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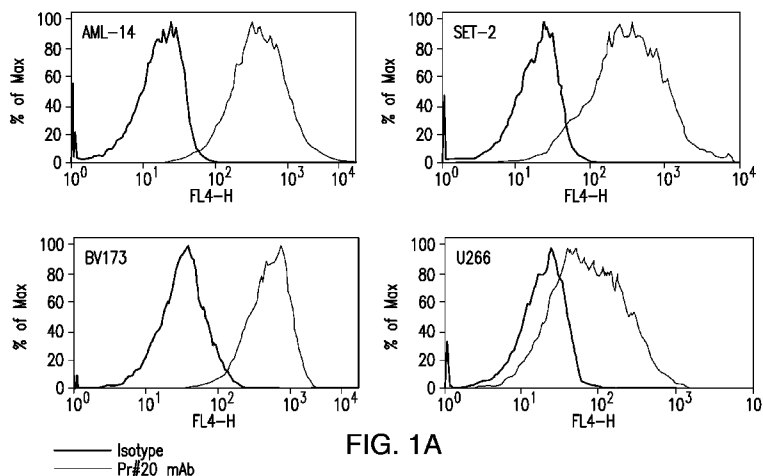
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Published:

— with international search report (Art. 21(3))

[Continued on next page]

(54) Title: T CELL RECEPTOR-LIKE ANTIBODIES SPECIFIC FOR A PRAME PEPTIDE



(57) Abstract: The presently disclosed subject matter provides antigen-binding proteins that specifically bind to Preferentially expressed antigen of melanoma (PRAME), including humanized, chimeric and fully human antibodies against PRAME, antibody fragments (e.g., scFv, Fab and F(ab)₂), chimeric antigen receptors (CARs), fusion proteins, and conjugates thereof. The antigen-binding proteins and antibodies bind to a PRAME peptide/HLA class I molecule complex. Such antibodies, fragments, fusion proteins and conjugates thereof are useful for the treatment of PRAME associated diseases, including for example, breast cancer, ovarian cancer, melanoma, lung cancer, gastrointestinal cancer, brain tumor, head and neck cancer, renal cancer, myeloma, neuroblastoma, mantle cell lymphoma, chronic myelocytic leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), acute myeloid/myelogenous leukemia (AML), Non-Hodgkin lymphoma (NHL), and Chronic lymphocytic leukemia (CLL). The antibodies or antigen binding proteins may comprise one or more framework region amino acid substitutions designed to improve protein stability, antibody binding and/or expression levels.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
27 April 2017

— *with sequence listing part of description (Rule 5.2(a))*

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/33430

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.: 8-31, 34-38, 41-44
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:

-----please see extra 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 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.:
claims 1-7, 32-33 limited to SEQ ID NOs: 49 and 50 and
claim 32 limited to SEQ ID NOs: 55 and 56
- 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.:

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/33430

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 16/18, C07K 16/30, A61K 39/395 (2017.01)

CPC - C07K 16/18, C07K 16/30, A61K 39/39558

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)

IPC(8) - C07K 16/18, C07K 16/30, A61K 39/395 (2017.01)

CPC - C07K 16/18, C07K 16/30, A61K 39/39558

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

CPC - C07K 16/28, A61K 39/3955, A61K 39/395

(keyword limited; terms below)

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

PatBase, Google Patents, Google Scholar

Search terms: PRAME, preferentially expressed antigen of melanoma, antibody, antibodies, major histocompatibility complex, MHC, human leukocyte antigen, HLA, HLA-A*0201

