CLAIMS

~~What is claimed is:~~

1. An isolated~~, e.g., recombinant,~~ nucleic acid ~~comprising a transgene~~ encoding a β-glucocerebrosidase (GBA) protein comprising~~, wherein~~ the nucleotide sequence of SEQ ID NO: 1773 or~~encoding the GBA protein comprises~~ a nucleotide sequence that is at least 90% identical thereto~~to the nucleotide sequence of SEQ ID NO: 1773~~.

2. The isolated nucleic acid of claim 1, comprising ~~wherein the nucleotide sequence encoding the GBA protein comprises the nucleotide sequence of SEQ ID NO: 1773, or~~ a nucleotide sequence that is at least 92% identical or at least 95% identical to the nucleotide sequence of SEQ ID NO: 1773.

3. The isolated nucleic acid of claim 1 or claim 2, ~~which~~ further ~~comprises a nucleotide sequence encoding a miR binding site that reduces expression of the GBA protein encoded by the nucleic acid in a cell or tissue where the corresponding miRNA is expressed, optionally wherein the encoded miRNA binding site is complementary, e.g., fully complementary or partially complementary, to a miRNA expressed in a cell or tissue of the DRG, liver, hematopoietic, or a combination thereof.~~

~~4. An isolated, e.g., recombinant viral genome comprising a nucleic acid~~ comprising a nucleotide sequence~~transgene encoding a GBA protein, and further comprising a nucleotide sequence encoding a miR binding site that modulates, e.g., reduces, expression of the encoded GBA protein in a cell or tissue of the DRG, liver, hematopoietic lineage, or a combination thereof.~~

~~5. The isolated nucleic acid of claim 3, or the viral genome of claim 4, wherein the encoded miR binding site comprises a miR183 binding site, a miR122 binding site, a miR-142-3p, or a combination thereof, optionally wherein:~~

~~(i) the encoded miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 1847, or a nucleotide sequence having at least 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1847;~~

~~(ii) the encoded miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 1865, or a nucleotide sequence having at least 85%, 90%, 92%, 95%, 97%, 98%, or 99%~~

sequence identity thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1865; and/or

(iii) the encoded miR-142-3p binding site comprises the nucleotide sequence of SEQ ID NO: 1869, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1869.

6. The isolated nucleic acid of any one of claims 1-3, or the viral genome of claim 4 or 5, wherein the nucleic acid further encodes an enhancement element, wherein the encoded enhancement element comprises one, two, or all of:

(a) a prosaposin polypeptide, Saposin C polypeptide, or functional fragment or variant thereof, optionally comprising the amino acid sequence of SEQ ID NOs: 1789, 1758, 1750, 1752, 1754, 1756-1758, 1784, or 1785, an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NOs: 1789, 1758, 1750, 1752, 1754, 1756-1758, 1784, or 1785; or an amino acid sequence at least 85%identical thereto;

(b) a cell penetrating peptide, optionally comprising the amino acid sequence of any of SEQ ID NOs: 1794, 1796, or 1798, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NOs: 1794, 1796, or 1798; or

(c) a lysosomal targeting sequence, optionally comprising the amino acid sequence of any of SEQ ID NOs: 1800, 1802, 1804, 1806, or 1808, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NOs: 1800, 1802, 1804, 1806, or 1808.

7. An isolated, e.g., recombinant, nucleic acid comprising a transgene encoding a GBA protein and an enhancement element, wherein the encoded enhancement element comprises one, two, or all of:

(a) a Saposin C polypeptide or functional fragment or variant thereof, optionally comprising the amino acid sequence of SEQ ID NO: 1789 or 1758, or an amino acid sequence at least 85% identical thereto;

(b) a cell penetrating peptide, optionally comprising the amino acid sequence of any of SEQ ID NOs: 1794, 1796, or 1798, or an amino acid sequence having at least one, two, or three

but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NOs: 1794, 1796, or 1798; or

(c) a lysosomal targeting sequence, optionally comprising the amino acid sequence of any of SEQ ID NOs: 1800, 1802, 1804, 1806, or 1808, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NOs: 1800, 1802, 1804, 1806, or 1808.

8. The isolated nucleic acid of claim 6 or 7, or the viral genome of claim 6, wherein:

(i) the encoded enhancement element comprises the amino acid sequence of SEQ ID NO: 1789, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 1789;

(ii) the nucleotide sequence encoding the enhancement element comprises the nucleotide sequence of 1787, or a nucleotide sequence or a nucleotide sequence at least 85% identical thereto;

(ii) the encoded enhancement element comprises the amino acid sequence of 1802, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 1802;

(iii) the nucleotide sequence encoding the enhancement element comprises the nucleotide sequence of 1801, or a nucleotide sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 1801;

(iv) the encoded enhancement element comprises the amino acid sequence of 1794, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 1794; or

(v) the nucleotide sequence encoding the enhancement element comprises the nucleotide sequence of 1793, or a nucleotide sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 1793.

9. The isolated nucleic acid of claim 7 or 8, or the viral genome of any one of claims 4-6 or 8, wherein the nucleotide sequence encoding the GBA protein comprises the nucleotide sequence of any one of SEQ ID NOs: 1773, 1777, or 1781, or a nucleotide sequence at least 90% (e.g., at least 92%, 95%, 97%, 98%, or 99%) identical thereto.

