

CLAIMS

1. An antibody comprising a polypeptide comprising a variant of an IgG Fc polypeptide or a functional fragment thereof,
wherein the variant is derived from or comprises a human IgG1 isotype;
wherein the variant comprises:
 - (a) an alanine (A) at EU position 236 and a leucine (L) at EU position 300, or
 - (b) an alanine (A) at EU position 236, a proline (P) at EU position 292, and a leucine (L) at EU position 300; andwherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 11 or 12, or the amino acid sequence of SEQ ID NO: 11 or 12 with one or more modifications that enhances binding to the human FcRn as compared to (1) a reference polypeptide that comprises a wild-type human IgG1 Fc polypeptide having the sequence of SEQ ID NO: 1 or (2) the polypeptide without the one or more modification.
2. The antibody of claim 1, wherein the polypeptide, has increased binding to a human FcγRIIa
as compared to the binding of a reference polypeptide to the human FcγRIIa,
wherein the reference polypeptide comprises a fucosylated wild-type human IgG Fc polypeptide having the sequence of SEQ ID NO: 1 or a functional fragment thereof.
3. The antibody of claim 2, wherein binding is as determined using an electrochemiluminescence assay.
4. The antibody of claim 3, wherein binding is further determined using Meso Scale Discovery.
5. The antibody of any one of claims 2-4, wherein the increased binding to a human FcγRIIa comprises at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 11-fold, at least 12-fold, at least 13-fold, at least 14-fold, at least 15-fold, at least 16-fold, at least 17-fold, or at least 18-fold greater

binding to the human FcγRIIa as compared to the binding of a reference polypeptide comprising a fucosylated wild-type human IgG Fc polypeptide having the sequence of SEQ ID NO: 1, or functional fragment thereof, to the human FcγRIIa.

6. The antibody of any one of claims 2-5, wherein the human FcγRIIa comprises H131 and, optionally, the increased binding to the human FcγRIIa H131 comprises at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold, at least 11-fold, at least 12-fold, at least 13-fold, at least 14-fold, at least 15-fold, at least 16-fold, at least 17-fold, or at least 18-fold greater binding to the human FcγRIIa H131 as compared to the binding of a reference polypeptide comprising a fucosylated wild-type human IgG Fc polypeptide having the sequence of SEQ ID NO: 1, or functional fragment thereof, to the human FcγRIIa H131.

7. The antibody of any one of claims 2-6, wherein the human FcγRIIa comprises R131 and, optionally, the increased binding to the human FcγRIIa R131 comprises at least 4-fold greater binding to the human FcγRIIa R131 as compared to the binding of a reference polypeptide comprising a fucosylated wild-type human IgG Fc polypeptide having the sequence of SEQ ID NO: 1, or functional fragment thereof, to the human FcγRIIa R131.

8. The antibody of any one of claims 2-7, wherein

(1) a ratio of (i) the binding of the variant or polypeptide to a human FcγRIIa to (ii) the binding of the variant or polypeptide, respectively, to a human FcγRIIb is greater than

(2) a ratio of (iii) the binding of a reference polypeptide comprising a fucosylated wild-type human IgG Fc polypeptide having the sequence of SEQ ID NO: 1, or functional fragment thereof, to the human FcγRIIa to (iv) the binding of the reference polypeptide to the human FcγRIIb.

9. The antibody of claim 8, wherein the human FcγRIIa comprises H131.

10. The antibody of claim 8 or 9, wherein the human FcγRIIa comprises R131.

11. The antibody of any one of claims 8-10, wherein the ratio in (1) is at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 11-fold, at least 12-fold, at least 13-fold, at least 14-fold, at least 15-fold, at least 16-fold, or at least 17-fold greater than the ratio in (2).

12. The antibody of any one of claims 1-11, wherein the variant comprises an alanine (A) at EU position 236, and a leucine (L) at EU position 300.

13. The antibody of any one of claims 1-12, wherein the variant comprises an alanine (A) at EU position 236, a proline (P) at EU position 292, and a leucine (L) at EU position 300.

14. The antibody of claim 13, wherein the variant, and optionally the polypeptide, has increased binding to a human FcγRIIIa,

as compared to the binding of a reference polypeptide to the human FcγRIIIa,
wherein the reference polypeptide comprises a fucosylated wild-type human IgG Fc polypeptide having the sequence of SEQ ID NO: 1, or functional fragment thereof,
wherein, optionally, binding is as determined using an electrochemiluminescence assay, further optionally Meso Scale Discovery.

