CLAIMS

What is claimed is:

1. A protein comprising:

a. a first Fc polypeptide linked to an alpha-L-iduronidase (IDUA) amino acid sequence, an IDUA variant amino acid sequence, or a catalytically active fragment thereof; and

b. a second Fc polypeptide that comprises a sequence having at least 90% identity to SEQ ID NO: 28 and that is capable of specifically binding to a transferrin receptor (TfR).

2. The protein of claim 1, wherein the second Fc polypeptide comprises Ala at position 389, Glu at position 380; and Asn at position 390, according to EU numbering.

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

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

4. The protein of any one of claims 1-3, wherein the IDUA amino acid sequence comprises an amino acid sequence having at least 80%, 85%, 90%, or 95% identity to any one of SEQ ID NOS: 39, 40, 45, 78, and 99.

5. The protein of any one of claims 1-3, wherein the IDUA amino acid sequence comprises the amino acid sequence of any one of SEQ ID NOS: 41-44.

6. The protein of any one of claims 1-3, wherein the IDUA amino acid sequence comprises the amino acid sequence of any one of SEQ ID NOS: 46-49.

7. The protein of any one of claims 1-3, wherein the IDUA amino acid sequence comprises the amino acid sequence of any one of SEQ ID NOS: 79-82.

8. The protein of any one of claims 1-7, wherein the first Fc polypeptide is linked to the IDUA amino acid sequence, IDUA variant amino acid sequence, or a catalytically active fragment thereof, by a peptide bond or by a polypeptide linker.

9. The protein of any one of claims 1-8, wherein the N-terminus of the first Fc polypeptide is linked to the IDUA amino acid sequence, IDUA variant amino acid sequence, or a catalytically active fragment thereof.

10. The protein of any one of claims 1-8, wherein the C-terminus of the first Fc polypeptide is linked to the IDUA amino acid sequence, IDUA variant amino acid sequence, or a catalytically active fragment thereof.

11. The protein of any one of claims 1-10, which comprises a single IDUA amino acid sequence, IDUA variant amino acid sequence, or a catalytically active fragment thereof.

12. The protein of any one of claims 1-11, wherein the second Fc polypeptide forms an Fc dimer with the first Fc polypeptide.

13. The protein of any one of claims 1-12, wherein one of the Fc polypeptides has a T366W substitution and the other Fc polypeptide has T366S, L368A, and Y407V substitutions, according to EU numbering.

14. The protein of claim 13, wherein the first Fc polypeptide contains the T366S, L368A, and Y407V substitutions and the second Fc polypeptide contains the T366W substitution.

15. The protein of claim 14, wherein the first Fc polypeptide comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 9-16 and 19-22; and the second Fc polypeptide comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 25-32 and 35-38.

16. The protein of any one of claims 1-15, 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.

17. The protein of any one of claims 1-15, 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; Ala at position 234, Ala at position 235 and Gly at position 329; or Ala at position 234, Ala at position 235 and Ser at position 329, according to EU numbering.

18. The protein of claim 17, wherein the first Fc polypeptide comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 11-16, and 19-22.

19. The protein of claim 18, wherein the first Fc polypeptide comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 11, 12, 19, and 20; or wherein the first Fc polypeptide comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS:15, 16, 21, and 22.

20. The protein of claim 17, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 50-69 and 83-92.

21. The protein of claim 20, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 50-53.

22. The protein of claim 20, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 54-57.

23. The protein of claim 20, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 83-86.

24. The protein of claim 20, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 58-61 and 91-92.

25. The protein of claim 20, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 62-65.

26. The protein of claim 20, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 87-90.

27. The protein of claim 20, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 66-67.

28. The protein of claim 20, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 68-69.

29. The protein of any one of claims 17-28, wherein the second Fc polypeptide comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 27-32 and 35-38.

30. The protein of claim 29, wherein the second Fc polypeptide comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS: 27, 28, 35 and 36; or wherein the second Fc polypeptide comprises an amino acid sequence having at least 95% or 100% identity to any one of SEQ ID NOS:31, 32, 37 and 38.

31. The protein of claim 1, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises the amino acid sequence of any one of SEQ ID NOS: 50-65 and 83-92; and wherein the second Fc polypeptide comprises the amino acid sequence of any one of SEQ ID NOS: 35-38.

