CLAIMS

~~WHAT IS CLAIMED IS:~~

~~1. A nucleic acid construct comprising:~~

~~(a) a nucleic acid sequence encoding a therapeutic protein, and~~

~~(b) a nucleic acid sequence encoding a variant IGF2 (vIGF2) peptide that is at least 95 % identical to at least one sequence selected from SEQ ID NO: 90-103.~~

~~2. The nucleic acid construct of claim 1, wherein the vIGF2 peptide has an amino acid sequence that is at least 98% identical to an IGF2 variant peptide selected from SEQ ID NOs:106, 109, 111, 119, 120, 121.~~

~~3. The nucleic acid construct of claim 1, wherein the vIGF2 peptide comprises an amino acid sequence that is at least 98% identical to an IGF2 variant peptide selected from the group consisting of SEQ ID NO:120 and SEQ ID NO:121.~~

~~4. The nucleic acid construct of any one of claim 1 to 3, further comprising a sequence encoding a linker having a sequence that is at least 98% identical to a sequence selected from the group consisting of SEQ ID NOs: 181-188.~~

~~5. The nucleic acid construct of any one of claims 1 to 4, wherein the vIGF2 peptide is capable of increasing expression and/or secretion of a therapeutic protein compared to a vIGF2 peptide having the amino acid sequence of SEQ ID NO:80.~~

~~6. The nucleic acid construct of any one of claims 1 to 4, wherein the vIGF2 peptide has increased affinity for the CI-MPR as compared to a vIGF2 peptide having the amino acid sequence of SEQ ID NO:80.~~

~~7. The nucleic acid construct of claims 1 to 4, wherein the vIGF2 peptide is capable of improving uptake of the therapeutic protein into a cell.~~

~~8. The nucleic acid construct of any one of claims 1 to 7, wherein the therapeutic protein is capable of replacing a defective or deficient protein associated with a genetic disorder in a subject having the genetic disorder.~~

~~9. The nucleic acid construct of claim 8, wherein genetic disorder is a lysosomal storage disorder.~~

~~10. The nucleic acid construct of claim 8, wherein the genetic disorder is selected from the group consisting of aspartylglucosaminuria, neuronal ceroid lipofuscinosis, CLN1/PPT1 disease, CLN2/PPT1 disease, cystinosis, Fabry disease, Gaucher disease type I, Gaucher disease type II, Gaucher disease type III, Pompe disease, Tay Sachs~~

disease, Sandhoff disease, metachomatic leukodystrophy, mucolipidosis type I, mucolipidosis type II, mucolipidosis type III, mucolipidosis type IV, Hurler disease, Hunter disease, Sanfilippo disease type A, Sanfilippo disease type B, Sanfilippo disease type C, Sanfilippo disease type D, Morquio disease type A, Morquio disease type B, Maroteau-Lamy disease, Sly disease, Niemann-Pick disease type A, Niemann-Pick disease type B, Niemann-Pick disease type C1, Niemann-Pick disease type C2, Schindler disease type I, Schindler disease type II, adenosine deaminase severe combined immunodeficiency (ADA-SCID), and neuronal ceroid lipofuscinosis.

11. The nucleic acid construct of claim 8 or claim 9, wherein the genetic disorder is selected from the group consisting of CLN1/PPT1 disease, CLN2/PPT1 disease, Pompe disease and MPS IIIB disease.

12. The nucleic acid construct of claim 11, wherein the genetic disorder is CLN1/PPT1 disease or CLN2/PPT1 disease.

13. The nucleic acid construct of any one of claims 1 to 12, wherein the therapeutic protein comprises a human enzyme selected from the group consisting of alpha-galactosidase (A or B), β-galactosidase, β-hexosaminidase (A or B), galactosylceramidase, arylsulfatase (A or B), β-glucocerebrosidase, glucocerebrosidase, lysosomal acid lipase, lysosomal enzyme acid sphingomyelinase, formylglycine-generating enzyme, iduronidase (e.g., alpha-L), acetyl-CoA:alpha-glucosaminide N-acetyltransferase, glycosaminoglycan alpha-L-iduronohydrolase, heparan N-sulfatase, N-acetyl-α-D-glucosaminidase (NAGLU), iduronate-2-sulfatase, galactosamine-6-sulfate sulfatase, N-acetylgalactosamine-6-sulfatase, N-sulfoglucosamine sulfohydrolase, glycosaminoglycan N-acetylgalactosamine 4-sulfatase, β-glucuronidase, hyaluronidase, alpha-N-acetyl neuraminidase (sialidase), ganglioside sialidase, phosphotransferase, alpha-glucosidase, alpha-D-mannosidase, beta-D-mannosidase, aspartylglucosaminidase, alpha-L-fucosidase, battenin, PPT1, TPP1, and other Batten-related proteins (e.g., ceroid-lipofuscinosis neuronal protein 6), or an enzymatically active fragment thereof.

