTGCCCATTATACGCGCGTATAATGGACTATTGTGTGCTGATATAGGGATAACAGGGTAATTCTAGAGCTAGCATATGGATCCATCGATTTGATGCGGTATTTTCTCCTTACGC ATCTGTGCGGTATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTC TTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGC CCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACTCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGTCTATTGGTT AAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCG CCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTA ATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATA TTGAAAAAGGAAGAGTATGAGCCATATTCAACGGGAAACGTCGAGGCCGCGATTAAATTCCAACATGGATGCTGATTTATATGGGTATAAATGGGCTCGCGATAATGTCGGGCAATCAGGTGCGACAATCTATCGCTTGTATGGG AAGCCCGATGCGCCAGAGTTGTTTCTGAAACATGGCAAAGGTAGCGTTGCCAATGATGTTACAGATGAGATGGTCAGACTAAACTGGCTGACGGAATTTATGCCTCTTCCGACCATCAAGCATTTTATCCGTACTCCTGATGATG CATGGTTACTCACCACTGCGATCCCCGGAAAAACAGCATTCCAGGTATTAGAAGAATATCCTGATTCAGGTGAAAATATTGTTGATGCGCTGGCAGTGTTCCTGCGCCGGTTGCATTCGATTCCTGTTTGTAATTGTCCTTTTAA CAGCGATCGCGTATTTCGTCTCGCTCAGGCGCAATCACGAATGAATAACGGTTTGGTTGATGCGAGTGATTTTGATGACGAGCGTAATGGCTGGCCTGTTGAACAAGTCTGGAAAGAATGCATAAACTTTTGCCATTCTCACCG GATTCAGTCGTCACTCATGGTGATTTCTCACTTGATAACCTTATTTTTGACGAGGGGAAATTAATAGGTTGTATTGATGTTGGACGAGTCGGAATCGCAGACCGATACCAGGATCTTGCCATCCTATGGAACTGCCTCGGTGAGT TTTCTCCTTCATTACAGAAACGGCTTTTTCAAAAATATGGTATTGATAATCCTGATATGAATAAATTGCAGTTTCATTTGATGCTCGATGAGTTTTTCTAAGCGTATAATGGTCTAGAGCTAGCATATGGATCCATCGATTCCAT TATACGCCTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCG TCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAA CTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTC GTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGC GCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTC GATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT
30	> coGAA plasmid construct TCTAGAGCTAGCATATGGATCCATCGATTTAGGGATAACAGGGTAATTATCAGCACACAATTGCCCATTATACGCGCGTATAATGGACTATTGTGTGCTGATATCTGTACACTTAAGGGCTAGATCTTAGCTTACGTCACTAGAG GGTCCACGTTTAGTTTTTAAGATCCATTGATCTCCTAAACGCTGCAAGATTCGCAACCTGGTATACTTAGCCTAGGCGCTAGGTCCTAGTGCAGCGGGACTTTTTTTCTAAAGTCGTTGAGAGGAGGAGTCGTCAGACCAGATAG CTTTGATGTCCTGATCGGAAGGATCGTTGGCCCCCCTGCAGGCAGCTGTTAATTAACTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGC GCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTTGTAGTTAATGATTAACCCGCCATGCTACTTATCTACGGCGCGCCACGCGTTCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCGAGCA TTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTTACTAGTTCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCGAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCT CAGGAGCACAAACATTCCTTACTAGTTCTAGAGCGGCCGCCAGTGTGCTGGAATTCGGCTTTTTTAGGGCTGGAAGCTACCTTTGACATCATTTCCTCTGCGAATGCATGTATAATTTCTACAGAACCTATTAGAAAGGATCACC CAGCCTCTGCTTTTGTACAACTTTCCCTTAAAAAACTGCCAATCCCACTGCTGTTTGGCCCAATAGTGAGAACTTTTTCCTGCTGCCTCTTGGTGCTTTTGCCTATGGCCCCTATTCTGCCTGCTGAAGACACTCTTGCCAGCAT GGACTTAAACCCCTCCAGCTCTGACAATCCTCTTTCTCTTTTGTTTTACATGAAGGGTCTGGCAGCCAAAGCAATCACTCAAAGTTCAAACCTTATCATTTTTTGCTTTGTTCCTCTTGGCCTTGGTTTTGTACATCAGCTTTGA AAATACCATCCCAGGGTTAATGCTGGGGTTAATTTATAACTGAGAGTGCTCTAGTTCTGCAATACAGGACATGCTATAAAAATGGAAAGATGTTGCTTTCTGAGAGATCAGGTGGATTCTTGGGCATTTGCTTAAGCTTGGTACC GCCACCATGGGGGTGAGGCACCCCCCCTGCTCTCACAGGCTGCTGGCTGTGTGTGCCCTGGTGAGCCTGGCCACTGCTGCTCTGCTGGGGCACATCCTGCTGCATGACTTCCTGCTGGTGCCCAGGGAGCTGTCTGGCAGCTCTC CTGTGCTGGAGGAAACTCATCCTGCCCATCAGCAGGGGGCCTCTAGGCCAGGCCCCAGGGATGCCCAGGCCCATCCTGGCAGGCCCAGAGCTGTGCCCACCCAGTGTGATGTGCCCCCCAACAGCAGGTTTGATTGTGCCCCTGA TAAGGCCATCACCCAGGAGCAGTGTGAGGCCAGGGGCTGCTGCTACATCCCTGCCAAGCAGGGGCTGCAGGGGGCCCAGATGGGCCAGCCCTGGTGCTTCTTCCCCCCTTCTTACCCCAGCTACAAGCTGGAGAACCTGTCTTCT TCTGAGATGGGCTATACTGCCACCCTGACCAGGACCACTCCCACCTTCTTCCCCAAGGACATCCTGACTCTGAGACTGGATGTGATGATGGAGACTGAGAACAGGCTGCACTTCACCATCAAGGACCCTGCCAACAGGAGGTATG AGGTGCCTCTGGAGACTCCTAGAGTGCACAGCAGGGCTCCCTCTCCCCTGTACTCTGTGGAGTTCTCTGAGGAGCCCTTTGGGGTGATTGTGCACAGACAGCTGGATGGGAGGGTGCTGCTGAACACCACTGTGGCCCCCCTGTT CTTTGCTGACCAGTTCCTGCAGCTGTCTACCTCTCTGCCCAGCCAGTACATTACTGGGCTGGCTGAACATCTGTCTCCCCTGATGCTGAGCACCAGCTGGACCAGGATCACTCTGTGGAACAGGACCTGGCCCCCACTCCTGGG

	GCCAATCTGTATGGGAGCCACCCATTCTACCTGGCCCTGGAGGATGGGGGCTCTGCCCATGGGGTGTTCCTGCTGAACAGCAATGCCATGCATGGTCGCAGCCTTCCCCTGCCCTGAGCTGGAGGTCTACTGGGGGCATCC
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	CATGGTTTACTCACCACTGCGATCCCCGGGAAAACAGCATTCCAGGTATTAGAAGAATATCCTGATTCAGGTGAAAATATTGTTGATGCGCTGGCAGTGTTCCTCGCCGCCAGTTGCTTCTGCCAGTGCGATCTGCTCACCG
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	GTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGC
	GCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTC
	GATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT
31	> ITR-to-ITR construct with coGAA GAA nucleic acid w/201 signal peptide
	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTTGTAGTTAATTGATTAA
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	ACTGCCCTGGCCTGGTGGAGGATATGGTGGCTGAGTTTCATGACCAGGTGCCCTTTGATGGCATGTGGATTGACATGAATGAGCCCAGCAACTTTATCAGGGCTCTGAGGTGCTGCAGAGGGGGCCTACACCCAGGTGATCTCCTGGCTAGGAATA
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	TGAGCGAGCGAGCGCGCAG
32	> ITR-to-ITR construct with coGAA GAA nucleic acid w/wtIL signal peptide
	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTTGTAGTTAATGATTAA
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	TCGACCAGCCAGCCGCCAG
33	> ITR-to-ITR construct with coGAA GAA nucleic acid w/ITmut signal peptide
	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTTGTAGTTAATGATTAA
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	TCGACCAGCCAGCCGCCAG
34	> ITR-to-ITR construct with coGAA GAA nucleic acid w/A2 signal peptide
	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTTGTAGTTAATGATTAA
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	TGGACCCTGCTATTTCTACTCTGGCCCTGCTGGCAGCTATAGGCCCTATGATGAGGGGCTGAGGAGGGGGTGTTCATCACTATAATGAGATCGGCCACGCCCTCATTGGCAAGTGTGCCCTACTGCCTTCCCTCATTC
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	CGGCCTCAGTGAGCGAGCGAGCGCGCAG
35	> ITR-to-ITR construct with coGAA GAA nucleic acid w/PXP signal peptide
	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTTGTAGTTAATGATTAA
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36	> dbDBA plasmid with M2 LSP and GAA nucleic acid
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37	> dbDBA plasmid with M3 LSP and GAA nucleic acid
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	GCAGCTGTGTGCGGCCTGGGGGTTGTTAAGTGCAATTATTTTTAATAAAAGGGGCATTTGGAAAAAAAAAAAAAAAGCTAGCACATCGACACATGATGAATTCTGCAGATCTGTGGCTTCTAGCTGCCGGGTGGCATCCCTGTGACCCC
	TCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGCCTTGTCCTCTAATAAAATTAAGTTGTCTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCA
	AGTTGGGAACAAGAGTCCACTATTGAAAGCACACAATCTTGGCTCACTGCAATCCGCCTCCTGGGTTCAACGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGG
	CATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTACAGGCGTGAACCACCT
	GCTCCCTTCCCTGTCCTTCTGATTTTAAAAAAAAGAAAATGTTCTGGCACCTGCACTTGCACTAGTTTGTTTTCGTTTTGTTTGATGGAGAGCGTATTGTTGTTTAAACGCGGCCGCGTAGA
	TAAGTAGCATGGCGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTGCGCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGA
	GCCAGCCAGCCGCCCACAGTTAATTAAGCGCCCCTAGGCCCGCACCCTTGACTCGTACTCAGTTCTATAAACCGACCATTCCATACACGACATCCCTACGATTCCGCCAATATACGACACGGTGCGACAGC
	TTGGTATCCTGAGCAGCAGTCGCGCGTCCGAATCTAGCTCTACTTTAGAGGCCCCGGATTCTGATGGTCGTAGACCGCAGAACCGATTGGGGGGATGAGATCTACTAGTTATCAGCACACAATTGCCCATTATACAGCGGCGTATAATG
	GACTATTGTTGTGCTGATATAGGATAACAGGGTAATTCTAGAGCTTAGCATTGATCGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAG
	CGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGC
	TCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTC
	TTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGTCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTAC
	AATTTTATTGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGA
	GCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGA
	ACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGCCATATTCAACGGGAAACGTCGAGGCCGCGATTAAATTCCAA
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	ATGAGATGGTCAGACTAAACTGGCTCGACGGAATTTATGCCTCTTCCGACCATCAAGCATTTTATCCGTACTCCTGATGATGCATGGTTACTCACCACTCGCGATCCCGGAAAAACAGCATTCCAGGTATTAGAAGAATATCCTGAT
	TCAGGTGAAAATATTGTTGATGCGCTGGCAGTGTTCCTGCGCCGGTTGCATTCGATTCCTGTTGTAATTGTCCTTTTAACAGCGATCGCGTATTTCGTCTCGCTCAGGCGCAATCACGAATGAATAACGGTTTGGTTGATGCGAG
	TGATTTTGATGACGAGCGTAATGGCTGGCCTGTTGAACAAGTCTGGAAAGAAATGCATAAACTTTTGCCATTCTCACCGGATTCAGTCGTCACTCATGGTGATTTCTCACTTGATAACCTTATTTTTGACGAGGGGAAATTAATAG
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	AAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTCTGCGCGTAATCTGCTGCTTGCTTG
	AAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAG
	AACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTC
	GTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGA
	GGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTG
	GCCTTTTGCTGGCCTTTTGCTCACATGT
38	> coGAA nucleic acid sequence w/o signal peptide
	CAGCAGGGGCCAGCAGGCCAGGCCCACCCTGGCAGACCCAGGCTGTGCCCACCCAGCAGATTTGACTGTGCCCCTGATAAGGCCATTACTCAGGAACAGTGTGAGGC
	CAGGGGCTGCTGCTATATCCCTGCCAAGCAGGGCCTGCAGGGGGCCCAGATGGGGCAGCCCTGGTGCTCTTCTCCCCCCCAGCTACCCCTCTTATAAGCTGGAGAATCTGAGCAGCTCTGAAATGGGCTACACTCTGACCA
	GGACTACCCCCACCTTCTCCCCAAGGATTCTGACTCTGAGGATTCCAAGGCATGCCCTGGTGCTCTTCACCCTCAAGGATCTCCCAGGTGCACTCT
	AGGGCCCCCAGCCCCCTGTATTCTGTGGAGTTCTCTGAGGAGCCTTTGGGGTCATTGTCCACAGGCAGCTGGATGGCAGGGTGTCGCTGTTCTTTGCTGACCAGTTCCTGCAGCTGAGCACCAG
	CCTGCCTTCTCAGTACATTACTGGCCTGGCTGAGCACCTCTGATGCTGAGCACCCTCTTGGACCAGAATCACCCTGTGGAACAGGGACCTGGCTCCCCACTCCTGGGGCCAACCTGTATGGCAGCCCACCCCTTCTACCTGG
	CCCTGGAGGATGGGGGCTCTGCCCATGGGGTGTTCCTGCTGAACAGCAATGCCATGATGTGGTGCTGCAGCCCTCTCCTGCCCTCTGCTTGGAGATCTACTGGGGGCATCCTGGATGTGTATATCTTCCTGGGGCCTGAGCCCAAG
	TCTGTGGTGCAGCAGTACCTGGATGTGGTGGCTACCCCTTCATGCCCCCTACTGGGCCTGGGCTTCCACCTGTCCAGCTGGCGTACTCTTCTACTCATCTACCAGGCAGGTGTGGAGAACATGACAGGCTCACTTCCC
	TCTGGATGTGCAGTGGAATGACCTGGACTACATGGACTTCACTTTTAATAAGGATGGGTTCAGGCAACTTCCATCAGGGGGGCAGGAGATATATGATGATTGTGGCACCCTGCTA
	TTTCTAGCTCTGGCCCTGCTGGCAGCTATAGGCCCTATGATGAGGGGCTGAGGAGGGGGGTGTTCATCACTAATGAGACTGGCCAGCCCCTGATTGCCTTCCCTGATTTCACCAACCCCACT
	GCCCTGGCCCTGGTGGAGGATATGGTGGCTCCATTTGACATGATGAATCGACCCCAGCAACTTTATCAGGCCTGAAGATGGCCTGGCTCCTCACAGGGCCCTGGTGAAGGCTAGGG
	TGTGCCTGGGGTGTGGGGGGCACCCTGCAGGCTGCCACCATCTGTGCCAGCAGCCACCACTATAACCTGCACACAACCTGTATGGCCATTGCCTCATCAGGGCCCTGGTGAAGGCTAGGG
	GGACTAGGCCCTTTGTGATCAGCAGGTCTACTTTTGCTGGCCAATGCCTGGCACTGGGGATGTGTGGTCTAGCTGGGAGCTGCCCAGCTGTGCTGAGCCTGCCCCAGGAGCCCTATTCTTTTCTGA
	CTGGTGGGGGCTGATGTGTGTGGCTTCCTGGCCAATACCTCTGAGGAGTGGTGTGAGGTGGACTCAGCTGGGGGCTTTCTACCCCTTCATGACAAACCACACAACTCTCTGCTGAGCCTGCCCCAGGAGCCCTATTCTTTTCTGA
	GCCTGCCCAGCAGGCTATGAGGAAGCCCTGCTGCCCACCTGTATACCCTGTTCCATCAGGCCCATGTGGCCAGACCTCTGTTCCTGGAGTTCCCCAAGGATAGCTCTACTT
	GGACTGTGGACCACCAGCTGCTGTGGGGGAGGCTCTGCTGTGCTGCAGGCTGAGGTGACTGGCTATTTCCCCCTGGGCACCTGGTGATCTGCAGACTGTGCCCATTGAGGCCCTGGCTCTCTG
	CCCCCTCCCCCTGCTGCCCCCAGGGAGCCTGCCATCCACTCTGAGGCCTGCCTGCCCCTCTGGACACTATCAATGTGCACCTGAGGCCCTGGCCTGAGGCCCTGGCTGAGTACCACTGA
	GTCTAGGCAGCAGCCCATGGCCCTGGCTGTGGCTCTGACCCAAGGGGGGGGAGGCCAGGGGGAGCTGTTCTGGAGTGATGGGGAGTCTCTGGAGTGCTGGAGTGATTCTTCCTGGCTAGGAATTAACA

