embodiment has a higher affinity towards human prostate specific membrane antigen than that of a binding protein which has the sequence set forth in SEQ ID NO: 4. In some cases, the prostate specific membrane antigen binding protein of the above embodiment further has a higher affinity towards cynomolgus prostate specific membrane antigen than that of a binding protein which has the sequence set forth in SEQ ID NO: 4.

[0012] One embodiment provides a method for the treatment or amelioration of prostate cancer, the method comprising administration of the PSMA binding protein comprising complementarity determining regions CDR1, CDR2, and CDR3, wherein (a) the amino acid sequence of CDR1 is as set forth in RFMISX_1YX_2MH (SEQ ID NO: 1); (b) the amino acid sequence of CDR2 is as set forth in X_3INPA$X_4$$X_5$TDYAE$X_6$VKG (SEQ ID NO: 2); and (c) the amino acid sequence of CDR3 is as set forth in DX_7YGY (SEQ ID NO: 3), to a subject in need thereof.

[0013] In some embodiments the PSMA binding protein is a single domain antibody. In some embodiments, said single domain antibody is part of a trispecific antibody.

[0013a] Another embodiment of the invention provides a prostate specific membrane antigen binding protein, comprising complementarity determining regions CDR1, CDR2, and CDR3,wherein

(a) the CDR1 comprises the sequence RFMISEYHMH (SEQ ID NO: 5), the CDR2 comprises the sequence TINPAGTTDYAESVKG (SEQ ID NO: 17), and the CDR3 comprises the sequence DSYGY (SEQ ID NO: 15);

(b) the CDR1 comprises the sequence RFMISPYSMH (SEQ ID NO: 6), the CDR2 comprises the sequence TINPAGTTDYAESVKG (SEQ ID NO: 17), and the CDR3 comprises the sequence DGYGY (SEQ ID NO: 18);

(c) the CDR1 comprises the sequence RFMISEYSMH (SEQ ID NO: 16), the CDR2 comprises the sequence TINPAGQTDYAESVKG (SEQ ID NO: 10), and the CDR3 comprises the sequence DGYGY (SEQ ID NO: 18);

(d) the CDR1 comprises the sequence RFMISEYSMH (SEQ ID NO: 16), the CDR2 comprises the sequence TINPAKTTDYAESVKG (SEQ ID NO: 9), and the CDR3 comprises the sequence DGYGY (SEQ ID NO: 18); or

(e) the CDR1 comprises the sequence RFMISEYHMH (SEQ ID NO: 5), the CDR2 comprises the sequence DINPAGTTDYAESVKG (SEQ ID NO: 8), and the CDR3 comprises the sequence DSYGY (SEQ ID NO: 15).

[0013b] Another embodiment of the invention provides a use of the PSMA binding protein as disclosed herein in the manufacture of a medicament for the treatment or amelioration of prostate cancer, wherein the medicament is to be administered to a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0015] **Figure 1** is schematic representation of an exemplary PMSA targeting trispecific antigen-binding protein where the protein has an constant core element comprising an anti-CD3ε single chain variable fragment (scFv) and an anti-HSA variable heavy chain region; and a PMSA binding domain that can be a VH, scFv, a non-Ig binder, or ligand.

[0016] **Figures 2A-B** compare the ability of exemplary PSMA targeting trispecific proteins (PSMA targeting TriTAC molecules) with different affinities for CD3 to induce T cells to kill human prostate cancer cells. **Figure 2A** shows killing by different PMSA targeting TriTAC molecules in prostate cancer model LNCaP. **Figure 2B** shows killing by different PMSA targeting TriTAC molecules in prostate cancer model 22Rv1. **Figure 2C** shows EC50 values for PMSA targeting TriTAC in LNCaP and 22Rv1 prostate cancer models.

[0017] **Figure 3** shows the serum concentration of PSMA targeting TriTAC C236 in Cynomolgus monkeys after i.v. administration (100 µg/kg) over three weeks.

CLAIMS

WHAT IS CLAIMED IS:

1. A prostate specific membrane antigen binding protein, comprising complementarity determining regions CDR1, CDR2, and CDR3, wherein

(a) the CDR1 comprises the sequence RFMISEYHMH (SEQ ID NO: 5), the CDR2 comprises the sequence TINPAGTTDYAESVKG (SEQ ID NO: 17), and the CDR3 comprises the sequence DSYGY (SEQ ID NO: 15);

(b) the CDR1 comprises the sequence RFMISPYSMH (SEQ ID NO: 6), the CDR2 comprises the sequence TINPAGTTDYAESVKG (SEQ ID NO: 17), and the CDR3 comprises the sequence DGYGY (SEQ ID NO: 18);

