

CLAIMS:

1. Use of a NRP-1 inhibitor in the manufacture of a medicament for increasing the amount of tumor infiltrating CD8+ T cells in a patient suffering from cancer.
- 5 2. The use of claim 1 wherein the NRP-1 inhibitor is an antibody having binding affinity for NRP-1, in particular an antibody which binds to the domain c of NRP-1, an antibody having binding affinity for the region of NRP-1 which binds to Semaphorin 3A or an antibody having binding affinity for the amino acid sequence ranging from the amino acid residue at position 1 to the amino acid residue at position 280 in SEQ ID NO:1.
- 10 3. The use of claim 2 wherein the antibody does not inhibit the binding of VEGF to NRP-1.
4. The use of claim 2 wherein the anti-NRP-1 antibody comprises:
 - a light chain variable domain comprising the following Complementary Determining Region (CDR) amino acid sequences: VL-CDR1 (RASQSISSYLA; SEQ ID NO:3), VL-CDR2 (GASSRAS; SEQ ID NO:4) and VL-CDR3 (QQYMSVPIT; SEQ ID NO:5) and
 - 15 - a heavy chain variable domain comprising the following CDR amino acid sequences: VH-CDR1 (GFSFSSEPIS; SEQ ID NO:6), VH-CDR2 (SSITGKNGYTTYADSVKG; SEQ ID NO:7) and VH-CDR3 (WGKKVYGMDV; SEQ ID NO: 8).
- 20 5. The use of claim 2 wherein the anti-NRP-1 antibody comprises the light chain variable domain sequence of SEQ ID NO:9 and/or the heavy chain variable domain sequence of SEQ ID NO:10.
6. The use of claim 2 wherein the anti-NRP-1 antibody cross-competes for binding to the NRP-1 isoform with the antibody that comprises:
 - 25 - a light chain variable domain comprising the following Complementary Determining Region (CDR) amino acid sequences: VL-CDR1 (RASQSISSYLA; SEQ ID NO:3), VL-CDR2 (GASSRAS; SEQ ID NO:4) and VL-CDR3 (QQYMSVPIT; SEQ ID NO:5) and

- a heavy chain variable domain comprising the following CDR amino acid sequences: VH-CDR1 (GFSFSSEPIS; SEQ ID NO:6), VH-CDR2 (SSITGKNGYTTYADSVKG; SEQ ID NO:7) and VH-CDR3 (WGKKVYGMDV; SEQ ID NO: 8).

- 5 7. The use of claim 1 wherein the NRP-1 inhibitor consists of a polypeptide which comprises the domain c of NRP-1; a polypeptide which comprises the transmembrane domain of NRP-1 or a polypeptide which comprises the amino acid sequence which ranges from the amino acid residue at position 1 to the amino acid residue at position 280 in SEQ ID NO:1.
- 10 8. The use of claim 1 wherein the NRP-1 inhibitor is an inhibitor of NRP-1 expression.
9. Use of a NRP-1 inhibitor in the manufacture of a medicament for treating cancer in a patient in need thereof.
10. The use of claim 9 comprising i) quantifying the density of CD8+ T cells in a tumor tissue sample obtained from the patient ii) comparing the density quantified at step i) with a predetermined reference value and iii) administering to the patient a therapeutically effective amount of a NRP-1 inhibitor.
- 15 11. Use of a NRP-1 inhibitor in the manufacture of a medicament for enhancing the potency of an immune checkpoint inhibitor administered to a patient as part of a treatment regimen, wherein a pharmaceutically effective amount of the NRP-1 inhibitor is used in combination with the immune checkpoint inhibitor.
- 20 12. Use of a combination of an immune checkpoint inhibitor with a NRP-1 inhibitor in the manufacture of a medicament for treating cancer in a patient in need thereof, wherein administration of the combination results in enhanced therapeutic efficacy relative to the administration of the immune checkpoint inhibitor alone.
- 25 13. The use of claim 12 wherein the immune checkpoint inhibitor is an antibody selected from the group consisting of anti-CTLA4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-PD-L2 antibodies anti-TIM-3 antibodies, anti-LAG3 antibodies, anti-B7H3 antibodies, anti-B7H4 antibodies, anti-BTLA antibodies, and anti-B7H6 antibodies.