	CCATTGTCAATGAGCTGGTGAGGGTGACCTCTGAGGGGCTGGCCTGCAGCTGCAGAAGGTGACTGTGCTGGGGGTGCCTACTGCCCCCCAGCAGGTGCTGAGCAACTTCACCTATAGCCCTGACACC AAGGTCGTCGACATCTGTCTGACGCCTGCTGATGGCGCAGCAGTTCCTCGTGAGCTGCTGCTAA
39	> coGAA GAA nucleic acid ATGGGAGTGAGGCACCCCCCCTGCTCCCATAGACTCCTGGCTGTCTGTCCCTTGGCTTGGCCAACAGCTGCACTC CAGCAGGGGCCAGCAGGCCAGGCCCACCCTGGCAGACCCAGGGCTGTGCCCACCCAGTGTGATGTGCCTCCCAACAGCAGATTTGACTGTGCCCCTGATAAGGCCATTACTCAGGAACAGTGTGAGG CCAGGGCTGCTGCTATATCCCTGCCAAGCAGGCCTGCAGGGCCCAGATGGGCAGCCCTGGTGTTCTTCCCCCCCAGCTACCCCTCTTATAAGCTGGACAATCTGAAATGGGCTACACTGCCACTCTGAC CAGGACTACCCCCACCTCTTCCCCAAGGATATTCTGACTCTGAGGCTGGATGATGGACTGCACTTCACCATCAAGGACAGGAGTATGAGGTGCCCCTGGAAACTCCCAGGGTGCAC TCTAGGGCCCCCAGCCCCCTGTATTCTGTGGAGTTCTTGGGGTCATTGTCCACAGGCAGCTGGATGGCAGGGTGCTGCTGAATACTACTGTGGCCCCCTCTGTTCTTTGCTGACCAGTTCCTGCAGCTGAGCA CCAGCCTGCCTTCTCAGTACATTACTGGCCTGGCTGAGCATCTCGAGCCCCCTCGATGCTGAGCACCTCTTGGACCAGAATCACCCTGTGGAACAGGGACCTGGCTCCCACTCCTGGGCCAACCTGTATGGCAGCCACCCCTCTA CCTGGCCCTGGAGGATGGGGGCTCTGCCCATGGGTGTTCCTGCTGAACAGCAATGCCATGGATGTGGTCTGCAGCCCTCTCCTGCCTGTCTTGGAGATCTACTGGGGGCATCCTGGATGTGTATATCTTCCTGGGGCCTGAG CCCAAGTCTGTGGTGCAGCAGTACCTGGATGTGGTGGGCTACCCCCCTCATGCCCCCCTACCTGTGCAGGTGGGCCTACTCTTCTACTGCTATCACCAGGCAGGTGGTGGAGAACATGACCAGGGCTC ACTTCCCTCTGGATCTGCAGTGCAATGACCTGGACTTACATGGAGACTTCACTTTTAATAAGGATGGCTTCAGGACTTTCCTGCCATGCTGCACGGAGCTGTGGCCAGACGTCTGTTCCTGGAGTTCCCCAA CCCTGCTATTTCTAGCTCTGGCCCTGCTGGCCAGCTATAGGCCCTATGATGAGGGGCTGAGAGGGGGTGTTCATCACTAATCAGACTGGCCACCAAGGTGTGGCCTGGCTCTACTGCCTTCCCTGATTCCACC AACCCCACTGCCCTGGCCTGGTGGGAGGATATGGTGGCTGAGTTTCATGACCAGGTGCCCTTTGATGGCATGTGGATTGCACATGAATGAGCCCACGCAACTTTATCAGGGCCTCTGAAGATGGCTGCCCCAACAATGAGCTGCGAGA ACCCCCCCTATGTGCCTGGGGTGGTGGGGGCACCCTGCAGCTGCCACCAGTCCTGACAGCACCCACTATAACCTGCACAACCTCTATGGCCTGACTGAGGCCATTGCCTCTCACAGGCCCTGGT GAAGGCTAGGGGGACTAGGCCCTTTGTGATCAGCAGGTCTACTTTTGCTGGCCATGGCAGGTATGCTGGCACTGGACTGGGAGCAGCTGGCCTGAGATCCTGCAGTTTAATCTG CTGGGGTGCCCCTGGTGGGGCTGATGTGTGTGAGGTGGATCTCAGCTGGGGGCTTTCTACCCCTTCATGAGAAACCACAACTCTGCTGAGCCTGCCCCAGGAGCCCT ATTCTTTTTCTGAGCCTGCCCACGCAGGCTATCGAGGTATGCCCTGCTGCCCACCTGTATACCCTGTTCCATCAGGCCCATGTGGCTGGGAGTTCCCAA GGATAGCTCTACTTGGACCTGGACCACCAGCTGCTGTGGGGGGAGGCTCTGCTGATCACCCCTGTGCTGCAGGCTGGGAAGGCTGAGGTCATGCTGCACATCAATCGTGCCCATTGAG GCCCTGGGCTCTCTGCCCCCTCCCCCTGCTGCCCCCAGGAGCCTGCCACTCTGAGGGCCAGTGGGTGACCCTGCCCCTCTGCCCCTCTGCACACTATCAATGTGCACCTGAGGGCCTGCAGGGCCCTG GCCTGACTACCACTCAGTCTAGGCAGCAGCCCATGGCCTGGCTCTGACCAAGGGGGGGAGGCCAGGGGCAGCTCTGTTCTGGCATGATGCGCAGTCTCTGGAGGTGCTGGAGGTGTCCTACACCCAGGTGATCTT CCTGGCTAGGAATAACACCATTGTCAATGAGCTGGTGAGGGTGACCTCTGAGGGGGCTGGCCTGCAGCTGCAGAAGGTGACTGTGCTGGGGGTGCCTGTGAGCAATGGGGTGCCTGTGAGCAACTTC ACCTATAGCCCTGACACCAAGGTGCTGGACATCTGTGTGAGCCTGCTGATGGGGGAGCAGTTCCTGGTGAGCTGGTGCTAA
40	>5'UTR|SERPINA7 CAGGTGGATTCTTGGGCATTTGCTTAAGCTTGGTACCGCCACC
41	> 5' UTR|24BP CAGGTGGATTCTTGGGCATTTGCT
42	>FL-POLYA ATCTGTGGCTTCTAGCTGCCCGGGTGGCATCCCTGTGACCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCT ATAATAATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGG
43	CTGTGGCTTCTAGCTGCCCGGGTGGCATCCCTGTGACCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTAT AATAATTATGGGGTGCAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGG
44	>FL-POLYA plus AATAA signal CTGTGGCTTCTAGCTGCCCGGGTGGCATCCCTGTGACCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTAT AATAATTATGGGGTGCAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGG
45	>REV RNA POLII TERMINATOR ACAGAAATGTTCTGCACCTGCACTTGCACTGGGGACAGCCTATTTTGTTTTGTTTCGTTTTGTTTTGATGGACAGCCGTATGTT
46	>Stuffer DNA with 48bp synthetic polyA GTCCTTCAACGTCGAACTGTAGCACTCTGGATAGCTTAGCTTAGATAGTTTCAAGGATAGCAACCAACAACACGATAGTTTAGAAATTGTTCTAGATCTTCTGCTACTACTCGAGAGATAGTTGACTTCTAGAAGACT CTGGATAGAGAGCTTCCTGTGGTTTCTATTTCAACACTTCGAGCGATTTAGATAGAGGCGTCAATTGAGAACAAAAACTGGACACCTGTTTCTAGAACACTAGTGCTAGTCTTCTCAAGGCTTGATACGTCCTGCCACTCACACA CAAAAAACCAACACACAGATTAATGAAAATAAAGATCTTTTATTAGAGACGGAGTGGATAGTTTAGACTTATCCTGTGTCCAACTAGCCAGAGTAGAGAGAGTGACTAGGTGGATCGAGATCGTCGTCT ATTTGACTGCTAGCCTGTCTCGTCGTAGTCCAAATCTTCAAATACTCTGGCGACTAGTAAACTTGAATCTGTGTATCTAACACGACAAGGCTACTCCTTTGAGTTTCTAGTGATAAAGTGCGACTGGATCTAGCTAGTTGAGTTT CTAGAAACTAGTCCCAAAGCTACTAGCACTA
47	>synthetic polyA CACACAAAAAACCAACACACAGATTAATGAAAATAAAGATCTTTTATT
48	>3'UTR AGCCCGCCGCAGTGTGTTAGTCTCTCCACAGCGAGCCTGGTTCCCCAGGCAACAGACGCCTGTGTCGCGGCCGCCTCGGCGTTG
49	>3'UTR CCGGGCGGAGTGTGTTAGTCTCTCCACAGAGGAGGCTGGTTCCCCAGGGAAGCAGAGCCTGTGTGCGGCCAGCAGCTGTGTGCGGCCTGGGGGTTG

50	>GAA 3'UTR CCGGCCGAGTGTGTTAGTCTCTCCACAGAGGAGGCTGGTTCCCCAGGGAAGCAGACAGGCCTGTGTGCGGGCAGCAGCTGTGTCGCCCGCCTGGGGGTTGTTAAGTCCAATTATTTTTAATAAAAGGGGCATTTGGAAAAAAAAAAAA AGGTAGCAGTCGACAGATGA
51	>endogenous wtGAA signal peptide ATGGGAGTGAGGCACCCCCCCTGCTCCCATAGACTCCTGGCTGTCTGTCCCTGGTGTCCTTGGCAACACGTGCACTC
52	>N-terminal deletion of GAA nucleic acid sequence ATGGGAGTGAGGCACCCCCCTGCTCCCATAGACTCCTGGCTGTCTGTCCCTGGTGTCCTTGGCAACACGTGCACTCCTGGGCACATCCTACTCCATGATTTCCTGCTGGTTCCCAGAGAGCTGAGTGGCTCCTCCCCAGTCC TGGAGGAGACTCACCCAGCTCAC
53	>nucleotide of codon optimized GAA signal peptide ATGGGAGTGAGGCACCGCCTGCTCCCACCGGCTCCTGGCCGTCTGCCCCTCGTGTCCTTGGCAACCGCTGCACTCCTG
54	>nucleotide of 201 signal peptide ATGGAGTTCGGCTGAGCTGGGTCTTTCTGGTGGCCCTGCTGAAGGGAGTCCAGTGCGAG
55	>nucleotide of wt Il2 signal peptide ATGTACCGTATGCAGCTGCTGTCCTGCATCGCACTGTCACTGGCACTGGTTACCAACTCA
56	>nucleotide of mut Il2 signal peptide ATGTACCGTATGCAGCTGCTGAGCTGCTGCATCGCACTGTCACTGGCACTGGTTACCAACTCA
57	>nucleotide of 2AM signal peptide ATGGGCAAGAACAAACTCCTTCATCCAAGTCGGTTCTTCCTCCTTGGTCCTCCCTGCCCACAGATGCC
58	>nucleotide of P2P signal peptide ATGAGAAAAGACAGACTTCTTCATTTATGTCTTGTGCTACTTCTTTATCCTGCTTTCTGCCAGTGACTCAAACTCT
59	>endogenous GAA signal peptide MGVRHPPCSHRLLAVCALVSLATAALL
60	>201 signal peptide MEFGLSWVFLVALLRGVQC
61	>wt Il2 signal peptide MYRMQLLSCIALSLALVTNS
62	>mut Il2 signal peptide MYRMQLLLIALSLALVTNS
63	>A2M signal peptide MGKNKLLHPSLVLLLLVLLPTDA
64	>P2P signal peptide MRKDRLLHLCLVLLLLTLLSASDSNS
65	>artificial signal peptide MWWRLWWLLLLLLLLWPMVWA
66	> cathpetsin L signal peptide LLLLAVLCLGT
67	>nucleotide of hAAT signal peptide ATGCCGTCTCTCTGTCTCGTGGGCATCCTCCTGCTGGCAGGCCTGTGCTGCCTGGTCCCTGTCTCCCTGGCT
68	> FIBrat Signal Peptide MLRGPGPGRLLLLAVLCLGTSVRCTETGKSKR
69	> FIBrat Signal Peptide MLRGPGPGRLLLLAVLCLGTSVRCTETGKSKRLALQIV
70	>FN1 human signal peptide MLRGPGPGLLLLAVQCLGTAVPSTGA
71	>FN1 x. leavis signal peptide MRRGALTGLLLVLCLSVVLRAAPSATSKKRR
72	>hIGF2 signal peptide ATGGGAATCCCAATGGGGAAGTCGATGCTGGTGCTTCTCACCTTCTTGGCCTTCGCCTCGTGCTGCATTGCT

73	>FN1 rat signal peptide ATGCTCAGGGGTCCGGGACCCGGCGCGGCTGCTGCTAGCAGTCCTGTGCCTGGGCACATCGGTCGCCTGCACCCAAACCCGGAAGACAGCAAGACGG
74	>FN1 rat signal peptide ATG CTC AGG GGT CCG GGA CCC GGG CGG CTG CTG CTA GCA GTC CTG TGC CTG GGG ACA TCG GTG CGC TGC ACC GAA ACC GGG AAG AGC AAG AGG CAG GCT CAG CAA ATC GTG-3'.
75	>FN1 human signal peptide ATGCTTAGGGGTCCGGGGCCCGGCTGCTGCTGGCCAGTGCCTGGGGACAGCGGTGCCCTCCACGGGAGCC
76	>FN1 x. leavis signal peptide ATG CGC CGG GGG GCC CTG ACC GGG CTG CTC CTG GTC CTG TGC CTG AGT GTT GTG CTA CGT GCA GCC CCC TCT GCA ACA AGC AAG AAG CGC AGG
77	> preprocathepsin L signal peptide (rat) MTPLLLLAVLCLGTALA
78	>prepro-alpha 2 type collagen signal peptide (homo sapiens) MLSFVDTRTLLLLAVTLCLATC
79	>SEQ 79 CTCGCGCCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGCCTCAGTGAGCGAGCGAGCGCGCAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCT
80	>SEQ 80 AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGCGCCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCCGGCTTTCCCCGGGCGCCTCAGTGAGCGAGCGAGCGCGCAG
81	>SEQ 81 CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGCCTCAGTGAGCGAGCGAGCGCGCAGAGGGAGTGGCCAACTCCATCACTAGGG
82	>SEQ 82 AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGCGCCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG
83	> MH-257 ITR AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGCGCCGCTCGCTCGCTCACTGAGGCAATTTGATAAAAAATCGTCAAATTATAAACAGGCTTTGCCTGTTTAGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCC AACTCCATCACTAGGGGTTCCT
84	>MH-258 ITR AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGCGCCGCTCGCTCACTGAGGGATAAAAATCCAGGCTTTGCCTGCCTCAGTCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCT
85	>MH Delta 258AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGCGCCGCTCGCTCACTGAGGGATAAAAATCCAGGCTTTGCCTGCCTCAGTCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCC T
100	>MH Telomere-1 ITR AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGGGATTGGGATTGGCGCTCGCTCGCGGGATTGGGATTGGCGATTGGATTGCATAAAAATCAATCCCAATCCCAATCCCAATCCC GCGAGCGAGCGCGCAATCCCAATCCCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCT
101	>MH Telomere-2 ITR AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGCGGCTCGCTCGGGATTGGGATTGGGATTGGGATTGGCGATTGATAAAAATCAATCCCAATCCCAATCCCAATCCCAATCCCAATCCC GCGCAGGAGAGGGAGTGGCCAACTCCCATCACTAGGGGTTCCTAAGCTTATTATA
102	>MH PolII 258 ITR AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGCGCCGCTCGCTCACTGAGGCGCCTATAAAGATAAAAATCCAGGCTTTGCCTGCCTCAGTTAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTA GGGGTTCCT
103	>MH 258 Delta D conservative CTAGTGATGGAGTTGGCCACTCCCTCTCGCGCCGCTCGCTCACTGAGGGATAAAAATCCAGGCTTTGCCTGCCTCAGTCGAGCGAGCCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAG
104	>5' AAV2-ITR TTGGCCACTCCCTCTCTGCGCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCACTGACCGACCACGCCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCT
105	>3' AAV2 ITR AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGCGCCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGCGCAGAGAGGGAGTGGCCAA
448	> ITR (145bp) AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGCGCCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGCGCAGAGAGGGAGTGGCCAA
449	> ITR (lacking 9bp) AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCGCGCCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGCGCAGAGAGGG

450	>CRE0052 GGCCATATAAAACAGGGCAAGGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCCAGCCACC
451	> pAAV-LSPhGAA |Actus101 plasmid CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTGGAGGGGTGGAGTCG TGACGTGAATTACGTCATAGGGTTAGGGAGGTCGGCCGCTCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCGAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTT ACTAGTTCTAGGAGTTAATTTTTAAAAAGCAGTCCAAAGTCCCTTCGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCCTTACTAGTTCTAGAGCGGCCGCCACCGCGGTGGCTCGAA TTCGGCTTTTTAGGGCTGGAAGCTACCTTTCGACATCATTTCCTCTGCGAATGCATGTATAATTTCTACAGAACCTATTAGAAAGGATCACCCAGCTCTGCTTTTGTACAACTTTCCCTTTAAAAAACTGCCAATCCCCACTGCTG TTTGGCCCAATAGTGAGAACTTTTTCCTGCTGCCTCTTGGTGCTTTTGCTTTGTTGTCCTCTTGGCCTTGGTTTTGTGAAGACACTCTTGCCCAGCATGGCAATCCTCTTCTCTTTGTTTTACATGA AGGGTCTGGCAGCCAAAGCAATCACTCAAAGTTTCAAACCTTATCATTTTTGCTTTGTTCCTCTTGGCCTTGGTTTTGTGAAGACACTCTTGCCCAGGGTTAATTTATAACTGAGAGTGCTCTA GTTCTGCAATACAGGACATGCTATAAAAATGGAAAGATCAGCTTACATGTGGTACCGAGCTCGGATCCACTAGTAACGGCCGCCAGTGTGCTGGAATTCGGCTTCTCCAAGCCATCTCCAACCATGGGA GTGAGGCACCCGCCCTGCTCCACCGGCTCCTGGCCCTCGTGTCCTTGGCAACCGCTGCACATCCTACTCCATGATTTCCTGCTGGTTCCCGAGAGCTGAGTGGCTCCTCCCCAGTCCTGGAGG AGACTCACCCAGCTCACCAGCAGGAGCCCAGGAGACCAGGGCCCGGCATGCCCAGGACACCCCGGCCGTCCCATCCCCCCCAACACGCCGCTTCGATTGCGCCCCTGACAAGGCCATCAC CCAGGAACAGTGCGAGGCCCGCCGCTGCTACATCCCTGCAAAGCAGGGGCTGCAGGAGCCCAGATGGGGCACGCCCTGGTGCTTCTCCCACCCACGCTACCCACCCTGGAGAACCTGACGCTCCTCTGAAATGGGC TACACGGCCACCCTCACCCGTACCCGCCCCACCTCCTTCCCCAAGGACATCCTGCGGCTGGACGTGATGATGACGGTTCCTCCACTTCACGATCAAAGATCCAGCTAACAGGCGGTACAGAGGTGCCGTTGG AGACCCCGCGTGTCCACAGCCGGCACCGTCCCCACTCTACAGCGTGGAGTTCTCCGAGGAGCCCTTCGGGGTCATCCTGCTGACTGAACACGACGGTGGCGCCCCTGTTCTTGCGGACCA GTTCCTTCAGCTGTCCACCTCGCTGCCCTCGCAGTATATCACAGGCCTCGCCGAGCACCTCAGTCCCCTGATGCTCAGCAACCAGGTGGAGCTGTGGAACCGGGACATTCGCGCCCACGGCCGGTGCGAACCTCTAC GGGTCTCACCCTTTCTACCTGGCGCTGGAGGACGGCGGGTGTTCCTGTCTAAACAGCAATGCCATGGTGTCCTGCAGCCGAGCCCTGCCCTTAGCTGGAGTCCTGGATGTCTACA TCTTCCTGGCGCAGCCCAAGAGCGTGGTGCAGCAGTACCTGGCAGTTGTGGGATACCGTTCATGCCGCCATCACTGTGGGCCTGTCCACCTGTGCCGCTGGGCGTGGTGGA GAACATGACCAGGGCCCACTTCCCCCTGGACGTCCGGAGGGACTTCACGTTCAACAAGGATGGCTTCCGGGCCATGGTGCAGGAGCTGCACCAGGGCGGCCGCGCGC TACATGATGATCGTGGATCCTGCCATCAGCAGCCCTACAGGCCTACAGGGCTGCGGAGGGGGTTTCATCACCAACAGACCGGCGATTGGGAAGGTATGGCCCGGGTCCACTG CCTTCCCCGACTTCACCAACCCCAGCCTGGCCTGGTGGGAGGACATGGTGGCTGAGTTCCATGACCAGGTGCCCTTCGACGGCATGTCGATTGACATGAACGACGGTCTGAGGACGGCTGCCC CAACAATGAGCTGGAGAACCCACCCTACGTGCCTGGGGTGTTGGGGGCACCCTCCAGCCGCCACCATCTGTGCCTCCAGCCACACTACAACCTGCACAACCTCTACGGCCTGACCGAACGCCATCGCC TCCCACAGGGCGCTGGTGAAGGCTCGGGGACACGCCCATTTGTGATCTCCCGCTCGACCTTTGCTGGCCACGGCCGATACACCGGCCGCCACTGGAGCAGCTCGCCTCCTCCGTGCCAGAAA TCCTGCCAGTTTAACCTGCTGGGGTGCCTCTGGTCGGGCCGACGTCTCCGGCTTCCTGGCCAACACCTCGCTATCGTCGACCCAGTGGCGCCCTTCTACCCCTTCATGCGGAACCCACAACAGCCTGCTCAG TTCCTGGAGTTCCCCAAGGACTCTAGCACCACGAGCTCCCTGCTGGGGGGAGGCCCTGCCGGTCAGCCAGCCACAGAAGTCTGCCAGCCGCCCCCTGGACACCATCAACGTCCACCTCCGGGGCTGGGTACATCAT AGACGGTGCCAATACGAGGCCCTTGGCAGCCTCCCACCCCCACCTGCAGCTCCCGTGAGCCAGCCATCCACAGCGAGGGCAGTGGGTGACGCTGCCGGCGCTGGGTACATCAT CCCCCTGCAGGGCCCTGGCCTCACAACCACAGAGTCCCGCCAGGCCATGGCCTGGCTGTGGCCATCGACCAAGGTGTGGAAGTGCTGGAAGTGGAGGGCCGCCACGCCGTG TACACACAGGTCATCTTCCTGGCCAGGAATAACACGATCGTGGTACGTGTGAGGGAGCTGGCCCTGCAGCTGCAGAAGTGATCTGCCTCTCCTCCAACGGTG TCCCTGTCTCCAACTTCACCTACAGCCCCGACACCAAGGTCCTGCTGTCTCGCTGTTCGATGGAGAGCAGTTTCTCGTCAGCTCGTCTTACCGCGGCGCGACTGTGGTTCCCCAGG GAAGCAGACCTGTCTGCGGCAGCAGCTGTCGTGCGGCCTGGGGTTCTTAAGTGCAATTATTTTAATAAAGGGCCATTTGGAAAAAAAAAAAAAGGTACAGTCGACAGATGTGTGGCTTCTACGCTG CCCGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCCTTCTGGGCAGCAATGATCCGCGAGCAGGGGCCGTGCCGTTCAACCC GGGGGGTGGTATGGAGCAAGGGCAAGTTGGGAAGACAACCTGAGTTGTTGGATTCCAGGCATCGCAGTAACTACTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGC GCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG	
97	>LSP|LSP_ACTUS_101 TCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCGAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTTACTAGTTCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAG TCCAAGTGCCCTTGCGAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTTACTAGTTCTAGAGCGGCCGCCACGTGTGCTGGAATTCGGCTTTTTAGGGCTGGAAGCTACCTTTCGACATCAT TTCCTCTGCGAATGCATGTATAATTTCTACAGAACCTATTAGAAAGGATCACCCAGCTCTGCTTTTGTACAACTTTCCCTTTAAAAAACTGCCAATCCCACTGCTGTTTTGGCCTCTTGCCTTGGTTTTGTGAAGACACTCTTGCCCAGCATGGCAATCCTCTTCTCTTTGTTTTACATGA GTGCTTTTGCCTATGGCCCCTATTCTGCCTGCTGAAGACACTCTTGCCAGCATGGACTTAAACCCCTCCAGCTCTGACAATCCCTCTTTCTCTTTGTTTTACATGAAGGGTCTGGCAGCCAAAGCAATCACTCAAAGTTCAAACC TTATCATTTTTTGCCTTTGTTCCTCTTGGCCTTGGTTTTGTACATCAGCTTTGAAAATACCATCCCAGGGTTAATTTATAACTGAGAGTGCTCTAGTTCTGCAATACAGGACATGCTATAAAAATGGAAAG ATGTTGCTTTCTGAGAGATCAGCTTACATGTG (SEQ ID NO: 437)	
99	>M3 LSP	

	TCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAAGTGCCCTTGCGAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTTACTAGTTCTAGGAGTTAATTTTTAAAAAGCAGTCAAAAG
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86	> CRM_SP0412
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87	> CRM_SP0239
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88	> CRM_SP0265 (CRM_LVR_131_A1)
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89	> CRM_SP0240
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90	> CRM_SP0246
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91	> SP0412
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92	> SP0422
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93	> SP0239
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94	> SP0265 (LVR_SP131_A1)
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95	>SP0240
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96	> SP0246
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	AACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGGCCCAGGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
144	> SP0131

	GGCCCGGGAGGCGCCTTTGGACCTTTGCAATCCTGGCGCACTGAACCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAA CATAGCGACAGACCTTAAGGCATGACTCAGTAACACAGATAAGCTTTCTGTCCTGCAGGCATATAAAACAGGGCAAGCCACACACTCATACCAGACCAATCACCACCAAGCCTGGAATAACTGCAGCCACC (SEQ ID NO: 144),
145	> CMV-IE 5′ UTR TCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCGGGAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGACTCTAT AGGCACACCCCTTTGGCTCTTATGCATGAACGGTGGAGGGCAGTGTAGTCTGAGCAGTACTCGTTGCTGCCGCGCGCCACCAGACATAATAGCTGACAGACTAACAGACCATGTTCCTTTCCATGGGTCTTTTCTGCAG (SEQ ID NO: 145),
146	> SP0265-UTR AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTGTACCGGCCCCGGGAGGCGCCCTTTGGACCTTTTGCAATCCTGGC GCACTGAACCCTTGACCCCTGCCCTGCAGCCCCGCAGCTTGCCCACACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGCAAAGTGCACTACAGCCTATAGGCATGACTCAGTAACACAGATAAG CTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCGGGAACGGTGCA TTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGAACGGTGGAGGGCAGTGTAGTCTGAGCAGTACTCGTTGCTGCCGCGCGCCACCAGACAT AATAGCTGACAGACTAACAGACTGTTCCTTTCCATGGGTCTTTTCTGCAGGCCACC (SEQ ID NO: 147
147	> SP0239-UTR CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCGTTGCCCGGCAACGGCCCAGCTCTGTGCCAAGTGTTTGAGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTT GGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAATCCTGGCCCTGCAGCCCCCGCAGCTTGCTGTTT GCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCACTCACTGAACCCTTGACCCCTGCCCTGCAGGCCATATAAACAGGGGCAAGGCACAGACTCA TAGCAGAGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCGGGAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATA GACTCTATAGGCACACCCCTTTGGCTCTTATGCATGAACGGTGGAGGGCAGTGTAGTCTGAGCAGTACTCGTTGCTGCCGCGCGCCACCAGACATAATAGCTGACAGACTAACAGACTGTTCCTTTCCATGGGTCTTTTCTGC AGGCCACC (SEQ ID NO: 147),
148	> SP0240-UTR CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCGTTGCCCGGCAACGGCCCAGCTCTGTGCCAAGTGTTTGAGCTTGGCAAAGGTCTTATCTC CCAGCTCGCCCAGGCCCAGTGTTCCAGGAATGTGACCTTGCTGCAGCCAGCCGCTGGAGGGGCAGAGGGGATGGGCTGGAGGTTGAGCAAACAGAGCAGCATTCCTCTTCTCCAGTGCCCTCCTTCCTGTCTC TGCCTCTCCCTCCCTTCCTCAGGCATCAGACGCGACACTTCAGGGACAGCCCAGCTTGCCAGGCACTGTCAGATCCGCCCATCCACCCTCTTTTCGACTCCATAGAAGACACCGGGACCGATCCAGCCTCCG CGGCCGGGAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGAACGGTGGAGGGCAGTGTAGTCTGAGCAGTACTCGTTGCTGCCG CGCGCGCCACCAGACATAATAGCTGACAGACTAACAGACTGTTCCTTTCCATGGGTCTTTTCTGCAGGCCACC (SEQ ID NO: 148
149	> SP0246-UTR AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAATCCTGGCGCACTG AACCCTTGACCCCTGCCCTGCAGCCCCGCAGCTTGCCCACACTCTATTTGCCCAGGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGAC CTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCGGGAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGAACGGTGGA GGGCAGTGTAGTCTGAGCAGTACTCGTTGCTGCCGCGCGCGCCACCAGACATAATAGCTGACAGACTAACAGACTGTTCCTTTCCATGGGTCTTTTCTGCAGGCCACC (SEQ ID NO: 149),
150	> SP0131_A1-UTR GGCCCGGGAGGCGCCTTTGGACCTTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAA CATAGGCAGACCTTAAGGGATGACTCAGTAACACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGAC ACCGGGACCGATCCAGCCTCCGCGGCCGGGAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGAACGGTGGAGGGCAGTGTAGTC TGAGCAGTACTCGTTGCTGCCGCGCGCGCCACCAGACATAATAGCTGACAGACTAACAGACTGTTCCTTTCCATGGGTCTTTTCTGCAGGCCACC (SEQ ID NO: 150),
154	>LVR412_askbioEU GCCATTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGGCGATCGGTGCGGGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTGCAAGGCGATTAAGTTGGGTAACGCCAGGGTTTTCCCAGTCACGACGTTGTAA AACGACGGCCAGTGAATTCCTCGAGATTTAAATGACGTTGGCCACACTCCCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGC AGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTGAGTTTAAACTTCGTCGAGGCCGCGACGGTAGGTTAATTTTTAAAAAGCAGTCAAAGTCGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATA ATCTCAGGAGCACAAACATTCCCCCTGTTCAAACATGTCCTAATACTCTGTCTCTGCAAGGGTCATCAGTAGTTTTCCATCTTACTCAACATCCCTCCCAGTGAGTCATATTGTTGCTCCATGTTAACAGGCATC CCTTAAACAGGATATAAAAGGACTTCAGCAGGACTGCTCGAAACATCCCACTCAGCCACCGCTCCCACCGGCTCCTGCGCCCTCGTGTCCTTGGCAACCGCTGCACTCCTGGGGC ACATCCTACTCCATGATTTCCTGCTGGTTCCCCGAGGTCATCCCCAGTCCTGGAGGAGACTCACCACGCTCACCAGGCCACAGCAGGCCCGGGATGCCCAGGCACACCCGGCGTCCAGAGC AGTGCCCACACAGTCGCGACGTCCCCCCCCAACAGCCCCTCCATTGCCGCCCCCTCACAAGGCCATCACCCACGCCCCGGCTGCTCTACATCCCTCGCAAGCAGGGCTCGCAGGAGCCCACGATGGGCACCCC TGGTGCTTCTTCCCACCCAGCTACCCCAGCTACAAGCTGAGGAACCTGAGCTCCTCTGAAATGGGCTACACGGCCACCCTGACCCGTGCGGCTGGCGTGGACGTGATGATTGG AGACTGAGAACCGCCTCCCACTTCACGATCAAAGATCCAGCTAACGAGGCGCTACGAGGTGCCCTTGGAGACCCCGCGTCCCACAGCCGGGCACCGTCCCCACTCTACAGCGTGGAGTTCTCCGAGAGACCCTTCGGGGTGATCGT GCACCGGCAGCTGGACGGCGGCGTGCTGTCAACACGACGGTGGCGCCCTGTTCTTTGCGGACCAGTTCCTTCAGCTGTCCCTCGCCGAGCACCTCAGTCCCTCGATGCTCAGC ACCAGCTGGACCAGGATCACCCTGTGGAACCGGGACCTTCGCCCACGCCCGGTCCTACCTTTCTACCTGGCGCTGGAGGACGGCGGTCTTCCTGCTAAACAGCAATGCCATGG ATGTGGTCCTCGCAGCCGAGCCCTGCCCTTAGCTGGAGGTCGACAGGTGGGATCCTGGATGTCTACATCTTCCTGGGCCCAAGAGCCCAAGACGGTGGTGCAGCAGTACCTGGACGCTTACGTGCCGCCATACTG

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	ACCTGGAATGCTGTTTTTCCGGGGATCGCCACGTGTGCAGTAACCATGCATCATCAGGAGTACGGATAAAATGCTTGATGGTCCCCAACAGGCCATTATAAATTCCTCCATCACACATTAGCCATCATTCGCCAA
	CGCTACCTTTGCCATGTTTCAGAAACAACTCTGGCGCATCGGGCTTCCCATACAAGCGATAGATTGTCGCACCTGATTGCCGCAGCCCATTTATACCCATATAAATCAGCATCCATGTTGGAATTTAATCGCGG
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	CAGATGCGTAAGGAGAAAATACCGCATCAGGC
158	>LVR422 Stuffer
	GCCATTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGGCGATCGGTGCGGGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTGCAAGGCGATTAAGTTGGGTAACGCCAGGGTTTTCCCAGTCACGACGTTGTAA
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	GCTGGACCCAGCTGGGGGCCTTCTACCCCTTCATGCGCCCAGGAGCCGTCACAGCTTCAGCGACGCCGGCCCAGCAGGCCATGAGGAAGGCCCTCACCCTCGCGCTACGCACTCCTCCCCCA
	CCTCTACACACTGTTCCACCAGGCCCACGTCGCGGGGGACGACCGTGGCCCGGCCCTCTTCCTGAGTTCCCCAAGGACTCTAGACCTGCAGTCCTCCACCCACCTCAGCTCCTCGTGGACCACCAGCTCCTGTCACATCACCCAGTCGCTC
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	AAATACCGCATCAGGC
	>LVRSP0412 insertion
	GGTACCGAGCTCGGATCCACTAGTAACGGCCGCCAGTGTGCTGGAAT
106	>mod GAA (H199R, R223H)
	MGVRHPPCSHRLLAVCALVSLATAALLGHILLHDFLLVPRELSGSSPVLEETHPAHQQGASRPGPRDAQAHPGRPRAVPTQCDVPPNSRFDCAPDKAITQEQCEARGCCYIPAKQGLQGAQMGQPWCFFPPSYPSYKLENLSSSE
	MGVTATLTRTPTFPPKDILTLRLDVMMETENRLHFTIKDPANRRYEVPLETPRVHSRAPSPLYSVEFSEEPFGVTVHRQLDGRVLLNTTVAPLFFADQFLQLSTSLPSQYITGLAEHLSPLMLSTSWTRITLWNRDLAPTPGAN
	LYGSHPFYLALEDGGSAHGVFLLNSNAMDVVLQPSPALSWRSTGGILDVYIFLGPEPKSVVQQYLDVVGYPFMPPYWGLGFHLCRWGYSSTAITRQVVENMTRAHFPLDVQWNDLDYMDSRRDFTFNKDGFRDFPAMVQELHQGG
	RRYMMIVDPAISSSGPAGSYRPYDEGLRRGVFITNETGQPLIGKVWPGSTAFPDFTNPTALAWWEDMVAEFHDQVPFDGMWIDMNEPSNFIRGSEDGCPNNELENPPYVPGVVGGTLQAATICASSHQFLSTHYNLHNLYGLTEA
	IASHRALVKARGTRPFVISRSTFAGHGRYAGHWTGDVWSSWEQLASSVPEILQFNLLGVPLVGADVCGFLGNTSEELCVRWTQLGAFYPFMRNHNSLLSLPQEPYSFSEPAQQAMRKALTLRYALLPHLYTLFHQAHVAGETVAR
	PLFLEFPKDSSTWTVDHQLLWGEALLITPVLQAGKAEVTGYFPLGTWYDLQTVPIEALGSLPPPPAAPREPAIHSEGQWVTLPAPLDTINVHLRAGYIIPLQGPGLTTTESRQQPMALAVALTKGGEARGELFWDDGESLEVLER
	GAYTQVIFLARNNTIVNELVRVTSEGAGLQLQKVTVLGVATAPQQVLSNGVPVSNFTYSPDTKVLDICVSLLMGEQFLVSWC
107	>mod GAA (H199R, H203L, R223H)

