

CLAIMS

WHAT IS CLAIMED IS:

1. A prostate specific membrane antigen binding protein, comprising complementarity determining regions CDR1, CDR2, and CDR3, wherein
 - (a) the amino acid sequence of CDR1 is as set forth in RFMISX₁YX₂MH (SEQ ID NO: 1);
 - (b) the amino acid sequence of CDR2 is as set forth in X₃INPAX₄X₅TDYAEX₆VKG (SEQ ID NO: 2); and
 - (c) the amino acid sequence of CDR3 is as set forth in DX₇YGY (SEQ ID NO: 3).
2. The prostate specific membrane antigen binding protein of claim 1, wherein said protein comprises the following formula:

$$f_1-r_1-f_2-r_2-f_3-r_3-f_4$$
 wherein, r₁ is SEQ ID NO: 1; r₂ is SEQ ID NO: 2; and r₃ is SEQ ID NO: 3; and wherein f₁, f₂, f₃ and f₄ 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 2, wherein X₁ is proline.
4. The prostate specific membrane antigen binding protein of claim 2, wherein X₂ is histidine.
5. The prostate specific membrane antigen binding protein of claim 2, wherein X₃ is aspartic acid.
6. The prostate specific membrane antigen binding protein of claim 2, wherein X₄ is lysine.
7. The prostate specific membrane antigen binding protein of claim 2, wherein X₅ is glutamine.
8. The prostate specific membrane antigen binding protein of claim 2, wherein X₆ is tyrosine.
9. The prostate specific membrane antigen binding protein of claim 2, wherein X₇ is serine.
10. The prostate specific membrane antigen binding protein of any one of claims 1-9, wherein the binding protein has a higher affinity towards a human prostate specific membrane antigen than that of a binding protein which has the sequence set forth as SEQ ID NO: 4.
11. The prostate specific membrane antigen binding protein of any one of claims 1-9, wherein X₁ is proline.
12. The prostate specific membrane antigen binding protein of any one of claims 1-9, wherein X₅ is glutamine.

13. The prostate specific membrane antigen binding protein of any one of claims 1-9, wherein X₆ is tyrosine
14. The prostate specific membrane antigen binding protein of any one of claims 1-9, wherein X₄ is lysine, and X₇ is serine.
15. The prostate specific membrane antigen binding protein of any one of claim 1-9, wherein X₂ is histidine, X₃ is aspartic acid, X₄ is lysine, and X₇ is serine.
16. The prostate specific membrane antigen binding protein of any one of claims 1-9, wherein X₁ is proline, X₂ is histidine, X₃ is aspartic acid, and X₇ is serine.
17. The prostate specific membrane antigen binding protein of any one claims 1-9, wherein X₂ is histidine, X₃ is aspartic acid, X₅ is glutamine, and X₇ is serine.
18. The prostate specific membrane antigen binding protein of any one claims 1-9, wherein X₂ is histidine, X₃ is aspartic acid, X₆ is tyrosine, and X₇ is serine.
19. The prostate specific membrane antigen binding protein of any one of claims 1-9, wherein X₂ is histidine, and X₇ is serine.
20. The prostate specific membrane antigen binding protein of any one of claims 1-9, wherein X₂ is histidine, X₃ is aspartic acid, and X₇ is serine.
21. The prostate specific membrane antigen binding protein of any one of claims 11-20, wherein the binding protein has a higher affinity towards a human prostate specific membrane antigen than that of a binding protein which has the sequence set forth in SEQ ID NO: 4.
22. The prostate specific membrane antigen binding protein of any one of claims 19-21, wherein the binding protein further has a higher affinity towards a cynomolgus prostate specific membrane antigen than that of a binding protein which has the sequence set forth in SEQ ID NO: 4.
23. The prostate specific membrane antigen binding protein of any one of claims 1-22, wherein r1 comprises SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7.
24. The prostate specific membrane antigen binding protein of any one of claims 1-23, wherein r2 comprises SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, or SEQ ID NO: 14.
25. The prostate specific membrane antigen binding protein of any one of claims 1-24, wherein r3 comprises SEQ ID NO: 15.
26. A prostate specific membrane antigen binding protein comprising CDR1, CDR2, and CDR3, comprising the sequence set forth as SEQ ID NO: 4 wherein one or more amino acid residues selected from amino acid positions 31, 33, 50, 55, 56, 62, and 97 are substituted.

