

CLAIMS

What is claimed is:

- 5 1. A vasoactive intestinal peptide receptor (VIP-R) antagonist comprising KPRRPYX¹X²X³X⁴TX⁵LRKQX⁶AVX⁷X⁸KYLX⁹X¹⁰ILN (SEQ ID NO: 3) or a fragment thereof, wherein

- X¹ is T or A;
X² is D, V, or S;
10 X³ is N or D;
X⁴ is Y or C;
X⁵ is R or S;
X⁶ is M or I;
X⁷ is K or N;
15 X⁸ is K;
X⁹ is N or M;
X¹⁰ is S, or L; and

- provided that the peptide is not KPRRPYTDNYTRLRKQMAVKKYLNSILN (SEQ ID NO: 1) or the combination wherein X¹ is T, X² is D, X³ is N; X⁴ is Y, X⁵ is R, X⁶ is M, X⁷ is K, X⁹ is N, and X¹⁰ is S.
- 20

2. A vasoactive intestinal peptide receptor (VIP-R) antagonist comprising KPRRPYX¹X²X³X⁴TX⁵LRKQX⁶AVX⁷KYLX⁸X⁹ILN (SEQ ID NO: 21) or a fragment thereof, wherein

- 25 X¹ is T or A;
X² is D, V, or S;
X³ is N or D;
X⁴ is Y or C;
X⁵ is R or S;
30 X⁶ is M or I;
X⁷ is K or N;
X⁸ is N or M;
X⁹ is S, or L; and

provided that the peptide is not KPRRPYTDNYTRLRKQMAVKKYLNSILN (SEQ ID NO:

1) or the combination wherein X¹ is T, X² is D, X³ is N; X⁴ is Y, X⁵ is R, X⁶ is M, X⁷ is K, X⁸ is N, and X⁹ is S.

3. The VIP-R antagonist of claim 1 or 2, wherein the VIP-R antagonist comprises the amino acid sequence:

KPRRPYADNYTRLRKQMAVNKYLNILN (SEQ ID NO: 6),
KPRRPYAVNYTRLRKQIAVKKYLMSILN (SEQ ID NO: 7),
KPRRPYAVNYTRLRKQMAVNKYLMSILN (SEQ ID NO: 8),
KPRRPYADNCTRLRKQIAVNKKYLNILN (SEQ ID NO: 9),
KPRRPYTVNYTSLRKQIAVKKYLMILN (SEQ ID NO: 10),
KPRRPYTDNCTSLRKQIAVNKYLNILN (SEQ ID NO: 11),
KPRRPYAVNCTSLRKQIAVNKYLNILN (SEQ ID NO: 12),
KPRRPYAVNCTSLRKQIAVKKYLMSILN (SEQ ID NO: 13),
KPRRPYTVNCTSLRKQIAVKKYLMILN (SEQ ID NO: 14),
KPRRPYTSDYTRLRKQMAVKKYLNILN (SEQ ID NO: 15),
KPRRPYTSDYTRLRKQMAVKKYLNILN (SEQ ID NO: 16), or a fragment thereof.

4. The VIP-R antagonist of any of Claims 1-3, wherein an amino, carboxyl, hydroxyl, or thiol group in the peptide is substituted.

5. The VIP-R antagonist of any of Claims 1-4, wherein the peptide is conjugated to and/or encapsulated within a nanoparticle.

6. A pharmaceutical composition comprising the vasoactive intestinal peptide receptor (VIP-R) antagonist of any of Claims 1-5 and a pharmaceutically acceptable carrier.

7. The pharmaceutical composition of Claim 6 in the form of a capsule, tablets, pill, powder, or granule.

8. The pharmaceutical composition of Claim 6 in the form of a sterilized pH buffered aqueous salt solution.

9. A method of *ex vivo* augmenting T cell activation and/or expansion, comprising mixing one or more T cells *in vitro* or *ex vivo* with the vasoactive intestinal peptide receptor (VIP-R) antagonist of any of Claims 1-5 or the pharmaceutical composition of any of Claims 6-8.
- 5
10. An *in vitro* cell culture composition, comprising one or more T cells, and the vasoactive intestinal peptide receptor (VIP-R) antagonist of any of Claims 1-5 or the pharmaceutical composition of any of Claims 6-8.
- 10
11. A therapeutically effective amount of the vasoactive intestinal peptide receptor (VIP-R) antagonist of any of Claims 1-5 or the pharmaceutical composition of any of Claims 6-8 or use in treating a microbial infection in a subject.
- 15
12. A therapeutically effective amount of the vasoactive intestinal peptide receptor (VIP-R) antagonist of any of Claims 1-5 or the pharmaceutical composition of any of Claims 6-8 for use in treating a cancer and/or metastasis in a subject.
- 20
13. A therapeutically effective amount of the vasoactive intestinal peptide receptor (VIP-R) antagonist of any of Claims 1-5 or the pharmaceutical composition of any of Claims 6-8 for use in enhancing an immune response to a cancer and/or metastasis in a subject.
- 25
14. A T cell expanded with the vasoactive intestinal peptide receptor (VIP-R) antagonist of any of Claims 1-5 or the pharmaceutical composition of any of Claims 6-8 for use in treating cancer in a subject, wherein the T cell is expanded by providing one or more T cells; mixing the one or more T cells with the vasoactive intestinal peptide receptor (VIP-R) antagonist thereby expanding the one or more T cells;
- 30
15. The method of Claim 9 or the composition of Claim 10, or the T cell for use of Claim 14, wherein mixing the one or more T cells is in combination with an anti-CD3 antibody and/or an anti-CD28 antibody.
16. The method of Claim 9 or 15 or the composition of Claim 10 or 15, or the antagonist