	MGVRHPPCSHRLLAVCALVSLATAALLGHILLHDFLLVPRELSGSSPVLEETHPAHQQGASRPGPRDAQAHPGRPRAVPTQCDVPPNSRFDCAPDKAITQEQCEARGCCYIPAKQGLQGAQMGQPWCFFPPSYPSYKLENLSSSE
	MGYTATLTRTTPTFFPKDILTLRLDVMMETENRLHFTIKDPANRYEVPLETPRVLSRAPSPLYSVEFSEEPFGVTVHRQLDGRVLLNTTVAPLFFADQFLQLSTSLPSQYITGLAEHLSPLMLSTSWTRITLWNRDLAPTPGAN
	LYGSHPFYLALEDGGSAHGVFLLNSNAMDVVLQPSPALSWRSTGGILDVYIFLGPEPKSVVQQYLDVVGYPFMPPYWGLGFHLCRWGYSSTAITRQVVENMTRAHFPLDVQWNDLDYMDSRRDFTFNKDGFRDFPAMVQELHQGG
	RRYMMIVDPAISSSGPAGSYRPYDEGLRRGVFITNETGQPLIGKVWPGSTAFPDFTNPTALAWWEDMVAEFHDQVPFDGMWIDMNEPSNFIRGSEDGCPNNELENPPYVPGVVGGTLQAATICASSHQFLSTHYNLHNLYGLTEAIASHRAL
	TASHRALVKARGTRPFVISRSTFAGHGRYAGHWTGDVWSSWEQLASSVPEILQFNLLGVPLVGADVCGFLGNTSEELCVRWTQLGAFYPFMRNHNSLLSLPQEPYSFSEPAQQAMRKALTLRYALLPHLYTLFHQAHVAGETVARPLFLEFP
	PLFLEFPKDSSTWTVDHQLLWGEALLITPVLQAGKAEVTGYFPLGTWYDLQTVPIEALGSLPPPPAAPREPAIHSEGQWVTLPAPLDTINVHLRAGYIIPLQGPGLTTTESRQQPMALAVALTKGGEARGELFWDDGESLEVLERGAYTQVI
	GAYTQVIFLARNNTIVNELVRVTSEGAGLQLQKVTVLGVATAPQQVLSNGVPVSNFTYSPDTKVLDICVSLLMGEQFLVSWC
108	>mod GAA w/201 signal peptide
	MEFGLSWVFLVALLKGVQCEGHILLHDFLLVPRELSGSSPVLEETHPAHQQGASRPGPRDAQAHPGRPRAVPTQCDVPPNSRFDCAPDKAITQEQCEARGCCYIPAKQGLQGAQMGQPWCFFPPSYPSYKLENLSSSEMGYTATL
	TRTTPTFFPKDILTLRLDVMMETENRLHFTIKDPANRYEVPLETPRVHSRAPSPLYSVEFSEEPFGVTVHRQLDGRVLLNTTVAPLFFADQFLQLSTSLPSQYITGLAEHLSPLMLSTSWTRITLWNRDLAPTPGANLYGSHPF
	YLALEDGGSAHGVFLLNSNAMDVVLQPSPALSWRSTGGILDVYIFLGPEPKSVVQQYLDVVGYPFMPPYWGLGFHLCRWGYSSTAITRQVVENMTRAHFPLDVQWNDLDYMDSRRDFTFNKDGFRDFPAMVQELHQGGRRYMMIV
	DPAISSSGPAGSYRPYDEGLRRGVFITNETGQPLIGKVWPGSTAFPDFTNPTALAWWEDMVAEFHDQVPFDGMWIDMNEPSNFIRGSEDGCPNNELENPPYVPGVVGGTLQAATICASSHQFLSTHYNLHNLYGLTEAIASHRAL
	VKARGTRPFVISRSTFAGHGRYAGHWTGDVWSSWEQLASSVPEILQFNLLGVPLVGADVCGFLGNTSEELCVRWTQLGAFYPFMRNHNSLLSLPQEPYSFSEPAQQAMRKALTLRYALLPHLYTLFHQAHVAGETVARPLFLEFP
	KDSSTWTVDHQLLWGEALLITPVLQAGKAEVTGYFPLGTWYDLQTVPIEALGSLPPPPAAPREPAIHSEGQWVTLPAPLDTINVHLRAGYIIPLQGPGLTTTESRQQPMALAVALTKGGEARGELFWDDGESLEVLERGAYTQVI
	FLARNNTIVNELVRVTSEGAGLQLQKVTVLGVATAPQQVLSNGVPVSNFTYSPDTKVLDICVSLLMGEQFLVSWC
109	>mod GAA w/wt IL2 signal peptide
	MYRMQLLSCIALSLALVTNSGHILLHDFLLVPRELSGSSPVLEETHPAHQQGASRPGPRDAQAHPGRPRAVPTQCDVPPNSRFDCAPDKAITQEQCEARGCCYIPAKQGLQGAQMGQPWCFFPPSYPSYKLENLSSSEMGYTATL
	TRTTPTFFPKDILTLRLDVMMETENRLHFTIKDPANRYEVPLETPRVHSRAPSPLYSVEFSEEPFGVTVHRQLDGRVLLNTTVAPLFFADQFLQLSTSLPSQYITGLAEHLSPLMLSTSWTRITLWNRDLAPTPGANLYGSHPF
	YLALEDGGSAHGVFLLNSNAMDVVLQPSPALSWRSTGGILDVYIFLGPEPKSVVQQYLDVVGYPFMPPYWGLGFHLCRWGYSSTAITRQVVENMTRAHFPLDVQWNDLDYMDSRRDFTFNKDGFRDFPAMVQELHQGGRRYMMIV
	DPAISSSGPAGSYRPYDEGLRRGVFITNETGQPLIGKVWPGSTAFPDFTNPTALAWWEDMVAEFHDQVPFDGMWIDMNEPSNFIRGSEDGCPNNELENPPYVPGVVGGTLQAATICASSHQFLSTHYNLHNLYGLTEAIASHRAL
	VKARGTRPFVISRSTFAGHGRYAGHWTGDVWSSWEQLASSVPEILQFNLLGVPLVGADVCGFLGNTSEELCVRWTQLGAFYPFMRNHNSLLSLPQEPYSFSEPAQQAMRKALTLRYALLPHLYTLFHQAHVAGETVARPLFLEFP
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	FLARNNTIVNELVRVTSEGAGLQLQKVTVLGVATAPQQVLSNGVPVSNFTYSPDTKVLDICVSLLMGEQFLVSWC
110	>mod GAA w/mut IL2 signal peptide
	MYRMQLLLIALSLALVTNSGHILLHDFLLVPRELSGSSPVLEETHPAHQQGASRPGPRDAQAHPGRPRAVPTQCDVPPNSRFDCAPDKAITQEQCEARGCCYIPAKQGLQGAQMGQPWCFFPPSYPSYKLENLSSSEMGYTATL
	TRTTPTFFPKDILTLRLDVMMETENRLHFTIKDPANRYEVPLETPRVHSRAPSPLYSVEFSEEPFGVTVHRQLDGRVLLNTTVAPLFFADQFLQLSTSLPSQYITGLAEHLSPLMLSTSWTRITLWNRDLAPTPGANLYGSHPF
	YLALEDGGSAHGVFLLNSNAMDVVLQPSPALSWRSTGGILDVYIFLGPEPKSVVQQYLDVVGYPFMPPYWGLGFHLCRWGYSSTAITRQVVENMTRAHFPLDVQWNDLDYMDSRRDFTFNKDGFRDFPAMVQELHQGGRRYMMIV
	DPAISSSGPAGSYRPYDEGLRRGVFITNETGQPLIGKVWPGSTAFPDFTNPTALAWWEDMVAEFHDQVPFDGMWIDMNEPSNFIRGSEDGCPNNELENPPYVPGVVGGTLQAATICASSHQFLSTHYNLHNLYGLTEAIASHRAL
	VKARGTRPFVISRSTFAGHGRYAGHWTGDVWSSWEQLASSVPEILQFNLLGVPLVGADVCGFLGNTSEELCVRWTQLGAFYPFMRNHNSLLSLPQEPYSFSEPAQQAMRKALTLRYALLPHLYTLFHQAHVAGETVARPLFLEFP
	KDSSTWTVDHQLLWGEALLITPVLQAGKAEVTGYFPLGTWYDLQTVPIEALGSLPPPPAAPREPAIHSEGQWVTLPAPLDTINVHLRAGYIIPLQGPGLTTTESRQQPMALAVALTKGGEARGELFWDDGESLEVLERGAYTQVI
	FLARNNTIVNELVRVTSEGAGLQLQKVTVLGVATAPQQVLSNGVPVSNFTYSPDTKVLDICVSLLMGEQFLVSWC
111	>codon optimized GAA signal peptide
	ATGGGATGAGGCACCCGCCCTGCTCCCACCGGCTCCTGCGCCGTCTGCCCCTCTTGGCCAACCGCTGCACTCCTACGCCGGCACACGTCCTCCCGACGTCC
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112	> M2 pJAL130 dbDNA_MYO_GAA_CUP_Stop TCTAGAGCTACGATATGGATCCATCGATTTAGGGATAACAGGGTAATTATCAGCACACAATTGCCCATTATACGCGCGTATAATGGACTATTGTGTGCTGATATCTGTACTTACGTTACGTTAGCTTACTAGTCACTAGAG GGTCCCAGGTTTAGTTTTAAGATCCATTGATCCTCCTAAACCGTCGCAACGATTCCGCAACCTGGTATACTTACCTAGGCCCTAGTCCATGTCCTAGCGGACTTTTTTTCTAAAGTCGTTGAGAGGAGGAGTCGTCAGACCAGATAG CTTTGATGTCCTGATCGGAAAGATCGTTGCCCCCCTGCAGGCAGCTGTTAATTAACTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGC GCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTTGTAGTTAATGATTAACCCGCCATGCTACTTATCTACGTAGCCATCCACGCGTTCTAGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCGAGCA TTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTTACTATGTTCTAGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCGAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCT CAGGAGCACAAACATTCCTTACTATGTTCTAGAGCGGCCGCCAGTGTGCTGGAATTCGCCCTTGAGCTCGAGATCTGAGTCCGGTAGCGCTAGCGGATCCACTAGTAACGGCCGCCAGTGTGCTGGAATTCTGCAGATATCCAGCA 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271	> CRM_SP0109 CCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGGGATGGGAAGAGGTGGGGCAGGAGAGGGACATAAAAGGGCTCTGAGGCATTGTA CTGTGAATTCCTTCAGTCTCCCTGTTTGGAGAAGACAGAGCCCTCGTTCCAGGGAAACAGAATATGCTCAGCATGACGCAGCACTCCCTGAACTTTCCGGTTACATCACCCAATAGCTGAGATCAGA
273	> CRM_SP0111 AGGTTAATTTTTAAAAGCAGTCAAAAGTCCCAAGTGCCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGCAGCACAAACATTCCTTTCGAGAAGACAGCCCCTCGTTCCAGGGAAACAG AATATGCTCAGCATGACGCAGCACTCCCTGAACTTTCCGGTTACATCACCCAATAGCTGAGATCAGA
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276	> CRM_SP0115 CCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGGGATGGGAAGAGGGTGGGGCAGGAGAGGGACATAAAAGGGCTCTGAGGCATTGTA CTGTGAATTCCTTCAGTCTCCCTGCTCTGCAGCCCTGCCTCCCTTGTTTAGGACCACACAGCACTGTCGGGTGTCTGCCTTTCCTTG
277	> CRM_SP0116 CCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGGGATGGGAAGAGGGTGGGGCAGGAGAGGGACATAAAAGGGCTCTGAGGCATTGTA CTGTGAATTCCTTCAGTCTCCTG
278	> CRM_SP0121 CCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCACCCTGGACAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACT CAGTAACAGATAAGCTTTGTGTGCCTGCA
279	> CRM_SP0124 CACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGAGGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGC TTTGTGTGCCTGCA
280	> CRM_SP0127 (CRM_LVR_127)

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281	> CRM_SP0127A1(CRM_LVR_127_A1)
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282	> CRM_SP0127V1 (CRM_LVR_127_V1)
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	CCTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGGGACAGAGCTGATCCTTGAACTCTTAAGTTCCAC
283	> CRM_SP0127V2 (CRM_LVR_127_V2)
	GGCGCCCTTTGGACCTTTTGCAATCCTGGAGCAAACAGCAAACACTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAAT
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284	> CRM_SP0128
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	TGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAG
285	> CRM_SP0131 (CRM_LVR_131)
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286	> CRM_SP0132 (CRM_LVR_132
	AGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGACCTTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCAGCCCCCGCAGCTTGCTG
	TTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCACTAACAGATAAGCTTTGTGTGCCTGCA
287	>CRM_SP0133 (CRM_LVR_133)
	AGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGACCTTTTGCAATCCTGCCG
288	> CRM_SP0155
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289	> CRM_SP0158
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290	> CRM_SP0163
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291	> CRM_SP0236
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292	> CRM_SP0239
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293	> CRM_SP0240
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294	> CRM_SP0241
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295	> CRM_SP0242
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296	> CRM_SP0243

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297	> CRM_SP0244 CTTTGGACCTTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCTGCACGCCCCCGCAGCTTCGTGTTTGCCCACTCTATTTGCCCAGCCCCCAGTCAAATCCCTGCCATATATTAGTGCCCTGAAGTCCAAAGGTAGAGGAA CCGAGTGTTTAAAAATTACTGTGGCTGTGGAGTCAACATGATGTAAAAAAACAAACATTTGGATAACACCAAGAAGCCAGATATGGTTGACTGGTTGACAAAAATAATTTGGGTTGCTTAATGGTGCACAAAGGTAA TGCAAAA
298	> CRM_SP0246 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAAATCTCAGGAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCACTG AACCCTTGACCCCTGCCCTGCACGCCCCCGCAGCTTCGTGTTTGCCCACTCTATTTGCCCAGCCCCAG
299	> CRM_SP0247 GCTGGTTTCTTATAAAACTGATGGAAGATACAAACACTATTAAAGAACGTGTTTGCATGTTGCAAATGATGTCCAAAGTCCAAACATTGTTAATAATTAATACTCCAATAAACATCATGTCAGAATTTCTGTTTTCTTTTCCCTTT GAACCTTTGCAGGATTGCCACATCATCAGGACCACACCTTCATCAGGAATGAATATCAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTCTGCTAAACAAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGGTCT GTGCCAAGTGTTTG
300	> CRM_SP0248 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCACTG AACCCTTGACCCCTGCCCTGCACGCCCCCGCAGCTTCGTGTTTGCCCACTCTATTTGCCCAGCCCCAGCAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAA CGGCCAGGTCTGTGCCAAGTGTTTG
301	> CRM_SP0249 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCACTG AACCCTTGACCCCTGCCCTGCACGCCCCCGCAGCTTCGTGTTTGCCCACTCTATTTGCCCAGCCCCAGCAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAA CGGCCAGGTCTGTGCCAAGTGTTTG
302	> CRM_SP0250 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCACTG AACCCTTGACCCCTGCCCTGCACGCCCCCGCAGCTTCGTGTTTGCCCACTCTATTTGCCCAGCCCCAGCAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAA CCAAACATTGTTAATAATTAATATACTCCAATAAACATCATGTCAGAATTTCTGTTTTCTTTTCCCTTTGAACCTTTGCAGGATTGCCACATCATCAGGAATGAATATCAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAA
303	> CRM_SP0251 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCACTG AACCCTTGACCCCTGCCCTGCACGCCCCCGCAGCTTCGTGTTTGCCCACTCTATTTGCCCAGCCCCAGAAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCC
304	> CRM_SP0252 AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCCAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGGTCT GTGCCAAGTGTTTG
305	> CRM_SP0253 AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCCCAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGGTCT GTGCCAAGTGTTTG
306	> CRM_SP0254 AGGTTAATTTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGCAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCAGGC TTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGGTCTGTTTG
307	> CRM_SP0255 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGCAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCAGGC TTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGGTCTGTTTG
308	> CRM_SP0256 ATTGGCATCTTCTATTGCTTTTCCTGGTGACTTCATTTTTCACTCTTGGCTAAAAATGGGTCTCTGATGATTTATTCTATCCTGGGTGTTCACAAGCTCGAAGAAGTTGTGTGGGGCCTGCTGCCAGTAACCCTGGGTGACGAAGC GTGACTCACCACTCCGAGGTCAGTGGGGGGGATGGAAGGCAGGGAGTCAGCTGACAAGATCTGCTGCTTTGTCACCAGGCCTTCTGCCAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACC TTTACCCCGTTGCCCGGCAACGGCCAGGTCTGTGCCAAGTGTTTG
309	> CRM_SP0257

	CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGCTGTCGCCAAGTGTTTGGCTGGTTTCTTATAAAACTGATGGAAGATACAAACACTATTA AAGCAACTGTTTGCATGTTCGCAAATGATCCCAAAGTCCAAACATTGTTAATAATTAATACTCCAATAAACATCATCTGCAGAATTTCTGTTTTCTTTTCCCTTTCAACCTTTGCAGCGATTGCCACATCATCAGCGACCACACCTTCA TCAGGAATGAATAT
310	> CRM_SP0258 CTGTTTGCTGCTTGCTTGCAATGTTTGCCCATTTTAGGGAGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAAACATTCCGGCCCGGGAG GCGCCCTTTGCGACCTTTTCGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCCACTCTATTTGCCCCAGCCCCTGGAGAGTCCCTTTAGCAGGCCAAAGTGCCAACATAGGCAGA CCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCA
311	> CRM_SP0259 CTGTTTGCTGCTTGCAATGTTTGCCCATTTTAGGGGCTGGTTTCTTATAAAACTGATGGAAGATACAAACACTATTAAAGAACTGTTTGCATGTTGCAAATGATGTCCCAAAGTCCCAAACATTGTTTAATAATTAATACTCCAATAA ACATCATGTCAGAATTTCTGTTTTCTTTTCCCTTTGAACCTTTGCAGGATTGCCACATCATCAGGAATGAATAT
312	> CRM_SP0264 CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGCTGTCGCCAAGTGTTTG
313	> CRM_SP0265 (CRM_LVR_131_A1) AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAAACATTCCTGTACCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGC GCACTGAACCCTTGACCCCTGCCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTCGAGACTCCTTTACCAGCCAAAGTCCAACATAGGCAGACCTTAAGGCATGACTCAGTAACAGATAAG CTTTGTGTGCCTGCA
314	> CRM_SP0266 (CRM_LVR_131_V1) AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCCTGTACCGGCCCGGGAGGCGCCCTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCT GTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCA
315	> CRM_SP0267 (CRM_LVR_131_V2) GGCGCCTTTGGACCTTTTGCAATCCTGGAGCAAACAGCAAACACTGTACCGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAATCCTGGCCCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACT CTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCA
316	> CRM_SP0268 (CRM_LVR_132_A1) AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGA GGTAAACAACAGGACTATAAATGGCCCGGGAGCGCCTTTGGACCTTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCTGCCCTGCAGCCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGT CCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCA
317	> CRM_SP0269 (CRM_LVR_132_V1) AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCCTGTACCAGAATGAACATTGAACTTTGCACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGCGCCCTTTGGA CCTTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGCAAAGTGCCAACATAGGCAGACCTTAAGGCATG ACTCAGTAACAGATAAGCTTTGTGTGCCTGCA
318	> CRM_SP0270 (CRM_LVR_132_V2) GGCGCCTTTGGACCTTTTGCAATCCTGGAGCAAACAGCAAACACTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAAT CCTGGCGCACTGAACCCTTGACCCCTGCCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACA GATAAGCTTTGTGTGCCTGCA
319	> CRM_SP0271 (CRM_LVR_133_A1) AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGA GGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAATCCTGGCG
320	> CRM_SP0272 (CRM_LVR_133_V1) AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCCTGTACCAGAATGAACATTGAACTTTGCACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGA CCTTTTGCAATCCTGGCG
321	> CRM_SP0273 (CRM_LVR_133_V2) GGCGCCCTTTGGACCTTTTGCAATCCTGGAGCAAACAGCAAACACTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAAT CCTGGCG
322	> CRM_SP0368 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCC
323	> CRM_SP0373 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTGTACCGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAATCCTGGC G

324	> CRM_SP0378 TGCTCTCTGACAAACATACGGTGGGTCCCACTGATCGAACTGTGCTGCCACAGTAAATGTAGCCACTATGCCTATCTCCATTCTGCCCTGTTCAAACATGTCCTAATACTCTGTCTCTGCAAGGGTCATCAGTAGTTT TCCATCTTACTCAACATCCTCCCAGTG
325	> CRM_SP0379 CCTCCCCGTGTTCCTGCTCTTTGTCCCTCTGTCCTACTTAGACTAATATTTGCCTTGGGTACTGCAAACAGGAAATGGGGGAGGGACAGGAGTAGGGCCGCCCTGTTCAAACATGTCCTAATACTCTGTCTCTGCAAGGGTCATC AGTAGTTTTCCATCTTACTCCTCAACATCCTCCCAGTG
326	> CRM_SP0380 CCGCCCCCACTGAACCCTTGACCCCTGCCCTCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCCTGTTCAAACATGTCCTAATACTCTGTCTCTGCAAGGGTCATCAGTAGTTTTCCATCTTACTCA ACATCCTCCCAGTG
327	> CRM_SP0381 AAGCTTTCTGAACACGCCAAACAGAGATTCCAAAGTTCAGGCACCAAAGTTCAGACCCTAACAGTTATTTACAAGGGTCAGTTAACCCCTGTTCAAACATGTCCTAATACTCTGTCTCTGCAAGGGTCATCAGTAGTTTTCCATCT TACTCAACATCCTCCCAGTG
328	> CRM_SP0384 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGCAATCCTGGCG
329	> CRM_SP0388 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCC
330	> CRM_SP0396 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTGTACCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGC GCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGCATGACTCAGTAACAGATAAGCTTTCTGTGCCTCGCA
331	> CRM_SP0397 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTGTACCCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGGCAGCT TGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCA
332	> CRM_SP0398 CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGCTGTCTGTGCCAAGTGTTTGAGGTTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTT GGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTG GACCTTTTGCAAATCCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGACTTTCTTGTCCAGCAGGCAGACCTTAAGGGA TGACTCAGTAACAGATAAGCTTTGTGTGCCTCGCA
333	> CRM_SP0399 AGAATGAACATTGAACTTTGGACTATACCTGAGGGTGAGGTAAACAACAGGACTATAAAT
334	> CRM_SP0403 CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGCTGTCTGTGCCAAGTGTTTGAGGTTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCC CACTCTATTTGCCCTGTACCGGCCCGGGAGGCGCCCTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCGGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGACTCC TTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCA
335	> CRM_SP0404 CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGCTGTCTGTGCCAAGTGTTTGAGGTTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCC CACTCTATTTGCCCTGTACCGGCCCGGGAGGCGCCCTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCGGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGACTCC GCAGCCCCCGGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAG
336	> CRM_SP0405 CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGCTGTCTGTGCCAAGTGTTTGAGGTTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCC CACTCTATTTGCCCTGTACCGGCCCGGGAGGCGCCCTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCGGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGACTCC GCAGCCCCCGGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAG
337	> CRM_SP0406 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCGGCCCGGGAGGCGCCCTTTGCAATCCTGGCG
338	> CRM_SP0407 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCCAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAA CAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGGTCTGTGCCAAGTGTTTG
339	> CRM_SP0409

	AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCCCCTGTTCAAACATGTCCTAATACTCTGTCTCTGCAAGGGTCATC AGTAGTTTTCCATCTTACTCAACATCCTCCCAGTG
340	> CRM_SP0411 CCCTGTTCAAACATGTCCTAATACTCTGTCTCTGCAAGGGTCATCAGTAGTTTTCCATCTTACTCAACATCCTCCCAGTG
86	> CRM_SP0412 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCCCCTGTTCAAACATGTCCTAATACTCTGTCTCTGCAAGGGTCATC AGTAGTTTTCCATCTTACTCAACATCCTCCCAGTG (SEQ ID NO: 186)
341	> CRM_SP0413 AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTGTACCGGCCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGC G
342	> SP0107 CCCTGGAGAGTCCTTTAGCAGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGGGATGGGAAGAGGTGGGGCAGGAGAGGGACATAAAAGGGCTCTGAGGCATTGTA CTGTGAATTCCTTCAGTCTCCTGTTTGGAGAAGACAGAGCCAATGAGGCCCTCGTTCCAGGGAAACAGAATATGCTCAGCATCACCCAATAGCTGATCAGAGGCATATAA AACAGGGCAAGGCACAGACTCATAGCAGACGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
343	> SP0109 CCTGGAGAGTCCTTTAGCAGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGGGATGGGAAGAGGTGGGGCAGGAGAGGGACATAAAAGGGCTCTGAGGCATTGTAC TGTGAATTCCTTCAGTCTCCTGTTTGGAGAAGACAGAGCCAATGAGGCCCTCGTTCCAGGGAAACAGAATATGCTCAGCATCACCCAATAGCTGATCAGAGGCATATAAC AAAAAAATCAAATACTCAGTATTTCAGAAATAGATTAAATAGGTTACTTTTTACTCATGATAATGTGAAAGAATGATATAAAAACTTGATTTCCTCAACAACATTACTTCTTTGTAAATGTGGTTTCTACAAAGATGAAACTAC TAAACTTACAGGCCACC
344	> SP0111 AGGTTAATTTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGCAGCACAAACATTCCTTTCGAGAAGACAGAGCCAATGAGGCCCTCGTTCCAGGGAAACAG AATATGCTCAGCATGACGCAGCACTCCCTGAACTTTCCGGTTACATCACCCAATAGCTGAGATCAGAGGCATATAACTGCAGCCACC
345	> SP0112 CACTGAACCCTTGACCCCTGCCCTGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGAGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGT TAATAATCTCAGGAGCACAAACATTCCTTTGGAGAAGACAGAGCCAATGAGGCCCTCGTTCCAGGGAAACAGAATATGCTCAGCATCACCCAATAGCTGAGATCAGAGGCAT ATAAAACAGGGGCAAGGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
346	> SP0113 CACTGAACCCTTGACCCCTGCCCTGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGAGTCCTTTAGCAGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGC TTTGTGTGCCTGCAGGGGGATGGGAAGAGGGTGGGGCAGGAGAGGGACATAAAAGGGCTCTGAGGCATTGTACTCTCCTGGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGACGCAATCACCA CCAAGCCTGGAATAACTGCAGCCACC
347	> SP0115 CCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGGGATGGGAAGAGGGTGGGGCAGGAGAGGGACATAAAAGGGCTCTGAGGCATTGTA CTGTGAATTCCTTCAGTCTCCTGCTGCTCAGCCAGTCAGCCCTGCCTCCTTGTTTAGGACCACACAGCACTGCTGGGTGTCTGCCTTCTTGTGACTTAGCCCCTGTTTGCTCCTCCGATAACTGCAGGCGACGAGGACAGGGCCCTGTC ATATTCACCAGCAGGCCTCCCCCCGTTGCCCCTCTGGATCCACTGCTTAAATACGGACGAGGACAGGCCCTGTCTCCTCAGCTTCAGGCCACCACTGACCTGGGACAGTGAATCGCCACC
348	> SP0116 CCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGGGATGGGAAGAGGTGGGGCAGGAGAGGGACATAAAAGGGCTCTGAGGCATTGTA CTGTGAATTCCTTCAGTCTCCTGTGGACTTAGCCCCTGTTGCTCCTCCGATAACTGGGGTGACCTTGGTTAATATTCACCACGACGCCTCCCCCCGTTGCCCCTCTGGATCCACTGCTTAAATACGGACGAGGACAGGGCCCTGTC TCCTCAGCTTCAGGCACCACCACTGACCTGGCACAGTGAATCGCCACC
349	> SP0121 CCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCACCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACT CAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGACGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
350	> SP0124 CACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGC TTTGTGTGCCTGCACTCTTTGTTTTACATGAAGGGTCTGGCAGCCAAAGCAATCACTCAAAGTTCAAACCTTATCATTTTTGTTCCTCTTGGCCTTGGTTTTGTACATCAGCTTTGAAAATACCATCCCAGGGTTAAT GCTGGGGTTAATTTAATAACTAAGAGTGCTCTAGTTTTGCAATACAGGACATGCTATAAAAATGGAAAGATGTTGCTTTCTGAGACGATGCGCCACC
351	> SP0127 (LVR_SP127) AGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAATCCTGGCCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTG TTTGCCCACTCTATTTGCCCAGCCCCAGGGACAGACTGATCCTTGAACTCTTAAGTTCCACGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGACGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC

352	> SP0127A1 (LVR_SP127_A1) AGTTAATTTTTAAAAACAGTCAAAAGTCCAAGTGCCCCTTGCGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCACCAGCACACAAACATTCCTGTACCAGAATCAACATTGAACTTTGGACTATACCTGAGGGTGA GGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCTTTGCAATCCTGGCGCACTGAACCCTGCCCTGCAGCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGGGACAGAGCTG ATCCTTGAACTCTTAAGTTCCACGGGCATATAAAACAGGGCAAGGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGCAATAACTGCAGCCACC
353	> SP0127V1 (LVR_SP127_V1) AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCCTGTACCAGAATGAACATTGAACTTTGCACTATACCTGAGGGTCAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGA CCTTTGCAATCCTGGCGCACTGAACCCTGACCCCTGCCCTGCAGCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGGGACAGAGCTGATCCTTGAACTCTTAAGTTCCACGGGCATATAAAACAGGGCAA GGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
354	> SP0127V2 (LVR_SP127_V2) GGCGCCCTTTGCACCTTTGCAATCCTGGAGCAAACAGCAAACACTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTGCAAT CCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGGGACAGAGCTGATCCTTGAACTCTTAAGTTCCACGGGCATATAAAACAGGGGCAAGGCACAGACTC ATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
355	> SP0128 AGAATGAACATTGAACTTTGGACTATACCTGAGGGTGAGGTAAACAACAGGACTATAAATGAACATTGAACTTTGCACTATACCTGAGGGTCAGGTAAACAACAGGACTATAAATACTGAACCCTTGACCCCTGCCC TGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGGGGCATAAAACAGGGGCAAGGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
356	>SP0131 (LVR_SP131) GGCCCGGGAGGCGCCCTTTGGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGGGCATATAAAACAGGGGCAAGGCACAGAC CATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGCCACACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
357	> SP0132 (LVR_SP132) AGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCGCAGCTTGCTG TTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGAC TCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
358	> SP0133 (LVR_SP133) AGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAATCCTGGCGCTCTTTGTTTACATGAAGGGTCTGGCAGCCAAAGCAATCACT CAAAGTTCAAACCTTATCATTTTTTGCTTTGTTCCTCTTGGCCTTGGTTTTGTACATCAGCTTTGAAAATACCATCCCAGGGTTAATGCTGGGGTTAATTTATAACTAAGAGTGCTCTAGTTTTGCAATACAGGACATGCTATAA AAATGCAAACGATGTTGCTTTCTCAGAGATGCCCCACC
359	> SP0155 GCTGGTTTCTTATAAAACTGATGGAAGATACAAACACTATTAAAGAACTGTTTGCATGTTGCAAATGATGTCCAAAGTCCAAACATTGTTAATAATTAATACTCCAATAAACATCATGTCAGAATTTCTGTTTTCTTTTCCCTTT GAACCTTTGCAGGATTGCCACATCATCAGGACCACACCTTCATCAGGAATGAATATCCGATGACCTAATGATTCTGAGCTTGCCAAAGGTCTATCTCCCAGCTGCCGCCAGGCTCCAGGTTCCAGGAATGTGACCTTTGCTGCAG CAGCCGCTGGAGGGGGCAGAGGGATGGGCTGGAGGTTGAGCAAACAGAGCAGCAGTTCCTCTTCTCCAGTGCCCTCCTTCCCTGTCTCTCCCAGCTGCCGCCAGGCCCAGGCCAGCAGCGGAGACTTCAGGGAG ACCAGAGCCCAGCTTGCCAGGCACTGAGCTAGAAGCCCTGCCATG
360	> SP0158 ATTGGCATCTTCTATTGCTTTTCCTGGTGACTTCATTTTTCACTCTTGGCTAAAAATGGGTCTCTGATGATTTATTCTATCCTGGGTGTTGCACAAGCTGAAGAAGTTGTGTGGGGCCTGCTGCCAGTAACCCTGGGTGACGAAGC GTGACTCACCACTCCGAGGTCAGTGGGGGGATGGAAGGCAGGGGAGTCAGCTGACTAATGATTCTGAGCTTGGCAAAGGTCTTATCTCCCAGCTCGCCCAGGCC CAGTGTTCCAGGAATGTGACCTTTGCTGCAGCAGCCGCTGGAGGGGGCAGAGGGGATGGGCTGGAGGTTGAGCAAACAGCAGCAGTTCCTCTTCTCCAGTGCCCTCCTTCCCTGTCTCTCCCTCCTT CCTCAGCCATCAGACGCGAGACTTCAGCGACACCAGAGCCCAGCTTGCCAGGCACTGAGCTAGAAGCCCTGCCATG
361	> SP0163 TGAAATGCCTGCCATATATTAGTGCCCTGAAGTCCAAAGGTAGAGGAACCGAGTGTTTAAAAATTACTGTGGCTGTGCAGTCAACATGATGTAAAAAACAAACATTTGGATAACACCAAGAGGCAGATATGTTGGTTGAAATGTTG ACTGGTTGACAAAAATAATTTGGTTGCTTAATGGTGCACAAAGGTAATGCAAAACCGATGACCTAATGATTCTGAGCTTGGCAAAGGTCTTATCTCCCAGCTCGCCCAGGCCCAGTGTTCCAGGAATGTGACCTTTGCTGCAGC AGCCGCTGGAGGGGGCAGAGGGGATGGGCTGGAGGTTGAGCAAACAGAGCAGCAGTTCCTCTTCTCCAGTGCCCTCCTTCCCTGTCTCTCCCTCCTTCCCTGCCAGGCCCAGCCAGCAGCGGAGACTTCAGGGAGA CCAGAGCCCAGCTTGCCAGGCACTGAGCTAGAAGCCCTGCCATG
362	> SP0236 CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCGTTGCCCGGCAACGGCCCAGGTCTGTGCCAAGTGTTTGCCTTTGCAACAGCTTATCGGAAGCAAACAAGCTGAGGGGAAT TGAGCAAGAATTTCTGGGATACCAACAGCATAGGAGGAACAAAGGACGTAGAGGGAGGGTTGACTGTCTACACAGACAAAGCCAATGATTAACCAAACCTCTTGCAGATTTAAATAGGATGGGAACTAGGAGTGGCAGCAATCC TTTCTTTCAGCTGGAGTGCTCCTCAGGAGCCAGCCCCACCCTTAGAAAAG
93	> SP0239 CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCGTTGCCCGGCAACGGCCCAGGTCTGTGCCAAGTGTTTGAGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTT GGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCCACAAACATTCCGGCCCGGCAGGCGCCCTTTGCAACCTTTGCCAATCCTGGCCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCGCAGCTTGCTGTT

