

Claims

What is claimed is:

1. ~~— An isolated binder polypeptide which binds human MTP-2 and inhibits its enzymatic activity.~~
2. ~~— A binder polypeptide according to claim 1, which binds the serine protease catalytic domain of MTP-2.~~
3. ~~— A binder polypeptide according to claim 1 or claim 2, comprising an immunoglobulin domain in which a binding site for MTP-2 is formed by loop regions of the immunoglobulin domain.~~
4. ~~— A binder polypeptide according to any preceding claim, which is an antibody, optionally a human antibody.~~
5. ~~— A binder polypeptide according to any preceding claim, which binds and inhibits the enzymatic activity of human MTP-2 and mouse MTP-2.~~
6. ~~— A binder polypeptide according to any preceding claim, which binds human MTP-2 comprising sequence polymorphisms in which residue 253 is K or E and residue 736 is V or A.~~
7. ~~— A binder polypeptide according to any preceding claim, which does not bind MTP-1 and optionally does not bind other members of the type II transmembrane serine protease family.~~
8. ~~— A binder polypeptide according to any preceding claim, which exhibits dose-dependent inhibition of MTP-2 serine protease activity in an enzymatic assay with MTP-2 extracellular domain and 50 mM final concentration fluorescent MTP-2 substrate.~~
9. ~~— A binder polypeptide according to claim 8, which has an IC₅₀ less than 100 nM in an enzymatic assay against human MTP-2 extracellular domain and 50 pM final concentration fluorescent MTP-substrate, and/or which has an IC₅₀ less than 100 nM in an enzymatic assay against mouse MTP-2 extracellular domain and 50 pM final concentration fluorescent MTP-substrate.~~

~~10. — A binder polypeptide according to claim 9, which has an IC₅₀ in the enzymatic assay with mouse MTP-2 extracellular domain which is less than 100-fold different from its IC₅₀ in said assay with human MTP-2 extracellular domain.~~

~~11. — A binder polypeptide according to any preceding claim, which exhibits dose-dependent inhibition of MTP-2 serine protease activity in an enzymatic assay with HEK293 cell surface expressed human MTP-2 and 50 mM final concentration fluorescent MTP-2 substrate.~~

~~12. — A binder polypeptide according to claim 11, which has an IC₅₀ less than 100 nM in an enzymatic assay with HEK293 cell surface expressed human MTP-2 and 50 pM final concentration fluorescent MTP-2 substrate.~~

~~13. — A binder polypeptide according to any preceding claim, which competes with an IgG comprising the VH and VL domain of any of NORI-001 to NORI-033 for binding to human and/or mouse MTP-2, defined wherein~~

~~NORI-001 VH domain is SEQ ID NO: 35 and VL domain is SEQ ID NO: 44;
 NORI-002 VH domain is SEQ ID NO: 54 and VL domain is SEQ ID NO: 63;
 NORI-003 VH domain is SEQ ID NO: 67 and VL domain is SEQ ID NO: 63;
 NORI-004 VH domain is SEQ ID NO: 74 and VL domain is SEQ ID NO: 63;
 NORI-005 VH domain is SEQ ID NO: 83 and VL domain is SEQ ID NO: 90;
 NORI-006 VH domain is SEQ ID NO: 94 and VL domain is SEQ ID NO: 100;
 NORI-007 VH domain is SEQ ID NO: 107 and VL domain is SEQ ID NO: 114;
 NORI-008 VH domain is SEQ ID NO: 125 and VL domain is SEQ ID NO: 132;
 NORI-009 VH domain is SEQ ID NO: 142 and VL domain is SEQ ID NO: 151;
 NORI-010 VH domain is SEQ ID NO: 160 and VL domain is SEQ ID NO: 166;
 NORI-011 VH domain is SEQ ID NO: 170 and VL domain is SEQ ID NO: 166;
 NORM 1-M VH domain is SEQ ID NO: 176 and VL domain is SEQ ID NO: 166;
 NORI-012 VH domain is SEQ ID NO: 182 and VL domain is SEQ ID NO: 166;
 NORI-013 VH domain is SEQ ID NO: 194 and VL domain is SEQ ID NO: 151;
 NORI-014 VH domain is SEQ ID NO: 203 and VL domain is SEQ ID NO: 151;
 NORI-015 VH domain is SEQ ID NO: 194 and VL domain is SEQ ID NO: 216;
 NORI-016 VH domain is SEQ ID NO: 203 and VL domain is SEQ ID NO: 216;
 NORI-017 VH domain is SEQ ID NO: 231 and VL domain is SEQ ID NO: 240;~~

