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(54) Title: EPIOTOPE SPREADING ASSOCIATED WITH CAR T-CELLS

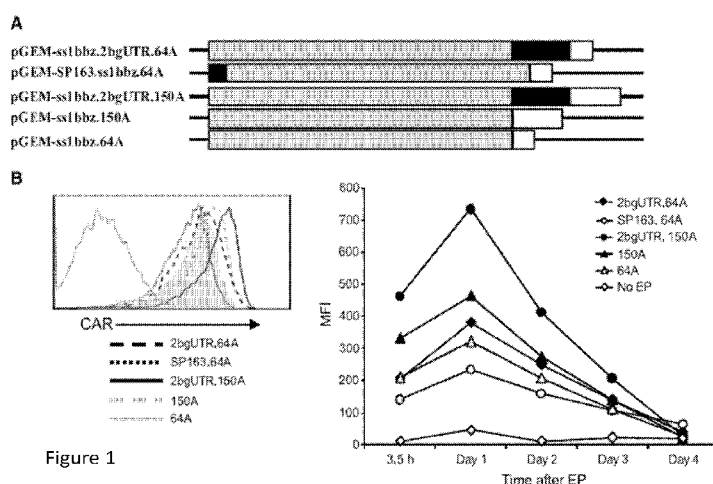


Figure 1

(57) Abstract: The present invention relates to compositions and methods for inducing epitope spreading by administering to a mammal an effective amount of a cell genetically modified to express a chimeric antigen receptor (CAR). The invention also relates to identification of antigens and antibodies involved in the epitope spreading associated with CAR T cells.

INTERNATIONAL SEARCH REPORT

51050283 24.02.2014
International application No.

PCT/US13/50283

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12N 5/07, 5/16; C12P 21/08 (2014.01)

USPC - 435/328, 326; 530/387.3

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): C12N 5/07, 5/16; C12P 21/08; A01N 63/00; A61K 48/00 (2013.01)

USPC: 435/328, 326, 325; 530/387.3, 387.1, 386, 380; 424/93.21, 93.2, 93.1

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)

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; ScienceDirect; ProQuest; cancer, immune, response, 'CAR,' 'antigen binding domain,' epitope

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2012/079000 A1 (JUNE, CH et al.) June 14, 2012; abstract; page 2, line 5; page 49, lines 6-10; page 49, lines 31-32	1, 5, 6, 10 ----- 2-4, 7-9
Y	WO 1999/051263 A2 (MACDONALD, GH et al.) October 14, 1999; page 12, lines 3-8; page 12, lines 22-23	2, 3, 7, 8
Y	KIM, CS et al. An RNA-Binding Protein, hnRNP A1, And A Scaffold Protein, Septin 6, Facilitate Hepatitis C Virus Replication. Journal of Virology. 17 January 2007. Vol. 81, No. 8; pages 3852-3865; page 3853, right column, second paragraph. DOI: 10.1128/JVI.01311-06.	3, 4, 8, 9

☐ 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

06 February 2014 (06.02.2014)

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24 FEB 2014

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US13/50283

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:

-Please See Supplemental Page-

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.:

Groups I+: Claims 1-10, septin 6, transcript variant II

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.

-***-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.

Groups I+: Claims 1-10 and an epitope from the antigen septin 6 (SEPT6), transcript variant II are directed toward a method for inducing at least a first and second epitope-specific immune response in a cancer patient, the method comprising administering to a patient in need thereof an effective amount of a cell genetically modified to express a chimeric antigen receptor (CAR) comprising an antigen binding domain, a transmembrane domain, and an intracellular signaling domain, wherein the first epitope-specific immune response is directed to a target epitope recognized by the CAR; and a method of treating a patient having a disease, disorder or condition associated with an elevated expression of a first tumor antigen by inducing at least a first and second epitope-specific immune response in the cancer patient, the method comprising administering to the patient an effective amount of a cell genetically modified to express a CAR, wherein the CAR comprises an antigen binding domain, and an intracellular signaling domain, wherein the first epitope-specific immune response is directed to a target epitope recognized by the CAR.

The method for inducing at least a first and second epitope-specific immune response in a cancer patient; and a method of treating a patient having a disease, disorder or condition associated with an elevated expression of a first tumor antigen by inducing at least a first and second epitope-specific immune response in a cancer patient will be searched to the extent that they encompass an epitope from the antigen septin 6 (SEPT6), transcript variant II. It is believed that Claims 1-10 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass an epitope from the antigen septin 6 (SEP6), transcript variant II. Applicants must 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/examined. An Exemplary Election would be: epitope from the antigen polymerase (DNA directed), lambda (POLL).

However, these shared technical features are previously disclosed by WO 2012/079000 A1 to June, et al. (hereinafter 'June'). June discloses a method for inducing at least a first and second epitope-specific immune response in a cancer patient (abstract; page 26, lines 22-39 to page 27, lines 1-10; page 31, lines 13-17), the method comprising administering to a patient in need thereof an effective amount of a cell genetically modified to express a chimeric antigen receptor (CAR) comprising an antigen binding domain (abstract), a transmembrane domain (abstract), and an intracellular signaling domain (Claim 10), wherein the first epitope-specific immune response is directed to a target epitope recognized by the CAR (Claim 45); and a method of treating a patient having a disease, disorder or condition associated with an elevated expression of a first tumor antigen (Claim 47) by inducing at least a first and second epitope-specific immune response in the cancer patient (abstract; page 26, lines 22-39 to page 27, lines 1-10; page 31, lines 13-17; Claim 47), the method comprising administering to the patient an effective amount of a cell genetically modified to express a CAR (Claims 45-47), wherein the CAR comprises an antigen binding domain (abstract), and an intracellular signaling domain (Claim 10), wherein the first epitope-specific immune response is directed to a target epitope recognized by the CAR (Claim 45).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the June reference, unity of invention is lacking.