

ENGINEERED POLYPEPTIDES

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is 930585_422WO_SEQUENCE_LISTING.txt. The text file is 71.6 KB, was created on May 20, 2022, and is being submitted electronically via EFS-Web.

BACKGROUND

Therapies involving antibodies and other molecules that include immunoglobulin Fc domains are developing. Fcs can interact with immune system proteins such as FcγRs and complement C1q, and the nature of such interactions can provide for different outcomes, such as, for example, activating or suppressing a host immune response against a pathogen.

SUMMARY

In one aspect, the present disclosure provides a polypeptide comprising a variant of: (i) an IgG CH2 polypeptide or (ii) an IgG Fc polypeptide or a fragment thereof, wherein the variant comprises an alanine (A) at EU position 236 and a leucine (L) at EU position 300.

In another aspect, the present disclosure provides a polypeptide comprising a variant of: (i) an IgG CH2 polypeptide or (ii) an IgG Fc polypeptide or a fragment thereof, 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.

In yet another aspect, the present disclosure provides an antibody comprising the polypeptide of the disclosure.

In yet another aspect, the present disclosure provides an antibody comprising a variant of an IgG Fc, wherein the variant comprises an alanine (A) at EU position 236 and a leucine (L) at EU position 300.

In yet another aspect, the present disclosure provides an antibody comprising a variant of an IgG Fc, 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.

In yet another aspect, the present disclosure provides a(n e.g. expression) vector comprising the polynucleotide of the disclosure.

In yet another aspect, the present disclosure provides a host cell comprising the polynucleotide or vector of the disclosure.

In yet another aspect, the present disclosure provides a host cell expressing: the polynucleotide and/or the antibody of the disclosure.

In yet another aspect, the present disclosure provides the polypeptide, the antibody, the polynucleotide, the vector, the host cell, and/or the composition of the disclosure for use in therapy.

In yet another aspect, the present disclosure provides the use of the polypeptide, the antibody, the polynucleotide, the vector, the host cell, and/or the composition of the disclosure 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 (optionally caused by a viral, bacterial, fungal, or parasitic infection), a cancer, a proliferative disorder, a neurodegenerative disease, an autoimmune disease, or any combination thereof.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Figures 1A-1E show that antibodies with certain Fc modifications have improved prophylactic effect against influenza A. Figure 1A shows the design of a study in which mice engineered to express human FcγRs were intravenously administered antibodies bearing variant Fcs two days prior to infection with a lethal intranasal dose of H1N1 PR8. Serum IgG levels were evaluated at the time of infection (day 0) and mice were evaluated for body weight and survival over fourteen days. Figure 1B shows maximum change in body weight in mice pre-treated with anti-FluA IgG1 antibody "F18" bearing G236A/A330L/I332E/M428L/N434S ("F18-LS-GAALIE") Fc mutations compared with mice pre-treated with F18 antibody bearing only M428L/N434S mutations in the Fc ("F18-LS"). Body weight change (Figure 1C) and survival (Figure 1D) were also evaluated in mice treated with antibody bearing G236A ("GA"), A330L/I332E ("ALIE"), G236A/A330L/I332E

("GAALIE"), or G237D/H268D/P271G/A330R ("V11") Fc mutations. Mice that were treated with antibody bearing wild-type Fc or afucosylated wild-type Fc, or treated with PBS, were evaluated as controls. The effect of the Fc mutation(s) on antibody binding to Fc γ RI,

CLAIMS

1. A polypeptide comprising a variant of: (i) an IgG CH2 polypeptide or (ii) an IgG Fc polypeptide or a fragment thereof,
wherein the variant comprises an alanine (A) at EU position 236 and a leucine (L) at EU position 300.
2. The polypeptide of claim 1, wherein the variant, and optionally the polypeptide, has increased binding to a human FcγRIIa
as compared to the binding of a reference polypeptide to the human FcγRIIa,
wherein, optionally, binding is as determined using an electrochemiluminescence assay, further optionally Meso Scale Discovery.
3. The polypeptide of claim 2, 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 wild-type human IgG Fc polypeptide or a fragment thereof to the human FcγRIIa.
4. The polypeptide of claim 2 or claim 3, 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 wild-type human IgG Fc polypeptide or a fragment thereof to the human FcγRIIa H131.
5. The polypeptide of any one of claims 2-4, 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 wild-type human IgG Fc polypeptide or a fragment thereof to the human FcγRIIa R131.