~~NORI-018 VH domain is SEQ ID NO: 250 and VL domain is SEQ ID NO: 259;~~
~~NORI-019 VH domain is SEQ ID NO: 267 and VL domain is SEQ ID NO: 273;~~
~~NORI-020 VH domain is SEQ ID NO: 283 and VL domain is SEQ ID NO: 292;~~
~~NORI-021 VH domain is SEQ ID NO: 302 and VL domain is SEQ ID NO: 311;~~
~~NORI-022 VH domain is SEQ ID NO: 321 and VL domain is SEQ ID NO: 330;~~
~~NORI-023 VH domain is SEQ ID NO: 339 and VL domain is SEQ ID NO: 346;~~
~~NORI-024 VH domain is SEQ ID NO: 356 and VL domain is SEQ ID NO: 365;~~
~~NORI-025 VH domain is SEQ ID NO: 372 and VL domain is SEQ ID NO: 377;~~
~~NORI-026 VH domain is SEQ ID NO: 387 and VL domain is SEQ ID NO: 396;~~
~~NORI-027 VH domain is SEQ ID NO: 406 and VL domain is SEQ ID NO: 412;~~
~~NORI-028 VH domain is SEQ ID NO: 422 and VL domain is SEQ ID NO: 427;~~
~~NORI-029 VH domain is SEQ ID NO: 437 and VL domain is SEQ ID NO: 444;~~
~~NORI-030 VH domain is SEQ ID NO: 453 and VL domain is SEQ ID NO: 462;~~
~~NORI-031 VH domain is SEQ ID NO: 472 and VL domain is SEQ ID NO: 481;~~
~~NORI-032 VH domain is SEQ ID NO: 491 and VL domain is SEQ ID NO: 497;~~
~~NORI-033 VH domain is SEQ ID NO: 507 and VL domain is SEQ ID NO: 513.~~

~~14. — A binder polypeptide according to claim 13, which competes with an IgG comprising the VH and VL domain of NORI-003, NORI-006, NORI-008 or NORI-011 for binding to the serine protease catalytic domain of human and/or mouse MTP-2.~~

~~15. — A binder polypeptide according to any preceding claim, which competes with aprotinin for binding to the serine protease catalytic domain of human and/or mouse MTP-2.~~

~~16. — A binder polypeptide according to claim 15, which has an IC₅₀ of less than 100 nM, less than 50 nM or less than 20 nM in a competition assay with labelled aprotinin for binding to human and/or mouse MTP-2.~~

~~17. — A binder polypeptide according to any preceding claim, which has an affinity (K_d) for human MTP-2 of less than 50 nM as determined by surface plasmon resonance, and/or has an affinity (K_d) for mouse MTP-2 of less than 50 nM as determined by surface plasmon resonance.~~

~~18. — A binder polypeptide according to claim 17, wherein the K_d for mouse MTP-2 is within 50-fold of the K_d for human MTP-2.~~

~~19. — A binder polypeptide according to any preceding claim, comprising an antibody heavy chain variable (VH) domain obtained by recombination of the set of germline v_H gene segments shown in Table G for any of NORI-001 to NORI-033 and/or an antibody light chain variable (VL) domain obtained by recombination of the set of germline v_L gene segments shown in Table G for any of NORI-001 to NORI-033.~~

