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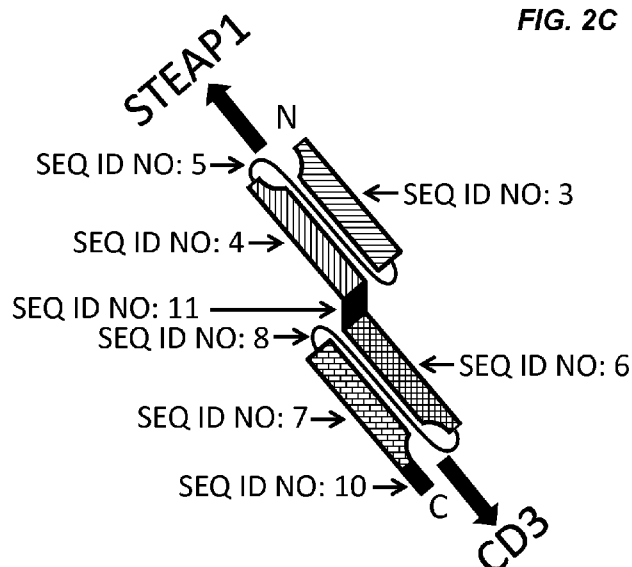
- with international search report (Art. 21(3))
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amendments (Rule 48.2(h))

[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR PREVENTING AND TREATING PROSTATE CANCER

STEAP1 x CD3 (TCT001)
(N-VL-VH-VH-VL-C)

FIG. 2C



(57) Abstract: Compositions, methods, and kits are provided for treating or preventing prostate cancer. In certain aspects, the compositions, methods, and kits are designed to kill prostate cancer cells. The compositions, methods, and kits can be useful to prevent or treat metastatic prostate cancer. The present invention provides a bispecific binding reagent comprising at least a first domain and a second domain, wherein the first domain specifically binds to a prostate cancer cell surface antigen, and wherein the second domain specifically binds to a T cell surface antigen. The bispecific binding reagent can be used to stimulate immune cell activity against the prostate cancer cell. In certain aspects, the present invention provides a plurality of bispecific binding reagents for co-stimulation of immune cells. Methods for preventing and/or treating metastatic prostate cancer in a subject in need thereof using one or more bispecific binding reagents of the present invention are also provided. In other aspects, the present invention provides isolated nucleic acids, vectors, processes of production, pharmaceutical compositions, and kits related to the bispecific binding reagents described herein. Exemplified are TCT001 against STEAP1 and CD3E and TCT002 against EpCam and CD28, as well as the combination of the two.



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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/033068

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 C07K16/30 C07K16/46 A61K39/395 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRIEDRICH MATTHIAS ET AL: "Regression of Human Prostate Cancer Xenografts in Mice by AMG 212/BAY2010112, a Novel PSMA/CD3-Bispecific BiTE Antibody Cross-Reactive with Non-Human Primate Antigens", MOLECULAR CANCER THERAPEUTICS, vol. 11, no. 12, December 2012 (2012-12), pages 2664-2673, XP002729091, ISSN: 1535-7163	1-9,17, 55-59, 71, 73-76,82
Y	the whole document ----- -/--	10,11, 60,69, 70,72,77



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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INTERNATIONAL SEARCH REPORT

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PCT/US2014/033068

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HO LYE LIN ET AL: "Androgen regulation of multidrug resistance-associated protein 4 (MRP4/ABCC4) in prostate cancer", PROSTATE, WILEY-LISS, NEW YORK, NY, US, vol. 68, no. 13, 1 September 2008 (2008-09-01), pages 1421-1429, XP008101316, ISSN: 0270-4137, DOI: 10.1002/PROS.20809 [retrieved on 2008-07-09] cited in the application figures 1-2 table 2	10,11, 60,69, 70,72,77
T	----- RUF PETER ET AL: "Two new trifunctional antibodies for the therapy of human malignant melanoma", INTERNATIONAL JOURNAL OF CANCER, JOHN WILEY & SONS, INC, US, vol. 108, no. 5, 20 February 2004 (2004-02-20), pages 725-732, XP002579122, ISSN: 0020-7136, DOI: 10.1002/IJC.11630 [retrieved on 2003-11-13] page 730	74-76
A	----- RAVINDRANATH MEPUR H ET AL: "Endogenous immune response to gangliosides in patients with confined prostate cancer", INTERNATIONAL JOURNAL OF CANCER, vol. 116, no. 3, September 2005 (2005-09), pages 368-377, XP002729092, ISSN: 0020-7136 figure 3C page 368, left-hand column	1-11,17, 55-60, 69-77,82
A	----- WU LISA Y ET AL: "Chemoaffinity capture of pre-targeted prostate cancer cells with magnetic beads", PROSTATE, vol. 72, no. 14, October 2012 (2012-10), pages 1532-1541, XP002729093, page 1532 ----- -/--	1-11,17, 55-60, 69-77,82

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/033068

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TAGAWA SCOTT T ET AL: "ANTI-PROSTATE SPECIFIC MEMBRANE ANTIGEN (PSMA)-BASED RADIOIMMUNOTHERAPY FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (CRPC): A DECADE OF EXPERIENCE WITH RADIOLABELED (RL)-J591", JOURNAL OF UROLOGY, vol. 187, no. 4, Suppl. S, April 2012 (2012-04), pages E387-E388, XP002729094, & ANNUAL MEETING OF THE AMERICAN-UROLOGICAL-ASSOCIATION (AUA); ATLANTA, GA, USA; MAY 19 -23, 2012 the whole document -----	1-11,17, 55-60, 69-77,82

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/033068

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-11, 17, 55-60, 69-77, 82(all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-11, 17, 55-60, 69-77, 82(all partially)

A bispecific binding reagent that simultaneously binds to an immune cell and a prostate cancer cell, wherein said bispecific binding reagent comprises a polypeptide molecule having a first domain that binds to an antigen expressed by the immune cell and a second domain that binds to an antigen expressed by the prostate cancer cell, wherein the antigen expressed by the prostate cancer cell is encoded by gene ABCC4.