~~10. The isolated nucleic acid of any one of claims 6-9, or the viral genome of any one of claims 6 or 8-9, wherein the encoded enhancement element and the encoded GBA protein are connected directly (e.g., without a linker) or are connected via an encoded linker.~~

~~11. The isolated nucleic acid or the viral genome of claim 10, wherein:~~

~~(i) the encoded linker comprises the amino acid sequence of any of SEQ ID NOs: 1854, 1855, 1843, 1845, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NOs: 1854, 1855, 1843, 1845;~~

~~(ii) the nucleotide sequence encoding the linker comprises any of the nucleotide sequences of Table 2, or a nucleotide sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the sequences of Table 2;~~

~~(iii) the nucleotide sequence encoding the linker comprises the nucleotide sequence of any one of SEQ ID NOs: 1724, 1726, 1729, or 1730, or a nucleotide sequence having at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NOs: 1724, 1726, 1729, or 1730;~~

~~(iv) the encoded linker comprises a furin cleavage site;~~

~~(v) the encoded linker comprises a T2A polypeptide;~~

~~(vi) the encoded linker comprises a (Gly4Ser)n linker, wherein n is 1-10, e.g., n is 3, 4, or 5; and/or~~

~~(vii) the encoded linker comprises a (Gly4Ser)3 linker.~~

~~12. The isolated nucleic acid of any one of claims 6-11, or the viral genome of any one of claims 6 or 8-11, wherein:~~

~~(i) the nucleotide sequence encoding the enhancement element is located 5' relative to the nucleotide sequence encoding the GBA protein; and/or~~

~~(ii) the nucleotide sequence encoding the enhancement element is located 3' relative to the nucleotide sequence encoding the GBA protein.~~

~~13. The isolated nucleic acid of any one of claims 1-3 or 5-12, or the viral genome of any one of claims 4-6 or 8-12, further~~ encoding a signal sequence, ~~optionally~~ wherein~~:~~

(i) the nucleotide sequence encoding theencoded signal sequence comprises the amino acid sequence of SEQ ID NO: 1853 or 1857, or an amino acid sequence at least 85% identical thereto; and/or

(ii) the nucleotide sequence encoding the signal sequence is located 5' relative to the nucleotide sequence encoding the GBA protein; and/or 5' relative to the encoded enhancement element.

14. The isolated nucleic acid of any one of claims 1-3 or 5-13, or the viral genome of any one of claims 4-6 or 8-13, wherein:

(i) the nucleic acid comprises in 5' to 3'order: a nucleotide sequence encoding a signal sequence comprising the nucleotide sequence of SEQ ID NO: 1850, or a nucleotide sequence that is at least 9585% identical thereto.; and a nucleotide sequence encoding a GBA protein comprising the nucleotide sequence of SEQ ID NO: 1773, or a nucleotide sequence at least 85% identical thereto; or

4. (ii) the nucleic acid encodes in 5' to 3'order: a signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; and a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto.

15. The isolated nucleic acid of any one of claims 1-3,7-13, or the viral genome of any one of claims 4-6 or 8-13, wherein the nucleic acid encodes in 5' to 3'order:

(i) a signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1800, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1800;

(ii) a signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; an enhancement element comprising the amino acid sequence of SEQ ID NO: 1802, or an amino acid sequence at least 85% identical thereto; and a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto;

(iii) a signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1804, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1804;

(iv) a signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1806, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1806;

(v) a signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; a linker comprising the amino acid sequence of SEQ ID NO: 1845, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1845; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1798, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1798;

(vi) a signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; a linker comprising the amino acid sequence of SEQ ID NO: 1845, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1845; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1794, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1794;

(vii) a first signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; a furin cleavage site comprising the amino acid sequence of SEQ ID NO: 1854, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1854; a T2A polypeptide comprising the amino acid

~~sequence of SEQ ID NO: 1855, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1855; a second signal sequence~~ comprising the nucleotide sequence of SEQ ID NO: 1772 or a~~1857, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1857; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1785, or an amino acid sequence at least 85% identical thereto;~~

~~(viii) a first signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; a furin cleavage site comprising the amino acid sequence of SEQ ID NO: 1854, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1854; a T2A polypeptide comprising the amino acid sequence of SEQ ID NO: 1855, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1855; a second signal sequence comprising the~~ nucleotide sequence that is at least 90% identical thereto.~~of SEQ ID NO: 1857, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1857; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1789, or an amino acid sequence at least 85% identical thereto;~~

5. A~~(ix) a first signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; a furin cleavage site comprising the amino acid sequence of SEQ ID NO: 1854, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1854; a T2A polypeptide comprising the amino acid sequence of SEQ ID NO: 1855, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1855; a second signal sequence comprising the nucleotide sequence of SEQ ID NO: 1857, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1857; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1758, or an amino acid sequence at least 85% identical thereto;~~

~~(x) a signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid~~

sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; a linker comprising the amino acid sequence of SEQ ID NO: 1845, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1845; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1796, or an amino acid sequence at least 85% identical thereto;

(xi) a signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; an enhancement element comprising the amino acid sequence of SEQ ID NO: 1794, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1794; a linker comprising the amino acid sequence of SEQ ID NO: 1845, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1845; and a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto;

(xii) a signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1808, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1808;

(xiii) a first signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a first enhancement element comprising the amino acid sequence of SEQ ID NO: 1802, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; a furin cleavage site comprising the amino acid sequence of SEQ ID NO: 1854, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1854; a T2A polypeptide comprising the amino acid sequence of SEQ ID NO: 1855, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1855; a second signal sequence comprising the nucleotide sequence of SEQ ID NO: 1857, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1857; and a second enhancement element comprising the amino acid sequence of SEQ ID NO: 1789, or an amino acid sequence at least 85% identical thereto;

