CLAIMS

What is claimed is:

1. A protein comprising:

a. a first Fc polypeptide linked to a first N-sulfoglucosamine sulfohydrolase (SGSH) amino acid sequence, an SGSH variant amino acid sequence, or a catalytically active fragment thereof; and

b. a second Fc polypeptide linked to a second SGSH amino acid sequence, an SGSH variant amino acid sequence, or a catalytically active fragment thereof, wherein the second Fc polypeptide is capable of specifically binding to a transferrin receptor (TfR); and wherein the second Fc polypeptide comprises a sequence having at least 80% identity to SEQ ID NO: 37 and has Ala at position 389, according to EU numbering.

2. The protein of claim 1, wherein the second Fc polypeptide further comprises at the following positions, according to EU numbering:

i. Glu at position 380;
ii. Tyr at position 384;
iii. Thr at position 386;
iv. Glu at position 387;
v. Trp at position 388;
vi. Asn at position 390;
vii. Thr at position 413;
viii. Glu at position 415;
ix. Glu at position 416; and
x. Phe at position 421.

3. The protein of claim 1 or 2, wherein the first and/or second SGSH amino acid sequence comprises an amino acid sequence having at least 80%, 85%, 90%, or 95% identity to any one of SEQ ID NOS:58-60.

4. The protein of claim 3, wherein the first and/or second SGSH amino acid sequence comprises the amino acid sequence of any one of SEQ ID NOS:58-60.

5. The protein of any one of claims 1-4, wherein the first Fc polypeptide is linked to the first SGSH amino acid sequence, SGSH variant amino acid sequence, or a catalytically active fragment thereof by a peptide bond or by a polypeptide linker; and/or wherein the second Fc polypeptide is linked to the second SGSH amino acid sequence, SGSH variant amino acid sequence, or a catalytically active fragment thereof by a peptide bond or by a polypeptide linker.

6. The protein of any one of claims 1-5, wherein the N-terminus of the first Fc polypeptide is linked to the first SGSH amino acid sequence, SGSH variant amino acid sequence, or a catalytically active fragment thereof; and/or wherein the N-terminus of the second Fc polypeptide is linked to the second SGSH amino acid sequence, SGSH variant amino acid sequence, or a catalytically active fragment thereof.

7. The protein of any one of claims 1-5, wherein the C-terminus of the first Fc polypeptide is linked to the first SGSH amino acid sequence, SGSH variant amino acid sequence, or a catalytically active fragment thereof; and/or wherein the C-terminus of the second Fc polypeptide is linked to the second SGSH amino acid sequence, SGSH variant amino acid sequence, or a catalytically active fragment thereof.

8. The protein of any one of claims 1-7, wherein the first Fc polypeptide and the second Fc polypeptide each contain modifications that promote heterodimerization.

9. The protein of claim 8, wherein the first Fc polypeptide contains the T366S, L368A, and Y407V substitutions and the second Fc polypeptide contains the T366W substitution, according to EU numbering; or wherein the first Fc polypeptide contains the T366W substitution and the second Fc polypeptide contains the T366S, L368A, and Y407V substitutions, according to EU numbering.

10. The protein of claim 9, wherein the first Fc polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 12-19 and 28-31; and the second Fc polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 34-41 and 54-57.

11. The protein of claim 9, wherein the first Fc polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 24-27; and the second Fc polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 48-53.

12. The protein of any one of claims 1-11, wherein the first Fc polypeptide and/or the second Fc polypeptide comprises a native FcRn binding site; or wherein the first Fc polypeptide and the second Fc polypeptide do not have effector function.

13. The protein of any one of claims 1-11, wherein the first Fc polypeptide and/or the second Fc polypeptide includes a modification that reduces effector function, wherein the modification that reduces effector function is the substitutions of Ala at position 234 and Ala at position 235, according to EU numbering; or the substitutions of Ala at position 234, Ala at position 235, and Ser at position 329, according to EU numbering.

14. The protein of claim 13, wherein the first Fc polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 14-19 and 26-31.

15. The protein of claim 14, wherein the first Fc polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 14, 15, 28, and 29; or wherein the first Fc polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS:18, 19, 30, and 31.