6. The polypeptide of any one of claims 2-5, 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 to the human FcγRIIa to (iv) the binding of the reference polypeptide to the human FcγRIIb, wherein the reference polypeptide comprises a wild-type human IgG Fc polypeptide or a fragment thereof.
7. The polypeptide of claim 6, wherein the human FcγRIIa comprises H131.
8. The polypeptide of claim 6 or 7, wherein the human FcγRIIa comprises R131.
9. The polypeptide of any one of claims 6-8, 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).
10. The polypeptide of any one of claims 1-9, further comprising a proline (P) at EU position 292.
11. The polypeptide of any one of claims 1-10, 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 to the human FcγRIIa to (iv) the binding of the reference polypeptide to the human FcγRIIb, wherein the reference polypeptide comprises a wild-type human IgG Fc polypeptide or a fragment thereof,

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

12. The polypeptide of claim 11, wherein the human FcγRIIa comprises H131.
13. The polypeptide of claim 11 or 12, wherein the human FcγRIIa comprises R131.
14. The polypeptide of any one of claims 11-13, wherein the ratio in (1) is more than 1-fold, at least 2-fold, at least 3-fold, 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, or at least 14-fold greater than the ratio in (2).
15. A polypeptide comprising a variant of: (i) an IgG CH2 polypeptide or (ii) an IgG Fc polypeptide or a fragment thereof,
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.
16. The polypeptide of claim 15, 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, optionally, binding is as determined using an electrochemiluminescence assay, further optionally Meso Scale Discovery.
17. The polypeptide of claim 16, wherein the increased binding to a human FcγRIIa comprises at least 2-fold, at least 3-fold, 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, or at least 14-fold greater binding to the human FcγRIIa as compared to the binding of a reference polypeptide comprising a wild-type human IgG Fc polypeptide or a fragment thereof to the human FcγRIIa.

18. The polypeptide of claim 16 or claim 17, wherein the human FcγRIIa comprises H131 and, optionally, the increased binding to the human FcγRIIa H131 comprises at least 2-fold, at least 3-fold, 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, or at least 14-fold greater binding to the human FcγRIIa H131 as compared to the binding of a reference polypeptide comprising a wild-type human IgG Fc polypeptide or a fragment thereof to the human FcγRIIa H131.

19. The polypeptide of any one of claims 15-18, wherein the human FcγRIIa comprises R131 and, optionally, the increased binding to the human FcγRIIa H131 comprises at least 2-fold greater binding to the human FcγRIIa R131 as compared to the binding of a reference polypeptide comprising a wild-type human IgG Fc polypeptide or a fragment thereof to the human FcγRIIa R131.

20. The polypeptide of any one of claims 15-19, 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 to the human FcγRIIa to (iv) the binding of the reference polypeptide to the human FcγRIIb, wherein the reference polypeptide comprises a wild-type human IgG Fc polypeptide or a fragment thereof,

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

21. The polypeptide of claim 20, wherein the human FcγRIIa comprises H131.

22. The polypeptide of claim 20 or 21, wherein the human FcγRIIa comprises R131.

23. The polypeptide of any one of claims 20-22, wherein the ratio in (1) is at least 2-fold, at least 3-fold, 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, or at least 15-fold greater than the ratio in (2).

24. The polypeptide of any one of claims 15-23, wherein the variant has increased binding to a human FcγRIIIa,
as compared to the binding of a reference polypeptide to the human FcγRIIIa,
wherein, optionally, binding is as determined using an electrochemiluminescence assay, further optionally Meso Scale Discovery.

25. The polypeptide of claim 24, wherein the human FcγRIII comprises V158, F158, or both.

26. The polypeptide of claim 24 or 25, 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 wild-type human IgG Fc polypeptide or a fragment thereof to the human FcγRIIIa.

27. The polypeptide of any one of claims 15-26, 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.

28. The polypeptide of any one of claims 1-27, 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).

29. The polypeptide of any one of claims 1-28, wherein the polypeptide comprises an antibody and 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 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 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 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-1β, 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 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 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.

30. The polypeptide of any one of claims 1-29, wherein the variant further comprises one or more modification that enhances or further enhances binding to a human FcRn

as compared to (1) a reference polypeptide that comprises a wild-type human IgG1 Fc polypeptide and/or to (2) the polypeptide of any one of claims 1-29 without the one or more modification.

31. The polypeptide of claim 30, 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).

32. The polypeptide of any one of claims 1-31, wherein the variant does not comprise any additional mutations as compared to the reference IgG Fc polypeptide or fragment thereof, the IgG CH2 polypeptide, the IgG hinge-CH2 polypeptide, or the IgG hinge-Fc polypeptide or fragment thereof, respectively.

