CLAIMS:

1. A prostate-specific membrane antigen (PSMA)-binding polypeptide comprising a humanized PSMA-binding domain wherein the PSMA binding domain comprises

(i) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3, and

(ii) an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3,

wherein the LCDR1, LCDR2 and LCDR3 has the amino acid sequences set forth in SEQ ID NO:15, 16 and 17, respectively, and the HCDR1, HCDR2, and HCDR3 has the amino acid sequences set forth in SEQ ID NO:9, 10 and 11, respectively.

2. The PSMA-binding polypeptide of claim 1, wherein said PSMA-binding polypeptide comprises from amino-terminus to carboxyl-terminus

(a) the PSMA binding domain,

(b) a first hinge region, and

(c) an immunoglobulin constant region.

3. The PSMA-binding polypeptide of claim 1, wherein said PSMA-binding polypeptide further comprises a second binding domain.

4. The PSMA-binding polypeptide of claim 3, wherein the PSMA-binding polypeptide comprises, in order from amino-terminus to carboxyl-terminus or in order from carboxyl-terminus to amino-terminus

(a) the PSMA binding domain,

(b) a first hinge region,

(c) an immunoglobulin constant region,

(d) a second hinge region, and

(e) a second binding domain.

5. The PSMA-binding protein of claim 3 or 4, wherein the second binding domain is amino-terminal to the second hinge region.

6. The PSMA-binding polypeptide of any one of the previous claims, wherein the immunoglobulin light chain variable region comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:5 or SEQ ID NO:23 and the heavy chain variable region comprises an amino acid sequence that is at least 95% or 100% identical to the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:25, or SEQ ID NO:27.

7. The PSMA-binding polypeptide of any one of the previous claims, wherein the PSMA-binding domain competes for binding to human PSMA with a single chain Fv (scFv) having the amino acid sequence set forth in SEQ ID NO:21.

8. The PSMA-binding polypeptide of any one of claims 2-6, wherein the first hinge region is derived from (i) a stalk region of a type II C lectin or (ii) an immunoglobulin hinge region.

9. The PSMA-binding polypeptide of any one of claims 4-7, wherein the second hinge region is derived from (i) a stalk region of a type II C lectin or (ii) an immunoglobulin hinge region.

10. The PSMA-binding polypeptide of any one of the previous claims, wherein the PSMA-binding domain is a single chain Fv (scFv).

11. The PSMA-binding polypeptide of claim 10, wherein said scFv comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, or SEQ ID NO:35.

12. The PSMA-binding polypeptide of any one of the preceding claims, wherein said PSMA-binding polypeptide comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:70, or SEQ ID NO:72.

13. The PSMA-binding polypeptide of any one of claims 3-12, wherein the second binding domain specifically binds a T cell, CD3, CD3ε or a T cell receptor (TCR) complex or a component thereof.

14. The PSMA-binding polypeptide of claim 13, wherein the second binding domain competes for binding to CD3ε with a monoclonal antibody selected from the group consisting of CRIS-7 and HuM291.

15. The PSMA-binding polypeptide of claim 13 or 14, wherein the second binding domain comprises an immunoglobulin light chain variable region and an immunoglobulin heavy chain

variable region derived from a monoclonal antibody selected from the group consisting of CRIS-7 and HuM291.

16. The PSMA-binding polypeptide of claim 15, wherein the light and heavy chain variable regions of the second binding domain are selected from the group consisting of

(a) a light chain variable region comprising an amino acid sequence that is at least 95% or 100% identical to the amino acid sequence set forth in residues 139-245 of SEQ ID NO:47 and a heavy chain variable region comprising an amino acid sequence that is at least 95% or 100% identical to the amino acid sequence set forth in residues 1-121 of SEQ ID NO:47; and

(b) a light chain variable region comprising an amino acid sequence that is at least 95% or 100% identical to the amino acid sequence set forth in residues 634-740 of SEQ ID NO:78 and a heavy chain variable region comprising an amino acid sequence that is at least 95% or 100% identical to the amino acid sequence set forth in residues 496-616 of SEQ ID NO:78.

17. The PSMA-binding polypeptide of claim 1, wherein said PSMA-binding polypeptide comprises an amino acid sequence that is at least 95% or 100% identical to the amino acid sequence set forth in SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, or SEQ ID NO:164.

18. A dimeric PSMA-binding protein comprising first and second polypeptide chains, wherein each of said polypeptide chains is the PSMA-binding polypeptide of any one of the previous claims.

19. An isolated nucleic acid encoding the PSMA-binding polypeptide of any one of the previous claims.

20. A recombinant host cell comprising the nucleic acid of claim 19.

21. A composition comprising the PSMA-binding protein of claim 18; and a pharmaceutically acceptable carrier, diluent, or excipient.