14. The nucleic acid construct of claim 13, wherein the therapeutic protein is alpha-glucosidase, or an enzymatically active fragment thereof.

15. The nucleic acid construct of claim 13, wherein the therapeutic protein is human PPT1.

16. The nucleic acid construct of claim 13, wherein the therapeutic protein is human TPP1

17. The nucleic acid construct of claim 13, wherein the therapeutic protein is human NAGLU.

18. The nucleic acid construct of claim 1, wherein the nucleic acid construct further comprises a sequence encoding a signal peptide.

19. The nucleic acid construct of claim 18, wherein the signal peptide is one of the sequences selected from the group consisting of SEQ ID NO:169-180.

20. The nucleic acid construct of any one of claims 1 to 19, wherein the vIGF2 encoding nucleic acid sequence is 5' to the nucleic acid sequence encoding a therapeutic protein.

21. The nucleic acid construct of any one of claims 1 to 19, wherein the vIGF2 encoding nucleic acid sequence is 3' to the nucleic acid sequence encoding a therapeutic protein.

22. A gene therapy vector comprising the nucleic acid construct of any one of claims 1 to 21.

23. The gene therapy vector of claim 22, wherein the gene therapy vector is a virus vector.

24. The gene therapy vector of claim 23, wherein the virus vector is an adenovirus vector, an adeno-associated virus (AAV) vector, a retrovirus vector, a lentivirus vector, a pox virus vector, a vaccinia virus vector, an adenovirus vector, or a herpes virus vector.

25. The nucleic acid construct of any one of claims 1 to 21, wherein the nucleic acid construct is a plasmid.

26. A pharmaceutical composition comprising a therapeutically effective amount of the nucleic acid construct of any one of claims 1 to 23 or the gene therapy vector of any one of claims 22 to 24, and a pharmaceutically acceptable carrier or excipient.

27. The pharmaceutical composition of claim 25, wherein the excipient comprises a non-ionic, low-osmolar compound, a buffer, a polymer, a salt, or a combination thereof.

28. A method for treating a genetic disorder comprising administering to a subject in need thereof the nucleic acid construct of any one of claims 1 to 23 or the pharmaceutical composition of claim 25 or claim 26.

29. The method of claim 27, wherein the genetic disorder is a lysosomal storage disorder.

30. The method of claim 27 or claim 28, wherein the genetic disorder is selected from the group consisting of aspartylglucosaminuria, neuronal ceroid lipofuscinosis, CLN1/PPT1 disease, CLN2/PPT1 disease , cystinosis, Fabry disease, Gaucher disease type I, Gaucher disease type II, Gaucher disease type III, Pompe disease, Tay-Sachs disease, Sandhoff disease, metachomatic leukodystrophy, mucolipidosis type I,

mucolipidosis type II, mucolipidosis type III, mucolipidosis type IV, Hurler disease, Hunter disease, Sanfilippo disease type A, Sanfilippo disease type B, Sanfilippo disease type C, Sanfilippo disease type D, Morquio disease type A, Morquio disease type B, Maroteau-Lamy disease, Sly disease, Niemann-Pick disease type A, Niemann-Pick disease type B, Niemann-Pick disease type C1, Niemann-Pick disease type C2, Schindler disease type I, Schindler disease type II, adenosine deaminase severe combined immunodeficiency (ADA-SCID), and chronic granulomatous disease (CGD).

31. The method of claim 29, wherein the genetic disorder is CLN1/PPT1 disease.

32. The method of claim 29, wherein the genetic disorder is CLN2/TPP1 disease.

33. The method of claim 29, wherein the genetic disorder is Sanfilippo type B.

34. The method of any one of claims 27 to 32, wherein the administering is performed intrathecally, intraocularly, intravitreally, retinally, intravenously, intramuscularly, intraventricularly, intracerebrally, intracerebellarly, intracerebroventricularly, intraperenchymally, subcutaneously, or a combination thereof.

35. The method of claim 31, wherein administering the nucleic acid, gene therapy vector or pharmaceutical composition prevents/reduces or reverses accumulation of autofluorescent storage material (ASM) in the brain.

