

CLAIMS

We claim:

1. An anti-TIGIT antibody or antigen-binding fragment thereof that specifically binds to human TIGIT, comprising
 - (a) a heavy chain variable region comprising a heavy chain (HC) complementarity determining region (CDR) 1 having at least 80% sequence identity to SEQ ID NO: 36, an HC-CDR2 having at least 80% sequence identity to SEQ ID NO: 37, and an HC-CDR3 having at least 80% sequence identity to SEQ ID NO: 38; and a light chain variable region comprising a light chain (LC) CDR1 having at least 80% sequence identity to SEQ ID NO: 39, an LC-CDR2 having at least 80% sequence identity to SEQ ID NO: 40, and an LC-CDR3 having at least 80% sequence identity to SEQ ID NO: 41;
 - (b) a heavy chain variable region comprising an HC-CDR1 having at least 80% sequence identity to SEQ ID NO: 42, an HC-CDR2 having at least 80% sequence identity to SEQ ID NO: 43, and an HC-CDR3 having at least 80% sequence identity to SEQ ID NO: 44; and a light chain variable region comprising an LC-CDR1 having at least 80% sequence identity to SEQ ID NO: 45, an LC-CDR2 having at least 80% sequence identity to SEQ ID NO: 46, and an LC-CDR3 having at least 80% sequence identity to SEQ ID NO: 47;
 - (c) a heavy chain variable region comprising an HC-CDR1 having at least 80% sequence identity to SEQ ID NO: 48, an HC-CDR2 having at least 80% sequence identity to SEQ ID NO: 49, and an HC-CDR3 having at least 80% sequence identity to SEQ ID NO: 50; and a light chain variable region comprising an LC-CDR1 having at least 80% sequence identity to SEQ ID NO: 51, an LC-CDR2 having at least 80% sequence identity to SEQ ID NO: 52, and an LC-CDR3 having at least 80% sequence identity to SEQ ID NO: 53;
 - (d) a heavy chain variable region comprising an HC-CDR1 having at least 80% sequence identity to SEQ ID NO: 54, an HC-CDR2 having at least 80% sequence identity to SEQ ID NO: 55, and an HC-CDR3 having at least 80% sequence identity to SEQ ID NO: 56; and a light chain variable region comprising an LC-CDR1 having at least 80% sequence identity to SEQ ID NO: 57, an LC-CDR2 having at least 80% sequence identity to SEQ ID NO: 58, and an LC-CDR3 having at least 80% sequence identity to SEQ ID NO: 59;

- (e) a heavy chain variable region comprising an HC-CDR1 having at least 80% sequence identity to SEQ ID NO: 60, an HC-CDR2 having at least 80% sequence identity to SEQ ID NO: 61, and an HC-CDR3 having at least 80% sequence identity to SEQ ID NO: 62; and a light chain variable region comprising an LC-CDR1 having at least 80% sequence identity to SEQ ID NO: 63, an LC-CDR2 having at least 80% sequence identity to SEQ ID NO: 64, and an LC-CDR3 having at least 80% sequence identity to SEQ ID NO: 65;
- (f) a heavy chain variable region comprising an HC-CDR1 having at least 80% sequence identity to SEQ ID NO: 60, an HC-CDR2 having at least 80% sequence identity to SEQ ID NO: 66, and an HC-CDR3 having at least 80% sequence identity to SEQ ID NO: 67; and a light chain variable region comprising an LC-CDR1 having at least 80% sequence identity to SEQ ID NO: 63, an LC-CDR2 having at least 80% sequence identity to SEQ ID NO: 68, and an LC-CDR3 having at least 80% sequence identity to SEQ ID NO: 65;
- (g) a heavy chain variable region comprising an HC-CDR1 having at least 80% sequence identity to SEQ ID NO: 69, an HC-CDR2 having at least 80% sequence identity to SEQ ID NO: 55, and an HC-CDR3 having at least 80% sequence identity to SEQ ID NO: 70; and a light chain variable region comprising an LC-CDR1 having at least 80% sequence identity to SEQ ID NO: 71, an LC-CDR2 having at least 80% sequence identity to SEQ ID NO: 68, and an LC-CDR3 having at least 80% sequence identity to SEQ ID NO: 65;
- (h) a heavy chain variable region comprising an HC-CDR1 having at least 80% sequence identity to SEQ ID NO: 72, an HC-CDR2 having at least 80% sequence identity to SEQ ID NO: 73, and an HC-CDR3 having at least 80% sequence identity to SEQ ID NO: 67; and a light chain variable region comprising an LC-CDR1 having at least 80% sequence identity to SEQ ID NO: 63, an LC-CDR2 having at least 80% sequence identity to SEQ ID NO: 68, and an LC-CDR3 having at least 80% sequence identity to SEQ ID NO: 65; or
- (i) a heavy chain variable region comprising an HC-CDR1 having at least 80% sequence identity to SEQ ID NO: 74, an HC-CDR2 having at least 80% sequence identity to SEQ ID NO: 75, and an HC-CDR3 having at least 80% sequence identity to SEQ ID NO: 67; and a light chain variable region comprising an LC-CDR1 having at least 80% sequence identity to SEQ ID NO: 63, an LC-CDR2 having at least 80%

