CLAIMS

1. An isolated immunogenic PSMA polypeptide, the amino acid sequence of which has 90%-99% identity to amino acids 15-750 of the human PSMA of SEQ ID NO: 1 and comprises amino acids of at least 10, 11, 12,13 ,14, 15, 16, 17, 18, or 19 of the conserved T cell epitopes of the human PSMA protein at corresponding positions.

2. The isolated immunogenic PSMA polypeptide according to claim 1, which comprises at least 15, 16, 17, 18, or 19 of the conserved T cell epitopes of the human PSMA.

3. The isolated immunogenic PSMA polypeptide according to claim 2, which has 94% - 97% identity to amino acids 15-750 of human PSMA of SEQ ID NO: 1.

4. The isolated immunogenic PSMA polypeptide according to claim 3, which comprises an amino acid sequence selected from the group consisting of:

a) amino acid sequence of SEQ ID NO: 3;

b) amino acid sequence of SEQ ID NO: 5;

c) amino acid sequence of SEQ ID NO: 7; and

d) the amino acid sequence of SEQ ID NO: 9.

5. The isolated immunogenic PSMA polypeptide according to claim 3, which consists of an amino acid sequence selected from the group consisting of:

a) amino acid sequence of SEQ ID NO: 3;

b) amino acid sequence of SEQ ID NO: 5;

c) amino acid sequence of SEQ ID NO: 7; and

d) the amino acid sequence of SEQ ID NO:9.

6. A composition comprising an isolated immunogenic PSMA polypeptide or a functional variant thereof according to any one of claims 1- 5 and a pharmaceutically acceptable excipient.

7. The composition according to claim 6, further comprising an immunogenic PSA polypeptide.

8. The composition according to claim 7, wherein the immunogenic PSA polypeptide consists of the amino acid sequence of SEQ ID NO:17.

9. The composition according to claim 8, wherein the immunogenic PSA polypeptide consists of the amino acid sequence of SEQ ID NO: 19.

10. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an immunogenic PSMA polypeptide according to any one of claims 1-5.

11. An isolated nucleic acid molecule comprising a nucleotide sequence, or a degenerate variant thereof, selected from the group consisting of:

a) the nucleotide sequence of SEQ ID NO:4;

b) the nucleotide sequence of SEQ ID NO:6;

c) the nucleotide sequence of SEQ ID NO:8; and

d) the nucleotide sequence of SEQ ID NO:10.

12. A plasmid construct comprising an isolated nucleic acid molecule according to claim 10 or claim 11.

13. A vector comprising a nucleic acid molecule according to claim 10 or claim 11.

14. A composition comprising an isolated nucleic acid molecule according to claim 10 or claim 11, a plasmid construct according to claim 12, or a vector according to claim 13.

15. The composition according to claim 14, further comprising a nucleic acid molecule that encodes an immunogenic PSA polypeptide consisting of amino acid sequence of SEQ ID NO:17 or amino acid sequence of SEQ ID NO:19.

16. The composition according to claim 15, further comprising a nucleic acid molecule that encodes the human PSCA protein.

17. The composition according to claim 16, which is a vaccine composition.

18. Use of an immune-effector-cell enhancer for the preparation of a medicament for enhancing the therapeutic effect of a vaccine for the treatment of a neoplastic disorder in a mammal, wherein the medicament is administered in combination with an immune-suppressive-cell inhibitor.

19. Use of an immune-effector-cell enhancer for the preparation of a medicament for enhancing immunogenicity of a vaccine for the treatment of a neoplastic disorder in a mammal, wherein the medicament is administered in combination with an immune- suppressive-cell inhibitor.

20. The use according to any one of claims 18-19, wherein the mammal is a human.

21. The use according to claim 20, wherein the neoplastic disorder is cancer.

22. The use according to claim 21, wherein the immune-suppressive-cell inhibitor is selected from a protein kinase inhibitor, a COX-2 inhibitor, or a PDE5 inhibitor; and wherein the immune-effector-cell enhancer is selected from a CTLA-4 inhibitor, a CD40 agonist, a TLR agonist, a 4-1BB agonist, a OX40 agonist, a GITR agonist, a PD-1 antagonist, or a PD-L1 antagonist.

23. The use according to claim 22, wherein:

1) the protein kinase inhibitor is selected from the group consisting of imatinib, sorafenib, lapatinib, zactima MP-412, dasatinib, lestaurtinib, lapatinib, sunitinib malate, axitinib, erlotinib, gefitinib, bosutinib, temsirolismus, and nilotinib;

2) the CTLA-4 inhibitor is selected from the group consisting of ipilimumab and Tremelimumab;

3) the CD40 agonist is an anti-CD40 antibody selected from the group consisting of G28-5, mAb89, EA-5 , S2C6, CP870893, and dacetuzumab; and

4) the TLR agonist is a CpG oligonucleotide selected from the group consisting of CpG 24555, CpG 10103, CpG7909, and CpG1018.