36. The method of claim 31, wherein administering the nucleic acid, gene therapy vector or pharmaceutical composition prevents/reduces or reverses elevation of glial fibrillary acidic protein (GFAP) in the brain.

37. The method of claim 35, wherein administering the nucleic acid, gene therapy vector or pharmaceutical composition prevents/reduces or reverses accumulation of autofluorescent storage material (ASM) in the cortex or thalamus.

38. The method of claim 36, wherein administering the nucleic acid, gene therapy vector or pharmaceutical composition prevents/reduces or reverses elevation of glial fibrillary acidic protein (GFAP) brain cortex or thalamus.

39. The method of any one of claims 31, 35 to 38, wherein the nucleic acid encodes a fusion protein having a sequence at least 98% identical to a sequence selected from the group consisting of SEQ ID NO:60-67.

40. The method of claim 32, wherein the nucleic acid encodes a fusion protein having a sequence at least 98% identical to a sequence selected from the group consisting of SEQ ID NO:47-53.

41. The nucleic acid of any one of claims 1 to 13, wherein the nucleic acid encodes a fusion protein comprising:

a. an amino acid sequence at least 98% identical to a sequence selected from the group consisting of SEQ ID NO:106, 109, 111, 119, 120 and 121; and

b. an amino acid sequence at least 95% identical to a sequence selected from the group consisting of SEQ ID NO:4, residues 21-306 of SEQ ID NO:4, residues 28-306 of SEQ ID NO:4, SEQ ID NO: 8, SEQ ID NO:54-59, residues 24-743 of SEQ ID NO:54, and SEQ ID NO:46.

42. The nucleic acid of claim 41 comprising a sequence encoding a fusion protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:120 and 121.

43. The nucleic acid of claim 41 to 42, further comprising a sequence encoding a lysosomal cleavage peptide.

44. The nucleic acid of any one of claim to 43 to 45, wherein the fusion protein has a sequence at least 95 % identical to a sequence selected from the group consisting of SEQ ID NO:60-67 and SEQ ID NO:47-53.

45. The nucleic acid of claim 44, wherein the fusion protein has a sequence at least 98% identical to a sequence selected from the group consisting of SEQ ID NO:60-67 and SEQ ID NO 47-53.

46. A pharmaceutical composition comprising the nucleic acid of any one of claim 41 to 44 and a pharmaceutically acceptable carrier or excipient.

47. A variant IGF2 (vIGF2) peptide that is at least 98 % identical to at least one sequence selected from the group consisting of SEQ ID NO: 90-103.

48. The variant IGF2 (vIGF2) peptide of claim 47, wherein the vIGF2 is at least 98% identical to at least one sequence selected from SEQ ID NOs:106, 109, 111, 119, 120, 121.

49. A fusion protein comprising the variant vIGF2 peptide of claim 47 or 48, further comprising a therapeutic protein having an amino acid sequence at least 95% identical to a sequence selected from the group consisting of SEQ ID NO:4, amino acid residues 21-306 of SEQ ID NO:4, amino acid residues 28-306 of SEQ ID NO:4, SEQ ID NO: 8, SEQ ID NO:46, SEQ ID NO:54 and amino acid residues 24-743 of SEQ ID NO:54.

50. The fusion protein of claim 49, having an amino acid sequence at least 95% identical to a sequence selected from the group consisting of SEQ ID NO:60-67, SEQ ID NO:47-53 and SEQ ID NO:54-59.

51. The fusion protein of any one of claims 49 to 50, wherein the fusion protein further comprises a lysosomal cleavage peptide.

52. The fusion protein of any one of claims 49 to 51, wherein the vIGF2 peptide is N terminal to the therapeutic protein.

53. The fusion protein of any one of claims 49 to 51, wherein the vIGF2 peptide is C terminal to the therapeutic protein.

54. The fusion protein of any one of claims 49 to 51, wherein the fusion protein comprises a signal sequence.

55. The fusion protein of claim 54, the signal sequence has an amino acid sequence at least 95% identical to a sequence selected from the group consisting of SEQ ID NO:169-180.

56. The fusion protein of claim 56, wherein the vIGF2 peptide is at least 98% identical to SEQ ID NO:120 or 121.

57. The fusion protein of claim 57, wherein the therapeutic protein is selected from the group consisting of PPT1 or an enzymatically active fragment thereof, TPP1 or an enzymatically active fragment thereof, and NAGLU or enzymatically active fragment thereof.