33. The polypeptide of any one of claims 1-32, which comprises a Fc polypeptide.

34. The polypeptide of any one of claims 1-33, which is a monomer comprised in a polypeptide dimer (*e.g.*, a Fc dimer).

35. The polypeptide of any one of claims 1-34, which is a monomer comprised in a polypeptide homodimer (*e.g.*, a Fc homodimer).

36. The polypeptide of any one of claims 1-34, which is a monomer comprised in a polypeptide heterodimer (*e.g.*, a Fc heterodimer, optionally comprising a protuberance in a first Fc of the heterodimer and a corresponding cavity in a second Fc of the heterodimer, and/or comprising one or more mutations that provide or contribute to an opposite charge in each of the two Fc monomers (*e.g.*, a positive charge in a region of a first monomer and a negative charge in a corresponding region of a second monomer), and/or comprising a heterologous amino acid sequence in one or both monomers, to promote dimerization of the two Fc monomers).

37. The polypeptide of any one of claims 1-36, which is comprised in an antibody.

38. An antibody comprising the polypeptide of any one of claims 1-37.

39. An antibody comprising a variant of an IgG Fc, wherein the variant comprises an alanine (A) at EU position 236 and a leucine (L) at EU position 300.

40. An antibody comprising a variant of an IgG Fc, 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.

41. The polypeptide of any one of claims 1-37 or the antibody of any one of claims 38-40, wherein the variant is derived from or comprises an IgG1 isotype, an IgG2 isotype, an IgG3 isotype, or an IgG4 isotype.

42. The polypeptide of any one of claims 1-37 and 41, or the antibody of any one of claims 38-41, wherein the variant is derived from or comprises a human Fc or a fragment thereof, or from a human antibody heavy chain or a fragment thereof.

43. The polypeptide of any one of claims 1-37, 41, and 42, or the antibody of any one of claims 38-42, wherein the variant is derived or comprises from a human IgG1 isotype, a human IgG2 isotype, a human IgG3 isotype, or a human IgG4 isotype.

44. The polypeptide of any one of claims 1-37 and 41-43, or the antibody of any one of claims 38-43, wherein the variant is derived from or comprises a human IgG1 isotype, optionally comprising a G1m3 allotype, a G1m17 allotype, a G1m3,1 allotype, or a G1m17,1 allotype.

45. The antibody of any one of claims 38-44, 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), optionally with binding that is increased by more than 1-fold, at least 2-fold, at least 3-fold, or at least 4-fold relative to the binding of an antibody comprising a reference Fc polypeptide;
- (v) has a higher T_m, and/or can be produced at a higher titer, and/or is capable of binding to a human FcγRIIIa (optionally, H131 and/or R131) with a higher affinity and/or avidity, and/or is capable of binding to a human FcγRIIIb with a lower affinity and/or avidity, as compared to
 - (1) a reference antibody that comprises a human IgG1 Fc comprising the amino acid substitutions G236A, S239D, A330L, and I330E (EU numbering), wherein the reference antibody optionally does not comprise any other amino acid substitutions relative in the Fc relative to the wild-type human IgG1 Fc,

- (2) a reference antibody that comprises a human IgG1 Fc comprising the amino acid substitutions G236A, A330L, and I330E (EU numbering), wherein the reference antibody optionally (a) further comprises M428L and N434S mutations or M428L and N434A mutations and/or (b) does not comprise any other amino acid substitutions in the Fc relative to the wild-type human IgG1 Fc and/or (c) does not comprise a S239D mutation,
- (3) a reference antibody comprising a human IgG1 Fc that comprises the amino acid substitution G236A or G236S (EU numbering), and optionally does not comprising any other amino acid substitutions on the Fc relative to a wild-type human IgG1 Fc,
- (4) a reference antibody that comprises a human IgG1 Fc comprising the amino acid substitutions A330L and I332E (EU numbering), wherein the reference antibody optionally does not comprise any other amino acid substitutions in the Fc relative to the wild-type human IgG1 Fc; and/or
- (5) a reference antibody comprising a wild-type human IgG1 Fc;
- (vi) is capable of promoting signaling through a FcγRa in a host cell, wherein, optionally, (a) signaling is increased as compared to the signaling promoted by a reference antibody and/or (b) wherein the FcγRa comprises FcγRIIa H131, FcγRIIa R131, FcγRIIIa V158, FcγRIIIa F158, or any combination thereof;
- (vii) is capable of promoting antibody-dependent cellular cytotoxicity (ADCC);
- (viii) is capable of promoting antibody-dependent phagocytosis (ADCP);
- (ix) is capable of promoting complement-dependent cytotoxicity (CDC);
- (x) is capable of forming an immune complex; or
- (xi) any combination of (i)-(x).