sequence identity to SEQ ID NO: 68, and an LC-CDR3 having at least 80% sequence identity to SEQ ID NO: 65.

2. The anti-TIGIT antibody or antigen-binding fragment thereof of claim 1, comprising
 - (a) a heavy chain variable region comprising an HC-CDR1 having an amino sequence comprising SEQ ID NO: 36, an HC-CDR2 having an amino sequence comprising SEQ ID NO: 37, and an HC-CDR3 having an amino sequence comprising SEQ ID NO: 38; and a light chain variable region comprising an LC-CDR1 having an amino sequence comprising identity to SEQ ID NO: 39, an LC-CDR2 having an amino sequence comprising SEQ ID NO: 40, and an LC-CDR3 having an amino sequence comprising SEQ ID NO: 41;
 - (b) a heavy chain variable region comprising an HC-CDR1 having an amino sequence comprising SEQ ID NO: 42, an HC-CDR2 having an amino sequence comprising SEQ ID NO: 43, and an HC-CDR3 having an amino sequence comprising SEQ ID NO: 44; and a light chain variable region comprising an LC-CDR1 having an amino sequence comprising SEQ ID NO: 45, an LC-CDR2 having an amino sequence comprising SEQ ID NO: 46, and an LC-CDR3 having an amino sequence comprising SEQ ID NO: 47;
 - (c) a heavy chain variable region comprising an HC-CDR1 having an amino sequence comprising SEQ ID NO: 48, an HC-CDR2 having an amino sequence comprising SEQ ID NO: 49, and an HC-CDR3 having an amino sequence comprising SEQ ID NO: 50; and a light chain variable region comprising an LC-CDR1 having an amino sequence comprising SEQ ID NO: 51, an LC-CDR2 having an amino sequence comprising SEQ ID NO: 52, and an LC-CDR3 having an amino sequence comprising SEQ ID NO: 53;
 - (d) a heavy chain variable region comprising an HC-CDR1 having an amino sequence comprising SEQ ID NO: 54, an HC-CDR2 having an amino sequence comprising SEQ ID NO: 55, and an HC-CDR3 having an amino sequence comprising SEQ ID NO: 56; and a light chain variable region comprising an LC-CDR1 having an amino sequence comprising SEQ ID NO: 57, an LC-CDR2 having an amino sequence comprising SEQ ID NO: 58, and an LC-CDR3 having an amino sequence comprising SEQ ID NO: 59;
 - (e) a heavy chain variable region comprising an HC-CDR1 having an amino sequence comprising SEQ ID NO: 60, an HC-CDR2 having an amino sequence comprising

SEQ ID NO: 61, and an HC-CDR3 having an amino sequence comprising SEQ ID NO: 62; and a light chain variable region comprising an LC-CDR1 having an amino sequence comprising SEQ ID NO: 63, an LC-CDR2 having an amino sequence comprising SEQ ID NO: 64, and an LC-CDR3 having an amino sequence comprising SEQ ID NO: 65;