27. The prostate specific membrane antigen binding protein of claim 26, comprising one or more additional substitutions at amino acid positions other than positions 31, 33, 50, 55, 56, 62, and 97.
28. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitution at position 31.
29. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitution at position 33.
30. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitution at position 50.
31. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitution at position 55.
32. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitution at position 56.
33. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitution at position 62.
34. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitution at position 97.
35. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitutions at amino acid positions 55 and 97.
36. The prostate specific membrane antigen binding protein of any one of claims 28-35, wherein the binding protein 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.
37. The specific membrane antigen binding protein of claim 26 or 27, comprising substitutions at amino acid positions 33 and 97.
38. The specific membrane antigen binding protein of claim 26 or 27, comprising substitutions at amino acid positions 33, 50, and 97.
39. The prostate specific membrane antigen binding protein of claim 37 or 38, wherein the binding protein has a higher affinity towards human prostate specific membrane antigen than that of a binding protein which has the sequence set forth as SEQ ID NO: 4.
40. The prostate specific membrane antigen binding protein of claim 37 or 38, wherein the binding protein 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.
41. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitutions at amino acid positions 31, 33, 50, and 97.

42. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitutions at amino acid positions 33, 50, 55, and 97.
43. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitutions in amino acid positions 33, 50, 56, and 97.
44. The prostate specific membrane antigen binding protein of claim 26 or 27, comprising substitutions at amino acid positions 33, 50, 62, and 97.
45. A prostate specific membrane antigen binding protein comprising a CDR1, CDR2 and CDR3, wherein CDR1 comprises the sequence as set forth is SEQ ID NO: 16.
46. A prostate specific membrane antigen binding protein comprising a CDR1, CDR2 and CDR3, wherein CDR2 comprises the sequence as set forth in SEQ ID NO: 17.
47. A prostate specific membrane antigen binding protein comprising a CDR1, CDR2 and CDR3, wherein CDR3 comprises the sequence as set forth in SEQ ID NO: 18.
48. A prostate specific membrane antigen binding protein comprising a sequence that is at least 80% identical to the sequence set forth in SEQ ID NO: 4.
49. A prostate specific membrane antigen binding protein comprising a CDR1, CDR2 and CDR3, wherein CDR1 has at least 80% identity to SEQ ID NO: 16, CDR2 has at least 85% identity to SEQ ID NO: 17, and CDR3 has at least 80% identity to SEQ ID NO: 18.
50. A prostate specific membrane antigen binding protein comprising a CDR1, CDR2 and CDR3, wherein CDR1 comprises the sequence set forth in SEQ ID NO: 16, CDR2 comprises the sequence set forth in SEQ ID NO: 17, and CDR3 comprises the sequence set forth in SEQ ID NO: 18.
51. The prostate specific membrane antigen binding protein of any one of claims 1-50, wherein said binding protein binds to one or both of human prostate specific membrane antigen and cynomolgus prostate specific membrane antigen.
52. The prostate specific membrane antigen binding protein of any one of claims 1-51, wherein said binding protein binds to human prostate specific membrane antigen and cynomolgus prostate specific membrane antigen with comparable binding affinities.
53. The prostate specific membrane antigen binding protein of any one of claims 1-51, wherein said binding protein binds to human prostate specific membrane antigen with a higher binding affinity than cynomolgus prostate specific membrane antigen.
54. A polynucleotide encoding a PSMA binding protein according to any one of claims 1-53.
55. A vector comprising the polynucleotide of claim 54.
56. A host cell transformed with the vector according to claim 55.

57. A pharmaceutical composition comprising (i) a PSMA binding protein according to any one of claims 1-53, the polynucleotide according to claim 54, the vector according to claim 55 or the host cell according to claim 56, and (ii) a pharmaceutically acceptable carrier.
58. A process for the production of a PSMA binding protein according to any one of claims 1-53, said process comprising culturing a host transformed or transfected with a vector comprising a nucleic acid sequence encoding a PSMA albumin binding protein according to any one of claims 1-53 under conditions allowing the expression of the PSMA binding protein and recovering and purifying the produced protein from the culture.
59. A method for the treatment or amelioration of a proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, a viral disease, an allergic reaction, a parasitic reaction, a graft-versus-host disease or a host-versus-graft disease comprising the administration of the PSMA binding protein according to any one of claims 1-53, to a subject in need thereof.
60. The method of claim 59, wherein the subject is human.
61. The method of claim 60, wherein the method further comprises administration of an agent in combination with the PSMA binding protein according to any one of claims 1-53.
62. A multispecific binding protein comprising the PSMA binding protein according to any one of claim 1, claim 26, or claims 45-50.
63. An antibody comprising the PSMA binding protein according to claim 1, claim 26, or claims 45-50.
64. A multispecific antibody, a bispecific antibody, an sdAb, a variable heavy domain, a peptide, or a ligand, comprising the PSMA binding protein according to claim 1, claim 26, or claims 45-50.
65. An antibody comprising the PSMA binding protein according to claim 1, claim 26, or claims 45-50, wherein said antibody is a single domain antibody.
66. The single domain antibody of claim 64, wherein said antibody is derived from a heavy chain variable region of IgG.
67. A multispecific binding protein or antibody comprising the PSMA binding protein according to any one of claim 1, claim 26, and claims 45-50 and a CD3 binding domain.
68. A method for the treatment or amelioration of a proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, a viral disease, an allergic reaction, a parasitic reaction, a graft-versus-host disease or a host-versus-graft disease comprising administration of the multispecific antibody according to any one of claims 64-68, to a subject in need thereof.