14. The use of claim 13 wherein the anti-PD-1 antibody is nivolumab or pembrolizumab.
15. Use of a multispecific antibody comprising at least one binding site that specifically binds to PD-1, and at least one binding site that specifically binds to NRP-1 in the manufacture of a medicament for treating cancer in a patient in need thereof.
- 5 16. The use of claim 15 wherein the multispecific antibody is a bispecific antibody.
17. Use of a NRP-1 inhibitor in the manufacture of a medicament for treating cancer in combination with a cancer vaccine in a patient in need thereof.
18. An ex vivo method of predicting whether a patient suffering from cancer will achieve a response with an immune checkpoint inhibitor comprising i) determining the expression
10 level of NRP-1 or Semaphorin 3A in a tumor sample from the patient and ii) comparing the expression level determined at step i) with a predetermined reference value and iii) concluding that the patient will achieve a response with the immune checkpoint inhibitor when the expression level determine at step i) is lower than the predetermined reference value or concluding that the patient will not achieve a response with the
15 immune checkpoint inhibitor when the expression level determined at step i) is higher than the predetermined reference value.
19. The method of claim 18 which further comprises determining the expression level of CD8.
20. Use of an immune checkpoint inhibitor in the manufacture of a medicament for treating
20 cancer in a patient in need thereof, comprising i) determining the expression level of NRP-1 or Semaphorin 3A in a tumor tissue sample obtained from the patient, ii) comparing the expression level determined at step i) with a predetermined reference value and iii) administering to the patient an immune checkpoint inhibitor when the expression level determined at step i) is lower than the predetermined reference level.
- 25 21. A multispecific antibody comprising at least one binding site that specifically binds to PD-1, and at least one binding site that specifically binds to NRP-1.
22. The multispecific antibody of claim 21 which a bispecific antibody.

23. The multispecific antibody of claim 21 comprising a first binding site that specifically binds to NRP-1 that comprises a light chain variable domain comprising the following Complementary Determining Region (CDR) amino acid sequences: VL-CDR1 (RASQSISSYLA; SEQ ID NO:3), VL-CDR2 (GASSRAS; SEQ ID NO:4) and VL-CDR3 (QQYMSVPIT; SEQ ID NO:5) and a heavy chain variable domain comprising the following CDR amino acid sequences: VH-CDR1 (GFSFSSEPIS; SEQ ID NO:6), VH-CDR2 (SSITGKNGYTTYADSVKG; SEQ ID NO:7) and VH-CDR3 (WGKKVYGM DV; SEQ ID NO: 8).
24. The multispecific antibody of claim 21 comprising a first binding site that specifically binds to NRP-1 that the light chain variable domain (VL) sequence of SEQ ID NO:9 and the heavy chain variable domain (VH) sequence of SEQ ID NO:10.
25. The multispecific antibody of claim 21 comprising a second binding site that specifically binds to PD-1 and that comprises the VH domain of SEQ ID NO:11 and the VL domain of SEQ ID NO: 12.
26. The multispecific antibody of claim 21 comprising a second binding site that specifically binds to PD-1 and that comprises the VH domain of SEQ ID NO:15 and the VL domain of SEQ ID NO: 16.
27. The multispecific antibody of claim 21 comprising:
- a first binding site that specifically binds to NRP-1 and that comprises the light chain variable domain (VL) sequence of SEQ ID NO:9 and the heavy chain variable domain (VH) sequence of SEQ ID NO:10 and,
 - a second binding site that specifically binds to PD-1 and that comprises the VH domain of SEQ ID NO:11 and the VL domain of SEQ ID NO: 12.
28. The multispecific antibody of claim 21 comprising:
- a first binding site that specifically binds to NRP-1 and that comprises the light chain variable domain (VL) sequence of SEQ ID NO:9 and the heavy chain variable domain (VH) sequence of SEQ ID NO:10 and,

- a second binding site that specifically binds to PD-1 and that comprises the VH domain of SEQ ID NO:15 and the VL domain of SEQ ID NO: 16.

29. The multispecific antibody of claim 21 for use in the treatment of cancer.

30. A population of cells engineered to express a chimeric antigen receptor (CAR) and wherein the expression of NRP-1 in said cells is repressed.

31. The population of cells of claim 30 wherein the cells are selected from the group consisting of T-cells such as tumor infiltrating cells (TILS), CD4+ T-cells or CD8+ T-cells and stem cells.

32. The population of cells of claim 30 wherein the expression of at least one immune checkpoint protein is also repressed.

33. An ex vivo method of manufacturing a CAR-expressing cell, comprising the steps consisting of i) introducing nucleic acid encoding a CAR into a cell and ii) contacting the cell with a endonuclease system so as to repress the expression of NRP-1.

34. The method of claim 33 comprising the steps consisting of i) introducing nucleic acid encoding a CAR into a cell and ii) contacting the cell with a Cas protein and with at least one guide RNA molecules (gRNA) comprising a sequence that targets the NRP-1 gene, and a sequence which is capable of binding to the Cas protein.

35. The method of claim 34 which further comprises contacting the cell at least one guide RNA molecule that comprising a sequence that targets a gene encoding for an immune checkpoint protein.

36. Use of a population of T cells as defined in claim 31 in the manufacture of a medicament for treating cancer in a patient in need thereof.