

CLAIMS

1. A protein comprising:
 - (a) a single progranulin polypeptide;
 - (b) a first Fc polypeptide that is linked to the progranulin polypeptide of (a); and
 - (c) a second Fc polypeptide that forms an Fc dimer with the first Fc polypeptide,wherein the protein comprises exactly one progranulin polypeptide,
wherein the first Fc polypeptide and/or the second Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and
wherein the first Fc polypeptide and/or the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering.
2. The protein of claim 1, wherein:
 - (i) the first Fc polypeptide and/or the second Fc polypeptide does not include an immunoglobulin heavy and/or light chain variable region sequence or an antigen-binding portion thereof; and/or
 - (ii) the progranulin polypeptide comprises an amino acid sequence having greater than 90% identity, or at least 95% identity to the amino acid sequence of SEQ ID NO:212, optionally wherein the progranulin polypeptide comprises the amino acid sequence of SEQ ID NO:212.
3. The protein of claim 1 or 2, wherein the first Fc polypeptide is linked to the progranulin polypeptide by a peptide bond or by a polypeptide linker, optionally wherein:
 - (i) the polypeptide linker is 1 to 50 amino acids in length; and/or
 - (ii) the polypeptide linker is a flexible polypeptide linker, optionally wherein the flexible polypeptide linker is a glycine-rich linker, optionally wherein the glycine-rich linker is G₄S (SEQ ID NO:277) or (G₄S)₂ (SEQ ID NO:276).

4. The protein of any one of claims 1 to 3, wherein the N-terminus or the C-terminus of the first Fc polypeptide is linked to the progranulin polypeptide.

5. A protein comprising:

(a) a first Fc polypeptide that is linked to a first progranulin polypeptide; and
(b) a second Fc polypeptide that is linked to a second progranulin polypeptide,
wherein the first Fc polypeptide and the second Fc polypeptide form an Fc dimer,
wherein the first Fc polypeptide and/or the second Fc polypeptide is modified to
specifically bind to a transferrin receptor (TfR), and

wherein the first Fc polypeptide and/or the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering.

6. The protein of claim 5, wherein:

(i) the first Fc polypeptide and/or the second Fc polypeptide does not include an immunoglobulin heavy and/or light chain variable region sequence or an antigen-binding portion thereof; and/or

(ii) each of the first and second progranulin polypeptides comprises an amino acid sequence having greater 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:212, optionally wherein each of the first and second progranulin polypeptides comprises the amino acid sequence of SEQ ID NO:212.

7. The protein of claim 5 or 6, wherein the first Fc polypeptide is linked to the first progranulin polypeptide by a peptide bond or by a polypeptide linker and wherein the second Fc polypeptide is linked to the second progranulin polypeptide by a peptide bond or by a polypeptide linker,

optionally wherein:

(i) the polypeptide linker is 1 to 50 amino acids in length; and/or

(ii) the polypeptide linker is a flexible polypeptide linker,

optionally wherein the flexible polypeptide linker is a glycine-rich linker,

optionally wherein the glycine-rich linker is G₄S (SEQ ID NO:277) or (G₄S)₂ (SEQ ID NO:276).

8. The protein of any one of claims 5 to 7, wherein:

(i) the N-terminus of the first Fc polypeptide is linked to the C-terminus of the first progranulin polypeptide and the N-terminus of the second Fc polypeptide is linked to the C-terminus of the second progranulin polypeptide; or

(ii) the N-terminus of the first Fc polypeptide is linked to the C-terminus of the first progranulin polypeptide and the C-terminus of the second Fc polypeptide is linked to the N-terminus of the second progranulin polypeptide; or

(iii) the C-terminus of the first Fc polypeptide is linked to the N-terminus of the first progranulin polypeptide and the C-terminus of the second Fc polypeptide is linked to the N-terminus of the second progranulin polypeptide.

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

optionally wherein the Fc dimer is an Fc heterodimer,

optionally 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,

optionally wherein:

(i) the first Fc polypeptide contains the T366S, L368A, and Y407V substitutions and the second Fc polypeptide contains the T366W substitution; or

(ii) the first Fc polypeptide contains the T366W substitution and the second Fc polypeptide contains the T366S, L368A, and Y407V substitutions.

