

## WHAT IS CLAIMED:

1. A TIM-3 binding protein comprising a TIM-3 binding domain, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the immunoglobulin variable (IgV) domain of TIM-3, for use in altering engagement between T-cell immunoglobulin and mucin domain containing protein-3 (TIM-3) and phosphatidylserine (PS) in a subject, wherein the TIM-3 binding protein is to be administered to the subject.

2. Use of a TIM-3 binding protein comprising a TIM-3 binding domain, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the immunoglobulin variable (IgV) domain of TIM-3, in the manufacture of a medicament for altering engagement between T-cell immunoglobulin and mucin domain containing protein-3 (TIM-3) and phosphatidylserine (PS) in a subject, wherein the TIM-3 binding protein is to be administered to the subject.

3. The TIM-3 binding protein for use of claim 1 or the use of claim 2, wherein administration of the TIM-3 binding protein increases anti-tumor activity in a subject relative to no antibody administration.

4. The TIM-3 binding protein for use of claim 1 or the use of claim 2, wherein administration of the TIM-3 binding protein increases anti-tumor activity in a subject relative to administration of a TIM-3 binding protein that binds to the PS binding cleft (FG and CC' loops) of the IgV domain of TIM-3.

5. A TIM-3 binding protein comprising TIM-3 binding domain, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the IgV domain of TIM-3, for use in increasing T cell mediated anti-tumor activity in a subject, wherein the TIM-3 binding protein is to be administered to the subject.

6. Use of a TIM-3 binding protein comprising TIM-3 binding domain, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the IgV domain of TIM-3, in the manufacture of a medicament for increasing T cell mediated anti-tumor activity in a subject, wherein the TIM-3 binding protein is to be administered to the subject.

7. The TIM-3 binding protein for use of claim 5 or the use of claim 6, wherein the T cell mediated anti-tumor activity in the subject is increased relative to no antibody administration.

8. The TIM-3 binding protein for use of claim 5 or the use of claim 6, wherein the T cell mediated anti-tumor activity in the subject is increased relative to administration of a TIM-3 binding protein that binds to the PS binding cleft (FG and CC' loops) of the IgV domain of TIM-3.

9. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7 and 8 or the use of any one of claims 2-4 and 6-8, wherein administration of the TIM-3 binding protein increases dendritic cell phagocytosis of apoptotic tumor cells in a subject relative to no antibody administration.

10. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7 and 8 or the use of any one of claims 2-4 and 6-8, wherein administration of the TIM-3 binding protein increases dendritic cell phagocytosis of apoptotic tumor cells in a subject relative to administration of a TIM-3 binding protein that binds to the PS binding cleft (FG and CC' loops) of the IgV domain of TIM-3.

11. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-10 or the use of any one of claims 2-4 and 6-10, wherein administration of the TIM-3 binding protein increases dendritic cell cross-presentation of tumoral antigen in a subject relative to no antibody administration.

12. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-10 or the use of any one of claims 2-4 and 6-10, wherein administration of the TIM-3 binding protein increases dendritic cell cross-presentation of tumoral antigen in a subject relative to administration of a TIM-3 binding protein that binds to the PS binding cleft (FG and CC' loops) of the IgV domain of TIM-3.

13. A TIM-3 binding protein comprising a TIM-3 binding domain, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the IgV domain of TIM-3, for use in promoting dendritic cell phagocytosis of tumor cells in a subject, wherein the TIM-3 binding protein is to be administered to the subject.

14. Use of a TIM-3 binding protein comprising a TIM-3 binding domain, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the IgV domain of TIM-3, in the manufacture of a medicament for promoting dendritic cell phagocytosis of tumor cells in a subject, wherein the TIM-3 binding protein is to be administered to the subject.

15. A TIM-3 binding protein comprising a TIM-3 binding domain, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the IgV domain of TIM-3, for use in increasing dendritic cell cross-presentation of tumor antigens in a subject, wherein the TIM-3 binding protein is to be administered to the subject.