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y — A	US 2013/0029359 A1 (KERTESZ et al.) 31 January 2013 (31.01.2013) para [0005], [0035]	1-7 — 32, 33
Y — A	US 2014/0348862 A1 (ACADEMISCH ZIEKENHUIS LEIDEN H.O.D.N. LUMC) 27 November 2014 (27.11.2014) para [0007], [0022], [0047]; SEQ ID NO: 21	1-7 — 32, 33
Y	— KESSLER et al., Efficient Identification of Novel Hla-A*0201-Presented Cytotoxic T Lymphocyte Epitopes in the Widely Expressed Tumor Antigen Prame by Proteasome-Mediated Digestion Analysis. J Exp Med. 1 January 2001, Vol 193, No 1, pp 73-88. Especially abstract	6, 7/6
A	WO 2011/147982 A2 (GENMAB AS et al.) 01 December 2011 (01.12.2011) Fig 1D, sequence of IgHV1-69-4	32-33
A	US 2004/0023864 A1 (ROCZNIAK et al.) 05 February 2004 (05.02.2004) SEQ ID NO: 22	32-33
A	US 2013/0295102 A1 (NOVARTIS AG) U/ November 2013 (07.11.2013) - SEQ ID NO: 91	32-33
A	US 2013/0171096 A1 (HSIEH et al.) 04 July 2013 (04.07.2013) SEQ ID NO: 4	32-33

 Further documents are listed in the continuation of Box C.

* 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"&" document member of the same patent family

Date of the actual completion of the international search

16 February 2017

Date of mailing of the international search report

13 MAR 2017

Name and mailing address of the ISA/US

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/33430

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S25754, GenPept Accession No S25754, Ig lambda chain - human (fragment), 21 January 2000 [online]. [Retrieved on 15 November 2016]. Retrieved from the internet <URL: https://www.ncbi.nlm.nih.gov/protein/S25754 > Entire document	32-33
A	A2NYV5, UniProtKB/TrEMBL entry A2NYV5_HUMAN, 01 April 2015 [online]. [Retrieved on 15 November 2016]. Retrieved from the internet <URL: http://www.uniprot.org/uniprot/A2NYV5.bxt?version=31 > Entire document	32-33
A	US 2011/0064726 A1 (LIU et al.) 17 March 2011 (17.03.2011) SEQ ID NO: 153	32-33
A	US 2003/0157109 A1 (CORVALAN et al.) 21 August 2003 (21.08.2003) SEQ ID NO: 42	32-33
A	US 2004/0141969 A1 (FLOEGE et al.) 22 July 2004 (22.07.2004) SEQ ID NO: 62	32-33
A	US 2007/0004910 A1 (SEXTON et al.) 04 January 2007 (04.01.2007) SEQ ID NO: 1161	32-33
A	US 2010/0303801 A1 (THROSBY et al.) 02 December 2010 (02.12.2010) SEQ ID NO: 22	32-33
A	US 2008/0095775 A1 (LEWIS et al.) 24 April 2008 (24.04.2008) SEQ ID NO: 100	32-33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/33430

— Continuation of Box No. III Observations where unity of invention is lacking—

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-7, 32-33, drawn to an isolated antibody which binds to a PRAME peptide bound to a major histocompatibility complex (MHC). The anti-PRAME/MHC antibody will be searched to the extent that the antibody competes with a reference antibody having a heavy chain variable region SEQ ID NO: 49 and a light chain variable region SEQ ID NO: 50 (see claim 32). It is believed that claims 1-7, 32-33 limited to SEQ ID NOs: 49 and 50, encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass SEQ ID NOs: 49 and 50. Additional antibodies will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected antibodies. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be an antibody that competes with a reference antibody having a heavy chain variable region SEQ ID NO: 51 and a light chain variable region SEQ ID NO: 52 (claims 1-7, 32-33).

Group II: Claim 39, drawn to a method for detecting PRAME.

Group III: Claim 40, drawn to a chimeric antigen receptor specific for a PRAME peptide.

The inventions listed as Groups I+, II, and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

Group I+ requires a composition comprising an isolated antibody, or an antigen-binding portion thereof, which binds to a PRAME peptide bound to a major histocompatibility complex (MHC) molecule, not required by Groups II and III. Further, the technical feature of each of the inventions listed as Group I+ is the specific antibody having a heavy chain variable region and a light chain variable region sequences, recited therein. Each invention requires a specific antibody, not required by any of the other inventions.

Group II requires method steps for detecting PRAME in a whole cell or tissue, not required by Groups I+ and III.

Group III requires a chimeric antigen receptor (CAR), not required by Groups I+ and II.

