

What is claimed is:

1. A polypeptide comprising the CH2 and CH3 domains of an Fc region, wherein the CH2 and CH3 domains of the Fc region comprises mutations in residues chosen from:

- (i) T256, Q311, and A378;
- (ii) H285, T307, and N315;
- (iii) H285, T307, and A378;
- (iv) T307, Q311, and A378;
- (v) T256, N286, T307, Q311, and A378; or
- (vi) T256, H285, T307, Q311, and A378.

2. The polypeptide of claim 1, wherein the CH2 and CH3 domains of the Fc region comprises mutations chosen from:

- (i) T256D, Q311V, and A378V;
- (ii) H285N, T307Q, and N315D;
- (iii) H285D, T307Q, and A378V;
- (iv) T307Q, Q311V, and A378V;
- (v) T256D, N286D, T307R, Q311V, and A378V; or
- (vi) T256D, H285D, T307R, Q311V, and A378V.

3. The polypeptide of claim 1 or 2, further comprising a mutation in a region other than the Fc region and/or further comprising a hinge region between the CH2 and CH3 domains of the Fc region.

4. The polypeptide of any of claims 1-3, which is an isolated polypeptide or a synthetic polypeptide.

5. The polypeptide of any of claims 1-4, which:

(i) is an antibody molecule, optionally wherein the antibody molecule is a chimeric antibody molecule, a murine antibody molecule, human antibody molecule, or a humanized antibody molecule;

(ii) further comprises a heavy chain immunoglobulin variable region, a light chain immunoglobulin variable region, or both;

(iii) is an immunoglobulin chain or a fragment thereof; or

(iv) is a fusion protein.

6. The polypeptide of any of claims 1-5, wherein the polypeptide has 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or all of the following properties:

a) has an increased binding affinity for a neonatal Fc receptor (FcRn) at a pH between 6.0 and 6.5, compared to a reference polypeptide;

5 b) has a higher binding affinity for FcRn at a pH between 6.0 and 6.5 than the binding affinity at a pH between 7.0 and 7.4;

c) binds to an FcRn at a pH between 6.0 and 6.5 with a dissociation constant (K_d) of 300 nM or less;

d) binds to the FcRn at a pH between 7.0 and 7.4 with a K_d of 50 nM or more;

10 e) has the same, substantially the same, or increased binding affinity for an Fc γ receptor, compared to a reference polypeptide;

f) has the same, or substantially the same, thermal stability, compared to a reference polypeptide;

15 g) has the same, substantially the same, or increased binding affinity for C1q, compared to a reference polypeptide;

h) has the same, substantially the same, or increased binding affinity for TRIM21, compared to a reference polypeptide.

i) has an effector function that is the same, substantially the same, or increased, compared to a reference polypeptide;

20 j) has an increased half-life *in vivo*, compared to a reference polypeptide;

k) has a biological function, *in vitro*, *ex vivo*, or *in vivo*, that is the same, substantially the same, or increased, compared to a reference polypeptide;

l) has a developability characteristic that is the same or substantially the same, compared to a reference polypeptide;

25 m) has the same, substantially the same, or increased binding affinity, specificity, or both, for an epitope, compared to a reference polypeptide; or

n) increases mucosal uptake, compared to a reference polypeptide, and wherein the polypeptide has at least properties a), b), and one, two, three, four, or all of properties e), f), g), h), or i).

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7. The polypeptide of any of claims 1-6,

(i) which has at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, or 50-fold increase in the binding affinity for the FcRn at pH 6.0, compared to a reference polypeptide, as determined by an octet-based assay or a cell-based assay;

(ii) which has at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, or 50-fold higher in the binding affinity for the FcRn at pH 6.0 than that at pH 7.4, as determined by an octet-based assay or a cell-based assay;

(iii) which binds to the FcRn at pH 6.0 with a dissociation constant (K_d) of 250 nM or less, 200 nM or less, 150 nM or less, 100 nM or less, 50 nM or less, 25 nM or less, 10 nM or less, 5 nM or less, 2 nM or less, 1 nM or less, 0.5 nM or less, 0.2 nM or less, 0.1 nM or less, 0.05 nM or less, 0.02 nM or less, 0.01 nM or less, between 25 nM and 0.1 nM, between 20 nM and 0.5 nM, between 15 nM and 1 nM, between 10 nM and 5 nM, or between 20 nM and 10 nM, as determined by an octet-based assay or a cell-based assay;