24. The use according to claim 23, wherein the immune-suppressive-cell inhibitor is a protein kinase inhibitor and wherein the immune-effector-cell enhancer is a CTLA-4 inhibitor.

25. The use according to claim 24, wherein the protein kinase inhibitor is selected from sorafenib, dasatinib, imatinib, axitinib or sunitinib malate and wherein the CTLA-4 inhibitor is Tremelimumab.

26. Use of an immune-effector-cell enhancer for the preparation of a medicament for treating a neoplastic disorder in a human, wherein the medicament is administered in combination with a vaccine and an immune-suppressive-cell inhibitor, and wherein the vaccine is capable of eliciting an immune response against a tumor-associated antigen associated with the neoplastic disorder.

27. The use according to claim 26, wherein the neoplastic disorder is prostate cancer.

28. The use according to claim 27, wherein the vaccine comprises a nucleic acid molecule encoding an immunogenic PSMA polypeptide selected from the group consisting of:

1) polypeptide consisting of the amino acid sequence of SEQ ID NO:9;

2) polypeptide consisting of the amino acids 4- 739 of SEQ ID NO:3;

3) polypeptide consisting of the amino acids 4 -739 of SEQ ID NO:5; and

4) polypeptide consisting of the amino acids 4 – 739 of SEQ ID NO:7.

29. The method according to claim 28, wherein the isolated nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of:

1) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:4;

2) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:6;

3) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:8; and

4) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:10, or a degenerate variant of any of the nucleotide sequences,

30. The use according to claim 28, wherein the vaccine further comprises a nucleic acid molecule encoding an immunogenic PSA polypeptide and wherein the immunogenic PSA polypeptide is selected from the group consisting of:

1) a polypeptide comprising the amino acid sequence of SEQ ID NO:17 or amino acids 4-240 of SEQ ID NO:17;

2) a polypeptide consisting of the amino acid sequence of SEQ ID NO:17 or amino acids 4-240 of SEQ ID NO:17;

3) a polypeptide comprising the amino acid sequence of SEQ ID NO:19 or amino acids 4-281 of SEQ ID NO:19; and

4) a polypeptide consisting of the amino acid sequence of SEQ ID NO:19 or amino acids 4-281 of SEQ ID NO:19.

31. The use according to claim 30, wherein the vaccine further comprises a nucleic acid molecule encoding the human PSCA polypeptide.

32. The use according to claim 31, wherein the immunogenic PSCA polypeptide is the full length human PSCA.

33. The use according to claim 27, wherein the vaccine comprises a multi-antigen construct encoding at least two immunogenic PAA polypeptides selected from

the group consisting of immunogenic PSMA polypeptide, an immunogenic PSA polypeptide, and an immunogenic PSCA polypeptide,

34. The use according to claim 27, wherein the vaccine comprises a multi-antigen construct encoding at least three immunogenic PAA polypeptides selected from the group consisting of an immunogenic PSMA polypeptide, an immunogenic PSA polypeptide, and an immunogenic PSCA polypeptide.

35. The use according to claim 33 or claim 34, wherein the immunogenic PSMA polypeptide is selected from the group consisting of:

1) a polypeptide consisting of the amino acid sequence of SEQ ID NO:9;

2) a polypeptide consisting of the amino acids 4- 739 of SEQ ID NO:3;

3) a polypeptide consisting of the amino acids 4 -739 of SEQ ID NO:5; and

4) a polypeptide consisting of the amino acids 4 – 739 of SEQ ID NO:7,

wherein the immunogenic PSA polypeptide is selected from the group consisting of:

1) a polypeptide comprising the amino acid sequence of SEQ ID NO:17 or amino acids 4-240 of SEQ ID NO:17;

2) a polypeptide consisting of the amino acid sequence of SEQ ID NO:17 or amino acids 4-240 of SEQ ID NO:17;

3) a polypeptide comprising the amino acid sequence of SEQ ID NO:19 or amino acids 4-281 of SEQ ID NO:19; and

4) a polypeptide consisting of the amino acid sequence of SEQ ID NO:19 or amino acids 4-281 of SEQ ID NO:19; and

wherein the immunogenic PSCA polypeptide is the full length human PSCA.