16. The protein of claim 13, wherein the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 61-88 and 117-118.

17. The protein of claim 16, wherein the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 61-68, 73-76, 81-84 and 117-118.

18. The protein of any one of claims 13-17, wherein the second Fc polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 36-41 and 50-57.

19. The protein of claim 18, wherein the second Fc polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 36, 37, 54 and 55; or wherein the second Fc polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS:40, 41, 56 and 57.

20. The protein of any one of claims 13-17, wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 89-116 and 119-120.

21. The protein of claim 20, wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS: 89-96, 101-104, 109-112 and 119-120.

22. The protein of any one of claims 1-21, wherein the first Fc polypeptide and/or the second Fc polypeptide comprises amino acid changes relative to the native Fc sequence that extend serum half-life, wherein the amino acid changes comprise substitutions of Tyr at position 252, Thr at position 254, and Glu at position 256, according to EU numbering; or wherein the amino acid changes comprise substitutions of Leu at position 428 and Ser at position 434, according to EU numbering; or wherein the amino acid changes comprise a substitution of Ser or Ala at position 434, according to EU numbering.

23. The protein of claim 1, wherein:

1) the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence of any one of SEQ ID NOS: 61-68, 73-76, and 81-84; and wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence of any one of SEQ ID NOS: 89-96, 101-104, and 109-112; or

2) wherein the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence of SEQ ID NO: 118; and wherein the second Fc polypeptide

linked to the second SGSH amino acid sequence comprises an amino acid sequence of SEQ ID NO: 120.

24. The protein of claim 23, wherein:

1) the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence of any one of SEQ ID NOS: 61-64; and wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence of any one of SEQ ID NOS: 89-92; or

2) the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence of SEQ ID NO: 75 or 76; and wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence of SEQ ID NO: 103 or 104; or

3) the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence of SEQ ID NOS: 83 or 84; and wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence of SEQ ID NO: 111 or 112; or

4) the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence of any one of SEQ ID NOS: 65-68; and wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence of any one of SEQ ID NOS: 93-96.

25. The protein of claim 24, wherein the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence of SEQ ID NO: 63 or 64; and wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence of SEQ ID NO: 91 or 92.

26. The protein of claim 6, wherein the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence having at least 90% identity to any one of SEQ ID NOS: 67-68; and wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence having at least 90% identity to any one of SEQ ID NOS: 95-96.

27. The protein of claim 26, wherein the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence having at least 95% identity to any one of SEQ ID NOS: 67-68; and wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence having at least 95% identity to any one of SEQ ID NOS: 95-96.

28. The protein of claim 27, wherein the first Fc polypeptide linked to the first SGSH amino acid sequence comprises an amino acid sequence of SEQ ID NO: 67 or 68; and wherein the second Fc polypeptide linked to the second SGSH amino acid sequence comprises an amino acid sequence of SEQ ID NO: 95 or 96.

29. The protein of any one of claims 1-28, wherein the protein does not include an immunoglobulin heavy and/or light chain variable region sequence or an antigen-binding portion thereof.

30. A polypeptide comprising a Fc polypeptide linked to an SGSH amino acid sequence, an SGSH variant amino acid sequence, or a catalytically active fragment thereof, wherein the Fc polypeptide i) is capable of specifically binding to a transferrin receptor (TfR); ii) comprises a sequence having at least 90% identity to SEQ ID NO: 37; iii) has one or more modifications that promote its heterodimerization to another Fc polypeptide; and iv) has Ala at position 389, according to EU numbering.

31. The polypeptide of claim 30, wherein the Fc polypeptide further comprises at the following positions, according to EU numbering:

i. Glu at position 380;
ii. Tyr at position 384;
iii. Thr at position 386;
iv. Glu at position 387;
v. Trp at position 388;
vi. Asn at position 390;
vii. Thr at position 413;
viii. Glu at position 415;
ix. Glu at position 416; and

x. Phe at position 421.

32. The polypeptide of claim 30 or 31, wherein the Fc polypeptide further comprises Ala at position 234 and Ala at position 235, according to EU numbering; or Ala at position 234, Ala at position 235, and Ser at position 329, according to EU numbering.