16. Use of a TIM-3 binding protein comprising a TIM-3 binding domain, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the IgV domain of TIM-3, in the manufacture of a medicament for increasing dendritic cell cross-presentation of tumor antigens in a subject, wherein the TIM-3 binding protein is to be administered to the subject.

17. The TIM-3 binding protein for use of claim 15 or the use of claim 16, wherein the level of dendritic cell cross-presentation is increased relative to no antibody administration.

18. The TIM-3 binding protein for use of claim 15 or the use of claim 16, wherein the level of dendritic cell cross-presentation is increased relative to administration of a TIM-3 binding protein that binds to the PS binding cleft (FG and CC' loops) of the IgV domain of TIM-3.

19. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-18 or the use of any one of claims 2-4 and 6-12, 14 and 16-18, wherein administration of the TIM-3 binding protein increases IL-2 secretion upon engagement to TIM-3 positive T cells in a subject relative to no antibody administration.

20. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-18 or the use of any one of claims 2-4 and 6-12, 14 and 16-18, wherein administration of the TIM-3 binding protein increases IL-2 secretion upon engagement to TIM-3 positive T cells in a subject relative to administration of a TIM-3 binding protein that binds to the PS binding cleft (FG and CC' loops) of the IgV domain of TIM-3.

21. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-20 or the use of any one of claims 2-4 and 6-12, 14 and 16-20, wherein administration of the TIM-3 binding protein results in inhibition of tumor growth in the subject.

22. The TIM-3 binding protein for use or the use of claim 21, wherein the tumor is an advanced or metastatic solid tumor.

23. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-22 or the use of any one of claims 2-4 and 6-12, 14 and 16-22, wherein the subject has 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, lung cancer, esophageal cancer, gastric cancer, biliary tract tumors, urothelial carcinoma, Hodgkin lymphoma, non-hodgkin lymphoma, myelodysplastic syndrome, and acute myeloid leukemia.

24. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-23 or the use of any one of claims 2-4 and 6-12, 14 and 16-23, wherein the subject has immunology (IO) acquired resistance.

25. A TIM-3 binding protein comprising a TIM-3 binding domain, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the IgV domain of TIM-3, for use in treating a cancer in a subject with IO acquired resistance, wherein the TIM-3 binding protein is to be administered to the subject.

26. Use of a TIM-3 binding protein comprising a TIM-3 binding domain, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the IgV domain of TIM-3, in the manufacture of a medicament for treating a cancer in a subject with IO acquired resistance, wherein the TIM-3 binding protein is to be administered to the subject.

27. The TIM-3 binding protein for use of claim 25 or the use of claim 26, 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, lung cancer, esophageal cancer, gastric cancer, biliary tract tumors, urothelial carcinoma, Hodgkin lymphoma, non-hodgkin lymphoma, myelodysplastic syndrome, and acute myeloid leukemia.

28. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-25 and 27 or the use of any one of claims 2-4 and 6-12, 14 and 16-24 and 26-27, wherein the subject is a human.

29. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-25 and 27-28 or the use of any one of claims 2-4 and 6-12, 14 and 16-24 and 26-28, wherein the subject has documented Stage III which is not amenable to curative surgery or radiation, or Stage IV non-small cell lung carcinoma (NSCLC).

30. The TIM-3 binding protein for use or the use of claim 29, wherein the NSCLC is squamous or non-squamous NSCLC.

31. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, 17-25, 27-30, 50 and 52 or the use of any one of claims 2-4 and 6-12, 14 and 16-24 and 26-30, 51 and 53, wherein the subject has a radiologically documented tumor progression or clinical deterioration following initial treatment with an anti-PD-1/PD-L1 therapy for a minimum of 3-6 months, as monotherapy or in combination with chemotherapy, and had signs of initial clinical benefit, i.e. disease stabilization or regression.