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95	> SP0240
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363	> SP0241
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364	> SP0242
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365	> SP0243
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366	> SP0244
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96	> SP0246
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367	> SP0247
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368	> SP0248
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369	> SP0249
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370	> SP0250
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371	> SP0251
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372	> SP0252
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373	> SP0253
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374	> SP0254
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375	> SP0255
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376	> SP0256
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377	> SP0257
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378	> SP0258
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379	> SP0259
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380	> SP0264
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94	> SP0265(LVR_SP131_A1) AGGTTAATTTTTAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCACGAGCACAAACATTCCTGTACCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGC GCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCAGCCCTGGAGAGTCCTTTACCAGGCCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAG CTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
381	> SP0266(LVR_SP131_V1) AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCCTGTACCGGCCCGGCAGGCGCCCTTTGCAATCCTGCCCTGCACCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCT GTTTGCCCACTCTATTTGCCCAGCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACAGA CTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
382	> SP0267(LVR_SP131_V2) GGCGCCCTTTGGACCTTTGCAATCCTGGAGCAAACAGCAAACACTGTACCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCCTGCCCTGCACCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACT CTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGA GCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
383	> SP0268 (LVR_132_A1) AGGTTAATTTTTAAAAAGCAGTCAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGCAGACAAACATTCCTGTACCAGAATGAACATTTGGACTATACCTCAGGGGTGA GGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCCTGCCCTGCACCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGT CCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
384	> SP0269 (LVR_132_V1) AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCCTGTACCAGAATGAACATTGAACTTTGCCCTGCACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGA CCTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGGGATGACCTTAAGGGATG ACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
385	> SP0270 (LVR_132_V2) GGCGCCCTTTGGACCTTTGCAATCCCTGGAGCAAACAGCAAACACTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTGCAAT CCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACA GATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
386	> SP0271 (LVR_133_A1) AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGCAGACAAACATTCCTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGA GGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCACTCTTTCTATTTGCCCAGCCCAAAGCAATCACTCAAAGTTCAAACCTTATCATTTTTTGCTTTGTTCCTCTT GGCCTTGGTTTTGTGCCTCGAGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
387	> SP0272 (LVR_133_V1) AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCCTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGA CCTTTTGCAATCCTGGCGCTCTTTGTTTTACATGAAGGGTCTGGCAGGCCAAAGCAATCACTCAAAGTTCAAACCTTATCATTTTTTGCTTTGTTCCTCTTGGCCTTGGTTTTGTGCCTCGAGGCATGTGCTCTAGTTTTGCAATACAGGACATGTTGCTTTCTGAGAGATGCGCCACC TTAATTTTATAACTAAGAGTGCTCTAGTTTTGCAATACAGCACATGCTATAAAAATGGAAACATGTTGCTTTCTGAGACATGCCCCACC
388	> SP0273 (LVR_133_V2) GGCGCCCTTTGGACCTTTGCAATCCTGGAGCAAACAGCAAACACTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTGCAAT CCTGGCGCTCTTTGTTTTACATGAAGGGTCTGGCAGCCAAAGCAATCACTCAAAGTTCAAACCTTATCATTTTTTGCTTTGTTCCTCTTGGCCTTGGTTTTGTGCCTCGAGGCATGTGCTCTAGTTTTGCAATACAGCACATGCTATAAAAATGGAAACATGTTGCTTTCTGAGACATGCCCCACC
389	> SP0256 ATTGGCATCTTCTATTGCTTTTCCTGGTGACTTCATTTTTCACTCTTGGCTAAAAATGGGTCTCTGATGATTTATTCTATCCTGGGTGTTCACAAGCTCAAGAAGTTGTGTGGGGCCTGCTGCCAGTAACCCTGGGTGACGAAGC GTGACTCACCACTCCGAGGTCAGTGGGGGATGGAAGGCAGGGGAGTCAGCTGACAAGATCTGCTGTTGTCACCAGGCCTTCGCCAACTTACAAGGCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAACGCGCCAGGTCTGTGCCAAGTGTTTGCCGATGACCTAATGATTCTGAGCTTGGCAAAGGTCTTATCTCCCACGTCCGCCCAGGCCCAGTGTCTCCAGCGAATGTGACCTTTGCTGCAGCAGCGCCGTGGA GGGGGCAGAGGGGATGGGCTGGAGGTTGAGCAAACAGAGCAGCAGAAAAGGCAGTTCCTCTTCTCCAGTGCCCTCCTTCCCTGTCTCTGCCTCCCTCCCTCCTTCCTCAGGCATCAGAGCGGAGACTTCAGGGAGACCAGAGCCCA GCTTGCCAGGCACTGAGCTAGAAGCCCTGCC
390	> SP0257 CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCCGTTGCCCGGCAACGGCCAGGTCTGTGCCAAGTGTTTGCTTCTATAAAACTGATGGAAGATACAAACACTATTA AAGAACTGTTTGCATGTTGCAAATGATGTCCAAAGTCCAAACATTAATTAATACTCCAATAAACATCATGTCAGAATTTCTGTTTTCTTTTCCCTTTCGAACCTTTGCAGGATTGCCACATCATCAGGACCACACCTTCA TCAGGAATGAAATATCCGATGACCTAATCATTCTGAGCTTGCCAAGGTCTTTCCACGAATGTCACCTTTGCTCCACCACGCCGCTGCAGCGGCAGACGGGATGGGCTGGAGTTCAGCAAACAGCAGCAGAAAAGGCAGTTCCTCTTCTCCAGTGCCCTCCTTCCCTGTCTCTGCCTCCCTCCCTCCTTCCTCAGGCATCAGAGCGGAGACTTCAGGGAGACCAGAGCCCA

391	> SP0258 CTGTTTGCTGCTGCTTGCAATGTTTGCCCATTTTAGGGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGCCACGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACACAAACATTCCGGCCCCGGGAG GCGCCCTTTGGACCTTTCGAATCCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGA CCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
392	> SP0259 CTGTTTGCTGCTGCTTGCAATGTTTGCCCATTTTAGGGGCTGGTTTCTTATAAAACTGATGGAAGATACAAACACTATTAAAGAACTGTTTGCATGTTGCAAATGATGTCCAAAGTCCCAAACATTGTTATAATTAATTACTCCCAATAA ACATCATGTCAGAATTTCTGTTTCTTTTCCCTTTGAACCTTTGCAGGATTCGCCACATCATCAGGAATGAATATCCGATGACCTAATGATTCTGAGCTTGGCAAAGGTCTTATCTCCCAGCTCGCCCA GGCCCAGTGTTCCAGGAATGTGACCTTTGCTGCAGCAGCCGCTGGAGGGGGCAGAGGGGATGGGCTGGAGGTTGAGCAAACAGCAGCAGAAAAGGCAGTTCCTCTTCTCCCTGTCTCTGCCTCTCCCTC CCTTCCTCAGGCATCAGAGCGGAGACTTCAGGGAGACCAGAGCCCAGCTTGCCAGGCACTGAGCTAGAAGCCCTGCC
393	> SP0264 CAGGCTTTCACTTTCTCGCCAACTTACAAGGCCTTTCTGTGTAAACAATACCTGAACCTTTACCCGTTGCCCGGCAACGGCCAGCTCTGTGCCAAGTGTTTGCCTTGCAACAGCTTATCGGAAGCAAACAAGCTGAGGGAAT TGAGCAAGAATTTCTGGGATACCAACAGCATAGGAGGAAGCAAAGGACGTAGAGGGAGGGTTGACTGTCTACACAGGACAAAGCCAATGGATTAACCAAACCTCTTGCAGATTTAAATAGGATGGGAACTAGGAGTGGCAGCAATCC TTTCTTTCAGCTGGAGTGCTCCTCAGCAGCCCACCCTACCTTAGAAAAGCCACC
394	>SP0265(LVR_SP131_A1) AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACACAAACATTCCTGTACCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGC GCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAG CTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
395	> SP0266(LVR_SP131_V1) AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCCTGTACCGGCCCGGGAGGCGCCCTTTGCAATCCTGCCCTGCCCTGCAGCCCCGCAGCTTGCT GTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGA CTCATAGCAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
396	> SP0267(LVR_SP131_V2) GGCGCCCTTTGGACCTTTGCAATCCTGGAGCAAACAGCAAACACTGTACCGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCCACTGAACCCTTGACCCCTGCCCTGCAGCCCCGCAGCTTGCTGTTTGCCCACT CTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGCAA GCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
397	> SP0268 (LVR_132_A1) AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTGTACCGGCCCGGGAGGCGCCCTTTGGACTATACCTGAGGGTGA GGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCCACTGAACCCTTGACCCCTGCCCTGCAGCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGACGT CCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACACACTCATAGCAGCAATCACCACCAAGCCTGGAATAACTGC AGCCACC
398	> SP0269 (LVR_132_V1) AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCACTCTATTTGCCCTGTACCAGAATGAACATTGAACTTTGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGA CCTTTTGCAATCCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATG ACTCAGTAACAGATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
399	> SP0270 (LVR_132_V2) GGCGCCCTTTGGACCTTTGCAATCCTGGAGCAAACAGCAAACACTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTGCAAT CCTGGCGCACTGAACCCTTGACCCCTGCCCTGCAGCCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGAGTCCTTTAGCAGGGCAAAGTGCAACATAGGCAGACCTTAAGGGATGACTCAGTAACA GATAAGCTTTGTGTGCCTGCAGGGCATATAAAACAGGGGCAAGGCACAGACTCATAGCAGCAATCACCACCAAGCCTGGAATAACTGCAGCCACC
400	> SP0271 (LVR_133_A1) AGGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGGCCCTTGGCAGCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTGTACCGAATGAACTTTGGACTATACCTGAGGGGTGA GGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTGCAATCCTGGCGCCACTGAACCCTTGACCCCTGCCCTGCAGCCCCGCAGCTTGCTGTTTGCCCACTCTATTTGCCCAGCCCCAGCCCTGGAGACGT GGCCTTGGTTTTGTACATCAGCTTTGAAAATACCATCCCAGGGTTAATGCTGGGGTTAATTTATAACTAAGAGTGCTCTAGTTTTGCAATACAGCACATGCTATATAAAAATGGAAAGATGTTGCTTTCTGAGAGATGCGCCACC
401	> SP0272 (LVR_133_V1) AAGCAAATATTTGTGGTTATGGATTAACTCGAACTGTTTGCCCTGTACCAGAATGAACATTGAACTTTGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGA CCTTTTGCAATCCTGGCGCCACTGAAGGGTCTGGCAGCCAAAGCAATCACTCAAAGTTTCAACCTTATCATTTTTGCTTTGTTCCTCTTGGCCTTGGTTTTGTACATCAGCTTTGAAAATACCATCCCAGGGT TAATGCTGGGGTTAATTTATAACTAAGAGTGCTCTAGTTTTGCAATACAGGACATGCTATAAAAATGGAAAGATGTTGCTTTCTGAGAGATGCGCCACC
402	> SP0273 (LVR_133_V2)	

	GGCGCCCTTTGGACCTTTGCAATCCTGGAGCAAACAGCAAACACTGTACCAGAATGAACATTGAACTTTGGACTATACCTGAGGGGTGAGGTAAACAACAGGACTATAAATGGCCCGGGAGGCGCCCTTTGGACCTTTTGCAAT
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403	> SP0368
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404	> SP0373
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405	> SP0378
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406	> SP0379
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407	> SP0380
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408	> SP0381
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409	> SP0272 (LVR_133_V1)
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410	> SP0273 (LVR_133_V2)
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411	> SP0368
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412	> SP0373
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413	> SP0378
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414	> SP0379
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415	> SP0380
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416	> SP0381
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417	> SP0384

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418	> SP0388
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419	> SP0396
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420	> SP0397
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421	> SP0398
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422	> SP0399
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423	> SP0403
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424	> SP0404
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425	> SP0405
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426	>SP0406
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427	> SP0407
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428	> SP0409
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429	> SP0411
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91	> SP0412

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430	> SP0413
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431	>TTR promoter
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	GCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGTCACACAGA
432	> LP1
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433	> CMV-IE
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435	> TBG
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	GTACTGTTGGTAAAGCCACC
438	>CMV-IE 5′ UTR with 3′ Kozac GCCACC.
	TCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCGGGAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGACTCTAT
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439	> LVR_0243-5′UTR
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440	> LVR_0412-5'UTR AGG TTAATTTTTA AAAAGCAGTC AAAAGTCCAA GTGGCCCTTG GCAGCATTTA CTCTCTCTGT TTGCTCTGGT TAATAATCTC AGGAGCACAA ACATTCCCCC TGTTCAAACA TGTCCTAATA CTCTGTCTCT GCAAGGGTCA TCAGTAGTTT TCCATCTTAC TCAACATCCT CCCAGTGAGT CATATGTTTG CTCACTGAAG GTTACTAGTT AACAGCCATC CCTTAAACAG GATATAAAAG GACTTCAGCA GGACTGCTCG AAACATCCCA CT
441	> A1 promoter (LVR_SP0131_A1)-5'UTRs AGG TTAATTTTTA AAAAGCAGTC AAAAGTCCAA GTGGCCCTTG GCAGCATTTA CTCTCTCTGT TTGCTCTGGT TAATAATCTC AGGAGCACAA ACATTCCTGT ACCGGCCCGG GAGGCGCCCT TTGGACCTTT TGCAATCCTG GCGCACTGAA CCCTTGACCC CTGCCCTGCA GCCCCCGCAG CTTGCTGTTT GCCCACTCTA TTTGCCCAGC CCCAGCCCTG GAGAGTCCTT TAGCAGGGCA AAGTGCAACA TAGGCAGACC TTAAGGGATG ACTCAGTAAC AGATAAGCTT TGTGTGCCTG CAGGGCATAT AAAACAGGGG CAAGCCACAG ACTCCATAGCA GAGCAAT
442	> MVM Intron CTAGCCCTAAGGTAAGTTGGCGCCGTTTAAGGGATGGTTGGTTGGGGTATTAATGTTTAATTACCTTTTTTACAGGCCTCGAA
443	> HBB2 intron sequence GTACACATAT TGACCAAATC AGGGTAATTT TGCATTTGTA ATTTTAAAAA ATGCTTTCTT CTTTTAATAT ACTTTTTTGT TTATCTTATT TCTCCTAATCT CTTTCTTTCA GGGCAATAAT GATACAATGT ATCATGCCTC TTTGCACCAT TCTAAACAAT AACACTGATA ATTTCTGGGT TAAGGCAATA CCAATATTTC TGCATATAAA TATTTCTGCA TATAAATTGT AACTGATGTA AGAGGTTTCA TATTGCTAAT AGCAGCTACA ATCCAGCTAC CATTCTGCTT TTATTTTCTG GTTGGGATAA GGCTGGATTA TTCTGAGTCC AAGCTAGGCC CTTTTGCTAA TCTTGTTCAT ACCTCTTATC TTCCTCCCAC AGCTCCTGGG CAACCTGCTG GTCTCTCTGC TGGCCCATCA CTTTGGCAAA G
444	>HBB INTRON TACTAGCAGCTACAATCCAGCTACCATTCTGCTTTTATTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATGTTCATACCTCTTATCCTTTTTCTTCCTCCACAGCTCCTGGGCAACGTGCTGG TCTGTGTGCTGGCCCATCACTTTGGCAAAGAATT
445	>UBC INTRON ACTTGGTGAGTAGCGGGCTGCTGGGCTGGCCGGGGCTTCGTGGCCGCCGGGCGCTCGGTGGGACGGAAGACGTGTGGAGACACCGCCAAGGGCTGTAGTCTGGGTCCGCGAGCAAGGTTGCCCTGAACTGGGGGTTGGGGGAG CGCAGCAAAATGGCGCTGTTCCCGAGTCTTGAATGGAAGACGCTTGTGAGGCGGGCTGTGAGGTCGTTGAAACAAGGTGGGGGGCATGGTGGCGGCAAGAACCCAAGGTCTTGAGGCCTTCGCTAATGCGGGAAAGCTCTTAT TCGGGTGAGATGGGCTGGGGCACCTGACGTGAAGTTTGTCACTGACTGGAGAACTCGGTTTGTCGTCTGTTGCGGGGCGGCAGTTATGCGGTGCCGTTGGGCAGTGCACCGTAACTTTGGGAGCGCGGCC CTCGTCGTGTCGTGACGTCACCCGTTCTGTTGGCTTATAATGCAGGGTGGGGCCACCTGCCCGGTAGGTGTGCGGTAGCTTTTCTCCGTCCCAGCACGCAGGCTTCCGTCAGTCTTCTCCTCGCCCCGGA CCTCTGGTGAGGGGAGGGATAAGTGAGGCGTCAGTTTCTTTGGTCGGTTTTATGTACCTATCTTCTTAAGTAGCTGAAGCTCCGGTTTTGAACTATGCGCTCGTCCGGCTGCGGCGAGTTTCTTCTTCTTT GAAATGTAATCATTTGGGTCAATATGTTAATTTTCAGTGTTAGACTAGTAAATTGTCCGCTAAATTCTGGCCGTTTTTGGCTTTTTTGTTAGAC
446	>MODIFIED CMVIE INTRON SEQUENCE. CAAGAGTGACGTAACGTACCGCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGCTATACTGTTTTGGCTTGGGGTCAGGTGAGGGCAGTGTAGTCTGAGCAGTACTCGTTGCTGCCGCGCGCGCCACCAGACATAATAGCTGACAGACTAACAGAC TGTTCCTTTCCATGGGTCTTTTCTGCAG
465	>termination sequence TGATAACTCGAG
464	> pAAV-LSPhGAA w/mod endogenous GAA signal peptide CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTGGAGGGGTGGAGTCG TCGACGTGAATTACGTCATAGGGTTATAGGGAGGTCGCGCCGCTCTAGCGAGTTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTCCCTTCCGACCATTTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAAACATTCCTT ACTAGTTCTAGAGTTAATTTTTAAAAAGCAGTCAAAAGTCCAAGTGCCCTTGCAGAATGCATGTATAATTTCTACAGAACCTATTAGAAAGCATCACCCACGCCTCTGCTTTTGTACAACTTCCCTTAAAAAACTGCCAATCCCACTCGCTG TTTGGCCCAATAGTCGAGAACTTTTCCTGCTGCCTCTTGGTGCTTTTGCCTATTCTGCCATGGACCCTCATTCTGCCAGCTGCATCCTCTTCTCTTTGTTTTACATGA AGGGTCTGGCAGCCAAAGCAATCACTCAAAGTTCAAACCTTATCATTTTTTGCTTTGTTCCTCTTGGCCTTTGTCGTCTTGGGTTATTTATACTGAGAGTGCTCTA GTTCTGCAATACAGGACATGCTATAAAAATGGAAAGATGTTGCTTTCTGAGAGATCAGCTTACATGTGCTAGCGTAGCCACCCGCCCTGCTCCCCACGGGCTCTGGCGCCCTCGTGTCCTT GGCAACCGCTCGCACTCCTGGGGCACATCCTACTCCATGATTTCCTGCTGTTCCCCGAGAGCTGAGTGGCTCCTCCCCAGTCCTGGAGGACACTCACCAGCTCACCAGCAGGGAGCCCAGGGCCCCGGGACGCCCAG GCACACCCGCGCCGTCCCAGAGCAGTGCCCACACAGTGCAGCTTCGATTGCGCCCTGACAAGGCCATCACCCAGGAACAGTGCGAGGCCCGGCTGCTACATCCCTGCAAAGCAGGGCTGC AGGGAGCCCAGATGGGGCAGCCCTGGTGCTTCTCCCACCCAGCTACAAGCTGGAGAACCTGAGCTCCCTCGACCGCCACCCTCGCCTTCTTCCCCAAGGACATCCTGAC CCTGCCGCCTGCACGTGATCATGCAGACTGAGACAACCCCCTCCACTTCACCATCAAAGATCCAGCTACAAGGCGCTACGAGGTCCCTTTGGACACCCCGCCGTCTCCCACTCTACAGCGTGGAGTTCTCC GAGGAGCCCTTCGGGGTGATCGTGCACCGGCAGCTGGACGCCGGTGCTGTCAACAGAGGTGGCGCCCTGTCCTTCAGCTGTCCCCTCGCAGTATATCACAGGCCTGCGCCAGC ACCTCAGTCCCCTGATGCTCAGCACCAGCTGGACCAGGATCACCCTGTGGAACCGGCACCTTCGCGCCCGCTGGTCAACGGCCGCCTGGCCACACCGGGTGTT CCTGCTAAACAGCAACGCCATGGACGTGGTCCTGCAGCCGACCCTGCCCTTAGCTGGACGTCCTGGAGGATCCTGGGGATCCTGGACGTCTACATCTTCCTGGCCCCACAGCCCCAAGAGCGTGGTGCAGCAGTACCTGGACGTGGGA