Common Technical Features

The feature shared by Groups I+, II, and III is an isolated antibody, or an antigen-binding portion thereof, which binds to a PRAME peptide bound to a major histocompatibility complex (MHC) molecule. Further, the feature shared by Groups I+ is the isolated antibody of claims 1 and 32.

However, these shared technical features do not represent a contribution over prior art, because the shared technical features are taught by US 2013/0029359 A1 to Kertesz et al. (hereinafter 'Kertesz') in view of US 2014/0348862 A1 to LUMC Ziekenhuis Leiden h.o.d.n. LUMC (hereinafter 'LUMC').

Kertesz discloses [claims 1 and 32] an isolated antibody, or an antigen-binding portion thereof, which binds to a PRAME peptide (para [0005] "antibodies that bind specifically to an epitope of the PRAME tumor-associated antigen"; para [0035] "In some embodiments, the disclosure relates to an isolated antibody, or antigen-binding fragment thereof, directed against PRAME antigen"). Kertesz does not specifically teach that the PRAME peptide is bound to a major histocompatibility complex (MHC) molecule. However, LUMC discloses that the human PRAME sequence comprises binding epitopes for human MHC (also known as HLA) (para [0022] "In a first aspect of the invention there is provided a peptide comprising a contiguous amino acid sequence selected from the 509 amino acid sequence of the human PRAME protein, depicted in SEQ ID No. 21, whereby the peptide preferably comprises at least one HLA class II Th cell epitope and preferably also at least one HLA class I cytotoxic T cell epitope"; para [0047] "A selection of PRAME peptides with a length of 8, 9, 10 or 11 amino acids with potential binding capacity for the HLA class I molecules that are most predominant was made using the peptide binding prediction algorithms ... These computer algorithms search for peptides contained in the full length PRAME protein complying to the binding motifs of the HLA class I molecule of interest"). Given that LUMC teaches epitopes of PRAME peptide that bind to MHC (HLA), and Kertesz teaches anti-PRAME antibodies (para [0005]) and methods of producing antibodies that target PRAME (para [0053]), one of ordinary skill in the art would have found it obvious to use the method of Kertesz to raise anti-PRAME antibodies against the PRAME epitopes disclosed by LUMC and thereby obtain an isolated antibody, or an antigen-binding portion thereof, which binds to a PRAME peptide bound to a MHC molecule.

Additionally, LUMC teaches the following PRAME peptide amino acid sequences:

PRA 100-108, SEQ ID NO: 2 (LUMC SEQ ID NO: 21, amino acids 100-108, exhibit 100% identity to claimed SEQ ID NO: 2),
PRA 142-151, SEQ ID NO: 3 (LUMC SEQ ID NO: 21, amino acids 142-151, exhibit 100% identity to claimed SEQ ID NO: 3),
PRA300-309, SEQ ID NO: 4, (LUMC SEQ ID NO: 21, amino acids 300-309, exhibit 100% identity to claimed SEQ ID NO: 4),
PRA 425-433, SEQ ID NO: 5 (LUMC SEQ ID NO: 21, amino acids 425-433, exhibit 100% identity to claimed SEQ ID NO: 5), and
PRA 435-443, SEQ ID NO: 6 (LUMC SEQ ID NO: 21, amino acids 435-443, exhibit 100% identity to claimed SEQ ID NO: 6).

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Groups I+, II, and III therefore lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

-----please see continuation on next extra sheet-----

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/33430

---continuation of Box No. III Observations where unity of invention is lacking---

Item 4 (continued)

Claims 8-31, 34-38, and 41-44 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Note, Claims 30 and 31 are written continuously without separation physically. Claims 30 and 31 are interpreted as follows:

Claim 30, The antibody or antigen-binding portion thereof of any one of claims 1-7 and 20-29, comprising: (a) a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 57, and a light chain variable region comprising an amino acid 25 sequence set forth in SEQ ID NO: 58; (b) a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 59, and a light chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 60; or (c) a heavy chain variable region comprising an amino acid sequence 30 set forth in SEQ ID NO: 61, and a light chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 62.

Claim 31, The antibody or antigen-binding portion thereof of any one of claims 20-30, comprising: a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 57, and a light chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 58.