

CLAIM(S):

1. ~~An isolated immunoglobulin heavy chain polypeptide which comprises the amino acid sequence Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Phe Xaa1 Ile Xaa2 Asp Asp Tyr Ile His Trp Val Xaa3 Gln Ala Pro Gly Lys Gly Leu Glu Trp Xaa4 Gly Trp Ile Asp Xaa5 Xaa6 Asn Xaa7 Asp Ser Xaa8 Tyr Xaa9 Ser Lys Phe Xaa10 Gly Arg Val Thr Ile Thr Val Asp Thr Ser Thr Xaa11 Thr Ala Tyr Met Xaa12 Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Tyr Ala Phe Gly Gly Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 181), wherein~~

- ~~(a) — Xaa1 is asparagine (Asn) or serine (Ser),~~
- ~~(b) — Xaa2 is lysine (Lys), tyrosine (Tyr), or asparagine (Asn),~~
- ~~(c) — Xaa3 is lysine (Lys) or glutamine (Gln),~~
- ~~(d) — Xaa4 is isoleucine (Ile) or methionine (Met),~~
- ~~(e) — Xaa5 is alanine (Ala) or proline (Pro),~~
- ~~(f) — Xaa6 is glutamic acid (Glu) or methionine (Met),~~
- ~~(g) — Xaa7 is glycine (Gly), asparagine (Asn), or aspartic acid (Asp),~~
- ~~(h) — Xaa8 is glutamic acid (Glu) or glutamine (Gln)~~
- ~~(i) — Xaa9 is alanine (Ala) or serine (Ser),~~
- ~~(j) — Xaa10 is glutamine (Gln) or arginine (Arg),~~
- ~~(k) — Xaa11 is aspartic acid (Asp) or asparagine (Asn), and~~
- ~~(l) — Xaa12 is glutamic acid (Glu) or lysine (Lys).~~

2. ~~The isolated immunoglobulin heavy chain polypeptide of claim 1, which comprises the amino acid sequence Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Phe Xaa1 Ile Xaa2 Asp Asp Tyr Ile His Trp Val Xaa3 Gln Ala Pro Gly Lys Gly Leu Glu Trp Xaa4 Gly Trp Ile Asp Xaa5 Glu Asn Xaa6 Asp Ser Glu Tyr Xaa7 Ser Lys Phe Xaa8 Gly Arg Val Thr Ile Thr Val Asp Thr Ser Thr Xaa9 Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Tyr Ala Phe Gly Gly Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 1), wherein~~

- ~~(a) — Xaa1 is asparagine (Asn) or serine (Ser),~~
- ~~(b) — Xaa2 is lysine (Lys), tyrosine (Tyr), or asparagine (Asn),~~

- (c) — ~~Xaa3 is lysine (Lys) or glutamine (Gln);~~
- (d) — ~~Xaa4 is isoleucine (Ile) or methionine (Met);~~
- (e) — ~~Xaa5 is alanine (Ala) or proline (Pro);~~
- (f) — ~~Xaa6 is glycine (Gly), asparagine (Asn), or aspartic acid (Asp);~~
- (g) — ~~Xaa7 is alanine (Ala) or serine (Ser);~~
- (h) — ~~Xaa8 is glutamine (Gln) or arginine (Arg), and~~
- (i) — ~~Xaa9 is aspartic acid (Asp) or asparagine (Asn).~~

3. — ~~The isolated immunoglobulin heavy chain polypeptide of claim 1 or 2, which comprises the amino acid sequence of any one of SEQ ID NO: 2 — SEQ ID NO: 34 or SEQ ID NO: 182-186.~~

4. — ~~An isolated immunoglobulin heavy chain polypeptide which comprises the amino acid sequence Gln Val Gln Leu Gln Gln Trp Gly Ala Xaa1 Leu Leu Lys Pro Ser Glu Thr Leu Ser Leu Xaa2 Cys Xaa3 Val Tyr Gly Gly Xaa4 Phe Xaa5 Gly Tyr Tyr Trp Xaa6 Trp Ile Arg Gln Pro Pro Xaa7 Lys Gly Leu Glu Trp Ile Gly Glu Ile Asn His Ser Gly Xaa8 Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Xaa9 Ser Leu Lys Leu Xaa10 Xaa11 Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Xaa12 Arg Glu Gly Xaa13 Tyr Gly Asp Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser (SEQ ID NO: 35), wherein~~

- (a) — ~~Xaa1 is arginine (Arg) or glycine (Gly);~~
- (b) — ~~Xaa2 is threonine (Thr) or isoleucine (Ile);~~
- (c) — ~~Xaa3 is threonine (Thr) or alanine (Ala);~~
- (d) — ~~Xaa4 is serine (Ser) or phenylalanine (Phe);~~
- (e) — ~~Xaa5 is serine (Ser) or phenylalanine (Phe);~~
- (f) — ~~Xaa6 is serine (Ser) or isoleucine (Ile);~~
- (g) — ~~Xaa7 is glycine (Gly) or arginine (Arg);~~
- (h) — ~~Xaa8 is serine (Ser) or asparagine (Asn);~~
- (i) — ~~Xaa9 is phenylalanine (Phe) or leucine (Leu);~~
- (j) — ~~Xaa10 is asparagine (Asn) or serine (Ser);~~
- (k) — ~~Xaa11 is serine (Ser) or phenylalanine (Phe);~~
- (l) — ~~Xaa12 is alanine (Ala) or valine (Val), and~~