2. claims: 1-11, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is ANO7.

3. claims: 35-42(completely); 1-13, 16, 17, 55-60, 69-77, 82(partially)

same as for INVENTION 1 except that the antigen is EPCAM.

4. claims: 1-12, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is FOLH1.

5. claims: 1-11, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is ORF51E1.

6. claims: 1-11, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is same as for INVENTION 1 except that the antigen is ORF51E2.

7. claims: 1-11, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is PSCA.

8. claims: 1-10, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is SLC30A4.

9. claims: 1-11, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is SLC45A3.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. claims: 1-12, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is SPON2.

11. claims: 24-31, 65-68, 79, 80(completely); 1-13, 16, 17, 55-60, 69-77, 82(partially)

same as for INVENTION 1 except that the antigen is STEAP1.

12. claims: 1-11, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is STEAP2.

13. claims: 1-11, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is TARP.

14. claims: 1-11, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is TMEFF2

15. claims: 1-11, 17, 55-60, 69-77, 82(all partially)

same as for INVENTION 1 except that the antigen is TMPR8.

16. claims: 14, 15(completely); 1-13, 17, 55-60, 69-77, 82(partially)

same as for INVENTION 1 except that the antigen is an NKG2D ligand.

17. claims: 1-9, 18-20, 55-60, 69-77, 82(all partially)

A bispecific binding reagent that simultaneously binds to an immune cell and a prostate cancer cell, wherein said bispecific binding reagent comprises a polypeptide molecule having a first domain that binds to an antigen expressed by the immune cell and a second domain that binds to an antigen expressed by the prostate cancer cell, wherein the antigen expressed by the immune cell is encoded by CD3D.

18. claims: 1-9, 18-20, 55-60, 69-77, 82(all partially)

same as for INVENTION 17 except that the antigen is CD3E.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

19. claims: 1-9, 18-20, 55-60, 69-77, 82(all partially)
same as for INVENTION 17 except that the antigen is CD247.

20. claims: 32-34(completely); 1-9, 18-20, 55-60, 69-77,
82(partially)
same as for INVENTION 17 except that the antigen is CD28.

21. claims: 21-23, 61-64, 78(completely); 1-9, 55-60, 69-77,
82(partially)
same as for INVENTION 17 except that the antigen is CD3.

22. claims: 1-9, 18, 55-60, 69-77, 82(all partially)
same as for INVENTION 17 except that the antigen is CD2.

23. claims: 1-9, 18, 55-60, 69-77, 82(all partially)
same as for INVENTION 17 except that the antigen is CD27.

24. claims: 1-9, 18, 55-60, 69-77, 82(all partially)
same as for INVENTION 17 except that the antigen is IL7R.

25. claims: 1-9, 18, 55-60, 69-77, 82(all partially)
same as for INVENTION 17 except that the antigen is CD69.

26. claims: 1-9, 18, 55-60, 69-77, 82(all partially)
same as for INVENTION 17 except that the antigen is ICOS.

27. claims: 1-9, 18, 55-60, 69-77, 82(all partially)
same as for INVENTION 17 except that the antigen is IL2RB.

28. claims: 1-9, 18, 55-60, 69-77, 82(all partially)
same as for INVENTION 17 except that the antigen is PTPRC.

29. claims: 1-9, 18, 55-60, 69-77, 82(all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

same as for INVENTION 17 except that the antigen is CD48.

30. claims: 1-9, 18, 55-60, 69-77, 82(all partially)

same as for INVENTION 17 except that the antigen is SELL.

31. claims: 1-9, 18, 19, 55-60, 69-77, 82(all partially)

same as for INVENTION 17 except that the antigen is CD137

32. claims: 1-9, 18, 19, 55-60, 69-77, 82(all partially)

same as for INVENTION 17 except that the antigen is CD134.

33. claims: 43, 45, 46(completely); 55-60, 69-77, 82(partially)

A bispecific binding reagent that simultaneously binds to an immune cell and a prostate cancer cell, wherein said bispecific binding reagent comprises a polypeptide molecule having a first domain that binds to an antigen expressed by the immune cell and a second domain that binds to an antigen expressed by the prostate cancer cell, wherein the second domain is derived from a ligand for a receptor, wherein the ligand is expressed on the surface of the prostate cancer cell.

34. claims: 44, 47-53(completely); 55-60, 69-77, 81, 82(partially)

A bispecific binding reagent that simultaneously binds to an immune cell and a prostate cancer cell, wherein said bispecific binding reagent comprises a polypeptide molecule having a first domain that binds to an antigen expressed by the immune cell and a second domain that binds to an antigen expressed by the prostate cancer cell, wherein the second domain is derived from a receptor that interacts with a ligand that is expressed on the surface of the prostate cancer cell.

35. claims: 54(completely); 55-60, 69-77, 81, 82(partially)

A bispecific binding reagent that simultaneously binds to an immune cell and a prostate cancer cell, wherein said bispecific binding reagent comprises a polypeptide molecule having a first domain that binds to an antigen expressed by the immune cell and a second domain that binds to an antigen expressed by the prostate cancer cell, wherein the first and/or the second domain comprises one or more disulfide bridges.