~~20. — A binder polypeptide according to claim 19, wherein the VH domain and the VL domain are each obtained by recombination of the set of germline gene segments shown in Table G for NORI-001, NORI-002, NORI-003, NORI-004, NORI-005, NORI-006, NORI-007, NORI-008, NORI-009, NORI-010, NORI-011, NORI-012, NORI-013, NORI-014, NORI-015, NORI-016, NORI-017, NORI-018, NORI-019, NORI-020, NORI-021, NORI-022, NORI-023, NORI-024, NORI-025, NORI-026, NORI-027, NORI-028, NORI-029, NORI-030, NORI-031, NORI-032 or NORI-033.~~

~~21. — A binder polypeptide according to any preceding claim, comprising an antibody heavy chain variable (VH) domain obtained by recombination of germline v_H gene segments:~~

~~IGHV3-9*01, IGHD4-17*01 and IGHJ6*02,~~

~~IGHV4-61*01, IGHD3-22*01 and IGHJ5*02,~~

~~IGHV3-49*05, IGHD3-9*01 and IGHJ4*02, or IGHV3-13*01, IGHD3-10*01 and IGHJ3*02.~~

~~22. — A binder polypeptide according to any preceding claim, comprising an antibody light chain variable (VL) domain obtained by recombination of germline v_L gene segments:~~

~~IGLV2-8*01 and IGLJ2*01,~~

~~IGKV1-D-33*01 and IGKJ5*01,~~

~~IGKV1-D-33*01 and IGKJ4*01, and IGKV3D-7*01 and IGKJ1*01.~~

~~23. — A binder polypeptide according to any preceding claim, comprising~~

1. A binder polypeptide that bind human MTP-2, comprising

(a) a variable heavy (VH) domain and a VL domain, the VH domain comprising a set of heavy chain complementarity determining regions (HCDRs) HCDR1, HCDR2 and HCDR3, wherein HCDR1 comprises an amino acid sequence of SEQ ID NO: 48, HCDR2 comprises an amino acid sequence of SEQ ID NO: 49, and HCDR3 comprises an amino sequence of SEQ ID NO: 50; and

(b) a variable light the (VL) domain comprising a set of light chain complementarity determining regions (LCDRs) LCDR1, LCDR2 and LCDR3, wherein the set of HCDRs is the set of HCDRs of any of NORI-001 to NORI-033 and/or wherein the set of LCDRs is the set of LCDRs of any of NORI-001 to NORI-033.

~~24. A binder polypeptide according to claim 23, wherein the set of HCDRs is the NORI-003 set of CDRs and the set of LCDRs is the NORI-003 set of LCDRs, wherein~~

~~HCDR1 is SEQ ID NO: 48,~~

~~HCDR2 is SEQ ID NO: 49,~~

~~HCDR3 is SEQ ID NO: 50,~~

~~LCDR1 iscomprises an amino acid sequence of SEQ ID NO: 58,~~

~~LCDR2 iscomprises an amino acid sequence of SEQ ID NO: 59 and~~

~~LCDR3 iscomprises an amino acid sequence of SEQ ID NO: 60.~~

~~252. A binder polypeptide according to claim 23~~ The binder polypeptide according to claim 1, wherein the set of HCDRs is the NORI-006 set of CDRs and the set of LCDRs is the NORI-006 set of LCDRs, wherein

~~(a) HCDR1 isconsists of the amino acid sequence of SEQ ID NO: 48,~~

~~HCDR2 isconsists of the amino acid sequence of SEQ ID NO: 49, and~~

~~HCDR3 isconsists of the amino acid sequence of SEQ ID NO: 8050, and~~

~~(b) LCDR1 isconsists of the amino acid sequence of SEQ ID NO: 9858,~~

~~LCDR2 isconsists of the amino acid sequence of SEQ ID NO: 59 and~~

~~LCDR3 isconsists of the amino acid sequence of -SEQ ID NO: 8860.~~

~~26. A binder polypeptide according to claim 23, wherein the set of HCDRs is the NORI-011 set of CDRs and the set of LCDRs is the NORI-011 set of LCDRs, wherein~~