10. The protein of any one of claims 1 to 9, wherein the first Fc polypeptide is linked to the progranulin polypeptide and comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the amino acid sequence of any one of SEQ ID NOS:213, 214, 225, and 226, and the second Fc polypeptide comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the amino acid sequence of SEQ ID NO:261.

11. The protein of any one of claims 1 to 10, wherein the first Fc polypeptide and/or the second Fc polypeptide comprises a native FcRn binding site.
12. The protein of any one of claims 1 to 11,
- (a) wherein:
- (i) the first Fc polypeptide and the second Fc polypeptide do not have effector function, or
- (ii) the first Fc polypeptide and/or the second Fc polypeptide includes a modification that reduces effector function, optionally wherein the modification that reduces effector function is the substitutions of Ala at position 234 and Ala at position 235, according to EU numbering; and/or
- (b) 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, optionally wherein:
- (i) the amino acid changes comprise substitutions of Leu at position 428 and Ser at position 434, according to EU numbering; or
- (ii) the amino acid changes comprise a substitution of Ser or Ala at position 434, according to EU numbering.
13. The protein of any one of claims 1 to 12, wherein the first Fc polypeptide and/or the second Fc polypeptide binds to the apical domain of the TfR.
14. The protein of any one of claims 1 to 13, wherein the first Fc polypeptide and/or the second Fc polypeptide has a CH3 domain with at least 90% identity, or at least 95% identity to amino acids 111-217 of any one of SEQ ID NOS:34-38, 58, 60-90, 136, and 137-210.
15. The protein of claim 14, wherein the first Fc polypeptide and/or the second Fc polypeptide comprises the amino acid sequence of any one of SEQ ID NOS:136-210, optionally wherein the first Fc polypeptide and/or the second Fc polypeptide comprises the amino acid sequence of any one of SEQ ID NOS:136, 138, 150, 162, 174, 186, and 198.

16. The protein of any one of claims 1 to 15, wherein:
- (i) the binding of the protein to the transferrin receptor does not substantially inhibit binding of transferrin to the transferrin receptor; and/or
 - (ii) the first Fc polypeptide and/or the second Fc polypeptide has an amino acid sequence identity of at least 90%, 92%, or 95%, as compared to the corresponding wild-type Fc polypeptide, optionally wherein the corresponding wild-type Fc polypeptide is a human IgG1, IgG2, IgG3, or IgG4 Fc polypeptide; and/or
 - (iii) uptake of the progranulin polypeptide into the brain is at least ten-fold greater as compared to the uptake of the progranulin polypeptide in the absence of the first Fc polypeptide and/or the second Fc polypeptide or as compared to the uptake of the progranulin polypeptide without the modifications to the first Fc polypeptide and/or the second Fc polypeptide that result in transferrin receptor binding.
17. The protein of any one of claims 1 to 16, wherein:
- (i) the first Fc polypeptide is not modified to bind to a blood-brain barrier receptor and the second Fc polypeptide is modified to specifically bind to a transferrin receptor; or
 - (ii) the first Fc polypeptide is modified to specifically bind to a transferrin receptor and the second Fc polypeptide is not modified to bind to a blood-brain barrier receptor.
18. The protein of any one of claims 1 to 17, wherein the progranulin polypeptide binds to sortilin or prosaposin,
optionally wherein the progranulin polypeptide binds to sortilin.
19. A protein comprising:
- (a) a first Fc polypeptide that is linked to a progranulin polypeptide through a polypeptide linker; and
 - (b) a second Fc polypeptide that forms an Fc dimer with the first Fc polypeptide,
wherein the first Fc polypeptide comprises hole mutations T366S, L368A, and Y407V and the second Fc polypeptide comprises a knob mutation T366W, according to EU numbering scheme,
wherein the first Fc polypeptide and/or the second Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and

wherein the first Fc polypeptide and/or the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering.

20. The protein of claim 19, wherein:

(i) (a) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of any one of SEQ ID NOS:213, 214, 225, and 226 and (b) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of SEQ ID NO:261; or

(ii) the second Fc polypeptide comprises TfR-binding mutations, and wherein (a) comprises the sequence of any one of SEQ ID NOS:213, 214, 225, and 226 and (b) comprises the sequence of SEQ ID NO:273.

