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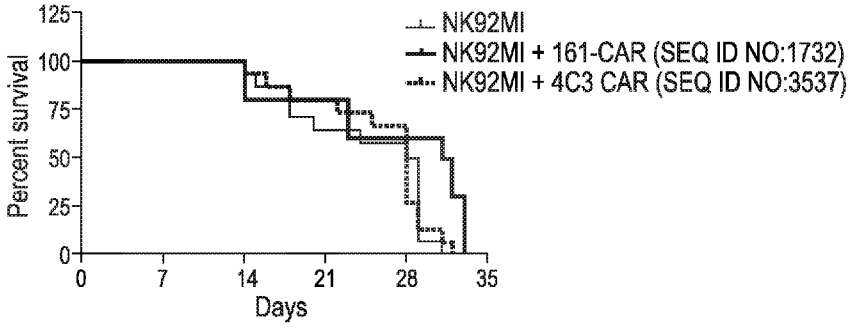
09 November 2017 (09.11.2017)

(54) Title: CHIMERIC ANTIGEN RECEPTORS TARGETING CANCER

Fig. 16



(57) Abstract: Provided herein is a composition comprising, a cell, comprising nucleic acids encoding a chimeric antigen receptor (CAR) and one or more of signaling proteins selected from K13-vFLIP, MC159-vFLIP, cFLIP-L, cFLIP-p22, HTLV1-Tax and HTLV2-Tax, wherein the CAR comprises an a) extracellular antigen specific domain, b) a transmembrane domain and c) an intracellular signaling domain comprising an immunoreceptor tyrosine-based activation motif (ITAM); wherein c) is located at the C-terminus of the chimeric receptor. In some embodiments, the CAR further comprises one or more co-stimulatory domains. Also provided herein are methods for treating diseases using the compositions described herein.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/24843

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 39/395, C07K 14/705, 14/725, 16/28 (2017.01)

CPC - A61K 39/395, 39/39533, 39/39558, 39/39583; C07K 14/7051, 16/2818, 16/2821, 16/283, 16/2851, 16/2896, 16/30, 16/3007, 16/3076

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.
Y	WO 2015/150526 A2 (CELLECTIS) 08 October, 2015; page 11, lines 1-9; page 12, lines 16-17; page 13, lines 3-7; page 15, lines 21-23; page 18, lines 17-28; page 19, line 12 – page 20, line 2; page 21, lines 12-14; page 37, line 15; page 41, lines 22-23	1-4, 5/1-4, 6/1-4, 7/6/1-4, 8/7/6/1-4, 10, 15-18, 19/17-18, 20/17-18
Y	(MATTA, H et al.) A Nuclear Role for Kaposi's Sarcoma-Associated Herpesvirus-Encoded K13 Protein in Gene Regulation. Oncogene. 12 May, 2008; Vol. 27, No. 39; pages 5243-5253; page 5244, column 2, paragraph 1; DOI: 10.1038/onc.2008.150	1-4, 5/1-4, 6/1-4, 7/6/1-4, 8/7/6/1-4, 10, 15-18, 19/17-18, 20/17-18
Y	US 2013/0017575 A1 (GARCIA-MARTINEZ, L et al.) 17 January, 2013; abstract; paragraphs [0014], [0017], [0451]; claims 138-139, 148	4, 5/4, 6/4, 7/6/4, 8/7/6/4
Y	US 2013/0143791 A1 (PETZELBAUER, P et al.) 06 June, 2013; paragraphs [0028], [0074]	5/1-4
Y	(POWNALL, ME et al.) An Inducible System for the Study of FGF Signalling in Early Amphibian Development. Development Biology. 01 April, 2013; Vol. 256, No. 1; pages 89-99; abstract; page 90, column 2, paragraph 2; page 91, column 2, paragraph 3 – page 92, column 1, paragraph 2	6/1-4, 7/6/1-4, 8/7/6/1-4
Y	(MAUDE, SL et al.) Chimeric antigen receptor T-cell therapy for ALL. Hematology. 18 November, 2014; Vol. 2014, No. 1; pages 559-564; page 562, column 1, paragraph 2; DOI: 10.1182/asheducation-2014.1.559	5/1-4

☒ 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	Date of mailing of the international search report
09 August 2017 (09.08.2017)	13 SEP 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/24843