22. A method for inducing redirected T-cell cytotoxicity (RTCC) against a cell expressing prostate-specific membrane antigen (PSMA), the method comprising contacting said PSMA-expressing cell with the PSMA-binding protein of claim 13, wherein said contacting is under

conditions whereby RTCC against the PSMA-expressing cell is induced wherein the method is not a method of treatment for the purposes of therapy carried out on the human or animal body.

23. Use of the dimeric PSMA-binding protein of claim 8 in the manufacture of a medicament for treating a disorder in a subject characterized by overexpression of prostate-specific membrane antigen (PSMA), wherein preferably, the disorder is a cancer, a prostate disorder, a neovascular disorder, a prostate cancer, colorectal cancer, gastric cancer, castrate-resistant prostate cancer, benign prostatic hyperplasia, solid tumor growth, clear cell renal carcinoma, colorectal cancer, bladder cancer, or lung cancer.

CLAIMS:

1. A prostate-specific membrane antigen (PSMA)-binding polypeptide comprising, in order from amino-terminus to carboxyl-terminus or in order from carboxyl-terminus to amino-terminus,

(a) a PSMA-binding domain that specifically binds human PSMA,

(b) a hinge region, and

(c) an immunoglobulin constant region.

2. The PSMA-binding polypeptide of claim 1, wherein the PSMA-binding domain competes for binding to human PSMA with a single chain Fv (scFv) having the amino acid sequence set forth in SEQ ID NO:21.

3. The PSMA-binding polypeptide of claim 1 or 2, wherein the PSMA-binding domain comprises (i) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3, and (ii) an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3.

4. The PSMA-binding polypeptide of claim 3, wherein LCDR3 has the amino acid sequence set forth in SEQ ID NO:17 and HCDR3 has the amino acid sequence set forth in SEQ ID NO:11.

5. The PSMA-binding polypeptide of claim 4, wherein LCDR1 and LCDR2 have the amino acid sequences as set forth in SEQ ID NO:15 and SEQ ID NO:16, respectively, and HCDR1 and HCDR2 have the amino acid sequences as set forth in SEQ ID NO:9 and SEQ ID NO:10, respectively.

6. The PSMA-binding polypeptide of any of claims 3 to 5, wherein at least one of the light chain variable and heavy chain variable regions is humanized.

7. The PSMA-binding polypeptide of any of claims 3 to 6, wherein the light chain variable region comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:5 or SEQ ID NO:23.

8. The PSMA-binding polypeptide of claim 7, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:5 or SEQ ID NO:23.

9. The PSMA-binding polypeptide of any of claims 3 to 8, wherein the heavy chain variable region comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:25, or SEQ ID NO:27.

10. The PSMA-binding polypeptide of claim 9, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:25, or SEQ ID NO:27.

11. The PSMA-binding polypeptide of any of claims 3 to 10, wherein the PSMA-binding domain is an scFv.

12. The PSMA-binding polypeptide of claim 11, wherein said scFv comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, or SEQ ID NO:35.

13. The PSMA-binding polypeptide of claim 12, wherein said scFv comprises the amino acid sequence set forth in SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, or SEQ ID NO:35.

14. The PSMA-binding polypeptide of claim 11, wherein the heavy chain variable region of said scFv is carboxy-terminal to the light chain variable region.

15. The PSMA-binding polypeptide of claim 14, wherein said scFv comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:21, SEQ ID NO:30, or SEQ ID NO:31.

16. The PSMA-binding polypeptide of claim 15, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO:21, SEQ ID NO:30, or SEQ ID NO:31.

17. The PSMA-binding polypeptide of claim 11 or 14, wherein the light chain variable region and heavy chain variable region of the scFv are joined by an amino acid sequence comprising $(Gly_4Ser)_n$, wherein n = 1-5 (SEQ ID NO:165).

18. The PSMA-binding polypeptide of any of claims 1 to 17, wherein the hinge region is derived from an immunoglobulin hinge region.

19. The PSMA-binding polypeptide of any of claims 1 to 18, wherein the immunoglobulin constant region comprises immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2 or IgD.

20. The PSMA-binding polypeptide of claim 19, wherein the hinge region is derived from an immunoglobulin hinge region and the immunoglobulin constant region comprises immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, or IgG4.

21. The PSMA-binding polypeptide of any of claims 1 to 20, wherein the PSMA-binding polypeptide comprises at least one effector function selected from the group consisting of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

22. The PSMA-binding polypeptide of claim 1, wherein said PSMA-binding polypeptide comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:70, or SEQ ID NO:72.

23. The PSMA-binding polypeptide of claim 22, wherein said PSMA-binding polypeptide comprises the amino acid sequence set forth in SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:70, or SEQ ID NO:72.