21. A protein comprising:

(a) a first Fc polypeptide that is linked to a progranulin polypeptide through a polypeptide linker; and

(b) a second Fc polypeptide that forms an Fc dimer with the first Fc polypeptide, wherein the first Fc polypeptide comprises a knob mutation T366W and the second Fc polypeptide comprises hole mutations T366S, L368A, and Y407V, according to EU numbering scheme,

wherein the first Fc polypeptide and/or the second Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and

wherein the first Fc polypeptide and/or the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering.

22. The protein of claim 21, wherein the first Fc polypeptide comprises TfR-binding mutations, and wherein (a) comprises the sequence of SEQ ID NO:274 or 275 and (b) comprises the sequence of SEQ ID NO:267.

23. A protein comprising:

(a) a first Fc polypeptide that is linked to a first progranulin polypeptide through a polypeptide linker; and

(b) a second Fc polypeptide that is linked to a second progranulin polypeptide through a polypeptide linker,

wherein the first and second Fc polypeptides form an Fc dimer, the first Fc polypeptide comprises hole mutations T366S, L368A, and Y407V, the second Fc polypeptide comprises a knob mutation T366W,

wherein the N-terminus of the first progranulin polypeptide is linked to the C-terminus of the first Fc polypeptide through the polypeptide linker and the N-terminus of the second progranulin polypeptide is linked to the C-terminus of the second Fc polypeptide through the polypeptide linker,

wherein the first Fc polypeptide and/or the second Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and

wherein the first Fc polypeptide and/or the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering.

24. The protein of claim 23, wherein the second Fc polypeptide comprises TfR-binding mutations, and wherein (a) comprises the sequence of SEQ ID NO:213 or 214 and (b) comprises the sequence of SEQ ID NO:274.

25. A protein comprising:

(a) a first Fc polypeptide that is linked to a first progranulin polypeptide through a polypeptide linker; and

(b) a second Fc polypeptide that is linked to a second progranulin polypeptide through a polypeptide linker,

wherein the first and second Fc polypeptides form an Fc dimer, the first Fc polypeptide comprises hole mutations T366S, L368A, and Y407V, the second Fc polypeptide comprises a knob mutation T366W,

wherein the C-terminus of the first progranulin polypeptide is linked to the N-terminus of the first Fc polypeptide through the polypeptide linker and the C-terminus of the second progranulin polypeptide is linked to the N-terminus of the second Fc polypeptide through the polypeptide linker,

wherein the first Fc polypeptide and/or the second Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and

wherein the first Fc polypeptide and/or the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering.

26. The protein of claim 25, wherein the second Fc polypeptide comprises TfR-binding mutations, and wherein (a) comprises the sequence of SEQ ID NO:225 or 226 and (b) comprises the sequence of SEQ ID NO:275.

27. A protein comprising:

(a) a first Fc polypeptide that is linked to a first progranulin polypeptide through a polypeptide linker; and

(b) a second Fc polypeptide that is linked to a second progranulin polypeptide through a polypeptide linker,

wherein the first and second Fc polypeptides form an Fc dimer, the first Fc polypeptide comprises hole mutations T366S, L368A, and Y407V, the second Fc polypeptide comprises a knob mutation T366W,

wherein the N-terminus of the first progranulin polypeptide is linked to the C-terminus of the first Fc polypeptide through the polypeptide linker and the C-terminus of the second

progranulin polypeptide is linked to the N-terminus of the second Fc polypeptide through the polypeptide linker,

wherein the first Fc polypeptide and/or the second Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and

wherein the first Fc polypeptide and/or the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering.

28. The protein of claim 27, wherein the second Fc polypeptide comprises TfR-binding mutations, and wherein (a) comprises the sequence of SEQ ID NO:213 or 214 and (b) comprises the sequence of SEQ ID NO:275.

29. A protein comprising:

(a) a first Fc polypeptide that is linked to a progranulin polypeptide through a polypeptide linker; and

(b) a second Fc polypeptide that forms an Fc dimer with the first Fc polypeptide,

wherein the first Fc polypeptide comprises hole mutations T366S, L368A, and Y407V and the second Fc polypeptide comprises a knob mutation T366W, according to EU numbering scheme, and TfR-binding mutations, and

wherein the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering.