(xiv) a first signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; a linker comprising the amino acid sequence of SEQ ID NO: 1845, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1845; a first enhancement element comprising the amino acid sequence of SEQ ID NO: 1798, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1798; a furin cleavage site comprising the amino acid sequence of SEQ ID NO: 1854, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1854; a T2A polypeptide comprising the amino acid sequence of SEQ ID NO: 1855, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1855; a second signal sequence comprising the nucleotide sequence of SEQ ID NO: 1857, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1857; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1789, or an amino sequence at least 85% identical thereto; or

(xv) a first signal sequence comprising the amino acid sequence of SEQ ID NO: 1853, or an amino acid sequence at least 85% identical thereto; a first enhancement element comprising the amino acid sequence of SEQ ID NO: 1802, or an amino acid sequence at least 85% identical thereto; a GBA protein comprising the amino acid sequence of SEQ ID NO: 1775, or an amino acid sequence at least 85% identical thereto; a linker comprising the amino acid sequence of SEQ ID NO: 1845, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1845; a first enhancement element comprising the amino acid sequence of SEQ ID NO: 1798, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1798; a furin cleavage site comprising the amino acid sequence of SEQ ID NO: 1854, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1854; a T2A polypeptide comprising the amino acid sequence of SEQ ID NO: 1855, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g., substitutions, relative to SEQ ID NO: 1855; a second signal sequence comprising the nucleotide sequence of SEQ ID NO: 1857, or an amino acid sequence having at least one, two, or three but no more than four modifications, e.g.,

substitutions, relative to SEQ ID NO: 1857; and an enhancement element comprising the amino acid sequence of SEQ ID NO: 1789, or an amino acid sequence at least 85% identical thereto.

16. An isolated, e.g., recombinant, viral genome comprising the isolated a promoter operably linked to the nucleic acid of any one of claims 1-4. 3 or 7-15.

6. The recombinant viral genome of claim 5, further comprising:

(i) at least one17. The viral genome of claims 4-6 or 7-15, further comprising a promoter operably linked to the nucleic acid comprising the transgene encoding the GBA protein, wherein the promoter comprises a tissue specific promoter or a ubiquitous promoter.

18. The viral genome of claim 16 or 17, wherein the promoter comprises:

(i) a chicken β-actin (CBA) promoter and/or its derivative CAG, an EF-1a promoter, a CMV immediate-early enhancer and/or promoter, a β glucuronidase (GUSB) promoter, a ubiquitin C (UBC) promoter, a neuron-specific enolase (NSE), a platelet-derived growth factor (PDGF) promoter, a platelet-derived growth factor B-chain (PDGF-β) promoter, an intercellular adhesion molecule 2 (ICAM-2) promoter, a synapsin (Syn) promoter, a methyl-CpG binding protein 2 (MeCP2) promoter, a Ca2+/calmodulin-dependent protein kinase II (CaMKII) promoter, a metabotropic glutamate receptor 2 (mGluR2) promoter, a neurofilament light (NFL) or heavy (NFH) promoter, a β-globin minigene nβ2 promoter, a preproenkephalin (PPE) promoter, an enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2) , a glial fibrillary acidic protein (GFAP) promoter, a myelin basic protein (MBP) promoter, a cardiovascular promoter (e.g., αMHC, cTnT, and CMV-MLC2k), a liver promoter (e.g., hAAT, TBG), a skeletal muscle promoter (e.g., desmin, MCK, C512) or a fragment, e.g., a truncation, or a functional variant thereof; and/or

(ii) the nucleotide sequence of any of SEQ ID NOs: 1832, 1833, 1834, 1835, 1836, 1839, 1840, or a nucleotide sequence at least 95% identical thereto.

19. The viral genome of any one of claims 16-18, wherein the promoter or functional variant thereof comprises:

(i) the nucleotide sequence of SEQ ID NO: 1834, or a nucleotide sequence at least 95% identical thereto; or

(ii) the nucleotide sequence of SEQ ID NO: 1839 or 1840, or a nucleotide sequence at least 95% identical thereto.

20. The viral genome of any one of claims 4-6 or 8-19, which further comprises an enhancer, optionally comprising the nucleotide sequence of SEQ ID NO: 1831, or a nucleotide sequence at least 95% identical thereto.

21. The viral genome of claim 4-6 or 8-20, which comprises an enhancer comprising the nucleotide sequence of SEQ ID NO: 1831, or a nucleotide sequence at least 95% identical thereto, and a promoter comprising the nucleotide sequence of SEQ ID NO: 1834, or a nucleotide sequence at least 95% identical thereto.

22. The viral genome of any one of claims 4-6 or 8-20, which further comprises:

(i) an inverted terminal repeat (ITR) sequence, optionally wherein the ITR sequence is positioned 5' relative to the transgene encoding the GBA protein and/or the ITR sequence is positioned 3' relative to the transgene encoding the GBA protein;

(ii) a promoter operably linked to the nucleotide sequence encoding the GBA protein;

(iii) an enhancer;

(iv) an intron;

(v) at least one microRNA (miRNA) binding site; and/or

(vi) (ii) a polyadenylation (polyA) sequence.signal region;

7. (iii) an intron region;

(iv) an exon region, e.g., at least one, two, or three exon regions;

(v) a Kozak sequence

23. The recombinant viral genome of claim 622, wherein:

(i) the promoterITR comprises a chicken beta actin (CB) promoter.nucleotide sequence of SEQ ID NO: 1829 or 1830, or a nucleotide sequence at least 95% identical thereto; or

8. The recombinant viral genome of claim 7, wherein the CB promoter (ii) the ITR positioned 5' relative to the nucleic acid comprising the transgene encoding the GBA

~~protein~~ comprises the nucleotide sequence of SEQ ID NO: 1834 or a nucleotide sequence that is at least 95% identical thereto.