- (f) a heavy chain variable region comprising an HC-CDR1 having an amino sequence comprising SEQ ID NO: 60, an HC-CDR2 having an amino sequence comprising SEQ ID NO: 66, and an HC-CDR3 having an amino sequence comprising SEQ ID NO: 67; and a light chain variable region comprising an LC-CDR1 having an amino sequence comprising SEQ ID NO: 63, an LC-CDR2 having an amino sequence comprising SEQ ID NO: 68, and an LC-CDR3 having an amino sequence comprising SEQ ID NO: 65;
- (g) a heavy chain variable region comprising an HC-CDR1 having an amino sequence comprising SEQ ID NO: 69, an HC-CDR2 having an amino sequence comprising SEQ ID NO: 55, and an HC-CDR3 having an amino sequence comprising SEQ ID NO: 70; and a light chain variable region comprising an LC-CDR1 having an amino sequence comprising SEQ ID NO: 71, an LC-CDR2 having an amino sequence comprising SEQ ID NO: 68, and an LC-CDR3 having an amino sequence comprising SEQ ID NO: 65;
- (h) a heavy chain variable region comprising an HC-CDR1 having an amino sequence comprising SEQ ID NO: 72, an HC-CDR2 having an amino sequence comprising SEQ ID NO: 73, and an HC-CDR3 having an amino sequence comprising SEQ ID NO: 67; and a light chain variable region comprising an LC-CDR1 having an amino sequence comprising SEQ ID NO: 63, an LC-CDR2 having an amino sequence comprising SEQ ID NO: 68, and an LC-CDR3 having an amino sequence comprising SEQ ID NO: 65; or
- (i) a heavy chain variable region comprising an HC-CDR1 having an amino sequence comprising SEQ ID NO: 74, an HC-CDR2 having an amino sequence comprising SEQ ID NO: 75, and an HC-CDR3 having an amino sequence comprising SEQ ID NO: 67; and a light chain variable region comprising an LC-CDR1 having an amino sequence comprising SEQ ID NO: 63, an LC-CDR2 having an amino sequence comprising SEQ ID NO: 68, and an LC-CDR3 having an amino sequence comprising SEQ ID NO: 65.

3. The anti-TIGIT antibody or antigen-binding fragment thereof of claim 1 or 2, comprising
- (a) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 1, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 2;
 - (b) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 3, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 4;
 - (c) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 5, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 6;
 - (d) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 7, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 8;
 - (e) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 9, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 10;
 - (f) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 11, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 12;
 - (g) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 13, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 14;
 - (h) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 15, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 16;
 - (i) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 17, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 12;
 - (j) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 76, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 77;
 - (k) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 78, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 77;

- (l) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 76, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 79; or
- (m) a heavy chain variable region having at least 80% sequence identity to SEQ ID NO: 78, and a light chain variable region having at least 80% sequence identity to SEQ ID NO: 79.
4. The anti-TIGIT antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein the anti-TIGIT antibody or antigen-binding fragment thereof is a monoclonal antibody.
 5. The anti-TIGIT antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the anti-TIGIT antibody or antigen-binding fragment thereof is a chimeric, humanized, or veneered antibody.
 6. The anti-TIGIT antibody or antigen-binding fragment thereof of claim 5, wherein the chimeric antibody comprises human IgG1/kappa Fab constant domain.
 7. The anti-TIGIT antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein the anti-TIGIT antibody or antigen-binding fragment thereof is a human antibody.
 8. The anti-TIGIT antibody or antigen-binding fragment thereof of any one of proceeding claims, wherein the anti-TIGIT antibody or antigen binding fragment thereof inhibits binding of TIGIT to CD155, optionally wherein the anti-TIGIT antibody or antigen binding fragment thereof inhibits the binding with an IC_{50} of about 0.1 nM to about 10 nM, about 0.1 nM to about 5 nM, about 0.2 nM to about 2 nM, about 0.2 nM to about 0.8 nM, about 0.4 nM to about 0.8 nM, or about 0.6 nM to about 0.8 nM, measured as in Example 1.
 9. The anti-TIGIT antibody or antigen binding fragment thereof of any one of claims 1-5 or 7-8, wherein the antibody further comprises a variant heavy chain constant region selected from variant human IgG1, variant human IgG2, variant human IgG3, or variant human IgG4, and optionally a human light chain constant region.
 10. The anti-TIGIT antibody or antigen binding fragment thereof of claim 9, wherein the variant heavy chain constant region has enhanced or decreased effector function with reference to the wild type heavy chain constant region.