~~HCDR1 is SEQ ID NO: 155,~~

~~HCDR2 is SEQ ID NO: 137,~~

~~HCDR3 is SEQ ID NO: 156,~~

~~LCDR1 is SEQ ID NO: 164,~~

~~LCDR2 is SEQ ID NO: 147 and~~

~~LCDR3 is SEQ ID NO: 148.~~

~~27. A binder polypeptide according to claim 23, wherein the set of HCDRs is the NORI-008 set of CDRs and the set of LCDRs is the NORI-008 set of LCDRs, wherein~~

~~HCDR1 is SEQ ID NO: 118,~~

~~HCDR2 is SEQ ID NO: 119,~~

~~HCDR3 is SEQ ID NO: 120,
 LCDR1 is SEQ ID NO: 128,
 LCDR2 is SEQ ID NO: 59 and
 LCDR3 is SEQ ID NO: 129.~~

~~283. A binder polypeptide according to any preceding claim~~The binder polypeptide according to claim 1 or 2, wherein

~~(a) comprising a the VH domain comprises an amino acid sequence having at least 90% amino acid sequence identity with the VH domain of any of NORI-001 to NORI-033 to SEQ ID NO.67, and~~

~~(b) and/or a the VL domain having comprises amino acid sequence having at least 90% identity to SEQ ID NO. 63. amino acid sequence identity with the VL domain of any of NORI-001 to NORI-033, defined wherein NORI-001 VH domain is SEQ ID NO: 35 and VL domain is SEQ ID NO: 44;~~

~~NORI-002 VH domain is SEQ ID NO: 54 and VL domain is SEQ ID NO: 63;
 NORI-003 VH domain is SEQ ID NO: 67 and VL domain is SEQ ID NO: 63;
 NORI-004 VH domain is SEQ ID NO: 74 and VL domain is SEQ ID NO: 63;
 NORI-005 VH domain is SEQ ID NO: 83 and VL domain is SEQ ID NO: 90;
 NORI-006 VH domain is SEQ ID NO: 94 and VL domain is SEQ ID NO: 100;
 NORI-007 VH domain is SEQ ID NO: 107 and VL domain is SEQ ID NO: 114;
 NORI-008 VH domain is SEQ ID NO: 125 and VL domain is SEQ ID NO: 132;
 NORI-009 VH domain is SEQ ID NO: 142 and VL domain is SEQ ID NO: 151;
 NORI-010 VH domain is SEQ ID NO: 160 and VL domain is SEQ ID NO: 166;
 NORI-011 VH domain is SEQ ID NO: 170 and VL domain is SEQ ID NO: 166;
 NORI-11-M VH domain is SEQ ID NO: 176 and VL domain is SEQ ID NO: 166;
 NORI-012 VH domain is SEQ ID NO: 182 and VL domain is SEQ ID NO: 166;
 NORI-013 VH domain is SEQ ID NO: 194 and VL domain is SEQ ID NO: 151;
 NORI-014 VH domain is SEQ ID NO: 203 and VL domain is SEQ ID NO: 151;
 NORI-015 VH domain is SEQ ID NO: 194 and VL domain is SEQ ID NO: 216;
 NORI-016 VH domain is SEQ ID NO: 203 and VL domain is SEQ ID NO: 216;
 NORI-017 VH domain is SEQ ID NO: 231 and VL domain is SEQ ID NO: 240;
 NORI-018 VH domain is SEQ ID NO: 250 and VL domain is SEQ ID NO: 259;
 NORI-019 VH domain is SEQ ID NO: 267 and VL domain is SEQ ID NO: 273;
 NORI-020 VH domain is SEQ ID NO: 283 and VL domain is SEQ ID NO: 292;
 NORI-021 VH domain is SEQ ID NO: 302 and VL domain is SEQ ID NO: 311;
 NORI-022 VH domain is SEQ ID NO: 321 and VL domain is SEQ ID NO: 330;~~