9. The recombinant viral genome of any one of claims 6-8, wherein the enhancer comprises a CMV immediate-early (CMVie) enhancer comprising the nucleotide sequence of SEQ ID NO: 1831~~1829,~~ or a nucleotide sequence that is at least 95% identical thereto.~~; and/or the ITR positioned 3' relative to the nucleic acid comprising the transgene encoding the GBA protein comprises the nucleotide sequence of SEQ ID NO: 1830, or a nucleotide sequence at least 95% identical thereto.~~

10. ~~24.~~ The recombinant viral genome of any one of claims 6-9~~claim 22 or 23~~, wherein~~:~~

~~(i) the polyadenylation (polyA) signal region comprises the nucleotide sequence of SEQ ID NO: 1846, or a nucleotide sequence at least 95% identical thereto;~~

~~(ii) the intron comprises a beta-globin intron; and/or~~

~~(iii)~~ the intron comprises the nucleotide sequence of SEQ ID NO: 1842~~,~~ or a nucleotide sequence that is at least 95% identical thereto.

11. ~~—~~

~~25.~~ The recombinant ~~isolated nucleic acid of any one of claims 3, 5-6, or 8-24, or the~~ viral genome of any one of claims 6-10, wherein the polyA sequence~~4-6 or 8-24, which~~ comprises the nucleotide sequence of SEQ ID NO: 1846 or a nucleotide sequence that is ~~:~~

~~(i)~~ at least 95% identical thereto.~~1-5 copies of the encoded miR binding site, e.g., at least 1, 2, 3, 4, or 5 copies;~~

12. ~~(ii) at least 4 copies of an encoded miR binding sites, optionally wherein all four copies comprise the same miR binding site, or at least one, two, three, or all of the copies comprise a different miR binding site, optionally wherein the 4 copies of the encoded miR binding sites are continuous, e.g., not separated by a spacer; or are separated by a spacer.~~

~~26.~~ The recombinant ~~isolated nucleic acid of any one of claims 3, 5-6, or 8-25, or the~~ viral genome of any one of claims 6-11, wherein the at least one ITR sequence comprises:

(i) the nucleotide sequence of SEQ ID NO: 1829 or a nucleotide sequence that is at least 95% identical to SEQ ID NO: 1829; and/or

(ii) the nucleotide sequence of SEQ ID NO: 1830 or a nucleotide sequence that is at least 95% identical to SEQ ID NO: 1830.

13. The recombinant viral genome of any one of claims 6-124-6 or 8-25, wherein the at least one ITR sequenceviral genome comprises:

(i) a 5' ITR sequence and a 3' ITR sequence, wherein the 5' ITR sequence comprises the nucleotide sequence of SEQ ID NO: 1829 and the 3' ITR sequence comprises the nucleotide sequence of SEQ ID NO: 1830.

14. The recombinant viral genome of any one of claims 6-13, wherein the at least one miRNA binding site comprises at least onefirst encoded miR183 binding site comprising:

(i) the nucleotide sequence of SEQ ID NO: 1847;

(ii) a , or a nucleotide sequence having at least 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity thereto; or a nucleotide sequence that ishaving at least 85% identical to SEQ ID NO: 1847; or

(iii) a nucleotide sequence having up toone, two, three, four, five, six, or seven modifications relative to, but no more than ten modifications of SEQ ID NO: 1847.;

15. The recombinant viral genome of any one of claims 6-14, wherein the at least one miRNA binding site comprises at least four miR183 binding sites, wherein each of the at least four miR183 binding sites is separated by a spacer.

16. The recombinant viral genome of claim 15, wherein the spacer comprises (ii) a first spacer sequence comprising the nucleotide sequence of SEQ ID NO: 1848, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications relative toof SEQ ID NO: 1848.;

17. The recombinant viral genome of any one of claims 6-13, wherein the at least one miRNA binding site comprises a (iii) a second encoded miR183 binding site series comprising:

(i) the nucleotide sequence of SEQ ID NO: 1849;

(ii) a nucleotide sequence that is at least 90% identical to SEQ ID NO: 1849;1847, or

(iii) a nucleotide sequence having up to ten modifications relative to SEQ ID NO: 1849.at least 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity thereto; or a nucleotide sequence

~~having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1847;~~

18. A recombinant viral genome comprising:

(i) a 5' inverted terminal repeat (ITR)~~ (iv) a second spacer~~ sequence comprising the nucleotide sequence of SEQ ID NO: 1829~~1848,~~ or a nucleotide sequence that is at least 95% identical thereto; ~~having at least one, two, or three modifications, but no more than four modifications of SEQ ID NO: 1848;~~

(ii~~v~~) a CMV immediate-early (CMVie) enhancer comprising the nucleotide sequence SEQ ID NO: 1831 or a nucleotide sequence that is at least 95% identical thereto;

(iii) a chicken beta actin (CB) promoter~~third encoded miR183 binding site~~ comprising the nucleotide sequence of SEQ ID NO: 1834~~1847, or a nucleotide sequence having at least 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity thereto;~~ or a nucleotide sequence that is~~having~~ at least 95% identical thereto~~one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1847~~;