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TAATCAGCGACTGATCCACCCAGTCCCAGAACGAAGCGCGCCGTCTGAAACGGGCGAACAGGCGAGCGCAACGCAATTAATGTGAGTTACCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTG
CCAGGTAGCGAAAGCCTTTTTTGATCGACCTTTCGGCACAGCGCGGCGTAACAAGGGCGAAATAATATCGGTGGCCGTGGTGTCGGCTCCGCCGCTTCAACTGCACCGGGCGGGAAGGATCGACAGATTTCGATCCACCGCATT
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CGGATCACGGTCAGACGATTCGTTGGCACGATCCGTGGGTTTCAATACTGGCTTCAAACCACCACCGTAACCAGGCCGTTACCACGAAAAGGTCCGTGAGGCCGCACGGCGTTAAAGTTGTT
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AACCGACAACGCAGGCTTCTGCTTCAATCAGCGTCCGGCGGTGTGCAGTTCAACCACCGCACGATAGAGATTCGGGATTTCGGCGCTCCACAGTTTCGGGTTTCGACGTTCAGACGTAGTGTGACGCGATCTGCAAACC
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	AATCGTCTTAAAGCGAGTGGCAACTGGAAATCGCTGATTGTGTAGTCGGTTTATGCAGCAACGAGACGTTCACGGAAATCCGCTAATCCGCCACAGATCCTGATCTTCCAGATAACTGCCGTCACTCCAACGCAGCACCTTCACC
	GCCAGCGGTTTCTCCGCCGCCGTAAAAATCCGCTCAGTCAAATTCAGACGGCAAACCACTGTCCTGCCGTTACCCACGCCCCGCTTCGCACCACACATTCAAACGCCGAGTTTACCGCCTCAAAAATAATTCCGCTCTGGCC
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	GCTATTACGCCAGCTTGCGAAAGGGGGTAGTGCTGCAAGGCGATTAAGTTGGGTAACGCCAGGGTTTTCCCAGTCACGACGTTGGATCTGGCCCACTCCCTCT
463	> AAV3B CAPSID NUCLEOTIDE SEQUENCE
	ATGGCTGCTGACGGTTATCTTCCAGATTGGCTCGAGGACAACCTTTCTGAAGGCATTCGTGAGTGGTGGGCTCTGAAACCTGGAGCCCTCCCTCAACCCAAAGCGAACCAACAGGACAACCGTCGGGGTCTTGTGCTTCCGG
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	CCCCCACAAGTTTGGGATCTAATACAATGGCTTCAGGCGGTGGCGCACCAATGGCACGAGGTGCCGATGCGAGTGGGTAATTCCTCAGGAAATTGGCATTGCGATTCCCAATGGCTGGGCACAGATCATCACCAC
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	TTCTCACCACGTGACTGGCAGCGACTCATTAACAACAACTGGGGATTCCGGCCCAAGAAACTCAGCTTCAAGCTCTTCAACATCCAAGTTAAAGAGGTCACGCAGAACGACTATTGCCAATAACCTTACCAGCA
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	CCTATTGGAACCGGTATCTCACACGAAACTTG
452	> AAV3B CAPSID AMINO ACID SEQUENCE
	MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKYLGPGNGLDKGEPVNEADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLQEDTSFGGNLGRAVFQAKKRILEPLGLVEEAAKTAPGKKRP
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	PIGTRYLTRNL
453	> AAV3B 265D CAPSID NUCLEOTIDE SEQUENCE
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	CCCCCACAAGTTTGGGATCTAATACAATGGCTTCAGGCGGTGGCGCACCAATGGCACGAGGTGCCGATGCGAGTGGGTAATTCCTCAGGAAATTGGCATTGCGATTCCCAATGGCTGGGCACAGATCATCACCAC
	CAGCACCAGAACCTGGGCCCTGCCCACTTACAAGCAAATCTCCAGCCAATCAGGAGCTTCAAACGACAACCACTACTTTGGCTACAGCACCCCTTGGGGGTATTTTGACTTTAACAGATTCCACTGCCAC
	TTCTCACCACGTGACTGGCAGCGACTCATTAACAACAACTGGGGATTCCGGCCCAAGAAACTCAGCTTCAAGCTCTTCAACATCCAAGTTAAAGAGGTCACGCAGAACGACTATTGCCAATAACCTTACCAGCA
	CGGTTCAAGTGTTTACGGACTCCGGAGTATCAGCTCCCGTCTCCGCCGTTCCAGCGGACGTCTTCATGGTCCCTCAGTATGGATACCTCACCCTGAACGACGAGTCAAGCGGT
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	CCTCTTATTGATCAGTATCTGTACTACCTGAACAGAACGCAAGGAACAACCTGGAACAACCAATCACGGCTGCTTTTTAGCCAGGCTGGCCCTCAGTCTATGTCTTGCTAGGCCCTGCT
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	CCTATTGGAACCGGTATCTCACACGAAACTTG
454	> AAV3B 265D CAPSID AMINO ACID
	MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKYLGPGNGLDKGEPVNEADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLQEDTSFGGNLGRAVFQAKKRILEPLGLVEEAAKTAPGKKRP
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455	> AAV3B ST (S663V+T492V) CAPSID NUCLEOTIDE SEQUENCE ATGGCTGCTGACGGTTATCTTCCAGATTGGCTCGAGGACAACCTTTCTGAAGGCATTCGTGAGTGGTGGGCTCTGAAACCTGGAGTCCCTCAACCCAAAGCGAACCAACAACACCAGGACAACCGTCGGGGTCTTGTGCTTCCGG GTTACAAATACCTCGGACCCGGTAACGGACTCGACAAAGGAGAGCCGGTCAACGAGGCGGACGCGGCAGCCCTCGAACACGACAAAGCTTACGACCAGCAGCTCAAGGCCGGTGACAACCCGTACCTCAAGTACAACCACGCCGA CGCCGAGTTTCAGGAGCGTCTTCAAGAAGATACGTCTTTTGGGGGCAACCTTGGCAGAGCAGTCTTCCAGGCCAAAAAGAGGATCCTTGAGCCTCTTGGTCTGGTTGAGGAAGCAGCTAAAACGGCTCCTGGAAAGAAGAGGCCT GTAGATCAGTCTCCTCAGGAACCGGACTCATCATCTGGTGTTGGCAAATCGGGCAAACAGCCTGCCAGAAAAAGACTAAATTTCGGTCAGACTGGCGACTCAGAGTCAGTCCCAGACCCTCAACCTCTCGGAGAACCACCAGCAG CCCCCACAAGTTTGGGATCTAATACAATGGCTTCAGGCGGTGGCGCACCAATGGCAGACAATAACGAGGGTGCCGATGGAGTGGGTAATTCCTCAGGAAATTGGCATTGCGATTCCCAATGGCTGGGCGACAGAGTCATCACCAC CAGCACCAGAACCTGGGCCCTGCCCACTTACAACAACCATCTCTACAAGCAAATCTCCAGCCAATCAGATGCTTCAAACGACAACCACTACTTTGGCTACAGCACCCCTTGGGGGTATTTTGACTTTAACAGATTCCACTGCCAC TTCTCACCACGTGACTGGCAGCGACTCATTAACAACAACTGGGGATTCCGGCCCAAGAAACTCAGCTTCAAGCTCTTCAACATCCAAGTTAAAGAGGTCACGCAGAACGATGGCACGACGACTATTGCCAATAACCTTACCAGCA CGGTTCAAGTGTTTACGGACTCGGAGTATCAGCTCCCGTACGTGCTCGGGTCGGCGCACCAAGGCTGTCTCCCGCCGTTTCCAGCGGACGTCTTCATGGTCCCTCAGTATGGATACCTCACCCTGAACAACGGAAGTCAAGCGGT GGGACGCTCATCCTTTTACTGCCTGGAGTACTTCCCTTCGCAGATGCTAAGGACTGGAAATAACTTCCAATTCAGCTATACCTTCGAGGATGTACCTTTTCACAGCAGCTACGCTCACAGCCAGAGTTTGGATCGCTTGATGAAT CCTCTTATTGATCAGTATCTGTACTACCTGAACAGAACGCAAGGAACAACCTCTGGAACAACCAACCAATCACGGCTGCTTTTTAGCCAGGCTGGGCCTCAGTCTATGTCTTTGCAGGCCAGAAATTGGCTACCTGGGCCCTGCT ACCGGCAACAGAGACTTTCAAAGGTAGCTAACGACAACAACAACAGTAACTTTCCTTGGACAGCGGCCAGCAAATATCATCTCAATGGCCGCGACTCGCTGGTGAATCCAGGACCAGCTATGGCCAGTCACAAGGACGATGAAGA AAAATTTTTCCCTATGCACGGCAATCTAATATTTGGCAAAGAAGGGACAACGGCAAGTAACGCAGAATTAGATAATGTAATGATTACGGATGAAGAAGAGATTCGTACCACCAATCCTGTGGCAACAGAGCAGTATGGAACTGTG GCAAATAACTTGCAGAGCTCAAATACAGCTCCCACGACTAGAACTGTCAATGATCAGGGGGCCTTACCTGGCATGGTGTGGCAAGATCGTGACGTGTACCTTCAAGGACCTATCTGGGCAAAGATTCCTCACACGGATGGACACT TTCATCCTTCTCCTCTGATGGGAGGCTTTGGACTGAAACATCCGCCTCCTCAAATCATGATCAAAAATACTCCGGTACCGGCAAATCCTCCGACGACTTTCGTACCGGCCAAGTTTGCTTCATTTATCACTCAGTACTCCACTGG ACAGGTCAGCGTGGAAATTGAGTGGGAGCTACAGAAAGAAAACAGCAAACGTTGGAATCCAGAGATTCAGTACACTTCCAACTACAACAAGTCTGTTAATGTGGACTTTACTGTAGACACTAATGGTGTTTATAGTGAACCTCGC CCTATTGGAACCCGGTATCTCACACGAAACTTG
456	> AAV3B ST (S663V+T492V) AMINO ACID SEQUENCE MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKYLGPGNGLDKGEPVNEADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLQEDTSFGGNLGRAVFQAKKRILEPLGLVEEAAKTAPGKKRP VDQSPQEPDSSSGVGKSGKQPARKRLNFGQTGDSESVPDPQPLGEPPAAPTSLGSNTMASGGGAPMADNNEGADGVGNSSGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISSQSGASNDNHYFGYSTPWGYFDFNRFHCH FSPRDWQRLINNNWGFRPKKLSFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMVPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYTFEDVPFHSSYAHSQSLDRLMN PLIDQYLYYLNRTQGTTSGTTNQSRLLFSQAGPQSMSLQARNWLPGPCYRQQRLSKVANDNNNSNFPWTAASKYHLNGRDSLVNPGPAMASHKDDEEKFFPMHGNLIFGKEGTTASNAELDNVMITDEEEIRTTNPVATEQYGTV ANNLQSSNTAPTTRTVNDQGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPPQIMIKNTPVPANPPTTFVPAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYNKSVNVDFTVDTNGVYSEPR PIGTRYLTRNL
457	> AAV3B265D549A CAPSID NUCLEOTIDE SEQUENCE GAAACCTGGAGTCCCTCAACCCAAAGCGAACCAACAACACCAGGACAACCGTCGGGGTCTTGTGCTTCCGGGTTACAAATACCTCGGACCCGGTAACGGACTCGACAAAGGAGAGCCGGTCAACGAGGCGGACGCGGCAGCCCTC GAACACGACAAAGCTTACGACCAGCAGCTCAAGGCCGGTGACAACCCGTACCTCAAGTACAACCACGCCGACGCCGAGTTTCAGGAGCGTCTTCAAGAAGATACGTCTTTTGGGGGCAACCTTGGCAGAGCAGTCTTCCAGGCCA AAAAGAGGATCCTTGAGCCTCTTGGTCTGGTTGAGGAAGCAGCTAAAACGGCTCCTGGAAAGAAGAGGCCTGTAGATCAGTCTCCTCAGGAACCGGACTCATCATCTGGTGTTGGCAAATCGGGCAAACAGCCTGCCAGAAAAAG ACTAAATTTCGGTCAGACTGGCGACTCAGAGTCAGTCCCAGACCCTCAACCTCTCGGAGAACCACCAGCAGCCCCCACAAGTTTGGGATCTAATACAATGGCTTCAGGCGGTGGCGCACCAATGGCAGACAATAACGAGGGTGCC GATGGAGTGGGTAATTCCTCAGGAAATTGGCATTGCGATTCCCAATGGCTGGGCGACAGAGTCATCACCACCAGCACCAGAACCTGGGCCCTGCCCACTTACAACAACCATCTCTACAAGCAAATCTCCAGCCAATCAGGAGCTT CAAACGACAACCACTACTTTGGCTACAGCACCCCTTGGGGGTATTTTGACTTTAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCAGCGACTCATTAACAACAACTGGGGATTCCGGCCCAAGAAACTCAGCTTCAAGCT CTTCAACATCCAAGTTAAAGAGGTCACGCAGAACGATGGCACGACGACTATTGCCAATAACCTTACCAGCACGGTTCAAGTGTTTACGGACTCGGAGTATCAGCTCCCGTACGTGCTCGGGTCGGCGCACCAAGGCTGTCTCCCG CCGTTTCCAGCGGACGTCTTCATGGTCCCTCAGTATGGATACCTCACCCTGAACAACGGAAGTCAAGCGGTGGGACGCTCATCCTTTTACTGCCTGGAGTACTTCCCTTCGCAGATGCTAAGGACTGGAAATAACTTCCAATTCA GCTATACCTTCGAGGATGTACCTTTTCACAGCAGCTACGCTCACAGCCAGAGTTTGGATCGCTTGATGAATCCTCTTATTGATCAGTATCTGTACTACCTGAACAGAACGCAAGGAACAACCTCTGGAACAACCAACCAATCACG GCTGCTTTTTAGCCAGGCTGGGCCTCAGTCTATGTCTTTGCAGGCCAGAAATTGGCTACCTGGGCCCTGCTACCGGCAACAGAGACTTTCAAAGACTGCTAACGACAACAACAACAGTAACTTTCCTTGGACAGCGGCCAGCAAA TATCATCTCAATGGCCGCGACTCGCTGGTGAATCCAGGACCAGCTATGGCCAGTCACAAGGACGATGAAGAAAAATTTTTCCCTATGCACGGCAATCTAATATTTGGCAAAGAAGGGACAACGGCAAGTAACGCAGAATTAGATA ATGTAATGATTACGGATGAAGAAGAGATTCGTACCACCAATCCTGTGGCAACAGAGCAGTATGGAACTGTGGCAAATAACTTGCAGAGCTCAAATACAGCTCCCACGACTAGAACTGTCAATGATCAGGGGGCCTTACCTGGCAT GGTGTGGCAAGATCGTGACGTGTACCTTCAAGGACCTATCTGGGCAAAGATTCCTCACACGGATGGACACTTTCATCCTTCTCCTCTGATGGGAGGCTTTGGACTGAAACATCCGCCTCCTCAAATCATGATCAAAAATACTCCG GTACCGGCAAATCCTCCGACGACTTTCAGCCCGGCCAAGTTTGCTTCATTTATCACTCAGTACTCCACTGGACAGGTCAGCGTGGAAATTGAGTGGGAGCTACAGAAAGAAAACAGCAAACGTTGGAATCCAGAGATTCAGTACA CTTCCAACTACAACAAGTCTGTTAATGTGGACTTTACTGTAGACACTAATGGTGTTTATAGTGAACCTCGCCCTATTGGAACCCGGTATCTCACACGAAACTTG
458	> AAV3B265D549A CAPSID AMINO ACID SEQUENCE MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKYLGPGNGLDKGEPVNEADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLQEDTSFGGNLGRAVFQAKKRILEPLGLVEEAAKTAPGKKRP VDQSPQEPDSSSGVGKSGKQPARKRLNFGQTGDSESVPDPQPLGEPPAAPTSLGSNTMASGGGAPMADNNEGADGVGNSSGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISSQSDASNDNHYFGYSTPWGYFDFNRFHCH FSPRDWQRLINNNWGFRPKKLSFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMVPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYTFEDVPFHSSYAHSQSLDRLMN PLIDQYLYYLNRTQGTTSGTTNQSRLLFSQAGPQSMSLQARNWLPGPCYRQQRLSKTANDNNNSNFPWTAASKYHLNGRDSLVNPGPAMASHKDDEEKFFPMHGNLIFGKEGTAASNAELDNVMITDEEEIRTTNPVATEQYGTV