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	(WU, Z et al.) TPO-Induced Metabolic Reprogramming Drives Liver Metastasis of Colorectal Cancer CD110+ Tumor- Initiating Cells. Cell Stem Cell. 02 July, 2015; Vol. 17, No. 1; pages 47-59; abstract; page 47, column 2, paragraph 2; DOI: 10.1016/j.stem.2015.05.016	9, 11, 13, 22-27
A	US 2006/0222588 A1 (SANDBERG, B et al.) 05 October, 2006; abstract; paragraph [0088]	9, 13, 22-27
A	(TETTAMANTI, S et al.) CD123 AML Targeting by Chimeric Antigen Receptors. Oncoimmunology. 1 May, 2014; Vol. 3; pages e28835-1-5; page e28835-2, column 3, paragraph 2; DOI: 10.4161/onci.28835	11
A	US 2014/0271635 A1 (BROGDON, J et al.) 18 September, 2014; abstract; paragraph [0006]	12, 14
A	(HOSING, C et al.) CARs in Chronic Lymphocytic Leukemia – Ready to Drive. Current Hematology Malignancy Reports. March, 2013; Vol. 8, No. 1; pages 1-17; page 6, paragraph 2; DOI: 10.1007/s11899-012-0145-y	12, 14
P, Y	WO 2017/103596 A1 (CELLULAR THERAPEUTICS LTD) 22 June, 2017; whole document	9, 11, 13, 22-27
P, Y	WO 2016/210447 A1 (UNIVERSITY OF SOUTH CALIFORNIA) 29 December, 2016; whole document	12, 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/24843

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.: 21
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 1-20, 22-27; SEQ ID NO: 2500 (scFv fragment)

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
Information on patent family members

International application No.
PCT/US17/24843

-***-Continued from 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 1-20, 22-27; SEQ ID NO: 2500 (scFv fragment) are directed toward a chimeric antigen receptor (CAR) and K13-vFLIP signaling protein.

The CAR will be searched to the extent that it encompasses an scFv encompassing SEQ ID NO: 2500 (first exemplary scFv fragment). Applicant is invited to elect additional scFv fragment(s), with specified SEQ ID NO: for each, to be searched. Additional scFv fragments (s) will be searched upon the payment of additional fees. It is believed that claims 1-12, 13 (in-part), 14-20, and 22-27 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 2500 (scFv fragment). 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 a CAR comprising a scFv fragment encompassing SEQ ID NO: 2501 (first exemplary elected scFv fragment).

No technical features are shared between the scFv fragment sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: a cell comprising nucleic acids encoding a chimeric antigen receptor (CAR) and K13-vFLIP signaling protein, wherein the CAR comprises an a) extracellular antigen specific domain, b) a transmembrane domain and c) an intracellular signaling domain comprising an immunoreceptor tyrosine-based activation motif (ITAM); wherein c) is located at the C-terminus of the chimeric receptor; nucleic acids comprising a first polynucleotide encoding the CAR and a second polynucleotide encoding the signaling protein; polypeptides encoded by the nucleic acids; vectors comprising nucleic acids; a method of treating a MPL-expressing cancer comprising administering to the subject, a therapeutically effective amount of the cell.

However, these shared technical features are previously shared by WO 2015/150526 A2 (CELLECTIS) (hereinafter 'Cellectis') in view of the article 'Role of MRIT/cFLIP in Protection Against Chemotherapy-Induced Apoptosis' by Matta et al. (hereinafter 'Matta').

Cellectis discloses a cell comprising nucleic acids encoding a chimeric antigen receptor (CAR) (a cell comprising nucleic acids encoding a chimeric antigen receptor (CAR); page 13, lines 5-8; claim 20) and a signaling protein (signaling domain; page 12, lines 16-17), wherein the CAR comprises an a) extracellular antigen specific domain (the CAR comprises an a) extracellular antigen specific domain; page 13, lines 1-2; page 15, lines 21-33), b) a transmembrane domain (page 15, lines 21-33) and c) an intracellular signaling domain comprising an immunoreceptor tyrosine-based activation motif (ITAM) (an intracellular signaling domain comprising an immunoreceptor tyrosine-based activation motif (ITAM); page 15, lines 21-33); wherein c) is located at the C-terminus of the chimeric receptor (cytoplasmic signaling sequence (wherein c) is located at the C-terminus of the chimeric receptor); page 18, lines 17-24); nucleic acids comprising a first polynucleotide encoding the CAR (page 37, lines 14-16) and a second polynucleotide encoding the signaling protein (a second polynucleotide encoding the signaling protein; page 24, lines 10-11; page 38, lines 3-12); polypeptides encoded by the nucleic acids (page 3, lines 9-13; page 24, lines 10-11); vectors comprising nucleic acids (page 13, lines 5-6); a method of treating a MPL-expressing cancer comprising administering to the subject a therapeutically effective amount of the cell (a method of treating leukemia (a MPL-expressing cancer) comprising administering to the subject a therapeutically effective amount of the cell; abstract; page 15, lines 10-13).

Cellectis does not disclose a K13-vFLIP signaling protein.

Matta discloses cancerous T cells expressing vFLIP (CEM cells (cancerous T cells) expressing vFLIP; page 653, first column, seventh paragraph - second column, first paragraph), wherein said cells escape drug-induced apoptosis (wherein said cells escape drug-induced apoptosis; Figure 3C).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the disclosure of Cellectics to include expression of K13-vFLIP, as disclosed by Matta, for providing a superior method of selectively activating the NF-KB pathway to promote the proliferation and survival of CAR-expressing T cells administered to a subject in need thereof, even in the presence of chemotherapeutic treatments.

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 a combination of the Cellectis and Thurau references, unity of invention is lacking.