11. The anti-TIGIT antibody or antigen binding fragment thereof of claim 10, wherein the variant human IgG heavy chain constant region comprises SEQ ID NO: 97, SEQ ID NO: 99, or SEQ ID NO: 101.
12. The anti-TIGIT antibody or antigen binding fragment thereof of any one of claims 1-5 or 7-8, wherein the antibody further comprises a wild-type human IgG heavy chain constant region, and optionally a human light chain constant region.
13. The anti-TIGIT antibody or antigen binding fragment thereof of claim 12, wherein the wild-type human IgG heavy chain constant region comprises SEQ ID NO: 94.
14. The anti-TIGIT antibody or antigen binding fragment thereof of claim 12 or 13 comprising a human light chain kappa constant region, optionally wherein the human light chain constant region comprises SEQ ID NO: 95.
15. The anti-TIGIT antibody or antigen binding fragment thereof of claim 1-5 or 7-8, wherein the antibody has a heavy chain and a light chain, wherein
 - (a) the heavy chain has an amino acid sequence comprising SEQ ID NO: 92, and the light chain has an amino acid sequence comprising SEQ ID NO: 93; or
 - (b) the heavy chain has an amino acid sequence comprising SEQ ID NO: 96, and the light chain has an amino acid sequence comprising SEQ ID NO: 93; or
 - (c) the heavy chain has an amino acid sequence comprising SEQ ID NO: 98, and the light chain has an amino acid sequence comprising SEQ ID NO: 93; or
 - (d) the heavy chain has an amino acid sequence comprising SEQ ID NO: 100, and the light chain has an amino acid sequence comprising SEQ ID NO: 93.
16. The anti-TIGIT antibody or antigen binding fragment thereof of any one of preceding claims, wherein the antibody or binding fragment thereof
 - (a) has an equilibrium binding constant (KD) of about 0.01×10^{-11} M to about 100×10^{-11} M, about 0.1×10^{-11} M to about 100×10^{-11} M, about 0.1×10^{-11} M to about 10×10^{-11} M, about 1×10^{-11} M to about 100×10^{-11} M or about 1×10^{-11} M to about 10×10^{-11} M, measured by surface plasmon resonance;
 - (b) blocks binding of soluble human CD155 ligand to cell surface human TIGIT with a half maximal inhibitor concentration (IC50) of about 0.2 nM to about 2 nM, about 0.2 nM to about 0.8 nM, about 0.6 nM to about 0.8 nM, or about 0.6 nM to about 0.8 nM, measured as in Example 1;
 - (c) binds to an epitope that includes at least the following residues of TIGIT:

- (i) D72 of SEQ ID NO: 80 and at least one of T55, Q56, N58, E60, S80, and K82 of SEQ ID NO: 80,
 - (ii) E60 and D72 of SEQ ID NO: 80 and optionally at least one of T55, Q56, N58, S80, and K82 of SEQ ID NO: 80,
 - (iii) D72 and K82 of SEQ ID NO: 80 and optionally at least one of T55, Q56, N58, E60, and S80 of SEQ ID NO: 80,
 - (iv) E60, D72 and K82 of SEQ ID NO: 80 and optionally at least one of T55, Q56, N58, and S80 of SEQ ID NO: 80, or
 - (v) T55, Q56, N58, E60, D72, S80, and K82 of SEQ ID NO: 80; or
 - (d) any combination of (a), (b) and (c).
17. The anti-TIGIT antibody or antigen binding fragment thereof of claim 16, wherein the antibody or antigen binding fragment thereof competes with the antibody or antigen-binding fragment thereof of any one of claims 1-17 for binding to TIGIT.
18. The anti-TIGIT antibody or antigen binding fragment thereof of claim 16 or 17, wherein an excess of the antibody or antigen-binding fragment thereof competes with a reference antibody for binding to TIGIT by at least about 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% as measured in a competitive binding assay, wherein the reference antibody comprises a heavy chain having an amino acid sequence comprising SEQ ID NO: 92 and a light chain having an amino acid sequence comprising SEQ ID NO: 93.
19. An anti-TIGIT antibody or antigen-binding fragment thereof that specifically binds to human TIGIT, comprising a heavy chain having an amino acid sequence comprising SEQ ID NO: 92 and a light chain having an amino acid sequence comprising SEQ ID NO: 93.
20. A method of inhibiting binding of TIGIT to CD155 comprising contacting TIGIT with the anti-TIGIT antibody or antigen-binding fragment thereof of any one of preceding claims.
21. A method of treating or effecting prophylaxis of cancer comprising administering to a subject having or at risk of cancer an effective regime or a therapeutically effective amount of any one of the anti-TIGIT antibodies or antigen-binding fragment thereof of any one of preceding claims.