(m) — ~~Xaa13 is aspartic acid (Asp) or asparagine (Asn).~~

5. — ~~The isolated immunoglobulin heavy chain polypeptide of claim 4, which comprises the amino acid sequence of any one of SEQ ID NO: 36 — SEQ ID NO: 56.~~

6. — ~~An isolated immunoglobulin light chain polypeptide which comprises the amino acid sequence Asp Xaa1 Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly Gln Pro Ala Ser Ile Ser Cys Arg Xaa2 Ser Gln Ser Leu Val His Ser Asp Xaa3 Xaa4 Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Xaa Xaa Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Xaa Gln Ser Thr Xaa Val Pro Tyr Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr (SEQ ID NO: 57), wherein~~

(a) — ~~Xaa1 is valine (Val) or isoleucine (Ile);~~

(b) — ~~Xaa2 is cysteine (Cys) or serine (Ser);~~

(c) — ~~Xaa3 is glycine (Gly) or serine (Ser);~~

(d) — ~~Xaa4 is asparagine (Asn) or aspartic acid (Asp);~~

(e) — ~~Xaa5 is lysine (Lys), glycine (Gly), asparagine (Asn), serine (Ser), or leucine (Leu);~~

(f) — ~~Xaa6 is valine (Val) or isoleucine (Ile);~~

(g) — ~~Xaa7 is serine (Ser), alanine (Ala), or glycine (Gly), and~~

(h) — ~~Xaa8 is histidine (His) or tyrosine (Tyr).~~

7. — ~~The isolated immunoglobulin light chain polypeptide of claim 6, which comprises the amino acid sequence of any one of SEQ ID NO: 58 — SEQ ID NO: 88 or 187-189.~~

8. — ~~An isolated immunoglobulin light chain polypeptide which comprises the amino acid sequence Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Xaa1 Xaa2 Xaa3 Xaa4 Xaa5 Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Val Tyr Tyr Cys Gln Gln Ser Tyr Ser Xaa6 Leu Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val (SEQ ID NO: 89), wherein~~

(a) the subsequence ~~Xaa1 Xaa2 Xaa3 Xaa4 Xaa5~~ is ~~deleted or is Tyr Asp Ala Ser Asn~~,
and

(b) ~~Xaa6~~ is ~~threonine (Thr) or isoleucine (Ile)~~.

9. — ~~The isolated immunoglobulin light chain polypeptide of claim 8, wherein the subsequence Xaa1 Xaa2 Xaa3 Xaa4 Xaa5 is Tyr Asp Ala Ser Asn.~~

10. — ~~The isolated immunoglobulin light chain polypeptide of claim 9, which comprises the amino acid sequence of SEQ ID NO: 90.~~

11. — ~~The isolated immunoglobulin light chain polypeptide of claim 8, wherein the subsequence Xaa1 Xaa2 Xaa3 Xaa4 Xaa5 is deleted.~~

12. — ~~The isolated immunoglobulin light chain polypeptide of claim 11, which comprises the amino acid sequence of SEQ ID NO: 91 or SEQ ID NO: 92.~~

13. — ~~An isolated immunoglobulin heavy chain polypeptide which comprises SEQ ID NO: 190 or 191.~~

14. — ~~The isolated immunoglobulin heavy chain polypeptide of claim 13 comprising any one of SEQ ID NOs: 192-195.~~

15. — ~~An isolated immunoglobulin light chain polypeptide which comprises SEQ ID NO: 196 or 197.~~

16. — ~~The isolated immunoglobulin light chain polypeptide of claim 15 comprising any one of SEQ ID NOs: 198-200.~~

17. — ~~An isolated nucleic acid sequence encoding the immunoglobulin heavy chain polypeptide of any one of claims 1-5, 13, or 14.~~

18. — ~~An isolated nucleic acid sequence encoding the immunoglobulin light chain polypeptide of any one of claims 6-12, 15, or 16.~~

19. — ~~A vector comprising the isolated nucleic acid sequence of claim 17 or claim 18.~~

20. — A Lymphocyte Activation Gene 3 (LAG-3) binding agent comprising the immunoglobulin heavy chain polypeptide of any one of claims 1-5, 13, or 14 and/or the immunoglobulin light chain polypeptide of any one of claims 6-12, 15, or 16.

21. — The LAG-3 binding agent of claim 20, which comprises the immunoglobulin heavy chain polypeptide of any one of claims 1-5, 13, or 14 and the immunoglobulin light chain polypeptide of any one of claims 6-12, 15, or 16.