36. The use according to claim 35, wherein the immune-suppressive-cell inhibitor is selected from protein kinase inhibitor, COX-2 inhibitor, or PDE5 inhibitor; and wherein the immune-effector-cell enhancer is selected from CTLA-4 inhibitor, CD40 agonist, TLR agonist, 4-1BB agonist, OX40 agonist, GITR agonist, PD-1 antagonist, or PD-L1 antagonist.

37. The use according to claim 22, wherein:

1) the protein kinase inhibitor is selected from the group consisting of imatinib, sorafenib, lapatinib, zactima MP-412, dasatinib, lestaurtinib, lapatinib, sunitinib malate, axitinib, erlotinib, gefitinib, bosutinib, temsirolismus, and nilotinib;

2) the CTLA-4 inhibitor is selected from the group consisting of Ipilimumab and Tremelimumab;

3) the CD40 agonist is an anti-CD40 antibody selected from the group consisting of G28-5, mAb89, EA-5 , S2C6, CP870893, and dacetuzumab; and

4) the TLR agonist is a CpG oligonucleotide selected from the group consisting of CpG 24555, CpG10103, CpG7909, and CpG1018.

38. The use according to claim 37, wherein the immune-suppressive-cell inhibitor is a protein kinase inhibitor and wherein the immune-effector-cell enhancer is a CTLA-4 inhibitor.

39. The use according to claim 38, wherein the protein kinase inhibitor is selected from sorafenib, dasatinib, imatinib, axitinib, bosutinib or sunitinib malate and wherein the CTLA-4 inhibitor is Tremelimumab.

40. The use according to claim 39, wherein the protein kinase inhibitor is sunitinib malate administered orally at about 1 - 25 mg/dose and Tremelimumab is administered intradermally or subcutaneously at about 10 - 150 mg/dose.

41. The use according to claim 39, wherein the protein kinase inhibitor is axitinib administered orally at about 1, 2, 3, 4, or 5 mg/dose twice per day and Tremelimumab is administered intradermally or subcutaneously at about 10 - 150 mg/dose.

42. A multi-antigen construct that comprises:

(a) at least one nucleotide sequence encoding an immunogenic PSA polypeptide;

(b) at least one nucleotide sequence encoding an immunogenic PSCA polypeptide; and

(c) at least one nucleotide sequence encoding an immunogenic PSMA polypeptide, wherein the immunogenic PSA polypeptide comprises amino acids 4 - 240 of SEQ ID NO:17, wherein the immunogenic PSCA polypeptide comprises the amino acid sequence of SEQ ID NO:21, and wherein the immunogenic PSMA polypeptide has at least 90% identity with amino acids 15-750 of the human PSMA of SEQ ID NO:1 and

comprises the amino acids of at least 10 conserved T cell epitopes of the human PSMA at corresponding positions.

43. The multi-antigen construct according to claim 42, wherein the immunogenic PSMA polypeptide is selected from the group consisting of:

1) a polypeptide comprising amino acids 15-750 of SEQ ID NO: 1;

2) a polypeptide comprising the amino acid sequence of SEQ ID NO:3;

3) a polypeptide comprising the amino acid sequence of SEQ ID NO:5;

4) a polypeptide comprising the amino acid sequence of SEQ ID NO:7;

5) a polypeptide comprising the amino acids 4 – 739 of SEQ ID NO:9;

6) a polypeptide comprising the amino acids 4 – 739 of SEQ ID NO:3;

7) a polypeptide comprising the amino acids 4 - 739 of SEQ ID NO:5;

8) a polypeptide comprising the amino acids 4 - 739 of SEQ ID NO:7; and

9) a polypeptide comprising the amino acid sequence of SEQ ID NO: 9.

44. The multi-antigen construct according to claim 43, wherein the nucleotide sequence encoding the immunogenic PSA polypeptide is set forth in SEQ ID NO:18, wherein the nucleotide sequence encoding the immunogenic PSCA polypeptide is set forth in SEQ ID NO:22, and wherein the nucleotide sequence encoding the immunogenic PSMA polypeptide is selected from the group consisting of:

1) the nucleotide sequence of SEQ ID NO:2;

2) the nucleotide sequence of SEQ ID NO:4;

3) the nucleotide sequence of SEQ ID NO:6;

4) the nucleotide sequence of SEQ ID NO:8;

5) the nucleotide sequence of SEQ ID NO:10;

6) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:4;

7) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:6;

8) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:8; and

9) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:10.

45. The multi-antigen construct according to claim 42, further comprising:

(a) a nucleotide sequence encoding a T2A peptide sequence; and

(b) a nucleotide sequence encoding a F2A peptide sequence.