22. The method of claim 21, wherein the cancer is a hematological malignancy, a solid tumor, Merkel cell carcinoma, urothelial cancer, head and neck squamous cell carcinoma, a B-cell lymphoma, uterine cancer, cervical cancer, testicular cancer, gastrointestinal tract cancer, bladder cancer, bone cancer, bone marrow, skin cancer, gall bladder cancer, heart cancer, lung cancer, salivary gland cancer, adrenal gland cancer, thyroid cancer, ganglia cancer, central nervous system (CNS) and peripheral nervous system (PNS) cancer, and a cancer of the hematopoietic system, a cancer of the immune system .
23. The method of claim 21 or 22, wherein the subject is administered tumor infiltrating T cells which are activated by the antibody or antigen-binding fragment thereof.
24. The method of any one of claims 21-23, wherein the subject is administered a vaccine inducing an immune response against the cancer, which is enhanced by the antibody or antigen-binding fragment thereof.
25. The method of claim 24, wherein the vaccine comprises an antigen or a fragment thereof expressed on the surface of cancer cells.
26. The method of any one of claims 21-25, wherein the subject is administered natural killer cells whose cytotoxicity against the cancer is enhanced by the antibody or antigen-binding fragment thereof.
27. The method of any one of claims 21-26, wherein the subject is further administered a second antibody against an antigen expressed on the surface of cells of cancer, whereby an effector mediated cytotoxicity of the second antibody against the cancer is enhanced by the antibody or antigen-binding fragment thereof.
28. The method of any one of claims 21-26, wherein the subject is further administered a second antibody against an antigen expressed on the surface of an immune cell.
29. The method of claim 28, wherein the immune cell is a T cell or a natural killer cell.
30. The method of claim 27 or 28, wherein the antigen is CTLA-4, PD-1 or PD-L1.
31. The method of any one of claims 21-30, wherein the subject is further administered one or more therapies selected from the group consisting of chemotherapy, radiation, cell-based therapy, and surgery.
32. The method of any one of claims 21-31, wherein the subject is further administered an inhibitor of one or more immune-checkpoint receptors or ligands.

33. The method of claim 30, wherein the one or more immune-checkpoint receptors or ligands are selected from the group consisting of CTLA-4, PD-1, PD-L1, TIM-3, LAG-3, PVRIG, BTLA, VISTA, CD96, A_{2a}R, A_{2b}R, A_{2a}/A_{2b}R, arginase, CD39, CD73, IDO and TDO.
34. The method of claim 32, wherein the inhibitor is selected from the group consisting of ipilimumab, tremelimumab, nivolumab, pembrolizumab, lambrolizumab, cemiplimab, tislelizumab, zimberelimab, durvalumab, and atezolizumab.
35. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-19 and a pharmaceutically acceptable carrier.
36. An anti-TIGIT antibody or antigen binding fragment thereof that binds to an epitope of human TIGIT comprising at least one of the following amino acid residues of SEQ ID NO 80: T55, Q56, N58, E60, D72, S80, and K82.
37. The anti-TIGIT antibody or antigen-binding fragment thereof of claim 36, wherein the antibody or antigen-binding fragment thereof binds to an epitope that includes at least the following residues of TIGIT:
- (i) D72 of SEQ ID NO: 80 and at least one of T55, Q56, N58, E60, S80, and K82 of SEQ ID NO: 80;
 - (ii) E60 and D72 of SEQ ID NO: 80 and optionally at least one of T55, Q56, N58, S80, and K82 of SEQ ID NO: 80;
 - (iii) D72 and K82 of SEQ ID NO: 80 and optionally at least one of T55, Q56, N58, E60, and S80 of SEQ ID NO: 80;
 - (iv) E60, D72 and K82 of SEQ ID NO: 80 and optionally at least one of T55, Q56, N58, and S80 of SEQ ID NO: 80; or
 - (v) T55, Q56, N58, E60, D72, S80, and K82 of SEQ ID NO: 80.
38. The anti-TIGIT antibody or antigen-binding fragment thereof of claim 36 or 37, wherein the antibody or antigen-binding fragment thereof competes with the antibody or antigen-binding fragment thereof of any one of claims 1-19 for binding to TIGIT.
39. The anti-TIGIT antibody or antigen-binding fragment thereof of claim 36 or 37, wherein an excess of the antibody or antigen-binding fragment thereof competes with a reference antibody for binding to TIGIT by at least about 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% as measured in a competitive binding

assay, wherein the reference antibody comprises a heavy chain having an amino acid sequence comprising SEQ ID NO: 92 and a light chain having an amino acid sequence comprising SEQ ID NO: 93.

40. An anti-TIGIT antibody or antigen binding fragment thereof of any one of claims 1-19, wherein the antibody or antigen binding fragment thereof binds to an epitope of human TIGIT comprising at least one of the following amino acid residues of SEQ ID NO 80: T55, Q56, N58, E60, D72, S80, and K82.