15. The antibody of claim 14, wherein the human FcγRIII comprises V158, F158, or both.

16. The antibody of claim 14 or 15, wherein the increased binding to a human FcγRIIIa comprises greater than 2-fold, at least 2.1-fold, at least 2.2-fold, at least 2.3-fold, at least 2.4-fold, at least 2.5-fold, at least 2.6-fold, at least 2.7-fold, at least 2.8-fold, at least 2.9-fold, at least 3.0 fold, at least 3.1-fold, at least 3.2-fold, at least 3.3-fold, at least 3.4-fold, at least 3.5-fold, at least 3.6-fold, or at least 3.7-fold greater binding to the human FcγRIIIa as compared to the binding of a reference polypeptide comprising a fucosylated wild-type human IgG Fc polypeptide having the sequence of SEQ ID NO: 1, or functional fragment thereof, to the human FcγRIIIa.

17. The antibody of any one of claims 13-16, wherein the variant, and optionally the polypeptide, is capable of binding to a human complement component 1q (C1q),

wherein, optionally, binding is as determined using an electrochemiluminescence assay, further optionally Meso Scale Discovery.

18. The antibody of any one of claims 1-17, which:

(i) is capable of binding to a human FcγRIIIa, wherein the human FcγRIIIa comprises a V158, a F158, or both;

(ii) is capable of binding to a human FcγRIIIb;

(iii) is capable of binding to a human FcRn, optionally at pH 6;

(iv) is capable of binding to a human complement component 1q (C1q);

(v) has a higher T_m and/or can be produced at a higher titer as compared to

(1) a reference polypeptide comprising a human IgG1 Fc polypeptide comprising the amino acid substitutions G236A, S239D, A330L, and I330E (EU numbering), and optionally not comprising any other amino acid substitutions relative to a wild-type human IgG1 Fc polypeptide,

(2) a reference polypeptide comprising a human IgG1 Fc polypeptide comprising the amino acid substitutions G236A, A330L, and I330E (EU numbering), and optionally further comprising M428L and N434S mutations or M428L and N434A mutations and/or not comprising any other amino acid substitutions and/or not comprising S239D, relative to a wild-type human IgG1 Fc polypeptide,

(3) a reference polypeptide comprising a human IgG1 Fc polypeptide comprising the amino acid substitution G236A or G236S (EU numbering), and optionally not comprising any other amino acid substitutions relative to a wild-type human IgG1 Fc polypeptide, and/or

(4) a reference polypeptide comprising a human IgG1 Fc polypeptide comprising the amino acid substitutions A330L and I332E (EU numbering), and optionally not comprising any other amino acid substitutions relative to a wild-type human IgG1 Fc polypeptide;

(vi) is capable of promoting signaling through a FcγRa in a host cell, wherein, optionally, (a) signaling is optionally increased as compared to the signaling promoted by a reference polypeptide and/or (b) the FcγRa comprises FcγRIIa H131, FcγRIIa R131, FcγRIIIa V158, FcγRIIIa F158, or any combination thereof;

(vii) at least when comprised in an antibody, is capable of promoting antibody-dependent cellular cytotoxicity (ADCC);

(viii) at least when comprised in an antibody, is capable of promoting antibody-dependent phagocytosis (ADCP);

(ix) at least when comprised in an antibody, is capable of promoting complement-dependent cytotoxicity (CDC);

(x) at least when comprised in an antibody, is capable of forming an immune complex; or

(xi) any combination of (i)-(x).

19. The antibody of any one of claims 1-18, wherein the antibody is capable of any one or more of the following:

(i) increasing specific lysis (e.g. via ADCC) by natural killer cells and/or PBMCs (e.g. expressing F158/V158 or V158/V158 FcγRIIIA) against antigen-expressing target cells, as compared to the antibody comprising a reference Fc polypeptide having the sequence of SEQ ID NO: 1 and not comprising the mutation(s) and/or fucosylation state (e.g. the antibody comprising a human IgG1 Fc comprising the mutations G236A, A330L, and I332E);

(ii) increasing ADCP by monocytes (e.g. CD14⁺ monocytes, optionally expressing F158/V158 FcγRIIA and R131/H131 FcγRIIA or F158/F158 FcγRIIA and R131/H131 FcγRIIA) against antigen-expressing target cells, as compared to the antibody comprising a reference Fc polypeptide having the sequence of SEQ ID NO: 1 and not comprising the mutation(s) and/or fucosylation state;