24. The PSMA-binding polypeptide of any of claims 1 to 23, further comprising

(d) a second hinge region carboxy-terminal to the immunoglobulin constant region, and

(e) a second binding domain carboxy-terminal to the second hinge region.

25. The PSMA-binding polypeptide of claim 24, wherein the second hinge region is derived from (i) a stalk region of a type II C lectin or (ii) an immunoglobulin hinge region.

26. A prostate-specific membrane antigen (PSMA)-binding polypeptide comprising

a first binding domain that specifically binds human PSMA, the first binding domain comprising (i) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3, and (ii) an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3;

wherein LCDR3 has the amino acid sequence set forth in SEQ ID NO:17 and HCDR3 has the amino acid sequence set forth in SEQ ID NO:11.

27. The PSMA-binding polypeptide of claim 26, wherein LCDR1 and LCDR2 have the amino acid sequences as set forth in SEQ ID NO:15 and SEQ ID NO:16, respectively, and HCDR1 and HCDR2 have the amino acid sequences as set forth in SEQ ID NO:9 and SEQ ID NO:10, respectively.

28. The PSMA-binding polypeptide of claim 26 or 27, wherein at least one of the light chain variable and heavy chain variable regions is humanized.

29. The PSMA-binding polypeptide of claim 27, wherein the light chain variable region has the amino acid sequence set forth in SEQ ID NO:5 or SEQ ID NO:23.

30. The PSMA-binding polypeptide of claim 27 or 29, wherein the heavy chain variable region has the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:25, or SEQ ID NO:27.

31. The PSMA-binding polypeptide of any of claims 26 to 30, wherein the first binding domain is a single chain Fv (scFv).

32. The PSMA-binding polypeptide of claim 31, wherein said scFv comprises the amino acid sequence set forth in SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, or SEQ ID NO:35.

33. The PSMA-binding polypeptide of claim 31, wherein the heavy chain variable region of said scFv is carboxy-terminal to the light chain variable region.

34. The PSMA-binding polypeptide of claim 33, wherein said scFv comprises the amino acid sequence set forth in SEQ ID NO:21, SEQ ID NO:30, or SEQ ID NO:31.

35. The PSMA-binding polypeptide of claim 31 or 33, wherein the light chain variable region and heavy chain variable region of the scFv are joined by an amino acid sequence comprising $(Gly_4Ser)_n$, wherein n = 1-5 (SEQ ID NO:165).

36. The PSMA-binding polypeptide of any of claims 26 to 35, wherein said PSMA-binding polypeptide further comprises an immunoglobulin constant region.

37. The PSMA-binding polypeptide of claim 36, wherein said immunoglobulin constant region comprises immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2 or IgD.

38. The PSMA-binding polypeptide of claim 36, wherein said PSMA-binding polypeptide further comprises at least one hinge region derived from (i) a stalk region of a type II C lectin or (ii) an immunoglobulin hinge region.

39. The PSMA-binding polypeptide of any of claims 26 to 38, wherein said PSMA-binding polypeptide further comprises a second binding domain.

40. The PSMA-binding polypeptide of claim 39, wherein said PSMA-binding polypeptide comprises, in order from amino-terminus to carboxyl-terminus or in order from carboxyl-terminus to amino-terminus,

(a) the first binding domain,
(b) a first hinge region,
(c) the immunoglobulin constant region,
(d) a second hinge region, and
(e) a second binding domain.

41. The PSMA-binding polypeptide of claim 36, wherein said PSMA binding polypeptide comprises, in order from amino-terminus to carboxyl-terminus,

(a) the first binding domain,
(b) a hinge region, and
(c) the immunoglobulin constant region.

42. The PSMA-binding polypeptide of claim 41, wherein said PSMA binding polypeptide further comprises

(d) a second hinge region carboxy-terminal to the immunoglobulin constant region, and
(e) a second binding domain carboxy-terminal to the second hinge region.

43. The PSMA-binding polypeptide of claim 36, wherein said PSMA binding polypeptide comprises, in order from amino-terminus to carboxyl-terminus,

(a) the immunoglobulin constant region,
(b) a hinge region, and

(c) the first binding domain.

44. The PSMA-binding polypeptide of claim 43, wherein said PSMA-binding polypeptide comprises

(d) a second hinge region amino-terminal to the immunoglobulin constant region, and

(e) a second binding domain amino-terminal to the second hinge region.

45. The PSMA-binding polypeptide of any of claims 24, 25, 39, 40, 42, and 44, wherein the second binding domain specifically binds a T cell.

46. The PSMA-binding polypeptide of claim 45, wherein the second binding domain specifically binds a T cell receptor (TCR) complex or a component thereof.