(iv) which binds to the FcRn at pH 7.4 with a K_d of 60 nM or more, 80 nM or more, 100 nM or more, 150 nM or more, 200 nM or more, 500 nM or more, between 50 nM and 500 nM, or between 100 nM and 250 nM, as determined by an octet-based assay or a cell-based assay;

(v) which decreases the binding affinity for one, two, or, all of FcγRI, FcγRIIa/b, or FcγRIII by no more than 10%, 20%, 30%, 40%, or 50%, or increases the binding affinity for one, two, or all of FcγRI, FcγRIIa/b, or FcγRIII by at least 1.5, 2, 3, 4, or 5-fold, compared to a reference polypeptide, as determined by an octet-based assay or a cell-based assay;

(vi) which increases or decreases the melting temperature by no more than 1°C, 2°C, 3°C, 4°C, 5°C, 6°C, 7°C, 8°C, 9°C, or 10°C, compared to a reference polypeptide, as determined by a sypro orange assay;

(vii) which decreases the binding affinity for C1q by no more than 10%, 20%, 30%, 40%, or 50%, or increases the binding affinity for C1q by at least 1.5, 2, 3, 4, or 5-fold, compared to a reference polypeptide, as determined by ELISA;

(viii) which decreases the binding affinity for TRIM21 by no more than 10%, 20%, 30%, 40%, or 50%, or increases the binding affinity for TRIM21 by at least 1.5, 2, 3, 4, or 5-fold, compared to a reference polypeptide, as determined by ELISA;

(ix) which decreases one, two, three, or all of a complement dependent cytotoxicity (CDC), an antibody dependent cell mediated cytotoxicity (ADCC), an antibody dependent cell mediated phagocytosis (ADCP), or an antibody dependent intracellular neutralization (ADIN) by no more than 10%, 20%, 30%, 40%, or 50%, or increases one, two, three, or all of a complement dependent cytotoxicity (CDC), an antibody dependent cell mediated cytotoxicity (ADCC), an antibody dependent cell mediated phagocytosis (ADCP), or an antibody dependent intracellular neutralization (ADIN) by at least 1.5, 2, 3, 4, or 5-fold, compared to a reference polypeptide;

(x) which has at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold increase in the half-life *in vivo*, compared to a reference polypeptide, as determined in an animal model;

(xi) which decreases the biological function, *in vitro*, *ex vivo*, or *in vivo* by no more than 10%, 20%, 30%, 40%, or 50%, or increases the biological function, *in vitro*, *ex vivo*, or *in vivo* by at least 1.5, 2, 3, 4, or 5-fold, compared to a reference polypeptide;

(xii) which alters one, two, three, or all of stability, solubility, aggregation, or expression level by no more than 10%, 20%, 30%, 40%, or 50%, compared to a reference polypeptide;

(xiii) which decreases the binding affinity, specificity, or both by no more than 10%, 20%, 30%, 40%, or 50%, or increases the binding affinity, specificity, or both by at least 1.5, 2, 3, 4, or 5-fold, compared to a reference polypeptide; and/or

(xiv) which increases mucosal uptake by at least 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold, compared to a reference polypeptide, as determined by a transcytosis assay.

8. The polypeptide of claim 6 or 7 wherein the reference polypeptide comprises a wild-type Fc region, an Fc region comprising the amino acid sequence of PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTIVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK (amino acids 121-330 of SEQ ID NO: 1 or amino acids 238-447 according to Fc numbering), or an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 1, 2, 5, 10, or 15 amino acid residues.

9. A composition comprising a polypeptide of any of claims 1-8, optionally further comprising a pharmaceutical acceptable carrier.

10. A nucleic acid molecule encoding a polypeptide of any of claims 1-8.

11. A vector comprising a nucleic acid molecule of claim 10.

12. A cell comprising a nucleic acid molecule of claim 10 or a vector of claim 11.

13. A kit comprising a polypeptide of any of claims 1-8 and instructions to use of the polypeptide.

14. A container comprising a polypeptide of any of claims 1-8.

5 15. A method of producing a polypeptide, the method comprising culturing a cell of claim 12 under conditions that allow production of an antibody molecule, thereby producing the polypeptide, optionally, wherein the method, further comprises isolating or purifying the polypeptide.

10 16. Use of a polypeptide of any of claims 1-8, or a composition of claim 9, in the manufacture of a medicament for the treatment of a disorder in a subject.

17. A method of detecting a molecule, the method comprising contacting a cell or a sample from a subject with a polypeptide of any of claims 1-180, thereby detecting the molecule.