(iv) an intron ~~(vi) a third spacer sequence~~ comprising the nucleotide sequence of SEQ ID NO: 1842~~1848,~~ or a nucleotide sequence that is~~having~~ at least 95% identical thereto;~~one, two, or three modifications, but no more than four modifications of SEQ ID NO: 1848; and~~

~~(vii) a fourth encoded miR183 binding site comprising the nucleotide sequence of SEQ ID NO: 1847, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1847.~~

~~27. An isolated, e.g., recombinant, viral genome comprising in 5' to 3' order:~~

~~(i) a 5' adeno-associated (AAV) ITR, optionally wherein the 5' AAV ITR comprises the nucleotide sequence of SEQ ID NO: 1829, or a nucleotide sequence at least 95% identical thereto;~~

~~(ii) a CMVie enhancer, optionally wherein the CMVie enhancer comprises the nucleotide sequence of SEQ ID NO: 1831, or a nucleotide sequence at least 95% identical thereto;~~

(iii) a CB promoter or functional variant thereof, optionally wherein the CB promoter or functional variant thereof comprises the nucleotide sequence of SEQ ID NO: 1834, or a nucleotide sequence at least 95% identical thereto;

(iv) an intron, optionally wherein the intron comprises the nucleotide sequence of SEQ ID NO: 1842, or a nucleotide sequence at least 95% identical thereto;

(v) a nucleotide sequence encoding a signal sequence, optionally wherein the nucleotide sequence encoding the signal sequence comprises the nucleotide sequence of SEQ ID NO: 1850, or a nucleotide sequence that is at least 95% identical thereto;

(vi) a nucleotide sequence transgene encoding a β-glucocerebrosidase (GBA) protein, wherein the nucleotide sequence encoding the GBA protein comprises the nucleotide sequence of SEQ ID NO: 1773 or a nucleotide sequence that is at least 9088% identical thereto to the nucleotide sequence of SEQ ID NO: 1773;

(vii) a polyadenylation (polyA) sequence comprising signal region, optionally wherein the polyA signal region comprises the nucleotide sequence of SEQ ID NO: 1846, or a nucleotide sequence that is at least 95% identical thereto; and

(viii) a 3' AAV ITR sequence comprising, optionally wherein the 3' AAV ITR comprises the nucleotide sequence of SEQ ID NO: 1830, or a nucleotide sequence that is at least 95% identical thereto.

19. The28. An isolated, e.g., recombinant, viral genome of any one of claims 5-13 or claim 18, comprising the nucleotide sequence of SEQ ID NO: 1812 or a nucleotide sequence that is at least 95% identical thereto.in 5' to 3' order:

20. A recombinant viral genome comprising:

(i) a 5' inverted terminal repeat (adeno-associated (AAV) ITR) sequence comprising, optionally wherein the 5' AAV ITR comprises the nucleotide sequence of SEQ ID NO: 1829, or a nucleotide sequence that is at least 95% identical thereto;

(ii) a CMV immediate-early (CMVie) enhancer comprising, optionally wherein the CMVie enhancer comprises the nucleotide sequence of SEQ ID NO: 1831, or a nucleotide sequence that is at least 95% identical thereto;

(iii) a chicken beta actin (CB) promoter comprising the nucleotide sequence of SEQ ID NO: 1834 or a nucleotide sequence that is at least 95% identical thereto;

(iv) an intron comprising the nucleotide sequence of SEQ ID NO: 1842 or a nucleotide sequence that is at least 95% identical thereto;

~~(iii) a CB promoter or functional variant thereof, optionally wherein the CB promoter or functional variant thereof comprises the nucleotide sequence of SEQ ID NO: 1834, or a nucleotide sequence at least 95% identical thereto;~~

~~(iv) an intron, optionally wherein the intron comprises the nucleotide sequence of SEQ ID NO: 1842, or a nucleotide sequence at least 95% identical thereto;~~

(v) a nucleotide sequence encoding a signal sequence, ~~optionally~~ wherein the nucleotide sequence encoding the signal sequence comprises ~~the nucleotide sequence of~~ SEQ ID NO: 1850~~,~~ or a nucleotide sequence that is at least 95% identical thereto;

(vi) a nucleotide sequence~~transgene~~ encoding a β-glucocerebrosidase (GBA) protein, ~~optionally~~ wherein the nucleotide sequence encoding the GBA protein comprises the nucleotide sequence of SEQ ID NO: 1773 or a nucleotide sequence that is at least 90% identical thereto;

(vii) a miR183 binding site series comprising the nucleotide sequence of SEQ ID NO: 1849; a nucleotide sequence that is at least 90~~88~~% identical to SEQ ID NO: 1849; or a~~the~~ nucleotide sequence having up to ten modifications relative to~~of~~ SEQ ID NO: 1849~~1773~~;

(viii) a polyadenylation (polyA) sequence comprising the ~~(vii) an encoded miR183 binding site, optionally wherein the encoded miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 1847, or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1847;~~

~~(viii) a spacer sequence, optionally wherein the spacer comprises the nucleotide sequence of SEQ ID NO: 1848, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of SEQ ID NO: 1848;~~

~~(ix) an encoded miR183 binding site, optionally wherein the encoded miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 1847, or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1847;~~

~~(x) a spacer sequence, optionally wherein the spacer comprises the nucleotide sequence of SEQ ID NO: 1848, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of SEQ ID NO: 1848;~~

~~(xi) an encoded miR183 binding site, optionally wherein the encoded miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 1847, or a nucleotide sequence having at~~

~~least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1847;~~

~~(xii) a spacer sequence, optionally wherein the spacer comprises the nucleotide sequence of SEQ ID NO: 1848, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of SEQ ID NO: 1848;~~

~~(xiii) an encoded miR183 binding site, optionally wherein the encoded miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 1847, or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1847;~~

~~(xiv) a polyA signal region, optionally wherein the polyA signal region comprises the~~ nucleotide sequence of SEQ ID NO: 1846~~,~~ or a nucleotide sequence that is at least 95% identical thereto; and

(ix~~xv~~) a 3' ~~AAV~~ ITR sequence comprising~~, optionally wherein the 3' AAV ITR comprises~~ the nucleotide sequence of SEQ ID NO: 1830~~,~~ or a nucleotide sequence that is at least 95% identical thereto.