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	PIGTRYLTRNL
459	> AAV3B549A CAPSID NUCLEOTIDE SEQUENCE
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	CCTATTGGAACCCGGTATCTCACACGAAACTTG
460	> AAV3B549A CAPSID AMINO ACID SEQUENCE
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461	> AAV3BQ263Y CAPSID NUCLEOTIDE SEQUENCE
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462	> AAV3BQ263Y CAPSID AMINO ACID SEQUENCE
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463	> pP112
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464	>pP113
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7741 tcacatgt (SEQ ID NO: 511)

pP157 (SEQ ID NO: 512)

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7681 ctggcctttt gctcacatgt (SEQ ID NO: 512)

ITR to ITR sequence of pP110, i.e., amino acids 1-4385 of SEQ ID NO: 502. (SEQ ID NO: 513)

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4381 atccg (SEQ ID NO: 513)
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ITR to ITR sequence of pP112, i.e., amino acids 1- 4439 of SEQ ID NO: 504. (SEQ ID NO: 514)

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 421 agttctagag cggccgccag tgtgctggaa ttcggctttt ttagggctgg aagctacctt
 481 tgacatcatt tcctctgcga atgcatgtat aatttctaca gaacctatta gaaaggatca
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2821 cgccggccac tggacggggg acgtgtggag ctcctgggag cagctcgcct cctccgtgcc
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```

(SEQ ID NO: 514)

ITR to ITR sequence of pP113, i.e., amino acids 1- 4433 of SEQ ID NO: 505. (SEQ ID NO: 515)

```
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(SEQ ID NO: 515)

END OF SEQUENCES

CLAIMS

1. A recombinant adenovirus associated (rAAV) vector comprising in its genome:
   a. 5' and 3' AAV inverted terminal repeats (ITR) sequences, and
   b. located between the 5' and 3' ITRs, a heterologous nucleic acid sequence encoding all or a portion of an endogenous GAA signal peptide, a heterologous signal peptide and an alpha-glucosidase (GAA) polypeptide,
   wherein the GAA polypeptide comprises amino acid residues 28-952 of SEQ ID NO: 1, 57-952 of SEQ ID NO: 1, or comprises a N-terminal GAA polypeptide fragment comprising amino acids 28, 28-29, 28-30, 28-31, 28-32, or 28-33 of SEQ ID NO: 1 and a deletion of any number of amino acids from the next about 5 amino acids to about 40 amino acids after the N terminal GAA polypeptide fragment of SEQ ID NO: 1, wherein the heterologous signal peptide can be inserted immediately after the N-terminal GAA polypeptide fragment and before the remaining amino acids of the GAA polypeptide, wherein the heterologous signal peptide is optionally fused at position 57 of the remaining amino acids of the GAA polypeptide, and where the GAA polypeptide can extend to amino acid 952 of SEQ ID NO: 1, or a functional fragment thereof, and
   wherein the nucleic acid sequence encoding the GAA polypeptide can be codon optimized, and
   wherein the heterologous nucleic acid is operatively linked to a liver-specific promoter.
2. The recombinant AAV vector of claim 1, where the codon optimized nucleic acid sequence encoding the GAA polypeptide is selected from the group consisting of SEQ ID NO: 1-18, or functional fragment thereofs.
3. The recombinant AAV vector of claim 1, wherein the nucleic acid encoding SEQ ID NO: 3 is wildtype.
4. The recombinant AAV vector of claim 1, further comprising at least one of a UTR or a reverse RNA polII terminator sequence.
5. The recombinant AAV vector of claim 1, which comprises the nucleic acid sequence of SEQ ID NO: 23, or a functional variant thereof.
6. The recombinant AAV vector of claim 1, wherein the heterologous nucleic acid sequence encodes a GAA protein comprising a signal peptide fused to the GAA polypeptide, wherein the signal peptide is an endogenous GAA signal peptide, or a heterologous signal peptide, or a combination thereof.
7. The recombinant AAV vector of any of claim 1-6, wherein the AAV genome comprises, in the 5' to 3' direction:
   a. a 5' ITR,
   b. a liver-specific promoter sequence,
   c. an 5' UTR sequence,
   d. a nucleic acid encoding a portion or all of the endogenous GAA signal peptide,

e. a nucleic acid encoding a heterologous signal peptide or the N-terminal GAA polypeptide fragment,
f. a nucleic acid encoding an alpha-glucosidase (GAA) polypeptide, wherein the GAA polypeptide is functionally active,
g. a poly A sequence, and
h. a reverse RNA pol II terminator sequence.

8. The recombinant AAV vector of any of claims 1-7, wherein the UTR is 5' or 3'.
9. The recombinant AAV vector of any of claims 1-8, wherein nucleic acid encoding the signal peptide encodes a signal sequence is selected from any of: an endogenous GAA signal peptide, a fibronectin signal peptide (FN1), a IL-2 wt signal peptide, modified IL-2 signal peptide, IL2(1-3) signal peptide, IgG signal peptide, a AAT signal peptide, a A2M signal peptide, or a PZP signal peptide, or an active fragment thereof having signal peptide activity.
10. The recombinant AAV vector of any of claims 1 to 9, wherein the nucleic acid sequence encodes a GAA polypeptide having the amino acid sequence of SEQ ID NO: 1, or a polypeptide having at least 80% sequence identity to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).
11. The recombinant AAV vector of any of claims 1-10, wherein the nucleic acid sequence encoding the GAA polypeptide is SEQ ID NO: 3, or a nucleic acid sequence having at least 80%, or at least 85%, or at least 90% sequence identity to SEQ ID NO: 3 that encodes a GAA polypeptide having at least 80% sequence identity to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).
12. The recombinant AAV vector of any of claims 1-10, wherein the 5' UTR sequence comprises SEQ ID NO: 41, or a nucleic acid having at least 80% sequence identity to SEQ ID NO: 41.
13. The recombinant AAV vector of any of claims 1-11, wherein the 5' UTR sequence comprises SEQ ID NO: 40, or a nucleic acid having at least 80% sequence identity to SEQ ID NO: 40.
14. The recombinant AAV vector of any of claims 1-13, further comprising an intron sequence located 5' of the nucleic acid sequence encoding the signal peptide, and 3' of the promoter.
15. The recombinant AAV vector of claim 14, wherein the intron sequence is selected from the group consisting of: MVM sequence, a HBB2 sequence, an CMVIE intron sequence, or a UBC intron sequence or a SV40 sequence.
16. The recombinant AAV vector of any of claims 1-15, wherein the GAA polypeptide is a N-terminal truncated GAA polypeptide selected from any disclosed in Table 1.
17. The recombinant AAV vector of any of claims 1-16, further comprising at least one polyA sequence located 3' of the nucleic acid encoding the GAA gene and 5' of the 3' ITR sequence.
18. The recombinant AAV vector of any of claims 1-17, wherein the heterologous nucleic acid sequence further comprises a 3' UTR sequence, wherein the 3' UTR sequence is located 3' of the nucleic acid

encoding the GAA polypeptide and 5' of the 3' ITR sequence, or is located between the nucleic acid encoding the GAA polypeptide and the poly A sequence, or RNA pol II terminator sequence.

19. The recombinant AAV vector of any of claims 1-18, wherein the heterologous nucleic acid sequence further comprises a 3' intron sequence, wherein the 3' intron sequence is located 3' of the nucleic acid encoding the GAA polypeptide and 5' of the 3' ITR sequence, or is located between the nucleic acid encoding the GAA polypeptide and the poly A sequence or RNA polII terminator sequence.
20. The recombinant AAV vector of any of claims 1-19, wherein the ITR comprises an insertion, deletion or substitution.
21. The recombinant AAV vector of claim 20, wherein one or more CpG islands in the ITR are removed.
22. The recombinant AAV vector of any of claims 1-21, wherein
    a. the nucleic acid encoding the signal peptide is selected from any of the group consisting of:
    AAT signal peptide (e.g., SEQ ID NO: 67), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 67;
    a fibronectin signal peptide (FN1) (e.g., SEQ ID NO: 73-75), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 73-75;
    an endogenous GAA signal peptide (SEQ ID NO: 51), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 51;
    an hIGF2 signal peptide (e.g., SEQ ID NO: 72), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 72;
    a IgG1 (201) signal peptide (SEQ ID NO: 54), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 54;
    wtIL2 leader peptide (SEQ ID NO: 55), or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 55;
    mutant IL2 leader peptide (SEQ ID NO: 56) or an active fragment thereof having secretory signal activity, e.g., a nucleic acid encoding an amino acid sequence that has at least about 75%, or 80%, or 85%, or 90%, or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 56; and
    b. the nucleic acid encoding the GAA polypeptide is selected from any of the group consisting of:
    SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO:

14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 or a nucleic acid sequence having at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% sequence identity to SEQ ID NOS: 1-18.

23. The recombinant AAV vector of claim 22, wherein the nucleic acid encoding the GAA polypeptide is selected from SEQ ID NO: 3, or a nucleic acid sequence having at least 60%, or 70%, or 80%, 85% or 90% or 95%, or 98%, or 99% sequence identity to SEQ ID NO: 3 which encodes a GAA polypeptide at least 85% sequence identity to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).
24. The recombinant AAV vector of any of claims 1-23, wherein the nucleic acid encoding the GAA polypeptide encodes a GAA polypeptide beginning at any of amino acid residues 35, 40, 50, 57, 60, 68, 69, 70, 72, 74, 779, 790, 791, 792, 793, or 796 of SEQ ID NO: 1 or a sequence 80% identical to SEQ ID NO: 1 where amino acid residue 199 is a R (199R), amino acid residue 223 is a H (223H) and amino acid residue 780 is a I (780I).
25. The recombinant AAV vector of claim 24, wherein the GAA polypeptide has an endogenous GAA signal peptide attached, or a heterologous signal peptide attached to the N-terminal of the GAA polypeptide, wherein the endogenous signal peptide has the amino acid sequence of SEQ ID NO: 59 or a sequence at least 80% sequence identity to SEQ ID NO: 59, and the heterologous signal peptide is selected from the group consisting of: SEQ ID NO: 60 (201 IgG signal peptide), or an IL2 wild type signal peptide (SEQ ID NO: 61), modified IL2 signal peptide (SEQ ID NO: 62), A2M signal peptide (SEQ ID NO: 63), or PZP signal peptide (SEQ ID NO: 64), or artificial signal peptide (SEQ ID NO: 65), or cathpetsin L signal peptide (SEQ ID NO: 66) or signal peptides at least 90% sequence identity to SEQ ID NOS: 60-66.
26. The recombinant AAV vector of any of claims 1-25, wherein the liver specific promoter is selected from any of: SEQ ID NOS: 86, 88, 91-96, 146-150 or 439-441, or a liver specific promoter having at least 80% sequence identity to SEQ ID NOs: 86, 88, 91-96, 146-150 or 439-441.
27. The recombinant AAV vector of any of claims 1-25, wherein the liver specific promoter is selected from any of: SEQ ID NOS: 98 or 99, or a liver specific promoter having at least 80% sequence identity to SEQ ID NOs: 98 or 99.
28. The recombinant AAV vector of any of claims 1-25, wherein the liver specific promoter is SEQ ID NOS: 97, or a liver specific promoter having at least 80% sequence identity to SEQ ID NO: 97.
29. The recombinant AAV vector of any of claims 1-28, wherein the recombinant vector is manufactured from the plasmid of SEQ ID NO: 27.
30. The recombinant AAV vector of any of claims 1-29, wherein the nucleic acid comprises SEQ ID NO: 25, or a functional fragment thereof.
31. The recombinant AAV vector of any of claims 1-30, wherein the recombinant AAV vector is a chimeric AAV vector, haploid AAV vector, a hybrid AAV vector or polyploid AAV vector.

32. The recombinant AAV vector of any of claims 1-31, wherein the recombinant AAV vector is a rational haploid vector, a mosaic AAV vector, a chemically modified AAV vector, or a AAV vector from any AAV serotypes.
33. The recombinant AAV vector of any of claims 1-32, wherein the recombinant AAV vector is selected from the group consisting of: a AAVXL32 vector, a AAVXL32.1 vector, a AAV8 vector, or a haploid AAV8 vector comprising at least one AAV8 capsid protein.
34. The recombinant AAV vector of any of claims 1-33, wherein the serotype is AAV3b.
35. The recombinant AAV vector of claim 34, wherein the AAV3b serotype comprises one or mutations in a capsid protein selected from any of: 265D, 549A, Q263Y.
36. The recombinant AAV vector of claim 35, wherein the AAV3b serotype is selected from any of: AAV3b265D, AAV3b265D549A, AAV3b549A or AAV3bQ263Y, or AAV3bSASTG.
37. The recombinant AAV vector of any of claims 1 to 36, wherein the poly A sequence is a full length HGF poly A sequence.
38. The recombinant AAV vector of claim 37, wherein poly A sequence is selected from SEQ ID NO: 42, 43 or 44, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 42-44.
39. The recombinant AAV vector of any of claims 1 to 38, wherein the reverse RNA pol II terminator sequence is SEQ ID NO: 45, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 45.
40. A pharmaceutical composition comprising the recombinant AAV vector of any one of the previous claims in a pharmaceutically acceptable carrier.
41. A method to treat a subject with Pompe Disease, or a a glycogen storage disease type II (GSD II, Acid Maltase Deficiency) or having a deficiency in alpha-glucosidase (GAA) polypeptide, comprising administering any of the recombinant AAV vector, or the rAAV genome or the nucleic acid sequence of any one of the previous claims to the subject.
42. The method of claim 41, wherein the AAV vector manufactured from the plasmid of SEQ ID NO: 27.
43. The method of any of claims 41-42, where the recombinant AAV vector comprises the nucleic acid sequence of SEQ ID NO: 3, or a functional fragment thereof.
44. The method of any of claims 41-43, where the recombinant AAV vector comprises the nucleic acid sequence of SEQ ID NO: 23, or a functional variant thereof.
45. The method of any of claims 41-44, wherein GAA polypeptide is secreted from the subject's liver and there is uptake of the secreted GAA by skeletal muscle tissue, cardiac muscle tissue, diaphragm muscle tissue or a combination thereof, wherein uptake of the secreted GAA results in a reduction in lysosomal glycogen stores in the tissue(s).
46. The method of claim 45, wherein the administering to the subject is selected from any of: intramuscular, sub-cutaneous, intraspinal, intracisternal, intrathecal, intravenous administration.
47. The method of any of claims 41-46, where the recombinant AAV vector is a chimeric AAV vector, haploid AAV vector, a hybrid AAV vector or polyploid AAV vector.

48. The method of any of claims 41-47, where the recombinant AAV vector is a rational haploid vector, a mosaic AAV vector, a chemically modified AAV vector, or a AAV vector from any AAV serotypes.
49. The method of any of claims 41-48, where the recombinant AAV vector is a AAVXL32 vector or a AAVXL32.1 vector or a AAV8 vector, or a haploid AAV8 vector comprising at least one AAV8 capsid protein.
50. The method of any of claims 41-49, where the recombinant AAV vector is a AAV8 vector.
51. The method of any of claims 41-50, where the recombinant AAV vector is administered at a dosage range of between 1.0E11vg/kg and 5.0E13 vg/kg.
52. The method of any of claims 41-51, further comprising receiving GAA protein enzyme replacement therapy, and withdrawing GAA protein enzyme replacement therapy (ERT) on the same day, a day after or, any time between day 1 and 26 weeks after administration of the recombinant AAV vector.
53. A nucleic acid construct comprising SEQ ID NO: 3, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 3.
54. The nucleic acid of claim 53, wherein the expression of the nucleic acid sequence of SEQ ID NO: 3 or a nucleic acid having 80% sequence identity thereto encodes a GAA polypeptide having at least 80% sequence identity to SEQ ID NO: 1 and wherein there is R at position 199, a H at position 223 and I at position 780.
55. A nucleic acid construct comprising SEQ ID NO: 23, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NO: 23.
56. The nucleic acid construct of claim 55, comprising SEQ ID NO: 3 or SEQ ID NO: 25, or a nucleic acid sequence at least 80% sequence identity to SEQ ID NOS: 3 or 25.
57. The nucleic acid of claim 56, wherein the expression of the nucleic acid sequence of SEQ ID NO: 3 or a nucleic acid having 80% sequence identity thereto encodes a GAA polypeptide having at least 80% sequence identity to SEQ ID NO: 1 and wherein there is R at position 199, a H at position 223 and I at position 780.
58. A recombinant AAV comprising the nucleic acid construct of any of claims 53-57.
59. The recombinant AAV vector of claim 1, wherein the AAV lacks at least 1 amino acids of the GAA N terminus.
60. The recombinant AAV vector of claim 1, wherein the AAV lacks at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 or mor amino acids of the GAA N terminus.
61. The recombinant AAV vector of claim 1, wherein the heterologous signal peptide is inserted immediately after the endogenous GAA signal peptide or a potion thereof.