~~NORI-023 VH domain is SEQ ID NO: 339 and VL domain is SEQ ID NO: 346;
 NORI-024 VH domain is SEQ ID NO: 356 and VL domain is SEQ ID NO: 365;
 NORI-025 VH domain is SEQ ID NO: 372 and VL domain is SEQ ID NO: 377;
 NORI-026 VH domain is SEQ ID NO: 387 and VL domain is SEQ ID NO: 396;
 NORI-027 VH domain is SEQ ID NO: 406 and VL domain is SEQ ID NO: 412;
 NORI-028 VH domain is SEQ ID NO: 422 and VL domain is SEQ ID NO: 427;
 NORI-029 VH domain is SEQ ID NO: 437 and VL domain is SEQ ID NO: 444;
 NORI-030 VH domain is SEQ ID NO: 453 and VL domain is SEQ ID NO: 462;~~

~~NORI-031 VH domain is SEQ ID NO: 472 and VL domain is SEQ ID NO: 481;
 NORI-032 VH domain is SEQ ID NO: 491 and VL domain is SEQ ID NO: 497;
 NORI-033 VH domain is SEQ ID NO: 507 and VL domain is SEQ ID NO: 513.~~

~~29. A binder polypeptide according to claim 28, comprising~~

~~a VH domain comprising the NORI-003 HCDRs, wherein HCDR1 is SEQ ID NO: 48, HCDR2 is SEQ ID NO: 49 and HCDR3 is SEQ ID NO: 50, and having at least 90% amino acid sequence identity with the VH domain of NORI-003 SEQ ID NO: 67, and~~

~~a VL domain comprising the NORI-003 LCDRs, wherein LCDR1 is SEQ ID NO: 58, LCDR2 is SEQ ID NO: 59 and LCDR3 is SEQ ID NO: 60, and having at least 90% amino acid sequence identity with the VL domain of NORI-003 SEQ ID NO: 63.~~

~~30. A binder polypeptide according to claim 29, comprising a NORI-003 antibody VH domain SEQ ID NO: 67 and a NORI-003 VL domain SEQ ID NO: 63.~~

4. The binder polypeptide according to any one of claims 1-3, wherein

(a) the VH domain comprises an amino acid sequence comprising SEQ ID NO. 67, and

(b) the VL domain comprises an amino acid sequence comprising SEQ ID NO. 63.

5. The binder polypeptide according to any one of claims 1-4, wherein

(a) the VH domain consists of an amino acid sequence comprising SEQ ID NO. 67, and

(b) the VL domain consists of an amino acid sequence comprising SEQ ID NO. 63.

~~31. A binder polypeptide according to claim 28, comprising~~

~~a VH domain comprising the NORI-011 HCDRs, wherein HCDR1 is SEQ ID NO: 155, HCDR2 is SEQ ID NO: 137 and HCDR3 is SEQ ID NO: 156 and having at least 90% amino acid sequence identity with the VH domain of NORI-011 SEQ ID NO: 170, and~~

~~a VL domain comprising the NORI-011 LCDRs, wherein LCDR1 is SEQ ID NO: 164, LCDR2 is SEQ ID NO: 147 and LCDR3 is SEQ ID NO: 148, and having at least 90% amino acid sequence identity with the VL domain of NORI-011 SEQ ID NO: 166.~~

~~326. A binder polypeptide according to any of claims 1 to 31~~The binder polypeptide according to any one of claim 1-5, wherein the binder polypeptide comprises an antibody constant region.

~~337. A binder polypeptide according to claim 32~~The binder polypeptide according to any one of claims 1-6, wherein the binder polypeptide is an IgG antibody.

~~348. A binder polypeptide according to claim 33~~The binder polypeptide according to any one of claims 1-7, wherein the binder polypeptide comprisingcomprises a human IgG4PE constant region.

~~359. A binder polypeptide according to claim 34~~The binder polypeptide according to any one of claims 1-7, comprising

~~(a) a NORI-003 antibody heavy chain comprising an amino acid sequence of SEQ ID NO: 69, and~~

~~(b) a NORI-003 antibody light chain comprising an amino acid of SEQ ID NO: 65.~~

10. The binder polypeptide according to any one of claims 1-9, comprising

(a) a heavy chain consisting of an amino acid sequence of SEQ ID NO. 69, and

(b) a light chain consisting of an amino acid sequence of SEQ ID NO. 65.