or composition for use of any one of Claims 11-13 and 15, or the T cell for use of Claim 14 or 15, wherein mixing the one or more T cells is in combination with a phosphatidylinositol 3-kinase (PI3K) inhibitor; preferably, wherein the PI3K inhibitor is a PI3K α inhibitor, a PI3K β inhibitor, a PI3K δ inhibitor, or a PI3K γ inhibitor; more preferably, wherein the PI3K inhibitor
5 comprises idelalisib, copanlisib, duvelisib, alpelisib, umbralisib, buparlisib, copanlisib, dactolisib, leniolisib, parsaclisib, paxalisib, taselisib, zandelisib, inavolisib, apitolisib, bimiralisib, eganelisib, fimepinostat, gedatolisib, linperlisib, nemiralisib, pilaralisib, samotolisib, seletalisib, serabelisib, sonolisib, tenalisib, voxalisib, AMG 319, AZD8186, GSK2636771, SF1126, acalisib, omipalisib, AZD8835, CAL263, GSK1059615, MEN1611,
10 PWT33597, TG100-115, or ZSTK474.

17. The method of any one of Claims 9, 15 and 16, or the composition of any one of Claims 10, 15 and 16, or the antagonist or composition for use of any one of Claims 11-13, 15 and 16, or the T cell for use of any one of Claims 14, 15 and 16, wherein mixing the one or more T
15 cells is in combination with an immune checkpoint blockade; preferably, comprises a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, an anti-TIM3 inhibitor, an anti-LAG3 inhibitor, an anti-CD47 inhibitor, imiquimod, polyinosinic-polycytidylic acid-poly-L-lysine carboxymethylcellulose (poly-ICLC), pexidartinib, an anti-TIGIT inhibitor, an anti-B7-H3 inhibitor, an anti-B7-H4 inhibitor, an anti-A2aR inhibitor, an anti-CD73 inhibitor, an anti-
20 NKG2A inhibitor, an anti-PVRIG/PVRL2 inhibitor, an anti-CEACAM1 inhibitor, an anti-CEACAM5 inhibitor, an anti-CEACAM6 inhibitor, an focal adhesion kinase (FAK) inhibitor, a CCL2/CCR2 inhibitor, an anti-leukemia inhibitory factor (LIF) inhibitor, an anti-CD47/SIRP α inhibitor, an anti-colony-stimulating factor (CSF)-1 inhibitor, an anti-IL-1 inhibitor, an anti-IL-1R3 inhibitor, an anti-IL-8 inhibitor, an anti-semaphorin 4D (Sema4D)
25 inhibitor, an angiopoietin(Ang)-2 inhibitor, a CLEVER-1 inhibitor, Axl-targeted enapotamab vedotin (EnaV), or an anti-phosphatidylserine inhibitor; more preferably, wherein the immune checkpoint blockade comprises a PD-1 inhibitor, a PD-L1 inhibitor, or a CTLA-4 inhibitor; most preferably, wherein the immune checkpoint blockade comprises pembrolizumab, nivolumab, cemiplimab, dostarlimab, atezolizumab, avelumab, durvalumab, or ipilimumab.

30

18. The method of any one of Claims 9 and 15-17, or the composition of any one of Claims 10 and 15-17, or the antagonist or composition for use of any one of Claims 11-13 and 15-17, or the T cell for use of any one of Claims 14-17, wherein the one or more T cells are derived from the subject; preferably, wherein the one or more T cells comprises a chimeric antigen

receptor.

19. The method of any one of Claims 9 and 15-18, or the composition of any one of Claims 10 and 15-18, or the antagonist or composition for use of any one of Claims 11-13 and 15-18, or the T cell for use of any one of Claims 14-18, wherein the expanded T cells have increased levels of CD28 and/or CD27 compared with levels prior to expansion and/or decreased levels of PD-1, TIM-3, and/or Lag3 compared with levels prior to expansion.
20. The method of any one of Claims 9 and 15-19, or the composition of any one of Claims 10 and 15-19, or the antagonist or composition for use of any one of Claims 11-13 and 15-19, or the T cell for use of any one of Claims 14-19, further comprising the use of a PI3 kinase inhibitor or a VIP receptor antagonist, or an immune checkpoint blockade, or a combination thereof.