21. ~~29.~~ The recombinant viral genome of any one of claims 5-19, comprising~~4-6 or 8-28, which comprises~~ the nucleotide sequence of SEQ ID NO: 1828~~1812, 1829, 1759-1771, 1809-1811, 1813-1827, or 1870,~~ or a nucleotide sequence that is at least 95% identical thereto.

22. An AAV particle comprising an AAV capsid protein and the recombinant ~~30. The~~ viral genome of any one of claims 5-21.~~4-6 or 8-29, which:~~

23. The AAV particle of claim 22~~(i) is single stranded;~~

~~(ii) further comprises a nucleic acid encoding a capsid protein, e.g., a structural protein~~, wherein the AAV capsid protein is an AAV9 capsid protein or a variant thereof; ~~comprises a VP1 polypeptide, a VP2 polypeptide, and/~~or wherein~~a VP3 polypeptide, optionally wherein the VP1 polypeptide,~~ the AAV capsid protein is an AAV5 capsid protein ~~VP2 polypeptide, and/~~or a variant thereof.

24. A vector comprising the recombinant viral genome of any~~VP3 polypeptide are encoded by at least~~ one of claims 5-20, ~~Cap gene; and/~~or

~~(iii) further comprises a nucleic acid encoding a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a~~

~~Rep40 protein. optionally wherein the Rep78 protein, the Rep68 protein, the Rep52 protein, and/or the Rep40 protein are encoded by at least one Rep gene.~~

~~31. An isolated, e.g., recombinant GBA protein encoded by~~ the isolated nucleic acid of any one of claims 1-4~~3 or 5-15 or the viral genome of any one of claims 4-6 or 8-30~~.

25. A cell~~32. An isolated, e.g., recombinant, AAV particle~~ comprising~~:~~

~~(i) a capsid protein; and~~

~~(ii)~~ the recombinant viral genome of any one of claims 5-21,~~4-6 or 8-30.~~

~~33. The AAV particle of claim 32, wherein:~~

~~(i)~~ the isolated~~capsid protein comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 90% sequence identity thereto;~~

~~(ii) the capsid protein comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 138;~~

~~(iii) the capsid protein comprises the amino acid sequence of SEQ ID NO: 11, or an amino acid sequence with at least 90% sequence identity thereto;~~

~~(iv) the capsid protein comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 11;~~

~~(v) the capsid protein comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 90% sequence identity thereto; and/or~~

~~(vi) the nucleotide sequence encoding the capsid protein comprises the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 90% sequence identity thereto.~~

~~34. The AAV particle of claim 32 or 33, wherein the capsid protein comprises:~~

~~(i) an amino acid substitution at position K449, e.g., a K449R substitution, numbered according to SEQ ID NO:138;~~

~~(ii) an insert comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1262), optionally wherein the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO:138;~~

~~(iii) an amino acid other than "A" at position 587 and/or an amino acid other than "Q" at position 588, numbered according to SEQ ID NO: 138;~~

(iv) the amino acid substitution of A587D and/or Q588G, numbered according to SEQ ID NO:138.

35. The AAV particle of any one of claims 32-34, wherein:

(i) the capsid protein comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence having at least 90%, 92%, 95%, 97%, 98%, or 99% sequence identity thereto;

(ii) the capsid protein comprises an amino acid sequence comprising at least one, two, or three modifications but no more than 30, 20, or 10 modifications, e.g., substitutions, relative to the amino acid sequence of SEQ ID NO: 1;

(iii) the capsid protein comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 2 or a nucleotide sequence having at least 90%, 92%, 95%, 97%, 98%, or 99% sequence identity thereto; and/or

(iv) the nucleotide sequence encoding the capsid protein comprises the nucleotide sequence of SEQ ID NO: 2, or a nucleotide sequence having at least 90%, 92%, 95%, 97%, 98%, or 99% sequence identity thereto.

36. A vector comprising the viral genome of any one of claims 4-6 or 8-30 or the nucleic acid of any one of claims 1-43 or 5-15.

37. A cell comprising the viral genome of any one of claims 4-6 or 8-30, the viral particle of any one of claims 32-35, or the vector of claim 2436, optionally wherein the cell is a mammalian cell, e.g., an HEK293 cell, an insect cell, e.g., an Sf9 cell, or a bacterial cell.

26. 38. A method of making an isolated, e.g., recombinant, AAV particle, the method comprising :

(i) providing a host cell comprising the recombinant viral genome of any one of claims 5-20;4-6 or 8-30; and

(ii) incubating the host cell under conditions suitable to encapsulateenclose the recombinant viral genome in an AAVa capsid protein, e.g., a VOY101 capsid protein;

thereby making the isolated AAV particle.

27. 39. A pharmaceutical composition comprising the AAV particle of claim 22 or claim 23any one of claims 32-35, or an AAV particle comprising the viral genome of any one of claims 4-6 or 8-30, and a pharmaceutically acceptable excipient.