(iii) increasing the percentage of CD83⁺ cells (e.g. moDCs) and/or increasing expression of CD83 by moDCs in a sample when provided in combination with the antigen, as compared to the antibody comprising a reference Fc polypeptide having the sequence of SEQ ID NO: 1 and not comprising the mutation(s) and/or fucosylation state, when provided in combination with the antigen;

(iv) increasing production of one or more cytokine (optionally selected from the group consisting of IL-1 β , IFN- γ , IL-6, and TNF- α) by moDCs in a sample when provided in combination with the antigen, as compared to the antibody comprising a reference Fc polypeptide having the sequence of SEQ ID NO: 1 and not comprising the mutation(s) and/or fucosylation state, when provided in combination with the antigen; and

(v) increasing the ability of moDCs to stimulate antigen-specific CD4⁺ T cells when provided to the moDCs in combination with the antigen, as compared to the antibody comprising a reference Fc polypeptide having the sequence of SEQ ID NO: 1 and not comprising the mutation(s) and/or fucosylation state, when provided to the moDCs in combination with the antigen, wherein, optionally, (1) the moDCs and the CD4⁺ T cells are from the same (optionally antigen-vaccinated) subject and/or (2) stimulation of antigen-specific CD4⁺ T cells is determined by an increase in CD25 expression and/or an increase in proliferation (e.g. as determined by a reduction in CFSE staining over time) and/or an increase in expression of CD69 and/or an increase in expression of NFAT and/or an increase in expression of CD44, by the antigen-specific CD4⁺ T cells.

20. The antibody of claim 1, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 11.

21. The antibody of claim 1, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 12.

22. The antibody of any one of claims 1 to 19, wherein the one or more modification that enhances binding to the human FcRn comprises the amino acid substitutions:

- (i) M428L/N434S;
- (ii) M252Y/S254T/T256E;
- (iii) T250Q/M428L;
- (iv) P257I/Q311I;
- (v) P257I/N434H;
- (vi) D376V/N434H;

- (vii) T307A/E380A/N434A;
- (viii) N434A;
- (ix) M428L/N434A; or
- (x) any combination of (i)-(ix).

23. The antibody of any one of claims 1-22, wherein the variant does not comprise any additional mutations as compared to the reference polypeptide having the sequence SEQ ID NO: 1 or functional fragment thereof, the IgG CH2 polypeptide, the IgG hinge-CH2 polypeptide, or the IgG hinge-Fc polypeptide or functional fragment thereof, respectively.

24. The antibody of any one of claims 1-23, wherein the antibody is capable of specifically binding to:

- (i) a target (*e.g.*, an antigen) that is expressed or produced by a pathogen (*e.g.*, virus, bacterium, parasite, fungus) or by a cell infected with the pathogen, wherein, optionally, the pathogen comprises a virus and the virus comprises: a coronavirus; a betacoronavirus; a sarbecovirus; an embecovirus; a nobecovirus; a merbecovirus; a metapneumovirus; a hibecovirus; a SARS-CoV-2; a hepatitis B virus; a hepatitis D virus; an influenza A virus; a cytomegalovirus; a rhinovirus; a hepatitis C virus; an influenza B virus; a human immunodeficiency virus; a respiratory virus; a respiratory syncytial virus; a zika virus; a rabies virus; a dengue virus; a flavivirus; an ebolavirus; or any combination thereof;
- (ii) a target (*e.g.*, an antigen) that is expressed by, and/or is expressed on a cell surface of, a tumor cell, optionally a cancer cell or a cell of a proliferative or hyperproliferative disorder;
- (iii) a target (*e.g.*, an antigen) that is associated with an autoimmune disease;
- (iv) a target (*e.g.*, an antigen) that is associated with a neurodegenerative disease
- (v) an immune system signaling molecule, such as a cytokine;
- (vi) a target (*e.g.*, an antigen) that is associated with inflammation;
- (vii) a target (*e.g.*, an antigen) that is associated with a non-infectious disease; or
- (viii) any combination of (i)-(vii).

