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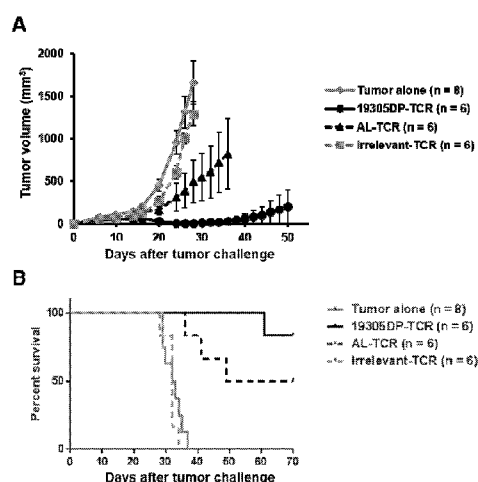
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(54) Title: COMPOSITIONS AND LIBRARIES COMPRISING RECOMBINANT T-CELL RECEPTORS AND METHODS OF USING RECOMBINANT T-CELL RECEPTORS

Figure 8



(57) **Abstract:** Provided are recombinant polynucleotides, including expression vectors encoding an alpha chain and/or a beta chain of a TCR having amino acid sequences from any of novel the AL, KQ, PP, 19305CD8, BB, KB, ST, JD, 19305DP, PB-P, PB-T, and PB 13.2 T Cell Receptors (TCRs) that are embodiments of the invention. Cells comprising the polynucleotides are provided, as are libraries of the recombinant polynucleotides and expression vectors. Methods are provided and involve administering to an individual modified human T cells that express a novel recombinant TCR. The methods are for prophylaxis and/or therapy of an individual diagnosed with, suspected of having or at risk for developing or recurrence of a cancer, wherein the cancer includes cancer cells which express NY-ESO-1 and/or its highly homologous LAGE-1 antigen.

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

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

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

(88) Date of publication of the international search report:

16 November 2017 (16.11.2017)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/12464

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/711, A61K 48/00, C12N 15/11, C12N 15/12, C12N 5/0783 (2017.01)
 CPC - C12N 2501/515, C07K 14/7051, C12N 15/11, C12N 15/09, C12N 5/0636

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)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0053184 A1 (MORGAN et al.) 26 February 2009 (26.02.3009) SEQ ID NOS: 6 and 8	1-8 and 15-18
A	JP 2008/263950 A (SHIZUOKA PREFECTURE) 6 November 2008 (06.11.2008) SEQ ID NOS: 24 and 51	1-8 and 15-18
A	US 2011/0070208 A1 (BERTOLETTI et al.) 24 March 2011 (24.03.2011) SEQ ID NOS: 12 and 24	1-8 and 15-18
A	US 2013/0273647 A1 (SAHIN et al.) 17 October 2013 (17.10.2013) SEQ ID NOS: 21 and 34	1-8 and 15-18

☐ 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

"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

23 May 2017

Date of mailing of the international search report

09 JUN 2017

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INTERNATIONAL SEARCH REPORT

International application No.

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
 - ☒ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/12464

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.: 11-14
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.:
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.:
1-8 and 15-18, limited to 10306DP and ECQ ID NOs: 1 and 2

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 17/12464

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 1-8, 15-19, drawn to a recombinant polynucleotide encoding an alpha chain and/or a beta chain of a T cell receptor (TCR) and library comprising said recombinant polynucleotide. The recombinant polynucleotide will be searched to the extent that the TCR encompasses 19305DP, comprising alpha chain sequence of SEQ ID NO: 1 and/or a beta chain sequence of SEQ ID NO:2. It is believed that claims 1-8 and 15-18, limited to 19305DP and SEQ ID NOs: 1 and 2, encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass a recombinant polynucleotide encoding an alpha chain and/or a beta chain of a TCR limited to 19305DP and SEQ ID NOs: 1 and 2. Additional TCRs and corresponding alpha and beta chain sequences will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected TCR(s) and corresponding alpha and beta chain sequences. 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 wherein the TCR encompasses AL, comprising alpha chain sequence of SEQ ID NO: 5 and/or a beta chain sequence of SEQ ID NO:6, i.e. claims 1, (4-6)/1, 15, 16, 19, limited to AL and SEQ ID NOs: 5 and 6.

