

WHAT IS CLAIMED IS:

1. A bispecific binding protein that specifically binds to PD-1 and TIGIT comprising:
 - a) a first binding domain that specifically binds to PD-1, wherein the first binding domain comprises a heavy chain variable domain comprising a HCDR1 having the amino acid sequence of SEQ ID NO: 1, a HCDR2 having the amino acid sequence of SEQ ID NO: 2, and a HCDR3 having the amino acid sequence of SEQ ID NO: 3, and a light chain variable domain comprising a LCDR1 having the amino acid sequence of SEQ ID NO: 4, a LCDR2 having the amino acid sequence of SEQ ID NO: 5 and a LCDR3 having the amino acid sequence of SEQ ID NO: 6; and
 - b) a second binding domain that specifically binds to TIGIT, wherein the second binding domain comprises a heavy chain variable domain comprising a HCDR1 having the amino acid sequence of SEQ ID NO: 11, a HCDR2 having the amino acid sequence of SEQ ID NO: 12, and a HCDR3 having the amino acid sequence of SEQ ID NO: 13, and a light chain variable domain comprising a LCDR1 having the amino acid sequence of SEQ ID NO: 14, a LCDR2 having the amino acid sequence of SEQ ID NO: 15, and a LCDR3 having the amino acid sequence of SEQ ID NO: 16.
2. The bispecific binding protein of claim 1, wherein the first binding domain that specifically binds to PD-1 comprises a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 7 and a light chain variable domain having the amino acid sequence of SEQ ID NO: 9.
3. The bispecific binding protein of claim 1, wherein first binding domain that specifically binds to PD-1 comprises a heavy chain variable domain having an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 7 and a light chain variable domain having an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 9.

4. The bispecific binding protein of any one of claims 1-3, wherein the first binding domain that specifically binds to PD-1 comprises a heavy chain having the amino acid sequence of SEQ ID NO: 8 and a light chain having the amino acid sequence of SEQ ID NO: 10.
5. The bispecific binding protein of any one of claims 1-3, wherein first binding domain that specifically binds to PD-1 comprises a heavy chain having an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 8 and a light chain having an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 10.
6. The bispecific binding protein of any one of claims 1-5, wherein the second binding domain that specifically binds TIGIT comprises a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 17 and a light chain variable domain having the amino acid sequence of SEQ ID NO: 19.
7. The bispecific binding protein of any one of claims 1-5, wherein the second binding domain that specifically binds to TIGIT comprises a heavy chain variable domain having an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 17 and a light chain variable domain having an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 19.
8. The bispecific binding protein of any one of claims 1-7, wherein the second binding domain that specifically binds to TIGIT comprises a heavy chain having the amino sequence of SEQ ID NO: 18 and a light chain having the amino acid sequence of SEQ ID NO: 20.
9. The bispecific binding protein of any one of claims 1-7, wherein the second binding domain that specifically binds to TIGIT comprises a heavy chain having an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 18 and a light chain having an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 20.

10. The bispecific binding protein of claim 4, wherein the light chain constant region is a kappa chain.
11. The bispecific binding protein of claim 8, wherein the light chain constant region is a lambda chain.
12. The bispecific binding protein of any one of claims 1-11, wherein the binding protein is an antibody.
13. The bispecific binding protein of claim 12, wherein the antibody is an IgG antibody.
14. The bispecific binding protein of claim 13, wherein the antibody is an IgG1 antibody.
15. The bispecific binding protein of either claim 13 or 14, wherein the antibody is human or humanized.
16. The bispecific binding protein of any one of claims 1-15, wherein the equilibrium dissociation constant (K_D) of the bispecific binding protein – human TIGIT interaction is less than or equal to 15 pM.
17. The bispecific binding protein of any one of claims 1-15, wherein the equilibrium dissociation constant (K_D) of the bispecific binding protein – human TIGIT interaction is less than or equal to 9 pM.
18. The bispecific binding protein of any one of claims 1-14, wherein the equilibrium dissociation constant (K_D) of the bispecific binding protein – human TIGIT interaction is from 9 pM to 15 pM.
19. The bispecific binding protein of any one of claims 1-18, wherein the equilibrium dissociation constant (K_D) of the bispecific binding protein – human PD-1 interaction is less than or equal to 0.4 nM.