30. The protein of claim 29, wherein:

(i) (a) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of any one of SEQ ID NOS:213, 214, 225, and 226 and (b) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of SEQ ID NO:273 or 281; or

(ii) the second Fc polypeptide further comprises L234A and L235A mutations with or without P329G mutation, and/or M428L and N434S mutations, according to EU numbering scheme,

optionally wherein (a) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of any one of SEQ ID NOS:213, 214, 225, and 226 and (b) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of any one of SEQ ID NOS: 210, 282-285, and 291-295; or

(iii) the first Fc polypeptide further comprises L234A and L235A mutations with or without P329G mutation, and/or M428L and N434S mutations, according to EU numbering scheme,

optionally wherein (a) comprises the sequence of any one of SEQ ID NOS:215-224 and 227-236 and (b) comprises the sequence of SEQ ID NO:273 or 281; or

(iv) each of the first and second Fc polypeptides further comprises L234A and L235A mutations with or without P329G mutation, and/or M428L and N434S mutations, according to EU numbering scheme,

optionally wherein (a) comprises the sequence of any one of SEQ ID NOS:215-224 and 227-236 and (b) comprises the sequence of SEQ ID NO: 210, 282-285, and 291-295.

31. A polypeptide comprising an Fc polypeptide that is linked to a progranulin polypeptide, wherein the Fc polypeptide contains one or more modifications that promote its heterodimerization to another Fc polypeptide, the Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and the Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering.

32. The polypeptide of claim 31, wherein the progranulin polypeptide comprises an amino acid sequence having greater than 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO:212, optionally wherein the progranulin polypeptide comprises the amino acid sequence of SEQ ID NO:212.

33. The polypeptide of claim 31 or 32, wherein the Fc polypeptide is linked to the progranulin polypeptide by a peptide bond or by a polypeptide linker,

optionally wherein:

(i) the polypeptide linker is 1 to 50 amino acids in length; and/or

(ii) the polypeptide linker is a flexible polypeptide linker,

optionally wherein the flexible polypeptide linker is a glycine-rich linker,

optionally wherein the glycine-rich linker is G₄S (SEQ ID NO:277) or (G₄S)₂ (SEQ ID NO:276),

optionally wherein the N-terminus or the C-terminus of the Fc polypeptide is linked to the progranulin polypeptide.

34. The polypeptide of any one of claims 31 to 33, wherein:

(i) the Fc polypeptide contains T366S, L368A, and Y407V substitutions, according to EU numbering,

optionally wherein the polypeptide comprises the amino acid sequence of any one of SEQ ID NOS:143-148, 155-160, 167-172, 179-184, 191-196, and 203-208; or

(ii) the Fc polypeptide contains a T366W substitution,

optionally wherein the polypeptide comprises the amino acid sequence of any one of SEQ ID NOS:137-142, 149-154, 161-166, 173-178, 185-190, and 197-202.

35. The polypeptide of any one of claims 31 to 34,

(a) wherein the Fc polypeptide comprises a modification that reduces effector function, optionally wherein the modification that reduces effector function is the substitutions of Ala at position 234 and Ala at position 235, according to EU numbering; and/or

(b) wherein the Fc polypeptide comprises amino acid changes relative to the native Fc sequence that extend serum half-life, optionally wherein the amino acid changes comprise substitutions of Leu at position 428 and Ser at position 434, according to EU numbering.

36. The polypeptide of any one of claims 31 to 35, wherein:

(i) the Fc polypeptide further comprises TfR-binding mutations; and/or

(ii) the progranulin polypeptide binds to sortilin or prosaposin,

optionally wherein the progranulin polypeptide binds to sortilin.

37. Use of the protein of any one of claims 1 to 30 or the polypeptide of any one of claims 31 to 36 in the manufacture of a medicament for treating a progranulin associated disorder in a patient in need thereof, wherein the progranulin-associated disorder is selected from the group consisting of a neurodegenerative disease, atherosclerosis, a disorder associated with TDP-43, and age-related macular degeneration (AMD).