Group II: Claims 9-10, 20 drawn to a method of treating or preventing, a cancer that expresses NY-ESO-1/LAGE-I antigen in an individual; and to a method of testing a sample from an individual to determine whether or not the individual has a NY-ESO-1/LAGE-I positive cancer.

The inventions listed as Groups I+ and II 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

The invention listed as Group I+ requires a composition of matter comprising a recombinant polynucleotide encoding an alpha chain and/or a beta chain of a TCR, not required by Group II. Further, the technical feature of each of the inventions listed as Group I+ is the specific TCR and corresponding alpha and beta chain sequences recited therein. Each invention requires a TCR and corresponding alpha and beta chain sequences, not required by any of the other inventions.

Group II requires method steps for treating or preventing a NY-ESO-1/LAGE-I positive cancer; and method steps for testing a sample from an individual to determine whether or not the individual has a NY-ESO-1/LAGE-I positive cancer; method steps not required by Group I+.

Common Technical Features

The feature shared by Groups I+ and II is a recombinant polynucleotide encoding an alpha chain and/or a beta chain of a TCR. The feature shared by the inventions listed by Group I+ is the recombinant polynucleotide of claim 1.

Another feature shared by Groups I+ and II is a library comprising a plurality of recombinant polynucleotides encoding the alpha chains and/or beta chain of TCR. Another feature shared by the inventions listed by Group I+ is the library of claim 15.

Another feature shared by Groups I+ and II is a recombinant polynucleotide present in an expression vector.

However, these shared technical features do not represent a contribution over prior art, because the shared technical features are taught by US 2009/0053184 A1 to Morgan et al. (hereinafter 'Morgan').

Morgan discloses [claim 1] a recombinant polynucleotide encoding an alpha chain and/or a beta chain of a T cell receptor (TCR) (para [0008] "The invention provides nucleic acids encoding polypeptides that are capable of forming a subunit of a T cell receptor (TCR)"; para [0019] "The nucleic acids encoding the TCR can be an .alpha.-chain or .beta.-chain of a T cell receptor or both or a portion thereof"; para [0033] "the vector of the invention contains a single chain TCR encoding both .alpha.-chain and .beta.-chain specific sequences in a single polypeptide"; para [0037] "Suitable methods of administering a vector of the invention to a mammal for purposes of gene therapy are known . . . The choice of excipient will be determined in part by the particular method used to administer the recombinant vector").

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INTERNATIONAL SEARCH REPORT

International application No.

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

Morgan discloses [claim 15] a library comprising a plurality of recombinant polynucleotides encoding the alpha chains and/or beta chain of T cell receptors (TCRs) (para [0027] "For example, the inventive nucleic acids can be mutated to derive other useful .alpha.- and .beta.-chains of T cell receptors capable of transforming T lymphocytes useful in the context of the invention. For example, the nucleic acids of SEQ ID NOS: 1, 3, 5, 7, 9, and 11 can be used to generate a library of mutant nucleic acids. One preferred method of generating this library is to clone a portion of one or more nucleic acids of SEQ ID NOS: 1, 3, 5, 7, 9, and 11 into a vector and propagating the same in the E. coli mutator strain XL1-Red (available from Strategene, La Jolla, Calif.). A library of yeast cells can be generated by transfecting yeast with the mutagenized nucleic acids of SEQ ID NOS: 1, 3, 5, 7, 9 and 11 under suitable conditions such that the yeast display the T cell receptors on their surface"; para [0033] "the vector of the invention contains a single chain TCR encoding both .alpha.-chain and .beta.-chain specific sequences in a single polypeptide"; para [0037] "recombinant vector").

Morgan discloses a recombinant polynucleotide present in an expression vector (para [0008] "The invention provides nucleic acids encoding polypeptides that are capable of forming a subunit of a T cell receptor (TCR)"; para [0033] "the vector of the invention contains a single chain TCR encoding both .alpha.-chain and .beta.-chain specific sequences in a single polypeptide"; para [0037] "the recombinant vector").

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