47. The PSMA-binding polypeptide of claim 46, wherein the second binding domain specifically binds CD3.

48. The PSMA-binding polypeptide of claim 47, wherein the second binding domain specifically binds CD3ε.

49. The PSMA-binding polypeptide of claim 48, wherein the second binding domain competes for binding to CD3ε with a monoclonal antibody selected from the group consisting of CRIS-7 and HuM291.

50. The PSMA-binding polypeptide of claim 49, wherein the second binding domain comprises an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region derived from a monoclonal antibody selected from the group consisting of CRIS-7 and HuM291.

51. The PSMA-binding polypeptide of claim 50, wherein the light and heavy chain variable regions of the second binding domain are humanized variable regions comprising, respectively, the light and heavy chain CDRs of the monoclonal antibody.

52. The PSMA-binding polypeptide of claim 50, wherein the light and heavy chain variable regions of the second binding domain are selected from the group consisting of

(a) a light chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in residues 139-245 of SEQ

ID NO:47 and a heavy chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in residues 1-121 of SEQ ID NO:47; and

(b) a light chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in residues 634-740 of SEQ ID NO:78 and a heavy chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in residues 496-616 of SEQ ID NO:78.

53. The PSMA-binding polypeptide of claim 50, wherein the light and heavy chain variable regions of the second binding domain are selected from the group consisting of

(a) a light chain variable region comprising the amino acid sequence set forth in residues 139-245 of SEQ ID NO:47 and a heavy chain variable region comprising the amino acid sequence set forth in residues 1-121 of SEQ ID NO:47; and

(b) a light chain variable region comprising the amino acid sequence set forth in residues 634-740 of SEQ ID NO:78 and a heavy chain variable region comprising the amino acid sequence set forth in residues 496-616 of SEQ ID NO:78.

54. The PSMA-binding polypeptide of any of claims 39, 40, 42, and 44 to 53, wherein the second binding domain is a scFv.

55. The PSMA-binding polypeptide of claim 50, wherein the second binding domain is a scFv comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of (i) the amino acid sequence set forth in residues 1-245 of SEQ ID NO:47, and (ii) the amino acid sequence set forth in residues 496-742 of SEQ ID NO:78.

56. The PSMA-binding polypeptide of claim 55, wherein the second binding domain comprises the amino acid sequence selected from the group consisting of (i) the amino acid sequence set forth in residues 1-245 of SEQ ID NO:47, and (ii) the amino acid sequence set forth in residues 496-742 of SEQ ID NO:78.

57. The PSMA-binding polypeptide of claim 54, wherein said PSMA-binding polypeptide comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, or SEQ ID NO:164.

58. The PSMA-binding polypeptide of claim 54, wherein said PSMA-binding polypeptide comprises the amino acid sequence set forth in SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, or SEQ ID NO:164.

59. A dimeric PSMA-binding protein comprising first and second polypeptide chains, wherein each of said polypeptide chains is a PSMA-binding polypeptide as in any one of claims 1 to 58.

60. A PSMA-binding polypeptide comprising, in order from amino-terminus to carboxyl-terminus,

(a) a binding domain that specifically binds human PSMA,
(b) a hinge region,
(c) an immunoglobulin constant region, and
(d) an immunoglobulin heterodimerization domain.

61. The PSMA-binding polypeptide of claim 60, wherein the binding domain competes for binding to human PSMA with a single chain Fv (scFv) having the amino acid sequence set forth in SEQ ID NO:21.

62. The PSMA-binding polypeptide of claim 60 or 61, wherein the binding domain comprises (i) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3, and (ii) and an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3.

63. The PSMA-binding polypeptide of claim 62, wherein LCDR3 has the amino acid sequence set forth in SEQ ID NO:17 and HCDR3 has the amino acid sequence set forth in SEQ ID NO:11.

64. The PSMA-binding polypeptide of claim 63, wherein LCDR1 and LCDR2 have the amino acid sequences as set forth in SEQ ID NO:15 and SEQ ID NO:16, respectively, and HCDR1 and HCDR2 have the amino acid sequences as set forth in SEQ ID NO:9 and SEQ ID NO:10, respectively.

65. The PSMA-binding polypeptide of any of claims 62 to 64, wherein at least one of the light chain variable and heavy chain variable regions is humanized.

66. The PSMA-binding polypeptide of any of claims 62 to 65, wherein the light chain variable region comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:5 or SEQ ID NO:23.

67. The PSMA-binding polypeptide of claim 66, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:5 or SEQ ID NO:23.

68. The PSMA-binding polypeptide of any of claims 62 to 67, wherein the heavy chain variable region comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:25, or SEQ ID NO:27.