25. The antibody of any one of claims 1-24, wherein the antibody is capable of specifically binding to human immunodeficiency virus.
26. The antibody of any one of claims 1-25, which comprises a chimeric antibody, a humanized antibody, a neutralizing antibody, a human antibody, an IgNAR, a camelid nanobody, or any combination thereof.
27. The antibody of any one of claims 1-26, wherein the antibody is a multispecific antibody, such as a bispecific antibody, a trispecific antibody, or a tetraspecific antibody.
28. The antibody of any one of claims 1-27, wherein the antibody is comprised in an antibody conjugate.
29. The antibody of any one of claims 1-28, wherein the polypeptide (1) comprises a Fc fusion protein; and/or (2) comprises an Fcab.
30. The antibody of claim 29, wherein the Fc fusion protein further comprises:
- (i) a receptor domain (*e.g.* an ectodomain of a receptor protein, or a ligand-binding portion thereof);
 - (ii) a ligand;
 - (iii) a replacement protein; or
 - (iv) any combination of (i)-(iii).
31. The antibody of any one of claims 1-30, which is conjugated, linked, or fused to a payload moiety.
32. The antibody of claim 31, wherein the payload moiety comprises: an antibody or an antigen-binding fragment thereof; a cytotoxic agent (*e.g.*, a chemotherapeutic agent); a detectable compound or detectable label; an oligonucleotide (*e.g.*, an antisense

oligonucleotide, a siRNA, or the like); a vector; an agent that stimulates an immune response; a growth factor; or any combination thereof.

33. The antibody of any one of claims 1-32, which: is afucosylated; has been produced in a host cell that is incapable of fucosylation or that is inhibited in its ability to fucosylate a polypeptide; has been produced under conditions that inhibit fucosylation thereof by a host cell; or any combination thereof.

34. The antibody of any one of claims 1-33, comprising an amino acid mutation that (1) inhibits fucosylation as compared to a reference polypeptide or antibody, respectively, and/or (2) that abrogates a fucosylation site that is present in the reference polypeptide or antibody, respectively.

35. An antibody comprising the amino acid sequence of SEQ ID NO: 11 or 12, or a variant derived from or comprises a human IgG1 isotype consisting of the modifications:

- (i) G236A, Y300L, M428L and N434S, or
- (ii) G236A, R292P, Y300L, M428L and N434S.

36. The antibody of any one of claims 1 to 35, wherein the antibody is afucosylated.

37. A polynucleotide encoding the antibody of any one of claims 1-36.

38. The polynucleotide of claim 37, wherein the polynucleotide is codon optimized for expression by a host cell.

39. A vector comprising the polynucleotide of claim 37 or 38.

40. A host cell comprising the polynucleotide of claim 37 or 38 or the vector of claim 39.

41. A host cell expressing the antibody of any one of claims 1-36.
42. A composition comprising:
- (i) the antibody of any one of claims 1-36; and/or
 - (ii) the polynucleotide of claim 37 or 38; and/or
 - (iii) the vector of claim 39; and/or
 - (iv) the host cell of claim 40 or 41,
- and a pharmaceutically acceptable carrier, excipient, or diluent.
43. The antibody of any one of claims 1-36, the polynucleotide of claim 37 or 38, the vector of claim 39, the host cell of claim 40 or 41, and/or the composition of claim 42, for use in therapy.
44. Use of the antibody of any one of claims 1-36, the polynucleotide of claim 37 or 38, the vector of claim 39, the host cell of any one of claims 40 or 41, and/or the composition of claim 42, in the manufacture of a medicament for treating or preventing a disease or disorder in a subject, wherein the disease or disorder comprises an infectious disease, a cancer, a proliferative disorder, a neurodegenerative disease, an autoimmune disease, or any combination thereof.
45. The use of claim 44, wherein the infectious disease comprises: a coronavirus infection, a betacoronavirus infection, a sarbecovirus infection, an embecovirus infection, a nobecovirus infection, a merbecovirus infection, a metapneumovirus infection, a hibecovirus infection, a SARS-CoV-2 infection, a hepatitis B virus infection, a hepatitis D virus infection, a hepatitis C virus infection, a cytomegalovirus infection, an influenza A virus infection, an influenza B virus infection, a human immunodeficiency virus infection, a respiratory virus infection, a respiratory syncytial virus infection, a zika virus infection, a rabies virus infection, a dengue virus infection, a flavivirus infection, an ebolavirus infection, or any combination thereof.

46. The use of claim 45, wherein the infectious disease is a human immunodeficiency virus infection.