46. The multi-antigen construct according to claim 45, wherein the order of the nucleotide sequences on the multi-antigen construct is shown in formula (I):

PSA-T2A-PSCA-F2A-PSMA (I)

wherein in formula (I);

PSA is the nucleotide sequence encoding the immunogenic PSA polypeptide;

PSCA is the nucleotide sequence encoding the immunogenic PSCA polypeptide;

PSMA is the nucleotide sequence encoding the immunogenic PSMA polypeptide;

T2A is the nucleotide sequence encoding the T2A peptide sequence; and

F2A is the nucleotide sequence encoding the F2A peptide sequence.

47. The multi-antigen construct according to claim 46, wherein the immunogenic PSMA polypeptide comprises the amino acid sequence of SEQ ID NO: 9.

48. The multi-antigen construct according to claim 47, which the nucleotide sequence encoding the immunogenic PSMA polypeptide is set forth in SEQ ID NO:10.

49. A multi-antigen construct comprising the nucleotide sequence of SEQ ID NO:35 or a degenerate variant of the nucleotide sequence of SEQ ID NO:35.

50. The multi-antigen construct according to claim 49, which comprises the nucleotide sequence of SEQ ID NO:35.

51. The multi-antigen construct according to claim 49, which is a degenerate variant of the nucleotide sequence of SEQ ID NO:35.

52. A vector comprising the multi-antigen construct according to any one of claims 42, 45, and 49.

53. A composition comprising the multi-antigen construct according to any one of claims 42, 45, and 49.

54. Composition according to any one of claims 6-9, 14-17, 42, 45, and 49 for use in the inhibition of abnormal cell proliferation in a mammal.

55. Composition according to any one of claims 6-9, 14-17, 42, 45, and 49 for use in the elicitation of an immune response in a mammal.

56. Composition according to any one of claims 6-9, 14 -17, 42, 45, and 49 for use in the treatment of prostate cancer in a human.

CLAIMS

1. A multi-antigen DNA construct for expression of at least three separate immunogenic prostate-associated-antigen polypeptides comprising an immunogenic PSA polypeptide, an immunogenic PSCA polypeptide, and an immunogenic PSMA polypeptide, that comprises:

(a) at least one nucleotide sequence encoding the immunogenic PSA polypeptide;

(b) at least one nucleotide sequence encoding the immunogenic PSCA polypeptide; and

(c) at least one nucleotide sequence encoding the immunogenic PSMA polypeptide, wherein the immunogenic PSA polypeptide comprises amino acids 4 - 240 of SEQ ID NO:17, wherein the immunogenic PSCA polypeptide comprises the amino acid sequence of SEQ ID NO:21, and wherein the immunogenic PSMA polypeptide has at least 90% identity with amino acids 15-750 of the human PSMA of SEQ ID NO:1 and comprises the amino acids of at least 10 conserved T cell epitopes of the human PSMA at corresponding positions.

2. The multi-antigen DNA construct according to claim 1, wherein the immunogenic PSMA polypeptide is selected from the group consisting of:

1) a polypeptide comprising amino acids 15-750 of the amino acid sequence of SEQ ID NO: 1;

2) a polypeptide comprising the amino acid sequence of SEQ ID NO:3;

3) a polypeptide comprising the amino acid sequence of SEQ ID NO:5;

4) a polypeptide comprising the amino acid sequence of SEQ ID NO:7;

5) a polypeptide comprising the amino acids 4 – 739 of SEQ ID NO:9;

6) a polypeptide comprising the amino acids 4 – 739 of SEQ ID NO:3;

7) a polypeptide comprising the amino acids 4 - 739 of SEQ ID NO:5;

8) a polypeptide comprising the amino acids 4 - 739 of SEQ ID NO:7; and

9) a polypeptide comprising the amino acid sequence of SEQ ID NO: 9.

3. The multi-antigen DNA construct according to claim 2, wherein the nucleotide sequence encoding the immunogenic PSA polypeptide is set forth in SEQ ID NO:18, wherein the nucleotide sequence encoding the immunogenic PSCA polypeptide

is set forth in SEQ ID NO:22, and wherein the nucleotide sequence encoding the immunogenic PSMA polypeptide is selected from the group consisting of:

(1) a nucleotide sequence comprising nucleotides 43-2250 of the nucleotide sequence of SEQ ID NO:2;

(2) the nucleotide sequence of SEQ ID NO:4;

(3) the nucleotide sequence of SEQ ID NO:6;

(4) the nucleotide sequence of SEQ ID NO:8;

(5) the nucleotide sequence of SEQ ID NO:10;

(6) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:4;

(7) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:6;

(8) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:8; and

(9) a nucleotide sequence comprising nucleotides 10 – 2217 of SEQ ID NO:10.