(c) the CDR1 comprises the sequence RFMISEYSMH (SEQ ID NO: 16), the CDR2 comprises the sequence TINPAGQTDYAESVKG (SEQ ID NO: 10), and the CDR3 comprises the sequence DGYGY (SEQ ID NO: 18);

(d) the CDR1 comprises the sequence RFMISEYSMH (SEQ ID NO: 16), the CDR2 comprises the sequence TINPAKTTDYAESVKG (SEQ ID NO: 9), and the CDR3 comprises the sequence DGYGY (SEQ ID NO: 18); or

(e) the CDR1 comprises the sequence RFMISEYHMH (SEQ ID NO: 5), the CDR2 comprises the sequence DINPAGTTDYAESVKG (SEQ ID NO: 8), and the CDR3 comprises the sequence DSYGY (SEQ ID NO: 15).

2. The prostate specific membrane antigen binding protein of claim 1, wherein said protein comprises the following formula:

f1-r1-f2-r2-f3-r3-f4

wherein, r1 is the CDR1; r2 is the CDR2; and r3 is the CDR3; and wherein f_1, f_2, f_3 and f_4 are framework residues selected so that said protein is at least eighty percent identical to the amino acid sequence set forth in SEQ ID NO: 4.

3. The prostate specific membrane antigen binding protein of claim 1 or 2, wherein the CDR1 comprises the sequence RFMISEYHMH (SEQ ID NO: 5), the CDR2 comprises the sequence TINPAGTTDYAESVKG (SEQ ID NO: 17), and the CDR3 comprises the sequence DSYGY (SEQ ID NO: 15).

4. The prostate specific membrane antigen binding protein of claim 1 or 2, wherein the CDR1 comprises the sequence RFMISPYSMH (SEQ ID NO: 6), the CDR2 comprises the sequence TINPAGTTDYAESVKG (SEQ ID NO: 17), and the CDR3 comprises the sequence DGYGY (SEQ ID NO: 18).

5. The prostate specific membrane antigen binding protein of claim 1 or 2, wherein the CDR1 comprises the sequence RFMISEYSMH (SEQ ID NO: 16), the CDR2 comprises the sequence TINPAGQTDYAESVKG (SEQ ID NO: 10), and the CDR3 comprises the sequence DGYGY (SEQ ID NO: 18).

6. The prostate specific membrane antigen binding protein of claim 1 or 2, wherein the CDR1 comprises the sequence RFMISEYSMH (SEQ ID NO: 16), the CDR2 comprises the sequence TINPAKTTDYAESVKG (SEQ ID NO: 9), and the CDR3 comprises the sequence DGYGY (SEQ ID NO: 18).

7. The prostate specific membrane antigen binding protein of claim 1 or 2, wherein the CDR1 comprises the sequence RFMISEYHMH (SEQ ID NO: 5), the CDR2 comprises the sequence DINPAGTTDYAESVKG (SEQ ID NO: 8), and the CDR3 comprises the sequence DSYGY (SEQ ID NO: 15).

8. The prostate specific membrane antigen binding protein of claim 1 or 2, wherein the protein comprises a sequence selected from the group consisting of SEQ ID Nos. 21, 22, 24, 25, 31 and 32.

9. The prostate specific membrane antigen binding protein of claim 8, wherein the protein comprises a sequence of SEQ ID NO: 32.

10. The prostate specific membrane antigen binding protein of any one of claims 1-9, wherein said binding protein binds to one or both of human prostate specific membrane antigen and cynomolgus prostate specific membrane antigen.

11. The prostate specific membrane antigen binding protein of any one of claims 1-10, wherein said binding protein binds to human prostate specific membrane antigen and cynomolgus prostate specific membrane antigen with comparable binding affinities.

12. The prostate specific membrane antigen binding protein of any one of claims 1-11, wherein said binding protein binds to human prostate specific membrane antigen with a higher binding affinity than cynomolgus prostate specific membrane antigen.

13. A polynucleotide encoding a PSMA binding protein according to any one of claims 1-12.

14. A vector comprising the polynucleotide of claim 13.

15. A host cell transformed with the vector according to claim 14.

16. A pharmaceutical composition comprising (i) a PSMA binding protein according to any one of claims 1-12, the polynucleotide according to claim 13, the vector according to claim 14 or the host cell according to claim 15, and (ii) a pharmaceutically acceptable carrier.

17. Use of the PSMA binding protein according to any one of claims 1-12 in the manufacture of a medicament for the treatment or amelioration of prostate cancer, wherein the medicament is to be administered to a subject in need thereof.

18. The use of claim 17, wherein the subject is human.

19. The use of claim 18, wherein an agent is to be further administered in combination with the medicament.

20. A multispecific binding protein comprising the PSMA binding protein according to any one of claims 1-11.