28. The pharmaceutical composition of claim 27 or the AAV particle of claim 22 or claim 23 for use in ~~40. A method of~~ delivering a nucleic acid sequence encoding a β-glucocerebrosidase (GBA)~~an exogenous GBA~~ protein to a subject.

29. The pharmaceutical composition of claim 27 or the AAV particle of claim 22 or claim 23 for use in increasing the level of a β-glucocerebrosidase (GBA) protein in the central nervous system of a subject.

30. Use of the pharmaceutical composition of claim 27 or the AAV particle of claim 22 or claim 23 in the manufacture of a medicament for delivering a nucleic acid sequence encoding a β-glucocerebrosidase (GBA) protein to a subject.

31. Use of the pharmaceutical composition of claim 27 or the AAV particle of claim 22 or claim 23 in the manufacture of a medicament for increasing the level of a β-glucocerebrosidase (GBA) protein in the central nervous system of a subject.

32. The use of claim 30 or claim 31, wherein the subject has a β-glucocerebrosidase (GBA)-related disorder.

33. The pharmaceutical composition of claim 27 or the AAV particle of claim 22 or claim 23 for use in treating a subject having a β-glucocerebrosidase (GBA)-related disorder, wherein ~~,~~ ~~comprising administering~~ an effective amount of the pharmaceutical composition or the~~of claim 39, the AAV particle of any one of claims 32-35, an~~ AAV particle is to be administered~~comprising the viral genome of any one of claims 4-6 or 8-30, or an AAV particle comprising a viral genome comprising the nucleic acid of any one of claims 1-3 or 5-15, thereby delivering the exogenous GBA protein~~ to the subject.

34. The pharmaceutical composition of claim 27 or the AAV particle of claim 22 or claim 23 for use in treating a subject having Parkinson's disease (PD), Parkinson's disease dementia (PDD), dementia with Lewy Bodies (DLB), Gaucher disease (GD), spinal muscular atrophy (SMA), multiple system atrophy (MSA), or multiple sclerosis (MS).

35. The pharmaceutical composition of claim 27~~41. The method of claim 40, wherein the subject has, has been diagnosed with having, or is at risk of having:~~

~~(i) a disease associated with expression of GBA, e.g., aberrant or reduced GBA expression, e.g., expression of an GBA gene, GBA mRNA, and/or GBA protein;~~ or the AAV particle of claim 23

~~(ii) a neurodegenerative~~ or claim 23 for use in~~neuromuscular disorder.~~

~~42. A method of~~ treating a subject having Parkinson's disease (PD), wherein ~~or diagnosed with having a disease associated with GBA expression comprising administering~~ an effective amount of the pharmaceutical composition or the~~of claim 39, the AAV particle of any one of claims 32-35, an~~ AAV particle is to be administered to~~comprising~~ the subject.

36. The pharmaceutical composition~~viral genome~~ of claim 27~~any one of claims 4-6~~ or the~~8-30, or an~~ AAV particle ~~comprising a viral genome comprising the nucleic acid~~ of claim 22~~any one of claims 1-3~~ or claim 23 for use~~5-15 thereby treating the disease associated with GBA expression~~ in ~~the subject.~~

~~43. A method of~~ treating a subject having Gaucher's disease (GD), wherein~~or diagnosed with having a neurodegenerative or neuromuscular disorder, comprising administering~~ an effective amount of the pharmaceutical composition or~~of claim 39,~~ the AAV particle is to be administered to the subject.

37. The pharmaceutical composition of claim 27 or the~~of any one of claims 32-35, an~~ AAV particle ~~comprising the viral genome~~ of claim 22~~any one of claims 4-6~~ or claim 23, wherein the pharmaceutical composition~~8-30,~~ or ~~an~~ AAV particle is formulated for intravenous administration.

38. Use of the pharmaceutical composition of claim 27 or the AAV particle of claim 22 or claim 23 in the manufacture of a medicament for treating a subject having a β-glucocerebrosidase (GBA)-related~~comprising a viral genome comprising the nucleic acid of any one of claims 1-3 or 5-15, thereby treating the neurodegenerative or neuromuscular~~ disorder, wherein an effective amount of the pharmaceutical composition or the AAV particle is to be administered to ~~in~~ the subject.

39. ~~44. The~~ use~~method~~ of claim 32 or 38~~any one of claims 41-43~~, wherein the GBA-related~~disease associated with expression of GBA or the neurodegenerative or neuromuscular~~ disorder is~~comprises~~ Parkinson's disease~~Disease~~ (PD), Parkinson's disease dementia (PDD), dementia with Lewy Bodies (DLB), Gaucher disease (GD), spinal~~Spinal~~ muscular atrophy (SMA), multiple system atrophy~~Multiple System Atrophy~~ (MSA), or multiple~~Multiple~~ sclerosis (MS).

40. Use of the pharmaceutical composition of claim 27 or the AAV particle of claim 22 or claim 23 in the manufacture of a medicament for treating a subject having Parkinson's disease (PD), wherein an effective amount of the pharmaceutical composition or the AAV particle is to be administered to the subject.

41. The use of claim 39 or claim 40~~45. The method of claim 44~~, wherein the PD is:

(i) associated with a mutation in a GBA gene;

(ii) early onset PD (e.g., before 50 years of age) or juvenile PD (e.g., before 20 years of age);

(iii) a tremor dominant, postural instability gait difficulty PD (PIGD); or

(iv) a sporadic PD (e.g., a PD not associated with a mutation).