4. The multi-antigen DNA construct according to claim 1, further comprising at least one nucleotide sequence encoding a 2A-like peptide sequence.

5. The multi-antigen DNA construct according to claim 4, wherein the 2A-like peptide sequence is selected from the group consisting of FMDV 2A peptide, TAV 2A peptide, EMCV 2A peptide, ERAV 2A peptide, and PTV 2A peptide.

6. The multi-antigen DNA construct according to claim 5, wherein:

(1) the FMDV 2A peptide comprises the amino acid sequence QTLNFDLLKLAGDVESNPGP;

(2) the TAV 2A peptide comprises the amino acid sequence EGRGSLLTCGDVEENPGP;

(3) the EMCV 2A peptide comprises the amino acid sequence HYAGYFADLLIHDIETNPGP;

(4) the ERAV 2A peptide comprises the amino acid sequence QCTNYALL,KLAGDVESNPGP; and

(5) the PTV 2A peptide comprises the amino acid sequence ATNFSLLKQAGDVEENPGP.

7. The multi-antigen DNA construct according to claim 5, which comprises:

(1) a nucleotide sequence encoding a TAV 2A peptide sequence; and

(2) a nucleotide sequence encoding a FMDV 2A peptide sequence.

8. The multi-antigen DNA construct according to claim 7, wherein the order of the nucleotide sequences on the multi-antigen DNA construct is shown in formula (I):

PSA-T2A-PSCA-F2A-PSMA (I)

wherein in formula (I);

PSA is the nucleotide sequence encoding the immunogenic PSA polypeptide;

PSCA is the nucleotide sequence encoding the immunogenic PSCA polypeptide;

PSMA is the nucleotide sequence encoding the immunogenic PSMA polypeptide;

T2A is the nucleotide sequence encoding the TAV 2A peptide sequence; and

F2A is the nucleotide sequence encoding the FMDV 2A peptide sequence.

9. The multi-antigen construct according to claim 8, wherein the immunogenic PSMA polypeptide comprises amino acids 15-750 of the amino acid sequence of SEQ ID NO:1.

10. The multi-antigen construct according to claim 8, wherein the nucleotide sequence encoding the immunogenic PSMA polypeptide comprises nucleotides 43-2250 of the nucleotide sequence of SEQ ID NO:2.

11. A multi-antigen DNA construct comprising the nucleotide sequence of SEQ ID NO:35 or a degenerate variant of the nucleotide sequence of SEQ ID NO:35.

12. The multi-antigen DNA construct according to claim 11, which comprises the nucleotide sequence of SEQ ID NO:35.

13. The multi-antigen DNA construct according to claim 11, which is a degenerate variant of the nucleotide sequence of SEQ ID NO:35.

14. A vector comprising the multi-antigen DNA construct according to any one of claims 1-12.

15. The vector according to claim 14, which comprises a multi-antigen DNA construct comprising nucleotide sequence of SEQ ID NO:35 or a degenerate variant of the nucleotide sequence of SEQ ID NO:35.

16. A composition comprising the vector according to claim 14.

17. The composition according to claim 16 for use in the inhibition of-abnormal cell proliferation in a mammal.

18. The composition according to claim 16 for use in the elicitation of an immune response in a mammal.

19. The composition according to claim 18 for use in the treatment of prostate cancer in a human.

20. A composition comprising the multi-antigen DNA construct according to any one of claims 1 -13.

21. The composition according to claim 20, wherein the multi-antigen DNA construct comprises the nucleotide sequence of SEQ ID NO:35 or a degenerate variant of the nucleotide sequence of SEQ ID NO:35.

22. Composition according to any one of claims 1-13 for use in the inhibition of-abnormal cell proliferation in a mammal.

23. The composition according to claim 22, wherein the multi-antigen DNA construct comprises the nucleotide sequence of SEQ ID NO:35 or a degenerate variant of the nucleotide sequence of SEQ ID NO:35.

24. Composition according to any one of claims 1-13 for use in the elicitation of an immune response in a mammal.

25. The composition according to claim 24, wherein the multi-antigen DNA construct comprises the nucleotide sequence of SEQ ID NO:35 or a degenerate variant of the nucleotide sequence of SEQ ID NO:35.

26. Composition according to any one of claims 1-13 for use in the treatment of prostate cancer in a human.

27. The composition according to claim 26, wherein the multi-antigen DNA construct comprises the nucleotide sequence of SEQ ID NO:35 or a degenerate variant of the nucleotide sequence of SEQ ID NO:35.