32. The TIM-3 binding protein for use of any one of claims 24-25, 27-31, 50 and 52 or the use of any one of claims 24 and 26-31, 51 and 53, wherein the IO acquired resistance is defined as:

(i) Exposure of less than 6 months to anti-PD-1/PD-L1 monotherapy with initial best overall response (BOR) of partial regression or complete regression followed by disease progression during treatment or disease progression less than or equal to 12 weeks after anti-PD-1/PD-L1 treatment discontinuation; or

(ii) Exposure of greater than or equal to 6 months to anti-PD-1/PD-L1 therapy alone or in combination with chemotherapy with BOR of disease stabilization, partial regression, or complete regression followed by disease progression during treatment or disease progression less than or equal to 12 weeks after anti-PD-1/PD-L1 treatment discontinuation.

33. The TIM-3 binding protein for use of any one of claims 24-25, 27-32, 50 and 52 or the use of any one of claims 24, 26-32, 51 and 53, wherein the IO acquired resistance is

defined as exposure of greater than or equal to 6 months to anti-PD-1/PD-L1 therapy alone or in combination with chemotherapy; a best overall response (BOR) of disease stabilization, partial regression, or complete regression followed by disease progression during treatment or disease progression less than or equal to 12 weeks after anti-PD-1/PD-L1 treatment discontinuation.

34. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-25 and 27-33 or the use of any one of claims 2-4 and 6-12, 14 and 16-24 and 26-33, wherein the subject's PD-L1 tumor proportion score (TPS) is greater than or equal to 1%.

35. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-25 and 27-34 or the use of any one of claims 2-4 and 6-12, 14 and 16-24 and 26-34, wherein the subject has not received prior systemic therapy in a first-line setting.

36. The TIM-3 binding protein for use or the use of 35, wherein the prior systemic therapy is an IO therapy other than an anti-PD-1/PD-L1 therapy.

37. The TIM-3 binding protein for use or the use of claim 35, wherein the subject received prior neo/adjuvant therapy but did not progress for at least 12 months following the last administration of an anti-PD-1/PD-L1 therapy.

38. The TIM-3 binding protein for use or the use of claim 37, wherein the subject's PD-L1 TPS is greater than or equal to 50%.

39. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-25 and 27-38 or the use of any one of claims 2-4 and 6-12, 14 and 16-24 and 26-38, wherein the TIM-3 binding protein comprises Complementarity-Determining Regions (CDRs): HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1, 2, 3, 7, 8, and 9, respectively, or SEQ ID NOs: 1, 2, 3, 7, 8, and 13, respectively.

40. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-25 and 27-39 or the use of any one of claims 2-4 and 6-12, 14 and 16-24 and 26-39, wherein the TIM-3 binding domain specifically binds to epitopes on the IgV domain of TIM-3 and the epitopes comprises N12, L47, R52, D53, V54, N55, Y56, W57, W62, L63, N64, G65, D66, F67, R68, K69, D71, T75, and E77 of TIM-3 (SEQ ID NO: 29).

41. The TIM-3 binding protein for use of any one of claims 1, 3-5, 7-13, 15, and 17-25 and 27-40 or the use of any one of claims 2-4 and 6-12, 14 and 16-24 and 26-40, wherein the TIM-3 binding protein further comprises a Programmed cell death protein 1 (PD-1) binding domain.

42. The TIM-3 binding protein for use or the use of claim 41, the TIM-3 binding domain comprises a first set of Complementarity-Determining Regions (CDRs): HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1, 2, 3, 7, 8, and 9 or 1, 2, 3, 7, 8, and 13, respectively; and

the PD-1 binding domain comprises a second set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 4, 5, 6, 10, 11, and 12, respectively.

43. The TIM-3 binding protein for use or the use of claim 42, wherein the TIM-3 binding protein comprises a first heavy chain variable domain (VH) comprising the amino acid sequence of SEQ ID NO: 14, a first light chain variable domain (VL) comprising the amino acid sequence of SEQ ID NO: 17, a second heavy chain VH comprising the amino acid sequence of SEQ ID NO: 19, and a second light chain VL comprising the amino acid sequence of SEQ ID NO: 21.