58. The fusion protein of claim 57, wherein the fusion protein is taken up by target cells more efficiently than the corresponding protein lacking the vIGF2 peptide.

59. A pharmaceutical composition comprising the fusion protein of any one of claims 49 to 58, and a pharmaceutically acceptable carrier or excipient.

60. A method of treating a lysosomal storage disorder, comprising administering the pharmaceutical composition of claim 59 to a subject in need thereof.

61. The method of claim 60, wherein the lysosomal storage disorder is selected from the group consisting of CLN1/PPT1 disease, CLN2/TPP1 disease, and Sanfilippo Type B disease.

62. The method of any one of claims 60 to 61, wherein the administering is performed intrathecally, intraocularly, intravitreally, retinally, intravenously, intramuscularly,

~~intraventricularly, intracerebrally, intracerebellarly, intracerebroventricularly, intraperenchymally, subcutaneously, or a combination thereof.~~

~~63. The method of claim 61 or 62, wherein administering the pharmaceutical composition prevents/reduces or reverses accumulation of autofluorescent storage material (ASM) in the brain.~~

~~64. The method of claim 61 or 62, wherein administering the pharmaceutical composition prevents/reduces or reverses elevation of glial fibrillary acidic protein (GFAP) in the brain.~~

~~65. The method of claim 63, wherein administering the pharmaceutical composition prevents/reduces or reverses accumulation of autofluorescent storage material (ASM) in the cortex or thalamus.~~

~~66. The method of claim 64, wherein administering the pharmaceutical composition prevents/reduces or reverses elevation of glial fibrillary acidic protein (GFAP) brain cortex or thalamus.~~

~~67. A nucleic acid encoding a fusion protein comprising vIGF2 and a therapeutic protein, wherein the nucleic acid is at least 85% identical to a sequence selected from the group consisting of SEQ ID NO:189-250.~~

1. A nucleic acid construct comprising:

(a) a nucleic acid sequence encoding a therapeutic protein, and

(b) a nucleic acid sequence encoding a variant IGF2 (vIGF2) peptide that is at least 95 % identical to at least one sequence selected from SEQ ID NO: 90-103.

2. The nucleic acid construct of claim 1, wherein the vIGF2 peptide has an amino acid sequence that is at least 98% identical to an IGF2 variant peptide selected from SEQ ID NOs:106, 109, 111, 119, 120, 121.

3. The nucleic acid construct of claim 1, wherein the vIGF2 peptide comprises an amino acid sequence that is at least 98% identical to an IGF2 variant peptide selected from the group consisting of SEQ ID NO:120 and SEQ ID NO:121.

4. The nucleic acid construct of any one of claim 1 to 3, further comprising a sequence encoding a linker having a sequence that is at least 98% identical to a sequence selected from the group consisting of SEQ ID NOs: 181-188.

5. The nucleic acid construct of any one of claims 1 to 4, wherein the vIGF2 peptide is capable of increasing expression and/or secretion of a therapeutic protein compared to a vIGF2 peptide having the amino acid sequence of SEQ ID NO:80.

6. The nucleic acid construct of any one of claims 1 to 4, wherein the vIGF2 peptide has increased affinity for the CI-MPR as compared to a vIGF2 peptide having the amino acid sequence of SEQ ID NO:80.

7. The nucleic acid construct of claims 1 to 4, wherein the vIGF2 peptide is capable of improving uptake of the therapeutic protein into a cell.

8. The nucleic acid construct of any one of claims 1 to 7, wherein the therapeutic protein is capable of replacing a defective or deficient protein associated with a genetic disorder in a subject having the genetic disorder.

9. The nucleic acid construct of claim 8, wherein genetic disorder is a lysosomal storage disorder.

10. The nucleic acid construct of claim 8, wherein the genetic disorder is selected from the group consisting of aspartylglucosaminuria, neuronal ceroid lipofuscinosis, CLN1/PPT1 disease, CLN2/PPT1 disease, cystinosis, Fabry disease, Gaucher disease type I, Gaucher disease type II, Gaucher disease type III, Pompe disease, Tay Sachs disease, Sandhoff disease, metachomatic leukodystrophy, mucolipidosis type I, mucolipidosis type II, mucolipidosis type III, mucolipidosis type IV, Hurler disease, Hunter disease, Sanfilippo disease type A, Sanfilippo disease type B, Sanfilippo disease type C, Sanfilippo disease type D, Morquio disease type A, Morquio disease type B, Maroteau-Lamy disease, Sly disease, Niemann-Pick disease type A, Niemann-Pick disease type B, Niemann-Pick disease type C1, Niemann-Pick disease type C2, Schindler disease type I, Schindler disease type II, adenosine deaminase severe combined immunodeficiency (ADA-SCID), and neuronal ceroid lipofuscinosis.