20. The bispecific binding protein of any one of claims 1-19, wherein the equilibrium dissociation constant (K_D) of the bispecific binding protein – human PD-1 interaction is from 0.3 nM to 0.5 nM.
21. The bispecific binding protein of any one of claims 1-20, comprising a variant Fc region.
22. The bispecific binding protein of claim 21, wherein the bispecific binding protein does not trigger complement dependent cytotoxicity in vivo.
23. The bispecific binding protein of claim 21, wherein the bispecific binding protein has reduced complement dependent cytotoxicity compared to a bispecific binding protein having a wild type Fc region.
24. The bispecific binding protein of claim 21, wherein the bispecific binding protein does not trigger antibody dependent cellular cytotoxicity in vivo.
25. The bispecific binding protein of claim 21, wherein the bispecific binding protein has reduced antibody dependent cellular cytotoxicity compared to a bispecific binding protein having a wild type Fc region.
26. The bispecific binding protein of claim 21, wherein the variant Fc region comprises at least one substitution selected from 221K, 221Y, 225E, 225K, 225W, 228P, 234D, 234E, 234N, 234Q, 234T, 234H, 234Y, 234I, 234V, 234F, 235A, 235D, 235R, 235W, 235P, 235S, 235N, 235Q, 235T, 235H, 235Y, 235I, 235V, 235E, 235F, 236E, 237L, 237M, 237P, 239D, 239E, 239N, 239Q, 239F, 239T, 239H, 239Y, 240I, 240A, 240T, 240M, 241W, 241L, 241Y, 241E, 241R, 243W, 243L, 243Y, 243R, 243Q, 244H, 245A, 247L, 247V, 247G, 250E, 250Q, 251F, 252L, 252Y, 254S, 254T, 255L, 256E, 256F, 256M, 257C, 257M, 257N, 262I, 262A, 262T, 262E, 263I, 263A, 263T, 263M, 264L, 264I, 264W, 264T, 264R, 264F, 264M, 264Y, 264E, 265A, 265G, 265N, 265Q, 265Y, 265F, 265V, 265I, 265L, 265H, 265T, 266I, 266A, 266T, 266M, 267Q, 267L, 268E, 269H, 269Y, 269F, 269R, 270E, 280A, 284M, 292P, 292L, 296E, 296Q, 296D, 296N, 296S, 296T, 296L, 296I, 296H, 296G, 297S, 297D, 297E, 298A, 298H,

298I, 298T, 298F, 299I, 299L, 299A, 299S, 299V, 299H, 299F, 299E, 305I, 308F, 313F, 316D, 318A, 318S, 320A, 320S, 322A, 322S, 325Q, 325L, 325I, 325D, 325E, 325A, 325T, 325V, 325H, 326A, 326D, 326E, 326G, 326M, 326V, 327G, 327W, 327N, 327L, 328S, 328M, 328D, 328E, 328N, 328Q, 328F, 328I, 328V, 328T, 328H, 328A, 329F, 329H, 329Q, 330K, 330G, 330T, 330C, 330L, 330Y, 330V, 330I, 330F, 330R, 330H, 331G, 331A, 331L, 331M, 331F, 331W, 331K, 331Q, 331E, 331S, 331V, 331I, 331C, 331Y, 331H, 331R, 331N, 331D, 331T, 332D, 332S, 332W, 332F, 332E, 332N, 332Q, 332T, 332H, 332Y, 332A, 333A, 333D, 333G, 333Q, 333S, 333V, 334A, 334E, 334H, 334L, 334M, 334Q, 334V, 334Y, 339T, 370E, 370N, 378D, 392T, 396L, 416G, 419H, 421K, 428L, 428F, 433K, 433L, 434A, 434W, 434Y, 436H, 440Y and 443W as numbered by the EU index as set forth in Kabat.

27. The bispecific binding protein of claim 21, wherein the variant Fc region comprises one or more amino acid substitutions at positions selected from 428 and 434 as numbered by the EU index as set forth in Kabat.

28. The bispecific binding protein of any one of claims 21-27, wherein the variant Fc region comprises one or more amino acid substitutions selected from 428L, 428F, 434A, 434W, and 434Y.

29. The bispecific binding protein of any one of claims 21-28, wherein the variant Fc region comprises a YTE mutation.

30. The bispecific binding protein of any one of claims 21-29, wherein the Fc variant region has an increased binding affinity for FcRn.

31. The bispecific binding protein of any one of claims 21-30, wherein the Fc variant region comprises a L234F/L235E/P331S triple mutation (TM).

32. The bispecific binding protein of any one of claims 12-31 comprising an Fc region, wherein the Fc region is aglycosylated.