69. A method for the treatment or amelioration of a prostate condition comprising administration of the multispecific antibody according to any one of claims 64-68, to a subject in need thereof.

70. A method for the treatment or amelioration of a prostate condition comprising administration of the PSMA binding protein according to any one of claims 1-53, to a subject in need thereof.

71. The prostate specific membrane antigen binding protein of claim 1, comprising any combination of the following:

- (i) wherein X₁ is proline;
- (ii) wherein X₂ is histidine;
- (iii) wherein X₃ is aspartic acid;
- (iv) wherein X₄ is lysine;
- (v) wherein X₅ is glutamine;
- (vi) wherein X₆ is tyrosine; and
- (vii) wherein X₇ is serine.

72. The prostate specific membrane antigen binding protein of claim 71, wherein the binding protein has a higher affinity towards a human prostate specific membrane antigen than that of a binding protein which has the sequence set forth as SEQ ID NO: 4.

73. The prostate specific membrane antigen binding protein of claim 1, comprising any combination of the following:

- (i) wherein X₁ is proline; wherein X₅ is glutamine;
- (ii) wherein X₆ is tyrosine; wherein X₄ is lysine and X₇ is serine;
- (iii) wherein X₂ is histidine, X₃ is aspartic acid, X₄ is lysine, and X₇ is serine;
- (iv) wherein X₁ is proline, X₂ is histidine, X₃ is aspartic acid, and X₇ is serine;
- (v) wherein X₂ is histidine, X₃ is aspartic acid, X₅ is glutamine, and X₇ is serine;
- (vi) wherein X₂ is histidine, X₃ is aspartic acid, X₄ is lysine, and X₇ is serine;
- (vii) wherein X₁ is proline, X₂ is histidine, X₃ is aspartic acid, and X₇ is serine;
- (viii) wherein X₂ is histidine, X₃ is aspartic acid, X₅ is glutamine, and X₇ is serine;
- (ix) wherein X₂ is histidine, X₃ is aspartic acid, X₆ is tyrosine, and X₇ is serine; and
- (x) wherein X₂ is histidine, X₃ is aspartic acid, and X₇ is serine.

74. The prostate specific membrane antigen binding protein of claim 73, wherein the binding protein has a higher affinity towards a human prostate specific membrane antigen than that of a binding protein which has the sequence set forth in SEQ ID NO: 4.

75. The prostate specific membrane antigen binding protein of claim 74, wherein the binding protein further has a higher affinity towards a cynomolgus prostate specific membrane antigen than that of a binding protein which has the sequence set forth in SEQ ID NO: 4.

76. The prostate specific membrane antigen binding protein of claim 26, comprising any combination of the following:

- (i) substitution at position 31;
- (ii) substitution at position 50;
- (iii) substitution at position 55; substitution at position 56;
- (iv) substitution at position 62;
- (v) substitution at position 97;
- (vi) substitutions at positions 55 and 97;
- (vii) substitutions at positions 33 and 97;
- (viii) substitutions at 33, 50, and 97;
- (ix) substitutions at positions 31, 33, 50, and 97;
- (x) substitutions at positions 33, 50, 55, and 97;
- (xi) substitutions at positions 33, 50, 56, and 97; and
- (xiii) substitutions at positions 33, 50, 62, and 97.

77. The prostate specific membrane antigen binding protein of claim 76, wherein the binding protein 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.

78. The prostate specific membrane antigen binding protein of claim 77, wherein the binding protein 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.

79. 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 RFMISX₁YX₂MH (SEQ ID NO: 1);
- (b) the amino acid sequence of CDR2 is as set forth in X₃INPAX₄X₅TDYAEX₆VKG (SEQ ID NO: 2); and
- (c) the amino acid sequence of CDR3 is as set forth in DX₇YGY (SEQ ID NO: 3), to a

subject in need thereof.

80. An antibody comprising the PSMA binding protein according to claim 1, wherein said antibody is a single domain antibody.

81. The antibody comprising the PSMA binding protein according to claim 80, wherein said single domain antibody is part of a trispecific antibody.
82. An antibody comprising the PSMA binding protein according to claim 26, wherein said antibody is a single domain antibody.
83. The antibody comprising the PSMA binding protein according to claim 82, wherein said single domain antibody is part of a trispecific antibody.
84. An antibody comprising the PSMA binding protein according to claim 49, wherein said antibody is a single domain antibody.
85. The antibody comprising the PSMA binding protein according to claim 84, wherein said single domain antibody is part of a trispecific antibody.