32. The protein of claim 31, wherein:

1) the first Fc polypeptide linked to the IDUA amino acid sequence comprises the amino acid sequence of any one of SEQ ID NOS: 50-57 and 83-86; and wherein the second Fc polypeptide comprises the amino acid sequence of any one of SEQ ID NOS: 35-36; or

2) the first Fc polypeptide linked to the IDUA amino acid sequence comprises the amino acid sequence of any one of SEQ ID NOS: 58-65 and 87-92; and wherein the second Fc polypeptide comprises the amino acid sequence of any one of SEQ ID NOS: 37-38.

33. The protein of claim 1, wherein the first Fc polypeptide linked to the IDUA amino acid sequence comprises the amino acid sequence of any one of SEQ ID NOS: 66-69; and wherein the second Fc polypeptide comprises the amino acid sequence of any one of SEQ ID NOS: 35-38.

34. The protein of claim 33, wherein:

1) the first Fc polypeptide linked to the IDUA amino acid sequence comprises the amino acid sequence of any one of SEQ ID NOS: 66-67; and wherein the second Fc polypeptide comprises the amino acid sequence of any one of SEQ ID NOS: 35-36; or

2) the first Fc polypeptide linked to the IDUA amino acid sequence comprises the amino acid sequence of any one of SEQ ID NOS: 68-69; and wherein the second Fc polypeptide comprises the amino acid sequence of any one of SEQ ID NOS: 37-38.

35. The protein of any one of claims 1-34, wherein the protein does not include an immunoglobulin heavy and/or light chain variable region sequence or an antigen-binding portion thereof.

36. A polypeptide comprising an Fc polypeptide that is linked to an alpha-L-iduronidase (IDUA) amino acid sequence, an IDUA variant amino acid sequence, or a catalytically active fragment thereof, wherein the Fc polypeptide comprises a sequence having at least 90% identity to SEQ ID NO: 12 and contains one or more modifications that promote its heterodimerization to another Fc polypeptide.

37. A protein comprising the polypeptide and the other Fc polypeptide of claim 36.

38. A pharmaceutical composition comprising the protein of any one of claims 1-35 and 37 or the polypeptide of claim 36 and a pharmaceutically acceptable excipient.

39. A polynucleotide comprising a nucleic acid sequence encoding the polypeptide of claim 36.

40. A vector comprising the polynucleotide of claim 39.

41. A host cell comprising the polynucleotide of claim 39 or the vector of claim 40.

42. The host cell of claim 41, further comprising a polynucleotide comprising a nucleic acid sequence encoding the other Fc polypeptide of claim 36.

43. A method for producing a polypeptide comprising an Fc polypeptide that is linked to an IDUA amino acid sequence, IDUA variant amino acid sequence, or catalytically active fragment thereof, comprising culturing a host cell under conditions in which the polypeptide encoded by the polynucleotide of claim 39 is expressed.

44. A pair of polynucleotides comprising a first nucleic acid sequence encoding the first Fc polypeptide linked to an IDUA amino acid sequence, IDUA variant amino acid sequence, or catalytically active fragment thereof; and a second nucleic acid sequence encoding the second Fc polypeptide, as recited in any one of claims 1-35.

45. One or more vectors comprising the pair of polynucleotides of claim 44.

46. A host cell comprising the pair of polynucleotides of claim 44, or the one or more vectors of claim 45.

47. A method for producing a protein comprising a first Fc polypeptide linked to an IDUA amino acid sequence, IDUA variant amino acid sequence, or catalytically active fragment thereof, and a second Fc polypeptide, comprising culturing a host cell under conditions in which the pair of polynucleotides of claim 44 are expressed.

48. A protein as described in any one of claims 1-35 and 37 or a polypeptide as described in claim 36 for use in treating MPS I in a patient in need thereof.

49. The use of a protein as described in any one of claims 1-35 and 37 or a polypeptide as described in claim 36 in the preparation of a medicament for treating MPS I in a patient in need thereof.

50. A protein as described in any one of claims 1-35 and 37 or a polypeptide as described in claim 36 for use in decreasing the accumulation of a toxic metabolic product in a patient having MPS I, wherein the toxic metabolic product comprises heparan sulfate-derived oligosaccharides or dermatan sulfate-derived oligosaccharides.

51. The use of a protein as described in any one of claims 1-35 and 37 or a polypeptide as described in claim 36 in the preparation of a medicament for decreasing the accumulation of a toxic metabolic product in a patient having MPS I, wherein the toxic metabolic product comprises heparan sulfate-derived oligosaccharides or dermatan sulfate-derived oligosaccharides.