22. — The LAG-3 binding agent of claim 20, which comprises the immunoglobulin heavy chain polypeptide of any one of claims 1-5, 13, or 14 or the immunoglobulin light chain polypeptide of any one of claims 6-12, 15, or 16.

23. — The LAG-3 binding agent of claim 20, which comprises (a) an immunoglobulin heavy chain polypeptide of any of claims 1-3, and an immunoglobulin light chain polypeptide of claim 6 or 7; (b) an immunoglobulin heavy chain polypeptide of claim 4 or 5, and an immunoglobulin light chain polypeptide of any of claims 8-12; or (c) an immunoglobulin heavy chain polypeptide of claim 13 or 14, and an immunoglobulin light chain polypeptide of claim 15 or 16.

24. — The LAG-3 binding agent of any one of claims 20-23, which is an antibody, an antibody conjugate, or an antigen-binding fragment thereof.

25. — The LAG-3 binding agent of claim 24, which is a F(ab')₂ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

26. — The LAG-3 binding agent of any one of claims 20-25, which binds to the extracellular domain 1 (D1) and/or the extracellular domain 2 (D2) of the LAG-3 protein.

27. — The LAG-3 binding agent of any one of claims 20-26, wherein the LAG-3 binding agent comprises an Fc region with reduced or abrogated effector function.

28. — An isolated nucleic acid sequence encoding the LAG-3 binding agent of any one of claims 20-27.

- ~~29. — A vector comprising the isolated nucleic acid sequence of claim 28.~~
- ~~30. — An isolated cell comprising the vector of claim 29.~~
- ~~31. — A composition comprising (a) the LAG-3 binding agent of any one of claims 20-27 or the vector of claim 29 and (b) a pharmaceutically acceptable carrier.~~
- ~~32. — Use of a composition of claim 31 in the manufacture of a medicament for the treatment of a disorder that is responsive to LAG-3 inhibition.~~
- ~~33. — The use of claim 32, wherein the disorder is cancer.~~
- ~~34. — The use of claim 33, wherein the cancer is melanoma, renal cell carcinoma, lung cancer, bladder cancer, breast cancer, cervical cancer, colon cancer, gall bladder cancer, laryngeal cancer, liver cancer, thyroid cancer, stomach cancer, salivary gland cancer, prostate cancer, pancreatic cancer, or Merkel cell carcinoma.~~
- ~~35. — The use of claim 32, wherein the disorder is an infectious disease.~~
- ~~36. — The use of claim 35, wherein the infectious disease is caused by a virus or a bacterium.~~
- ~~37. — The use of claim 36, wherein the virus is human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), influenza virus, dengue virus, or hepatitis B virus (HBV).~~
- ~~38. — The use of any one of claims 32-37, wherein the half-life of the LAG-3 binding agent in the mammal is between 30 minutes and 45 days.~~
- ~~39. — The use of any one of claims 32-38, wherein the LAG-3 binding agent binds to LAG-3 with a K_D between about 1 picomolar (pM) and about 100 micromolar (μ M).~~
- ~~40. — The use of any one of claims 32-39, wherein the medicament is to be further administered to the mammal with a PD-1 binding agent and/or a TIM-3 binding agent.~~

~~41. The use of claim 40, wherein the PD-1 binding agent and/or TIM-3 binding agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof.~~

1. A Lymphocyte Activation Gene-3 (LAG-3) binding agent comprising:
an immunoglobulin light chain variable (V_L) region comprising a light chain CDR1, a light chain CDR2, and a light chain CDR3 of SEQ ID NO:88; and
an immunoglobulin heavy chain variable (V_H) region comprising a heavy chain CDR1, a heavy chain CDR2, and a heavy chain CDR3 of SEQ ID NO:182.
2. A Lymphocyte Activation Gene-3 (LAG-3) binding agent comprising:
an immunoglobulin light chain variable (V_L) region comprising SEQ ID NO:88; and
an immunoglobulin heavy chain variable (V_H) region comprising SEQ ID NO:182.
3. The LAG-3 binding agent of claim 1, wherein the LAG-3 binding agent is an antibody.
4. The LAG-3 binding agent of claim 1, wherein the LAG-3 binding agent is an antigen-binding antibody fragment.
5. The LAG-3 binding agent of claim 1, wherein the LAG-3 binding agent is an IgG4 antibody.
6. The LAG-3 binding agent of claim 2, wherein the LAG-3 binding agent is an antibody.
7. The LAG-3 binding agent of claim 2, wherein the LAG-3 binding agent is an antigen-binding antibody fragment.
8. The LAG-3 binding agent of claim 2, wherein the LAG-3 binding agent is an IgG4 antibody.
9. A pharmaceutical composition comprising the LAG-3 binding agent of claim 1 and a pharmaceutically acceptable carrier.
10. A pharmaceutical composition comprising the LAG-3 binding agent of claim 2 and a pharmaceutically acceptable carrier.