11. The nucleic acid construct of claim 8 or claim 9, wherein the genetic disorder is selected from the group consisting of CLN1/PPT1 disease, CLN2/PPT1 disease, Pompe disease and MPS IIIB disease.

12. The nucleic acid construct of claim 11, wherein the genetic disorder is CLN1/PPT1 disease or CLN2/PPT1 disease.

13. The nucleic acid construct of any one of claims 1 to 12, wherein the therapeutic protein comprises a human enzyme selected from the group consisting of alpha-galactosidase

(A or B), β-galactosidase, β-hexosaminidase (A or B), galactosylceramidase, arylsulfatase (A or B), β-glucocerebrosidase, glucocerebrosidase, lysosomal acid lipase, lysosomal enzyme acid sphingomyelinase, formylglycine-generating enzyme, iduronidase (e.g., alpha-L), acetyl-CoA:alpha-glucosaminide N-acetyltransferase, glycosaminoglycan alpha-L-iduronohydrolase, heparan N-sulfatase, N-acetyl-α-D-glucosaminidase (NAGLU), iduronate-2-sulfatase, galactosamine-6-sulfate sulfatase, N-acetylgalactosamine-6-sulfatase, N-sulfoglucosamine sulfohydrolase, glycosaminoglycan N–acetylgalactosamine 4-sulfatase, β-glucuronidase, hyaluronidase, alpha-N -acetyl neuraminidase (sialidase), ganglioside sialidase, phosphotransferase, alpha-glucosidase, alpha-D-mannosidase, beta-D-mannosidase, aspartylglucosaminidase, alpha-L-fucosidase, battenin, PPT1, TPP1, and other Batten-related proteins (e.g., ceroid-lipofuscinosis neuronal protein 6), or an enzymatically active fragment thereof.

14. The nucleic acid construct of claim 13, wherein the therapeutic protein is alpha-glucosidase, or an enzymatically active fragment thereof.

15. The nucleic acid construct of claim 13, wherein the therapeutic protein is human PPT1.

16. The nucleic acid construct of claim 13, wherein the therapeutic protein is human TPP1

17. The nucleic acid construct of claim 13, wherein the therapeutic protein is human NAGLU.

18. The nucleic acid construct of claim 1, wherein the nucleic acid construct further comprises a sequence encoding a signal peptide.

19. The nucleic acid construct of claim 18, wherein the signal peptide is one of the sequences selected from the group consisting of SEQ ID NO:169-180.

20. The nucleic acid construct of any one of claims 1 to 19, wherein the vIGF2 encoding nucleic acid sequence is 5’ to the nucleic acid sequence encoding a therapeutic protein.

21. The nucleic acid construct of any one of claims 1 to 19, wherein the vIGF2 encoding nucleic acid sequence is 3’ to the nucleic acid sequence encoding a therapeutic protein.

22. A gene therapy vector comprising the nucleic acid construct of any one of claims 1 to 21.

23. The gene therapy vector of claim 22, wherein the gene therapy vector is a virus vector.

24. The gene therapy vector of claim 23, wherein the virus vector is an adenovirus vector, an adeno-associated virus (AAV) vector, a retrovirus vector, a lentivirus vector, a pox virus vector, a vaccinia virus vector, an adenovirus vector, or a herpes virus vector.

25. The nucleic acid construct of any one of claims 1 to 21, wherein the nucleic acid construct is a plasmid.

26. A pharmaceutical composition comprising a therapeutically effective amount of the nucleic acid construct of any one of claims 1 to 23 or the gene therapy vector of any one of claims 22 to 24, and a pharmaceutically acceptable carrier or excipient.

27. The pharmaceutical composition of claim 25, wherein the excipient comprises a non-ionic, low-osmolar compound, a buffer, a polymer, a salt, or a combination thereof.

28. Use of the nucleic acid construct of any one of claims 1 to 23 or the pharmaceutical composition of claim 25 or claim 26, in the manufacture of a medicament for the treatment of a genetic disorder.

29. The use of claim 27, wherein the genetic disorder is a lysosomal storage disorder.

30. The nucleic acid construct of any one of claims 1 to 23 or the pharmaceutical composition of claim 25 or claim 26, for use in therapy.