33. The bispecific binding protein of any one of claims 12-31 comprising an Fc region, wherein the Fc region is deglycosylated.
34. The bispecific binding protein of any one of claims 12-31 comprising an Fc region, wherein the Fc region has reduced fucosylation or is afucosylated.
35. A pharmaceutical composition comprising bispecific binding protein of any one of claims 1-34 and a pharmaceutically acceptable carrier.
36. The pharmaceutical composition of claim 35, further comprising an anti-cancer compound selected from pemetrexed, carboplatin, gemcitabine, cisplatin, paclitaxel or combinations thereof.
37. A nucleic acid comprising a nucleotide sequence encoding the bispecific binding protein of any one of claims 1-34.
38. The nucleic acid of claim 37, wherein the nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO:21, a sequence at least 95% identical to SEQ ID NO:23, a sequence at least 95% identical to SEQ ID NO:25, and/or a sequence at least 95% identical to SEQ ID NO:27.
39. The nucleic acid of claim 37, wherein the nucleic acid sequence comprises SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, and/or SEQ ID NO:27.
40. The nucleic acid of claim 37, wherein the nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO:22, a sequence at least 95% identical to SEQ ID NO:24, a sequence at least 95% identical to SEQ ID NO:26, and/or a sequence at least 95% identical to SEQ ID NO:28.
41. The nucleic acid of claim 37, wherein the nucleic acid sequence comprises SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, and/or SEQ ID NO:28.

42. A vector comprising the nucleic acid of any one of claims 37-41.
43. A host cell comprising the vector of claim 42.
44. A host cell comprising a vector comprising a nucleic acid sequence at least 95% identical to SEQ ID NO:21, a nucleic acid sequence at least 95% identical to SEQ ID NO:23, a nucleic acid sequence at least 95% identical to SEQ ID NO:25, and a nucleic acid sequence at least 95% identical to SEQ ID NO:27.
45. A host cell according to claim 44, comprising a vector comprising a nucleic acid sequence at least 95% identical to SEQ ID NO:22, a nucleic acid sequence at least 95% identical to SEQ ID NO:24, a nucleic acid sequence at least 95% identical to SEQ ID NO:26, and a nucleic acid sequence at least 95% identical to SEQ ID NO:28.
46. A bispecific antibody expressed by the host cell of any one of claims 43-45.
47. The bispecific binding protein of any one of claims 1-34, the pharmaceutical composition of claims 35 or 36, or the nucleic acid of any one of claims 37-41 for use in treating a subject having a tumor.
48. The bispecific binding protein of any one of claims 1-34, the pharmaceutical composition of claims 35 or 36, or the nucleic acid of any one of claims 37-41 for use in treating cancer in a subject.
49. The bispecific binding protein for use, the pharmaceutical composition for use, or the nucleic acid for use of claim 48, wherein the cancer is one or more of ovarian cancer, breast cancer, colorectal cancer, prostate cancer, cervical cancer, uterine cancer, testicular cancer, bladder cancer, head and neck cancer, melanoma, pancreatic cancer, renal cell carcinoma, and lung cancer.

50. The bispecific binding protein for use, the pharmaceutical composition for use, or the nucleic acid for use of claim 48 or claim 49, wherein the cancer is non-small cell lung cancer (NSCLC).
51. The bispecific binding protein for use, the pharmaceutical composition for use, or the nucleic acid for use of claim 50, wherein the NSCLC is advanced or metastatic.
52. The bispecific binding protein of any one of claims 1-34, the pharmaceutical composition of claims 35 or 36, or the nucleic acid of any one of claims 37 -41 for use in enhancing an immune response in a subject.
53. A bispecific binding protein as defined in any one of claims 1-34 for use in therapy.
54. A bispecific binding protein as defined in any one of claims 1-34 for use in the treatment of cancer.
55. The use of a bispecific binding protein as defined in any one of claims 1-34 in the manufacture of a medicament for the treatment of cancer.
56. A nucleic acid as defined in any one of claims 37-41 for use in therapy.
57. A nucleic acid as defined in any one of claims 37-41 for use in the treatment of cancer.
58. The use of a nucleic acid as defined in any one of claims 37-41 in the manufacture of a medicament for the treatment of cancer.
59. The bispecific binding protein of any one of claims 1-34, the pharmaceutical composition of claims 35 or 36, or the nucleic acid of any one of claims 37-41 for use in treating a subject having a tumor, wherein a therapeutically effective amount of the bispecific binding protein, the pharmaceutical composition, or the nucleic acid is to be administered to the subject in

combination with an anti-cancer compound selected from pemetrexed, carboplatin, gemcitabine, cisplatin, paclitaxel or combinations thereof.

60. The bispecific binding protein of any one of claims 1-34, the pharmaceutical composition of claims 35 or 36, or the nucleic acid of any one of claims 37 -41 for use in combination with an anti-cancer compound selected from pemetrexed, carboplatin, gemcitabine, cisplatin, paclitaxel or combinations thereof for treating cancer in a subject.