69. The PSMA-binding polypeptide of claim 68, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:25, or SEQ ID NO:27.

70. The PSMA-binding polypeptide of any of claims 62 to 69, wherein the binding domain is an scFv.

71. The PSMA-binding polypeptide of claim 70, wherein said scFv comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, or SEQ ID NO:35.

72. The PSMA-binding polypeptide of claim 71, wherein said scFv comprises the amino acid sequence set forth in SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, or SEQ ID NO:35.

73. The PSMA-binding polypeptide of claim 70, wherein the heavy chain variable region of said scFv is carboxy-terminal to the light chain variable region.

74. The PSMA-binding polypeptide of claim 73, wherein said scFv comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:21, SEQ ID NO:30, or SEQ ID NO:31.

75. The PSMA-binding polypeptide of claim 74, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO:21, SEQ ID NO:30, or SEQ ID NO:31.

76. The PSMA-binding polypeptide of claim 70 or 73, wherein the light chain variable region and heavy chain variable region of the scFv are joined by an amino acid sequence comprising $(Gly_4Ser)_n$, wherein n = 1-5 (SEQ ID NO:165).

77. The PSMA-binding polypeptide of any of claims 60 to 76, wherein the immunoglobulin heterodimerization domain comprises an immunoglobulin CH1 domain or an immunoglobulin CL domain.

78. The PSMA-binding polypeptide of any of claims 60 to 77, wherein the immunoglobulin constant region comprises immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD or any combination thereof; an immunoglobulin CH3 domain of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, IgM or any combination thereof; or immunoglobulin CH3 and CH4 domains of IgE, IgM or a combination thereof.

79. The PSMA-binding polypeptide of claim 78, wherein the hinge region is derived from an immunoglobulin hinge region and the immunoglobulin constant region comprises immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, or IgG4.

80. The PSMA-binding polypeptide of any of claims 60 to 79, wherein the PSMA-binding polypeptide comprises at least one effector function selected from the group consisting of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

81. The PSMA-binding polypeptide of claim 60, wherein said PSMA-binding polypeptide comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:46, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, or SEQ ID NO:61.

82. The PSMA-binding polypeptide of claim 81, wherein said PSMA-binding polypeptide comprises the amino acid sequence set forth in SEQ ID NO:46, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, or SEQ ID NO:61.

83. A heterodimeric PSMA-binding protein comprising

(1) a first polypeptide chain comprising, in order from amino-terminus to carboxyl-terminus,

(a) first binding domain that specifically binds human PSMA,

(b) a first hinge region,

(c) a first immunoglobulin constant region, and

(d) a first immunoglobulin heterodimerization domain; and

(2) a second polypeptide chain comprising, in order from amino-terminus to carboxyl-terminus,

(a') a second hinge region,

(b') a second immunoglobulin constant region, and

(c') a second immunoglobulin heterodimerization domain that is different from the first immunoglobulin heterodimerization domain of the first single chain polypeptide,

wherein the first and second immunoglobulin heterodimerization domains associate with each other to form a heterodimer.

84. The heterodimeric PSMA-binding protein of claim 83, wherein the first binding domain competes for binding to human PSMA with a single chain Fv (scFv) having the amino acid sequence set forth in SEQ ID NO:21.

85. The heterodimeric PSMA-binding protein of claim 83 or 84, wherein the PSMA-binding domain comprises (i) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3, and (ii) and an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3.

86. The heterodimeric PSMA-binding protein of claim 85, wherein LCDR3 has the amino acid sequence set forth in SEQ ID NO:17 and HCDR3 has the amino acid sequence set forth in SEQ ID NO:11.

87. The heterodimeric PSMA-binding protein of claim 86, wherein LCDR1 and LCDR2 have the amino acid sequences as set forth in SEQ ID NO:15 and SEQ ID NO:16, respectively, and HCDR1 and HCDR2 have the amino acid sequences as set forth in SEQ ID NO:9 and SEQ ID NO:10, respectively.

88. The heterodimeric PSMA-binding protein of any of claims 85 to 87, wherein at least one of the light chain variable and heavy chain variable regions is humanized.

89. The heterodimeric PSMA-binding protein of any of claims 85 to 88, wherein the light chain variable region comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:5 or SEQ ID NO:23.

90. The heterodimeric PSMA-binding protein of claim 89, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:5 or SEQ ID NO:23.

91. The heterodimeric PSMA-binding protein of any of claims 85 to 90, wherein the heavy chain variable region comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:25, or SEQ ID NO:27.

92. The heterodimeric PSMA-binding protein of claim 91, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:25, or SEQ ID NO:27.