46. The antibody of any one of claims 38-45, 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 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 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 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-1β, 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 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 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.

47. The antibody of any one of claims 38-46, wherein the variant further comprises one or more modification that enhances binding to a human FcRn

as compared to (1) a reference antibody comprises a wild-type human IgG1 Fc polypeptide and/or to (2) the antibody of any one of claims 38-46 without the one or more modification.

48. The antibody of claim 47, 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;
- (i) P257I/Q311I;
- (ii) P257I/N434H;
- (iii) D376V/N434H;
- (iv) T307A/E380A/N434A;
- (v) M428L/N434A; or
- (vi) any combination of (i)-(x).

49. The antibody of any one of claims 38-48, wherein the variant does not comprise any additional mutations as compared to a reference wild-type IgG Fc.

50. The polypeptide of claim 37, or the antibody of any one of claims 38-49, 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).

51. The polypeptide of claim 37 or the antibody of any one of claims 38-49, wherein the antibody is capable of specifically binding to human immunodeficiency virus.

52. The polypeptide of any one of claims 37, 41-44, and 50, and 51, or the antibody of any one of claims 38-51, which comprises a chimeric antibody, a humanized antibody, a neutralizing antibody, a human antibody, an IgNAR, a camelid nanobody, or any combination thereof.

53. The polypeptide of any one of claims 37, 41-44, and 50-52, or the antibody of any one of claims 38-52, wherein the antibody is a multispecific antibody, such as a bispecific antibody, a trispecific antibody, or a tetraspecific antibody.

54. The polypeptide of any one of claims 37, 41-44, and 50-53, or the antibody of any one of claims 38-53, wherein the antibody is comprised in an antibody conjugate.

55. The polypeptide of any one of claims 1-37, 41-44, and 50-54, or the antibody of any one of claims 38-54, wherein the polypeptide or the Fc polypeptide: (1) comprises a Fc fusion protein; and/or (2) comprises an Fcab.

56. The polypeptide or antibody of claim 55, 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).

57. The polypeptide of any one of claims 1-37, 41-44, and 50-56, or the antibody of any one of claims 38-56, which is conjugated, linked, or fused to a payload moiety.

58. The polypeptide or antibody of claim 57, 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.

59. The polypeptide of any one of claims 1-37, 41-44, and 50-58, or the antibody of any one of claims 38-58, 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.

60. The polypeptide of any one of claims 1-37, 41-44, and 50-59, or the antibody of any one of claims 38-59, 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.

61. The polypeptide of any one of claims 1-9, 11-14, 28-37, 41-44 and 50-60, or the antibody of any one of claims 38, 39, and 41-60, comprising the amino acid sequence of SEQ ID NO:11.

62. The polypeptide of any one of claims 10-37, 41-44, and 50-60, or the antibody of any one of claims 38 and 40-60, comprising the amino acid sequence of SEQ ID NO:12.

63. A polynucleotide encoding the polypeptide of any one of claims 1-37, 41-44, and 50-62, or the antibody of any one of claims 38-62.

64. The polynucleotide of claim 63, wherein the polynucleotide is codon optimized for expression by a host cell.

65. A(n *e.g.* expression) vector comprising the polynucleotide of claim 63 or 64.

66. A host cell comprising the polynucleotide of claim 63 or 64 or the vector of claim 65.

67. A host cell expressing: the polypeptide of any one of claims 1-37, 41-44, and 50-62; and/or the antibody of any one of claims 38-62.

68. A composition comprising:

- (i) the polypeptide of any one of claims 1-37, 41-44, and 50-62; and/or
- (ii) the antibody of any one of claims 38-62; and/or
- (iii) the polynucleotide of claim 63 or 64; and/or
- (iv) the vector of claim 65; and/or
- (v) the host cell of claim 66-67,

and a pharmaceutically acceptable carrier, excipient, or diluent.

69. The polypeptide of any one of claims 1-37, 41-44, and 50-62, the antibody of any one of claims 38-62, the polynucleotide of claim 63 or 64, the vector of claim 65, the host cell of claim 66 or 67, and/or the composition of claim 68, for use in therapy.

70. Use of the polypeptide of any one of claims 1-37, 41-44, and 50-62, the antibody of any one of claims 38-62, the polynucleotide of claim 63 or 64, the vector of claim

65, the host cell of any one of claims 66 or 67, and/or the composition of claim 68, 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 (optionally caused by a viral, bacterial, fungal, or parasitic infection), a cancer, a proliferative disorder, a neurodegenerative disease, an autoimmune disease, or any combination thereof.

71. The use of claim 70, 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.

72. The use of claim 70, wherein the infectious disease is a human immunodeficiency virus infection.