Claims

1. An EphA3 binding agent, optionally isolated, comprising at least one complementarity determining region (CDR) having an amino acid sequence set forth in SEQ ID NOs: 13-72 and/or Tables 4-7 or an amino acid sequence at least 70% identical thereto, preferably wherein the EphA3 binding agent comprises

    a. a heavy chain immunoglobulin variable region (VH) polypeptide comprising a CDR 1 having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 13-17 or 43-47; a CDR 2 having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 18-22 or 48-52; and a CDR 3 having an amino acid sequence at least 70% identical to any one of SEQ ID NO: 23-27 or 53-57; and/or

    b. a light chain immunoglobin variable region (VL) polypeptide comprising a CDR 1 having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 28-32 or 58-62; a CDR 2 having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 33-37 or 63-67; and a CDR 3 having an amino acid sequence at least 70% identical to any one of SEQ ID NO: 38-42 or 68-72.

2. The EphA3 binding agent of Claim 1, wherein:

    a. the VH polypeptide comprises an amino acid sequence set forth in SEQ ID NO: 153 or 155 or an amino acid sequence at least 70% identical thereto; and/or

    b. the VL polypeptide comprises an amino acid sequence set forth in SEQ ID NO: 154 or 156 or an amino acid sequence at least 70% identical thereto.

3. The EphA3 binding agent of any one of the preceding claims, wherein the EphA3 binding agent is an antibody or antibody fragment, preferably wherein the antibody or antibody fragment is a 3C3-1 or 2D4-1 monoclonal antibody or fragment thereof, preferably wherein the EphA3 binding agent is a recombinant, human or humanized antibody or antibody fragment.

4. A chimeric antigen receptor (CAR) comprising an antigen-binding agent according to any one of claims 1-3.

5. A chimeric antigen receptor (CAR) comprising an antigen binding domain including at least one CDR having an amino acid sequence set forth in SEQ ID NOs:1-3 or an amino acid sequence at least 70% identical thereto, a transmembrane domain, preferably wherein the transmembrane domain comprises a CD8 transmembrane domain, preferably wherein the CD8 transmembrane domain comprises an amino acid sequence set forth in SEQ ID NO:159 or an amino acid sequence at least 70% identical thereto, and an intracellular T-cell signalling domain, preferably wherein the intracellular signalling domain comprises a CD3 zeta intracellular signalling domain, preferably wherein the intracellular signalling domain comprises a CD3 zeta amino acid sequence set forth in SEQ ID NO:162 or an amino acid sequence at least 70% identical thereto.

6. The CAR of Claim 5, wherein the antigen binding domain comprises, consists or consists essentially of:

(a) a heavy chain immunoglobulin variable region (VH) polypeptide comprising a CDR 1 having an amino acid sequence at least 70% identical to any one of SEQ ID NOs:13 to 17 or 43 to 47; a CDR 2 having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 18 to 22 or 48 to 52; and a CDR 3 having an amino acid sequence at least 70% identical to any one of SEQ ID NO: 23 to 27 or 53 to 57; and/or

(b) a light chain immunoglobulin variable region (VL) polypeptide comprising a CDR 1 having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 28 to 32 or 58 to 62; a CDR 2 having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 33 to 37 or 63 to 67; and a CDR 3 having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 38 to 42 or 68 to 72.

7. The CAR of Claim 6, wherein:

(a) the VH polypeptide comprises an amino acid sequence set forth in SEQ ID NO:153 or 155 or an amino acid sequence at least 70% identical thereto; and/or

(b) the VL polypeptide comprises an amino acid sequence set forth in SEQ ID NO:154 or 156 or an amino acid sequence at least 70% identical thereto.

8. The CAR according to any one of Claims 5 to 7, wherein the antigen binding domain comprises a linker, such as the linker having an amino acid sequence set forth in SEQ ID NO: 158 or an amino acid sequence at least 70% identical thereto, optionally further comprising a leader sequence, preferably wherein the leader sequence comprises, consists or consists essentially of an amino acid sequence set forth in SEQ ID NO: 157 or an amino acid sequence at least 70% identical thereto.

9. The CAR according to any one of Claims 4 to 8, further comprising one or more co-stimulatory domains, such as a CD28 co-stimulatory domain having the amino acid sequence set forth in SEQ ID NO:161 or an amino acid sequence at least 70% identical thereto and/or a CD137 co-stimulatory domain having the amino acid sequence set forth in SEQ ID NO:160 or an amino acid sequence at least 70% identical thereto.

10. An isolated nucleic acid encoding the EphA3 binding agent according to any one of Claims 1 to 3, or the CAR according to any one of Claims 4 to 9.

11. A genetic construct comprising the isolated nucleic acid of Claim 10.

12. An expression vector, or a plurality of expression vectors, comprising a nucleic acid or a plurality of nucleic acids according to claim 10..