93. The heterodimeric PSMA-binding protein of any of claims 85 to 92, wherein the PSMA-binding domain is an scFv.

94. The heterodimeric PSMA-binding protein of claim 93, wherein said scFv comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, or SEQ ID NO:35.

95. The heterodimeric PSMA-binding protein of claim 94, wherein said scFv comprises the amino acid sequence set forth in SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, or SEQ ID NO:35.

96. The heterodimeric PSMA-binding protein of claim 93, wherein the heavy chain variable region of said scFv is carboxy-terminal to the light chain variable region.

97. The heterodimeric PSMA-binding protein of claim 96, wherein the scFv comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:21, SEQ ID NO:30, or SEQ ID NO:31.

98. The heterodimeric PSMA-binding protein of claim 97, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO:21, SEQ ID NO:30, or SEQ ID NO:31.

99. The hererodimeric PSMA-binding protein of claim 93 or 96, wherein the light chain variable region and heavy chain variable region of the scFv are joined by an amino acid sequence comprising $(Gly_4Ser)_n$, wherein n = 1-5 (SEQ ID NO:165).

100. The heterodimeric PSMA-binding protein of any of claims 83 to 99, wherein the first immunoglobulin heterodimerization domain comprises a first immunoglobulin CH1 domain and the second immunoglobulin heterodimerization domain comprises a first immunoglobulin CL domain, or

wherein the first immunoglobulin heterodimerization domain comprises a first immunoglobulin CL domain and the second immunoglobulin heterodimerization domain comprises a first immunoglobulin CH1 domain.

101. The heterodimeric PSMA-binding protein of any of claims 83 to 100, wherein at least one of the first and second immunoglobulin constant regions comprises immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD or any combination thereof; an immunoglobulin CH3 domain of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, IgM or any combination thereof; or immunoglobulin CH3 and CH4 domains of IgE, IgM or a combination thereof.

102. The heterodimeric PSMA-binding protein of claim 101, wherein each of the first and second hinge regions is derived from an immunoglobulin hinge region and each of the first and second immunoglobulin constant regions comprises immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, or IgG4.

103. The heterodimeric PSMA-binding protein of any of claims 83 to 102, wherein at least one of the first and second polypeptide chains comprises at least one effector function selected from the group consisting of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

104. The heterodimeric PSMA-binding protein of any of claims 83 to 103, wherein said second polypeptide chain further comprises a second binding domain.

105. The heterodimeric PSMA-binding protein of claim 104, wherein the second binding domain is amino-terminal to the second hinge region.

106. The heterodimeric PSMA-binding protein of claim 104 or 105, wherein the second binding specifically binds a T cell.

107. The heterodimeric PSMA-binding protein of claim 106, wherein the second binding domain specifically binds a T cell receptor (TCR) complex or a component thereof.

108. The heterodimeric PSMA-binding protein of claim107, wherein the second binding domain specifically binds CD3.

109. The heterodimeric PSMA-binding protein of claim 108, wherein the second binding domain specifically binds CD3ε.

110. The heterodimeric PSMA-binding protein of claim 109, wherein the second binding domain competes for binding to CD3ε with a monoclonal antibody selected from the group consisting of CRIS-7 and HuM291.

111. The heterodimeric PSMA-binding protein of claim 110, wherein the second binding domain comprises an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region derived from a monoclonal antibody selected from the group consisting of CRIS-7 and HuM291.

112. The heterodimeric PSMA-binding protein of claim 111, wherein the light and heavy chain variable regions of the second binding domain are humanized variable regions comprising, respectively, the light chain CDRs and the heavy chain CDRs of the monoclonal antibody.

113. The heterodimeric PSMA-binding protein of claim 111, wherein the light and heavy chain variable regions of the second binding domain are selected from the group consisting of

(a) a light chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in residues 139-245 of SEQ ID NO:47 and a heavy chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in residues 1-121 of SEQ ID NO:47; and

(b) a light chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in residues 634-740 of SEQ ID NO:78 and a heavy chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in residues 496-616 of SEQ ID NO:78.

114. The heterodimeric PSMA-binding protein of claim 111, wherein the light and heavy chain variable regions are selected from the group consisting of

(a) a light chain variable region comprising the amino acid sequence set forth in residues 139-245 of SEQ ID NO:47 and a heavy chain variable region comprising the amino acid sequence set forth in residues 1-121 of SEQ ID NO:47; and

(b) a light chain variable region comprising the amino acid sequence set forth in residues 634-740 of SEQ ID NO:78 and a heavy chain variable region comprising the amino acid sequence set forth in residues 496-616 of SEQ ID NO:78.