38. Use of the protein of any one of claims 1 to 30 or the polypeptide of any one of claims 31 to 36 in the manufacture of a medicament for increasing the amount of a progranulin polypeptide in a patient having a progranulin-associated disorder, decreasing cathepsin D activity in a patient having a progranulin-associated disorder, or increasing lysosomal degradation in a patient having a progranulin-associated disorder, wherein the progranulin-associated disorder is selected from the group consisting of a neurodegenerative disease, atherosclerosis, a disorder associated with TDP-43, and age-related macular degeneration (AMD).

39. The use of claim 37 or 38, wherein:
(i) the progranulin-associated disorder is a neurodegenerative disease,
optionally wherein the neurodegenerative disease is selected from the group consisting of frontotemporal dementia (FTD), neuronal ceroid lipofuscinosis (NCL), Niemann-Pick disease type A (NPA), Niemann-Pick disease type B (NPB), Niemann-Pick disease type C (NPC), C9ORF72-associated amyotrophic lateral sclerosis (ALS)/FTD, sporadic ALS, Alzheimer's disease (AD), Gaucher's disease, and Parkinson's disease,
optionally wherein the neurodegenerative disease is frontotemporal dementia (FTD);
and/or

(ii) the patient has a mutation in a gene encoding the progranulin polypeptide.

40. A pharmaceutical composition comprising the protein of any one of claims 1 to 30 or the polypeptide of any one of claims 31 to 36 and a pharmaceutically acceptable carrier.

41. A protein comprising: (a) a modified Fc polypeptide dimer that specifically binds TfR, wherein one or both of the Fc polypeptides in the modified Fc polypeptide dimer comprise 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position

390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering; and (b) a progranulin polypeptide,

optionally wherein the protein further comprises: (c) a polypeptide linker, wherein the polypeptide linker links the modified Fc polypeptide dimer to the progranulin polypeptide.

42. The protein of claim 41, wherein:

(i) the modified Fc polypeptide dimer specifically binds to the apical domain of TfR; and/or

(ii) the modified Fc polypeptide dimer comprises a first Fc polypeptide CH3 domain with at least 90% identity, or at least 95% identity to amino acids 111-217 of any one of SEQ ID NOS:34-38, 58, 60-90, 136, and 137-210; and/or

(iii) the modified Fc polypeptide dimer comprises the amino acid sequence of any one of SEQ ID NOS:136-210; and/or

(iv) the modified Fc polypeptide dimer comprises the amino acid sequence of any one of SEQ ID NOS:136, 138, 150, 162, 174, 186, and 198; and/or

(v) the modified Fc polypeptide dimer comprises an Fc polypeptide having an amino acid sequence identity of at least 90%, 92%, or 95%, as compared to the corresponding wild-type Fc polypeptide; and/or

(vi) the modified Fc polypeptide dimer does not include an immunoglobulin heavy and/or light chain variable region sequence or an antigen-binding portion thereof.

43. The protein of claim 41 or 42, wherein the C-terminus of an Fc polypeptide in the modified Fc polypeptide dimer is linked to the N-terminus of the progranulin polypeptide,

optionally wherein the polypeptide linker links the C-terminus of the Fc polypeptide in the modified Fc polypeptide dimer to the N-terminus of the progranulin polypeptide.

44. The protein of claim 41 or 42, wherein the C-terminus of the progranulin polypeptide is linked to the N-terminus of an Fc polypeptide in the modified Fc polypeptide dimer,

optionally wherein the polypeptide linker links the C-terminus of the progranulin polypeptide to the N-terminus of the Fc polypeptide in the modified Fc polypeptide dimer.

45. Use of the protein of any one of claims 1 to 30 and 41 to 44 in the manufacture of a medicament for therapy or treating a neurodegenerative disease,

optionally wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, primary age-related tauopathy, lewy body dementia, progressive supranuclear palsy (PSP), frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, argyrophilic grain dementia, amyotrophic lateral sclerosis, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam (ALS-PDC), corticobasal degeneration, chronic traumatic encephalopathy, Creutzfeldt-Jakob disease, dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, familial British dementia, familial Danish dementia, Gerstmann-Straussler-Scheinker disease, globular glial tauopathy, Guadeloupean parkinsonism with dementia, Guadeloupean PSP, Hallevorden-Spatz disease, hereditary diffuse leukoencephalopathy with spheroids (HDLS), inclusion-body myositis, multiple system atrophy, myotonic dystrophy, Nasu-Hakola disease, neurofibrillary tangle-predominant dementia, Niemann-Pick disease type C, pallido-ponto-nigral degeneration, Parkinson's disease, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, subacute sclerosing panencephalitis, and tangle only dementia.