~~36. A binder polypeptide according to claim 34, comprising a NORI-006 antibody heavy chain SEQ ID NO: 96 and a NORI-006 antibody light chain SEQ ID NO: 100.~~

~~37. A binder polypeptide according to claim 34, comprising a NORI-011 antibody heavy chain SEQ ID NO: 172 and a NORI-011 antibody light chain SEQ ID NO: 168.~~

~~38. A binder polypeptide according to claim 34, comprising a NORI-008 antibody heavy chain SEQ ID NO: 126 and a NORI-008 antibody light chain SEQ ID NO: 134.~~

~~39. An isolated antibody comprising a VH domain and VL domain as defined in any of claims 19 to 31.~~

~~40. An isolated antibody comprising a VH domain and VL domain which are the VH and VL domain of any of NORI-001 to NORI-033, defined wherein~~

~~NORI-001 VH domain is SEQ ID NO: 35 and VL domain is SEQ ID NO: 44;
 NORI-002 VH domain is SEQ ID NO: 54 and VL domain is SEQ ID NO: 63;
 NORI-003 VH domain is SEQ ID NO: 67 and VL domain is SEQ ID NO: 63;
 NORI-004 VH domain is SEQ ID NO: 74 and VL domain is SEQ ID NO: 63;
 NORI-005 VH domain is SEQ ID NO: 83 and VL domain is SEQ ID NO: 90;
 NORI-006 VH domain is SEQ ID NO: 94 and VL domain is SEQ ID NO: 100;
 NORI-007 VH domain is SEQ ID NO: 107 and VL domain is SEQ ID NO: 114;
 NORI-008 VH domain is SEQ ID NO: 125 and VL domain is SEQ ID NO: 132;
 NORI-009 VH domain is SEQ ID NO: 142 and VL domain is SEQ ID NO: 151;
 NORI-010 VH domain is SEQ ID NO: 160 and VL domain is SEQ ID NO: 166;
 NORI-011 VH domain is SEQ ID NO: 170 and VL domain is SEQ ID NO: 166;
 NORM 1-M VH domain is SEQ ID NO: 176 and VL domain is SEQ ID NO: 166;
 NORI-012 VH domain is SEQ ID NO: 182 and VL domain is SEQ ID NO: 166;
 NORI-013 VH domain is SEQ ID NO: 194 and VL domain is SEQ ID NO: 151;
 NORI-014 VH domain is SEQ ID NO: 203 and VL domain is SEQ ID NO: 151;
 NORI-015 VH domain is SEQ ID NO: 194 and VL domain is SEQ ID NO: 216;
 NORI-016 VH domain is SEQ ID NO: 203 and VL domain is SEQ ID NO: 216;
 NORI-017 VH domain is SEQ ID NO: 231 and VL domain is SEQ ID NO: 240;
 NORI-018 VH domain is SEQ ID NO: 250 and VL domain is SEQ ID NO: 259;
 NORI-019 VH domain is SEQ ID NO: 267 and VL domain is SEQ ID NO: 273;
 NORI-020 VH domain is SEQ ID NO: 283 and VL domain is SEQ ID NO: 292;
 NORI-021 VH domain is SEQ ID NO: 302 and VL domain is SEQ ID NO: 311;
 NORI-022 VH domain is SEQ ID NO: 321 and VL domain is SEQ ID NO: 330;~~

~~NORI-023 VH domain is SEQ ID NO: 339 and VL domain is SEQ ID NO: 346;
 NORI-024 VH domain is SEQ ID NO: 356 and VL domain is SEQ ID NO: 365;
 NORI-025 VH domain is SEQ ID NO: 372 and VL domain is SEQ ID NO: 377;
 NORI-026 VH domain is SEQ ID NO: 387 and VL domain is SEQ ID NO: 396;~~