115. The heterodimeric PSMA-binding protein of any of claims 104 to 114, wherein the second binding domain is a scFv.

116. The heterodimeric PSMA-binding protein of claim 111, wherein the second binding domain is a scFv comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of (i) the amino acid sequence set forth in residues 1-245 of SEQ ID NO:47, and (ii) the amino acid sequence set forth in residues 496-742 of SEQ ID NO:78.

117. The heterodimeric PSMA-binding protein of claim 116, wherein the second binding domain scFv comprises the amino acid sequence selected from the group consisting of (i) the amino acid sequence set forth in residues 1-245 of SEQ ID NO:47, and (ii) the amino acid sequence set forth in residues 496-742 of SEQ ID NO:78.

118. The heterodimeric PSMA-binding protein of claim 115, wherein

(a) the first polypeptide chain comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 46 and the second polypeptide chain comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 47;

(b) the first polypeptide chain comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 58 and the second polypeptide chain comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 57;

(c) the first polypeptide chain comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 59 and the second polypeptide chain comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 57;

(d) the first polypeptide chain comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 60 and the second polypeptide chain comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 47; or

(e) the first polypeptide chain comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 61 and the second polypeptide chain comprises an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 47.

119. The heterodimeric PSMA-binding protein of claim 118, wherein

(a) the first polypeptide chain comprises the amino acid sequence set forth in SEQ ID NO: 46 and the second polypeptide chain comprises the amino acid sequence set forth in SEQ ID NO: 47;

(b) the first polypeptide chain comprises the amino acid sequence set forth in SEQ ID NO: 58 and the second polypeptide chain comprises the amino acid sequence set forth in SEQ ID NO: 57;

(c) the first polypeptide chain comprises the amino acid sequence set forth in SEQ ID NO: 59 and the second polypeptide chain comprises the amino acid sequence set forth in SEQ ID NO: 57;

(d) the first polypeptide chain comprises the amino acid sequence set forth in SEQ ID NO: 60 and the second polypeptide chain comprises the amino acid sequence set forth in SEQ ID NO: 47; or

(e) the first polypeptide chain comprises the amino acid sequence set forth in SEQ ID NO: 61 and the second polypeptide chain comprises the amino acid sequence set forth in SEQ ID NO: 47.

120. The PSMA-binding protein of any of claims 59 and 83 to 119, wherein the PSMA-binding protein exhibits increased serum half-life, reduced internalization by a cell expressing PSMA, and/or increased time of persistence on the surface of the cell expressing PSMA as compared to murine monoclonal antibody 107-1A4.

121. An isolated nucleic acid encoding the PSMA-binding polypeptide of any of claims 1 to 58 and 60 to 82.

122. The isolated nucleic acid of claim 121, wherein the nucleic acid comprises the nucleotide sequence set forth in SEQ ID NO NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:33,

SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:53, SEQ ID: NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:79, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, or SEQ ID NO:163.

123. An expression vector comprising a nucleic acid segment encoding the PSMA-binding polypeptide of any of claims 1 to 58 and 60 to 82, wherein the nucleic acid segment is operably linked to regulatory sequences suitable for expression of the nucleic acid segment in a host cell.

124. The expression vector of claim 123, wherein the nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:53, SEQ ID: NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:79, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, or SEQ ID NO:163.

125. A recombinant host cell comprising the expression vector of claim 123 or 124.

126. An expression vector comprising first and second expression units,

wherein the first and second expression units respectively comprise first and second nucleic acid segments encoding the first and second polypeptide chains of a heterodimeric PSMA-binding protein as set forth in any of claims 83 to 119, and

wherein the first and second nucleic acid segments are operably linked to regulatory sequences suitable for expression of the nucleic acid segments in a host cell.

127. The expression vector of claim 126, wherein

(a) the first nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO:44 and the second nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO:45;

(b) the first nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO:53 and the second nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO:52;

(c) the first nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO:54 and the second nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO:52;

(d) the first nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO:55 and the second nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO:45; or

(e) the first nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO:56 and the second nucleic acid segment comprises the nucleotide sequence set forth in SEQ ID NO:45.

128. A recombinant host cell comprising the expression vector of claim 126 or 127.

129. A method for producing a PSMA-binding polypeptide, the method comprising culturing a recombinant host cell comprising the expression vector of claim 123 or 124 under conditions whereby the nucleic acid segment is expressed, thereby producing the PSMA-binding polypeptide.

130. The method of claim 129, further comprising recovering the PSMA-binding polypeptide.

131. A method for producing a dimeric PSMA-binding protein, the method comprising culturing a recombinant host cell comprising an expression vector, wherein the expression vector comprises a nucleic acid segment encoding the PSMA-binding polypeptide of any of claims 1 to 58, wherein the nucleic acid segment is operably linked to regulatory sequences suitable for expression of the nucleic acid segment in the host cell, and

wherein said culturing is under conditions whereby the nucleic acid segment is expressed and the encoded PSMA-binding polypeptide is produced as a dimeric PSMA-binding protein.