46. Use of a protein in the manufacture of a medicament for treating a neurodegenerative disease, the protein comprising:

(1) (a) a first Fc polypeptide that is linked to a progranulin polypeptide through a polypeptide linker; and

(b) a second Fc polypeptide that forms an Fc dimer with the first Fc polypeptide, wherein (a) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of SEQ ID NO:215 and (b) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of SEQ ID NO:210, the second Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr

or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering; or

(2) (a) a first Fc polypeptide that is linked to a progranulin polypeptide through a polypeptide linker; and

(b) a second Fc polypeptide that forms an Fc dimer with the first Fc polypeptide, wherein (a) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of SEQ ID NO:227 and (b) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of SEQ ID NO:210, the second Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering; or

(3) (a) a first Fc polypeptide that is linked to a progranulin polypeptide through a polypeptide linker; and

(b) a second Fc polypeptide that forms an Fc dimer with the first Fc polypeptide, wherein (a) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of SEQ ID NO:215 and (b) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of SEQ ID NO:291, the second Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering; or

(4) (a) a first Fc polypeptide that is linked to a progranulin polypeptide through a polypeptide linker; and

(b) a second Fc polypeptide that forms an Fc dimer with the first Fc polypeptide, wherein (a) comprises an amino acid sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of SEQ ID NO:227 and (b) comprises an amino acid

sequence having at least 90% identity, at least 95% identity, or 100% identity to the sequence of SEQ ID NO:291, the second Fc polypeptide is modified to specifically bind to a transferrin receptor (TfR), and the second Fc polypeptide comprises 11 positions as follows: position 380 is Trp, Leu, or Glu; position 384 is Tyr or Phe; position 386 is Thr; position 387 is Glu; position 388 is Trp; position 389 is Ser, Ala, Val, or Asn; position 390 is Ser or Asn; position 413 is Thr or Ser; position 415 is Glu or Ser; position 416 is Glu; and position 421 is Phe, according to EU numbering,

optionally wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, primary age-related tauopathy, lewy body dementia, progressive supranuclear palsy (PSP), frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, argyrophilic grain dementia, amyotrophic lateral sclerosis, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam (ALS-PDC), corticobasal degeneration, chronic traumatic encephalopathy, Creutzfeldt-Jakob disease, dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, familial British dementia, familial Danish dementia, Gerstmann-Straussler-Scheinker disease, globular glial tauopathy, Guadeloupean parkinsonism with dementia, Guadeloupean PSP, Hallevorden-Spatz disease, hereditary diffuse leukoencephalopathy with spheroids (HDLS), inclusion-body myositis, multiple system atrophy, myotonic dystrophy, Nasu-Hakola disease, neurofibrillary tangle-predominant dementia, Niemann-Pick disease type C, pallido-ponto-nigral degeneration, Parkinson's disease, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, subacute sclerosing panencephalitis, and tangle only dementia.

47. One or more polynucleotides comprising one or more nucleic acid sequences encoding parts (a) and (b) of the protein of any one of claims 1 to 30 and 41 to 45.

48. One or more vector(s) comprising the one or more polynucleotide(s) of claim 47.

49. A host cell comprising the one or more polynucleotide(s) of claim 47 or the one or more vector(s) of claim 48.

50. A method for making the protein of any one of claims 1 to 30 and 41 to 44, comprising culturing the host cell of claim 49 under conditions suitable for expression of the protein.

51. A polynucleotide comprising a nucleic acid sequence encoding the polypeptide of any one of claims 31 to 36.

52. A vector comprising the polynucleotide of claim 51.

53. A host cell comprising the polynucleotide of claim 51 or the vector of claim 52.

54. A method for making the polypeptide of any one of claims 31 to 36, comprising culturing the host cell of claim 53 under conditions suitable for expression of the polypeptide.