33. The polypeptide of any one of claims 30-32, wherein the Fc polypeptide is linked to the SGSH amino acid sequence, SGSH variant amino acid sequence, or catalytically active fragment thereof by a peptide bond or by a polypeptide linker.

34. The polypeptide of claim 33, which is a fusion polypeptide comprising from N- to C-terminus: the SGSH amino acid sequence, SGSH variant amino acid sequence, or catalytically active fragment; the polypeptide linker; and the Fc polypeptide; or which is a fusion polypeptide comprising from N- to C-terminus: the Fc polypeptide; the polypeptide linker; and the SGSH amino acid sequence, SGSH variant amino acid sequence, or catalytically active fragment.

35. The polypeptide of any one of claims 30-34, wherein the Fc polypeptide contains T366S, L368A, and Y407V substitutions, according to EU numbering; or wherein the Fc polypeptide contains a T366W substitution.

36. The polypeptide of claim 35, wherein the polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS:97-100, 105-108, and 113-116.

37. The polypeptide of claim 35, wherein the polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95% or 100% identity to any one of SEQ ID NOS:89-96, 101-104, 109-112, and 119-120.

38. A protein comprising the polypeptide of any one of claims 30-37 and the other Fc polypeptide.

39. A pharmaceutical composition comprising the protein of any one of claims 1-29 and 38 or the polypeptide of any one of claims 30 to 37 and a pharmaceutically acceptable excipient.

40. A polynucleotide comprising a nucleic acid sequence encoding the polypeptide of any one of claims 30-37.

41. A vector comprising the polynucleotide of claim 40.

42. A host cell comprising the polynucleotide of claim 40 or the vector of claim 41.

43. The host cell of claim 42, further comprising a polynucleotide comprising a nucleic acid sequence encoding the other Fc polypeptide.

44. A method for producing a polypeptide comprising an Fc polypeptide that is linked to an SGSH amino acid sequence, SGSH variant amino acid sequence, or catalytically active fragment, comprising culturing a host cell under conditions in which the polypeptide encoded by the polynucleotide of claim 40 is expressed.

45. A pair of polynucleotides comprising a first nucleic acid sequence encoding the first Fc polypeptide linked to the first SGSH amino acid sequence, SGSH variant amino acid sequence, or catalytically active fragment; and a second nucleic acid sequence encoding the second Fc polypeptide linked to the second SGSH amino acid sequence, SGSH variant amino acid sequence, or catalytically active fragment, as recited in any one of claims 1-29.

46. One or more vectors comprising the pair of polynucleotides of claim 45.

47. A host cell comprising the pair of polynucleotides of claim 44 or the one or more vectors of claim 46.

48. A method for producing a protein comprising a first Fc polypeptide linked to a first SGSH amino acid sequence, SGSH variant amino acid sequence, or catalytically active fragment, and a second Fc polypeptide linked to a second SGSH amino acid sequence, SGSH variant amino acid sequence, or catalytically active fragment, comprising culturing a host cell under conditions in which the pair of polynucleotides of claim 45 is expressed.

49. A protein as described in any one of claims 1-29 and 38 or a polypeptide as described in any one of claims 30-37 for use in treating Sanfilippo syndrome A in a patient in need thereof.

50. The use of a protein as described in any one of claims 1-29 and 38 or a polypeptide as described in any one of claims 30-37 in the preparation of a medicament for treating Sanfilippo syndrome A in a patient in need thereof.

51. A protein as described in any one of claims 1-29 and 38 or a polypeptide as described in any one of claims 30-37 for use in decreasing the accumulation of a toxic metabolic product in a patient having Sanfilippo syndrome A, wherein the toxic metabolic product comprises heparan sulfate-derived oligosaccharides.

52. The use of a protein as described in any one of claims 1-29 and 38 or a polypeptide as described in any one of claims 30-37 in the preparation of a medicament for decreasing the accumulation of a toxic metabolic product in a patient having Sanfilippo syndrome A, wherein the toxic metabolic product comprises heparan sulfate-derived oligosaccharides.