132. The method of claim 131, further comprising recovering the dimeric PSMA-binding protein.

133. A method for producing a heterodimeric PSMA-binding protein, the method comprising

culturing a recombinant host cell comprising first and second expression units, wherein the first and second expression units respectively comprise first and second nucleic

acid segments encoding the first and second polypeptide chains of a heterodimeric PSMA-binding protein as set forth in any of claims 83 to 119, wherein the first and second nucleic acid segments are operably linked to regulatory sequences suitable for expression of the nucleic acid segments in a host cell, and

wherein said culturing is under conditions whereby the first and second nucleic acid segments are expressed and the encoded polypeptide chains are produced as the heterodimeric PSMA-binding protein.

134. The method of claim 133, further comprising recovering the heterodimeric PSMA-binding protein.

135. A composition comprising
the PSMA-binding protein of claim 59; and
a pharmaceutically acceptable carrier, diluent, or excipient.

136. A composition comprising
the heterodimeric PSMA-binding protein of any of claims 83 to 119; and
a pharmaceutically acceptable carrier, diluent, or excipient.

137. A method for inducing at least one of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) against a cell expressing prostate-specific membrane antigen (PSMA), the method comprising

contacting said PSMA-expressing cell with a dimeric PSMA-binding protein comprising first and second polypeptide chains, wherein each of said polypeptide chains is a PSMA-binding polypeptide as in claim 20 or 21, and wherein said contacting is under conditions whereby at least one of ADCC and CDC against the PSMA-expressing cell is induced.

138. A method for inducing at least one of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) against a cell expressing prostate-specific membrane antigen (PSMA), the method comprising

contacting said PSMA-expressing cell with a heterodimeric PSMA-binding protein as in claim 102 or 103, wherein said contacting is under conditions whereby at least one of ADCC and CDC against the PSMA-expressing cell is induced.

139. A method for inducing redirected T-cell cytotoxicity (RTCC) against a cell expressing prostate-specific membrane antigen (PSMA), the method comprising

contacting said PSMA-expressing cell with a dimeric PSMA-binding protein comprising first and second polypeptide chains, wherein each of said polypeptide chains is a PSMA-binding polypeptide as in any of claims 45 to 58, and wherein said contacting is under conditions whereby RTCC against the PSMA-expressing cell is induced.

140. A method for inducing redirected T-cell cytotoxicity (RTCC) against a cell expressing prostate-specific membrane antigen (PSMA), the method comprising

contacting said PSMA-expressing cell with a heterodimeric PSMA-binding protein as in any of claims 106 to 119, wherein said contacting is under conditions whereby RTCC against the PSMA-expressing cell is induced.

141. Use of a dimeric prostate-specific membrane antigen (PSMA)-binding protein of claim 59 in the manufacture of a medicament for treating a disorder in a subject, wherein said disorder is characterized by overexpression of prostate-specific membrane antigen (PSMA).

142. The use of claim 141, wherein the first and second polypeptide chains of the dimeric PSMA-binding protein is a PSMA-binding polypeptide as in any of claims 45 to 58, and wherein the dimeric PSMA-binding protein induces redirected T-cell cytotoxicity (RTCC) in the subject.

143. Use of a heterodimeric prostate-specific membrane antigen (PSMA)-binding protein as in any of claims 83 to 119 in the manufacture of a medicament for treating a disorder in a subject, wherein said disorder is characterized by overexpression of prostate-specific membrane antigen (PSMA).

144. The use of claim 143, wherein the heterodimeric PSMA-binding protein is the protein of any of claims 106 to 119, and wherein the heterodimeric PSMA-binding protein induces redirected T-cell cytotoxicity (RTCC) in the subject.

145. The use of any of claims 141 to 144, wherein the disorder is a cancer.

146. The use of claim 145, wherein the cancer is selected from the group consisting of prostate cancer, colorectal cancer, and gastric cancer.

147. The use of claim 146, wherein the cancer is prostate cancer.

~~148. The use of claim 147, wherein the prostate cancer is castrate-resistant prostate cancer.~~

149. The use of any of claims 141 to 144, wherein the disorder is a prostate disorder.

150. The use of claim 149, wherein the prostate disorder is selected from the group consisting of prostate cancer and benign prostatic hyperplasia.

151. The use of any of claims 141 to 144, wherein the disorder is a neovascular disorder.

152. The use of claim 151, wherein the neovascular disorder is a cancer characterized by solid tumor growth.

153. The use of claim 152, wherein the cancer is selected from the group consisting of clear cell renal carcinoma, colorectal cancer, bladder cancer, and lung cancer.