42. Use of the pharmaceutical composition of claim 27 or the AAV particle of claim 22 or claim 23 in the manufacture of a medicament for treating a subject having Gaucher's disease (GD) wherein an effective amount of the pharmaceutical composition or the AAV particle is to be administered to the subject.

43. The use of claim 39 or 42, wherein the GD is:

~~46. The method of claim 44, wherein the GD is:~~

(i) neuronopathic GD (e.g., affects~~affect~~ a cell or tissue of the CNS, e.g., a cell or tissue of the brain and/or spinal cord), non-neuronopathic GD (e.g., does not affect a cell or tissue of the CNS), or combination thereof; or

(ii) a Type I GD (GD1), a Type 2 GD (GD2), or a Type 3 GD (GD3), optionally wherein the GD1 is non- neuronopathic GD and the GD2 is a neuronopathic GD.

44. ~~47. The~~ use~~method~~ of any one of claims 30-32 and 38-43~~40-46~~, wherein the medicament is formulated for intravenous administration.~~subject:~~

45. ~~(i) has a mutation in a GBA gene, GBA mRNA, and/or GBA protein; and/or~~

~~(ii) is a human, optionally wherein the subject is a juvenile (e.g., between 6 years of age to 20 years of age) or an adult (e.g., above 20 years of age).~~

~~48.~~ The use~~method~~ of any one of claims 30-32 and 38-44~~40-47~~, wherein the pharmaceutical composition or AAV particle is used in combination with~~administered to the subject intravenously, intracerebrally, via intrathalamic (ITH) administration, intramuscularly, intrathecally, intracerebroventricularly, via intraparenchymal administration, via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration, via intra-cisterna magna injection (ICM), or via dual ITH and ICM administration.~~

~~49. The method of any one of claims 40-48, wherein the AAV particle is administered via intravenous administration, optionally wherein the intravenous administration is via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration.~~

~~50. The method of any one of claims 40-49, wherein the administration results in an increase in at least one, two, or all of:~~

~~(i) the level of GCase activity in a cell, tissue, (e.g., a cell or tissue of the CNS, e.g., the cortex, striatum, thalamus, cerebellum, and/or brainstem), and/or fluid (e.g., CSF and/or serum), of the subject, optionally wherein the level of GCase activity is increased by at least 3, 4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, or 5.5 fold, as compared to a reference level, e.g., a subject that has not received treatment, e.g., has not been administered the AAV particle;~~

~~(ii) the level of viral genomes (VG) per cell in a CNS tissue (e.g., the cortex, striatum, thalamus, cerebellum, brainstem, and/or spinal cord) of the subject, optionally wherein the VG level is increased by greater than 50 VGs per cell, as compared to a peripheral tissue, wherein the level of VGs per cell is at least 4-10 fold lower than the levels in the CNS tissue, e.g., as measured by an assay as described herein; and/or~~

~~(iii) the level of GBA mRNA expression in a cell or tissue (e.g. a cell or tissue of the CNS, e.g., the cortex, thalamus, and/or brainstem), optionally wherein the level of GBA mRNA is increased by at least 100-1300 fold, e.g., 100 fold, 200 fold, 500 fold, 600 fold, 850 fold, 900 fold, 950 fold, 1000 fold, 1050 fold, 1100 fold, 1150 fold, 1200 fold, 1250 fold, or 1300 fold as compared to a reference level, e.g., a subject that has not received treatment (e.g., has not been~~

~~administered the AAV particle), or endogenous GBA mRNA levels, e.g., as measured by an assay as described herein.~~

~~51. The method of any one of claims 40-50, further comprising administration of~~ an additional therapeutic agent and/or therapy suitable for treatment or prevention of the β-glucocerebrosidase (GBA)-related~~disease associated GBA expression, the neurodegenerative~~ disorder, PD, or GD~~and/or the neuromuscular disorder~~, optionally wherein the additional therapeutic agent comprises enzyme replacement therapy (ERT) (e.g., imiglucerase, velaglucerase alfa, or taliglucerase alfa); substrate reduction therapy (SRT) (e.g., eliglustat or miglustat), blood transfusion, levodopa, carbidopa, Safinamide, dopamine agonists (e.g., pramipexole, rotigotine, or ropinirole), anticholinergics (e.g., benztropine or trihexyphenidyl), cholinesterase inhibitors (e.g., rivastigmine, donepezil, or galantamine), an N-methyl-d-aspartate (NMDA) receptor antagonist (e.g., memantine), or a combination thereof.

~~52. The isolated nucleic acid of any one of claims 1-3 or 5-15, the viral genome of any one of claims 4-6 or 8-30, the AAV particle of any one of claims 32-35, or the pharmaceutical composition of claim 39, for use in the manufacture of a medicament.~~

~~53. The isolated nucleic acid of any one of claims 1-3 or 5-15, the viral genome of any one of claims 4-6 or 8-30, the AAV particle of any one of claims 32-35, or the pharmaceutical composition of claim 39, for use in the treatment of a disease associated with GBA expression, a neuromuscular and/or a neurodegenerative disorder.~~

~~54. Use of an effective amount of an AAV particle comprising the genome of any one of claims 4-6 or 8-30, an AAV particle comprising a genome comprising the nucleic acid of any one of claims 1-3 or 5-15, the AAV particle of any one of claims 32-35, or the pharmaceutical composition of claim 39, in the manufacture of a medicament for the treatment of a disease associated with GBA expression, a neuromuscular and/or a neurodegenerative disorder.~~