NORI-027 VH domain is SEQ ID NO: 406 and VL domain is SEQ ID NO: 412;
 NORI-028 VH domain is SEQ ID NO: 422 and VL domain is SEQ ID NO: 427;
 NORI-029 VH domain is SEQ ID NO: 437 and VL domain is SEQ ID NO: 444;
 NORI-030 VH domain is SEQ ID NO: 453 and VL domain is SEQ ID NO: 462;
 NORI-031 VH domain is SEQ ID NO: 472 and VL domain is SEQ ID NO: 481;
 NORI-032 VH domain is SEQ ID NO: 491 and VL domain is SEQ ID NO: 497;
 NORI-033 VH domain is SEQ ID NO: 507 and VL domain is SEQ ID NO: 513,
 or comprising said VH and VL domain in which one or more non-germline residues of
 framework regions are reverted to germline.

41. — An antibody according to claim 40, comprising the VH domain SEQ ID NO: 67 and VL domain SEQ ID NO: 63 of NORI-003 or comprising said VH and VL domain in which one or more non-germline residues of framework regions are reverted to germline.

42. — An antibody according to claim 40, comprising the VH domain SEQ ID NO: 170 and VL domain SEQ ID NO: 166 of NORI-011 or comprising said VH and VL domain in which one or more non-germline residues of framework regions are reverted to germline.

43. — An isolated antibody comprising the heavy chain and light chain of any of NORI-001 to NORI-033.

44. — A monoclonal IgG antibody comprising a NORI-003 VH domain and a NORI-003 VL domain, optionally wherein the antibody comprises a NORI-003 antibody heavy chain SEQ ID NO: 69 and a NORI-003 antibody light chain SEQ ID NO: 65.

4511. A Nucleic acid encoding a binder polypeptide as defined in any of claims 1 to 38 or an antibody as defined in any of claims 39 to 44 according to any one of claims 1-10.

4612. A host cell in vitro comprising nucleic acid as defined in claim 45 according to claim 11.

4713. A composition comprising a binder polypeptide as defined in any of claims 1 to 38 or an antibody as defined in any of claims 39 to 44 according to any one of claims 1-10, formulated with a pharmaceutically acceptable excipient, optionally wherein the composition is for subcutaneous administration.

~~48. — A composition comprising nucleic acid according to claim 45 which is for gene therapy in vivo.~~

~~49. — A composition according to claim 47 or claim 48 for use in treatment of the human or animal body by therapy.~~

~~50. — A combination of medicaments comprising (i) an inhibitor of MTP-2 and (ii) an antagonist of a TQRb superfamily ligand.~~

14. A composition comprising (i) the binder polypeptide of any one of claims 1-10, and (ii) an antagonist of a TGF β superfamily ligand.

15. The composition according to claim 14, wherein the TGF β superfamily ligand is selected from activin, GDF-11, and bone morphogenic proteins

16. A composition comprising (i) the binder polypeptide of any one of claims 1-10, and (ii) erythropoietin.

~~51. — A combination according to claim 51, for use in treating iron overload and normalising erythropoiesis in a patient.~~

~~52. — A method of treating iron overload and normalising erythropoiesis in a patient, comprising administering (i) an inhibitor of MTP-2 and (ii) an antagonist of a TQRb family ligand to the patient, wherein (i) and (ii) are administered simultaneously or sequentially.~~

~~53. — A combination according to claim 51 or a method according to claim 52, wherein the patient has beta-thalassaemia (optionally beta-thalassaemia major), MDS, Blackfan-Diamond anaemia, Type 1 haemochromatosis or Type 3 haemochromatosis.~~

~~54. — A combination or method according to any of claims 50 to 53, wherein the antagonist is an activin II receptor ligand trap, optionally an activin MB receptor Fc fusion protein.~~

~~55. — A combination or method according to claim 54, wherein the antagonist is luspaterecept.~~

~~56. — A combination or method according to claim 54, wherein the antagonist is an activin IIA receptor Fc fusion protein, optionally sotatercept.~~

57. — A combination of medicaments comprising (i) an inhibitor of MTP-2 and (ii) erythropoietin.