13. A host cell comprising the nucleic acid of Claim 10 and/or the genetic construct of Claim 11, wherein the host cell is or comprises a T cell.

14. A method of producing an isolated EphA3 binding agent or a CAR, said method comprising; (i) culturing the host cell of Claim 13; and (ii) isolating said EphA3 binding agent or CAR from said host cell cultured in step (i).

15. An antibody or antibody fragment which binds and/or is raised against:

(i) the EphA3 binding agent according to any one of Claims 1 to 3; and/or (ii) the CAR according to any one of Claims 4 to 9.

16. A composition comprising the EphA3 binding agent according to any one of Claim 1 to 3, the CAR according to any one of Claims 4 to 9, the isolated nucleic acid according to Claim 10, the genetic construct according to Claim 11 and/or the host cell according to Claim 13 and a pharmaceutically acceptable carrier diluent or excipient.

17. Use of the EphA3 binding agent according to any one of Claims 1 to 3, the CAR according to any one of Claims 4 to 9, the isolated nucleic acid according to Claim 10, the genetic construct according to Claim 11, the host cell according to Claim 13, and/or the composition of Claim 15, in the manufacture of a medicament for the treatment or prevention of cancer.

18. An *ex vivo* method of detecting EphA3 or a cell expressing EphA3, said method including the step of forming a complex between the EphA3 binding agent according to any one of Claims 1 to 3, or the CAR according to any one of Claims 4 to 9 and EphA3 to thereby detect EphA3 or the cell expressing EphA3, preferably wherein the cell is or comprises a cancer cell.

19. A human T-cell expressing: (a) a T-cell receptor (TCR) that is activated by binding to a CMV antigen; and (b) a chimeric antigen receptor (CAR) comprising an antigen-binding domain that binds to an epitope on EphA3, preferably wherein the antigen-binding domain is a scFv comprising a heavy chain variable (VH) region and a light chain variable (VL) region.

20. A T-cell that comprises (a) a T-cell receptor (TCR) that expresses a TCR that is specific for a CMV antigen; and (b) an antigen-binding molecule, for example a CAR, that binds to EphA3, preferably wherein the antigen-binding molecule is a scFv comprising a heavy chain variable (VH) region, wherein the VH region has the amino acid sequence set forth in SEQ ID NO: 153 or 155 and a light chain variable (VL) region, wherein the VL region has an amino acid sequence that is set forth in SEQ ID NO: 154 or 156.

21. The T-cell of any one of claim 19 or claim 20, wherein the CAR comprises a transmembrane domain selected from a CD4, CD8, or CD28 transmembrane domain and a costimulatory domain selected from a 4-1BB or CD28 co-stimulatory domain.

22. The T-cell of any one of claims 19 to 21, wherein the CMV antigen comprises a peptide derived from one or more of pp50, pp65, IE-I, gB and gH, preferably wherein the CMV antigen comprises a peptide selected from the amino acid sequences set forth in SEQ ID NO: 181 -211.

23. A method of preparing a bi-specific T-cell population that is useful in treating cancer, the method comprising:

    (a) providing an isolated population of cells comprising PBMC and treating the cells to obtain a subpopulation of T-cells that express a TCR that binds to a CMV antigen;

    (b) treating the subpopulation of cells to introduce a vector encoding a CAR that binds to an epitope of EphA3, thereby creating a population of bi-specific T-cells expressing a TCR that binds to a CMV antigen and a CAR that binds to an epitope on EphA3, preferably wherein the CAR comprises an antigen-binding domain that binds to an epitope on EphA3, a spacer, a transmembrane domain, for example CD4, CD8 or CD28 transmembrane, a co-stimulatory

domain, for example 41BB or CD28 co-stimulatory domain, and a CD3 zeta signalling domain ; and

(c) expanding the population of bi-specific T-cells.

24. The method of claim 23, wherein the antigen-binding domain is a scFv comprising a heavy chain variable region and a light chain variable region, preferably wherein the heavy chain variable (VH) region has the amino acid sequence set forth in SEQ ID NO: 153 or 155, and wherein the light chain variable (VL) region has an amino acid sequence that is set forth in SEQ ID NO: 154 or 156.

25. The method of any one of claim 23 or claim 24, wherein treating the cells in step (a) comprises exposing the T-cells to a pool of immunogenic peptides comprising HLA class I and class ll-restricted CMV peptide epitopes capable of inducing proliferation of peptide-specific T-cells, preferably wherein the T-cells express a TCR specific for a CMV antigen and are expanded in the presence of a T-cell antigen before administration to the subject, wherein the CMV antigen comprises one or more CMV peptides, or a CMV vaccine, wherein at least one CMV peptide is selected from pp50, p65, IE-I, gB and gH, preferably wherein at least one CMV peptide is selected form the amino acid sequence set forth in SEQ ID NO: 181 -211 .