44. The TIM-3 binding protein for use or the use of claim 42, wherein the TIM-3 binding protein comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 15, a first light chain comprising the amino acid sequence of SEQ ID NO: 18, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 20, and a second light chain comprising the amino acid sequence of SEQ ID NO: 22.

45. The TIM-3 binding protein for use or the use of claim 42, wherein the TIM-3 binding protein comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 23, a first light chain comprising the amino acid sequence of SEQ ID NO: 24, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 23, and a second light chain comprising the amino acid sequence of SEQ ID NO: 24.

46. The TIM-3 binding protein for use or the use of claim 42, wherein the TIM-3 binding protein comprises a first heavy chain comprising the amino acid sequence of SEQ ID

NO: 25, a first light chain comprising the amino acid sequence of SEQ ID NO: 26, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 25, and a second light chain comprising the amino acid sequence of SEQ ID NO: 26.

47. The TIM-3 binding protein for use or the use of any one of claims 29-31, wherein the TIM-3 binding protein comprises an aglycosylated Fc region.

48. The TIM-3 binding protein for use or the use of any one of claims 29-31, wherein the TIM-3 binding protein comprises a deglycosylated Fc region.

49. The TIM-3 binding protein for use or the use of any one of claims 29-33, wherein the TIM-3 binding protein comprises an Fc region which has reduced fucosylation or is afucosylated.

50. A bispecific binding protein comprising a PD-1 binding domain and a TIM-3 binding domain for use in treating NSCLC in a subject having advanced or metastatic NSCLC, wherein the bispecific binding protein is to be administered to the subject,

wherein the bispecific binding protein comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 15, a first light chain comprising the amino acid sequence of SEQ ID NO: 18, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 20, and a second light chain comprising the amino acid sequence of SEQ ID NO: 22,

and wherein the subject has IO acquired resistance.

51. Use of a bispecific binding protein comprising a PD-1 binding domain and a TIM-3 binding domain in the manufacture of a medicament for treating NSCLC in a subject having advanced or metastatic NSCLC, wherein the bispecific binding protein is to be administered to the subject,

wherein the bispecific binding protein comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 15, a first light chain comprising the amino acid sequence of SEQ ID NO: 18, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 20, and a second light chain comprising the amino acid sequence of SEQ ID NO: 22,

and wherein the subject has IO acquired resistance.

52. A bispecific binding protein comprising a PD-1 binding domain and a TIM-3 binding domain, for use in inhibiting growth of a non-small cell lung tumor in a subject having an advanced or metastatic tumor, wherein the bispecific binding protein is to be administered to the subject,

wherein the bispecific binding protein comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 15, a first light chain comprising the amino acid sequence of SEQ ID NO: 18, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 20, and a second light chain comprising the amino acid sequence of SEQ ID NO: 22,

and wherein the subject has IO acquired resistance.

53. Use of a bispecific binding protein comprising a PD-1 binding domain and a TIM-3 binding domain, in the manufacture of a medicament for inhibiting growth of a non-small cell lung tumor in a subject having an advanced or metastatic tumor, wherein the bispecific binding protein is to be administered to the subject,

wherein the bispecific binding protein comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 15, a first light chain comprising the amino acid sequence of SEQ ID NO: 18, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 20, and a second light chain comprising the amino acid sequence of SEQ ID NO: 22,

and wherein the subject has IO acquired resistance.

54. The bispecific binding protein for use of claim 50 or 52 or the use of claim 51 or 53, wherein the TIM-3 binding domain specifically binds to the C'C'' and DE loops of the IgV domain of TIM-3.

55. The bispecific binding protein for use of claim 50 or 52 or the use of claim 51 or 53, wherein the TIM-3 binding domain specifically binds to epitopes on the IgV domain of TIM-3 and the epitopes comprises N12, L47, R52, D53, V54, N55, Y56, W57, W62, L63, N64, G65, D66, F67, R68, K69, D71, T75, and E77 of TIM-3 (SEQ ID NO: 29).

56. The bispecific binding protein for use of any one of claims 50, 52 and 54-55 or the use of claims 51 and 53-55, wherein the NSCLC is squamous or non-squamous NSCLC.