58. — A combination according to claim 57, for use in treating anaemia associated with iron overload in a patient.

59. — A method of treating anaemia associated with iron overload in a patient, comprising administering (i) an inhibitor of MTP-2 and (ii) erythropoietin to the patient, wherein (i) and (ii) are administered simultaneously or sequentially.

60. — A combination or method according to any of claims 50 to 59, wherein the inhibitor of MTP-2 is a binder polypeptide as defined in any of claims 1 to 38 or an antibody as defined in any of claims 39 to 44.

61. — A method of: reducing absorption of dietary iron, treating iron overload, elevating expression of hepcidin from hepatocytes, reducing anaemia caused by iron overload, decreasing serum iron concentration and/or decreasing transferrin iron saturation, in a patient, the method comprising administering a composition according to claim 47 or claim 48 to the patient.

62. — A method according to claim 61, wherein the patient has beta-thalassaemia (e.g., beta-thalassaemia major or intermedia), 5q-MDS or RARS.

63. — A method according to claim 61 or claim 62, wherein the method further comprises administering an antagonist of a TQRb family ligand to the patient, optionally wherein the antagonist is an activin II receptor ligand trap, optionally: an activin MB receptor Fc fusion protein, e.g., luspaterecept, or an activin IIA receptor Fc fusion protein, e.g., sotatercept.

64. — A method according to claim 61 or claim 62, wherein the method further comprises administering an erythropoiesis stimulating agent to the patient, optionally wherein the erythropoiesis stimulating agent is erythropoietin.

65. — A method according to claim 61 or claim 62, wherein the method comprises administering a further therapeutic agent to the patient to reduce iron overload, e.g., luspaterecept.

~~66. — A composition according to claim 47 or claim 48 for use in a method as defined in any of claims 61 to 65.~~

~~67. — Use of a composition according to claim 47 or claim 48 for the manufacture of a medicament for treatment of a patient, said treatment comprising a method as defined in any of claims 61 to 65.~~

~~68. — A therapeutic agent which reduces iron overload, for use in a method of: reducing absorption of dietary iron, treating iron overload, elevating expression of hepcidin from hepatocytes, reducing anaemia caused by iron overload, decreasing serum iron concentration and/or decreasing transferrin iron saturation, in a patient, the method comprising administering the therapeutic agent and a composition according to claim 47 or claim 48 to the patient.~~

~~69. — A therapeutic agent comprising erythropoietin (epo), for use in a method of stimulating erythropoiesis in a patient, the method comprising administering the agent and a composition according to claim 47 or claim 48 to the patient.~~

~~70. — A therapeutic agent comprising an antagonist of a TQRb family ligand, for use in a method of promoting erythrocyte maturation in a patient, the method comprising administering the agent and a composition according to claim 47 or claim 48 to the patient.~~

~~71. — A method according to any of claims 63 to 65, a composition for use according to claim 66, use of a composition according to claim 67, a therapeutic agent for use according to any of claims 68 to 70, wherein the method comprises administering the therapeutic agent and the composition to the patient separately and sequentially.~~

17. Use of a composition according to claim 13 in the manufacture of a medicament for treating a disease or disorder associated with iron overload in a patient, the medicament is to be administered to the patient.

18. Use of a composition according to claim 13 in the manufacture of a medicament for treating anaemia caused by iron overload in a patient, the medicament is to be administered to the patient.

19. The use according to any one of claims 17 and 18, wherein the patient has beta-thalassaemia, myelodysplastic syndrome, polycythemia vera, haemochromatosis, or refractory anaemia with ring-sideroblasts (RARS).

20. Use of a composition according to claim 14 or 15 in the manufacture of a medicament for treating a disease or disorder associated with iron overload in a patient, wherein the medicament is to be administered to the patient.

21. Use of a composition according to claim 16 in the manufacture of a medicament for treating anaemia associated with iron overload in a patient, wherein the medicament is to be administered to the patient.