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(54) Title: COMPOSITIONS AND METHODS FOR INHIBITING T CELL EXHAUSTION

FIG. 1A

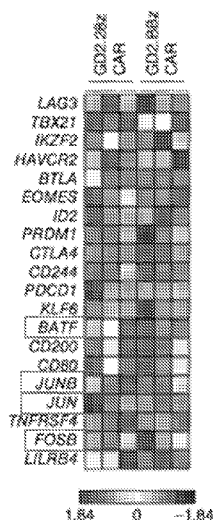
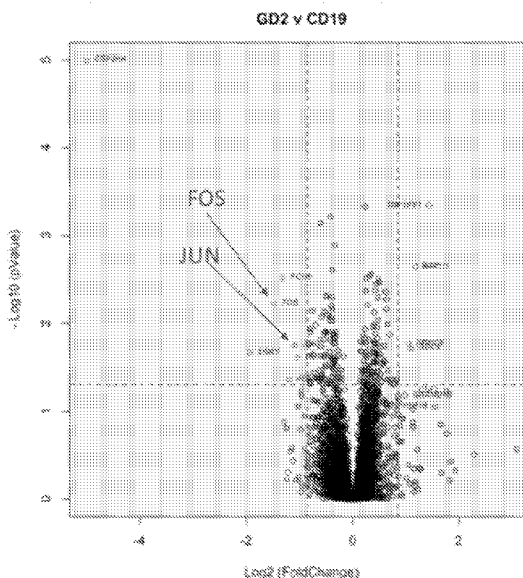


FIG. 1B



(57) Abstract: The present invention relates to T cell compositions and methods of using the same in the context of therapy and treatment. In particular, the invention provides T cells that are modified (e.g., genetically and/or functionally) to maintain functionality under conditions in which unmodified T cells display exhaustion. Compositions and methods disclosed herein find use in preventing exhaustion of engineered (e.g., chimeric antigen receptor (CAR) T cells) as well as non-engineered T cells thereby enhancing T cell function (e.g., activity against cancer or infectious disease).



MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US18/65801

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 35/17; C12N 5/0783, 5/10; A61P 35/00 (2019.01)

CPC - A61K 35/17; C12N 5/0638, 5/0636, 5/0646, 5/10; A61P 35/00

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.
X -- Y	WO 2016/179283 A1 (FATE THERAPEUTICS, INC.) 10 November 2016; paragraphs [0005], [0009]-[0010], [0022], [0036], [0081]-[0082], [0089], [0098], [00161], [00169], [00250]-[0251]; Claims 51-52	1-3, 5-12, 20-21, 25, 30, 34-35, 66 ----- 14, 16, 22-24, 39-41, 58-65
Y	◀ (BEHRENS, A et al.) Jun N-terminal kinase 2 modulates thymocyte apoptosis and T cell activation through c-Jun and nuclear factor of activated T cell (NF-AT). Proceedings of the National Academy of Sciences of the U.S.A. 13 February 2001, Vol. 98, No. 4; pages 1769-1774; page 1770, 1st column, 1st-2nd paragraphs; page 1771, 1st column, 1st paragraph to 2nd column, 2nd paragraph; DOI: 10.1073/pnas.98.4.1769	14, 16
Y	▶ (FINCH, S et al.) JunB negatively regulates AP-1 activity and cell proliferation of malignant mouse keratinocytes. Journal of Cancer Research and Clinical Oncology. January 2002, Epub 6 November 2001, Vol. 128, No. 1; pages 3-10; abstract; DOI: 10.1008/S00432-001-0298-x	22-24, 39-41, 58-65
A	— (JURADO, J et al.) Alternative splicing of c-fos pre-mRNA: contribution of the rates of synthesis and degradation to the copy number of each transcript isoform and detection of a truncated c-Fos immunoreactive species. BMC Molecular Biology. 21 September 2007, Vol. 8, No. 83; pages 1-14; page 7, 2nd column, 2nd paragraph; DOI: 10.1186/1471-2199-8-83	15

 Further documents are listed in the continuation of Box C.

 See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search

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Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US18/65801

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	(LIANG, G et al.) Characterization of Human Activating Transcription Factor 4, a Transcriptional Activator That Interacts with Multiple Domains of cAMP-responsive Element-binding Protein (CREB)-binding Protein (CBP). Journal of Biological Chemistry. 19 September 1997, Vol. 272, No. 38; pages 24088-24095; Figure 2; page 24091, 2nd column, 1st paragraph; DOI: 10.1074/jbc.272.38.24088	15
A	WO 2015/164594 A1 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 29 October 2015; paragraphs [0020], [00231]	31, 33, 67, 69
A	(FAHMY, TM et al.) Increased TCR Avidity after T Cell Activation: A Mechanism for Sensing Low-Density Antigen. Immunity. February 2001, Vol. 14, No. 2; pages 135-143; abstract; DOI: 10.1016/S1074-7613(01)00096-6	31, 67
A	US 2016/0317654 A1 (KING'S COLLEGE LONDON) 3 November 2016; paragraph [0080]	32, 68
A	(HU, G et al.) A Genome-wide Regulatory Network Identifies Key Transcription Factors for Memory CD8+ T Cell Development. Nature Communications. 123 December 2013, Vol. 4, No. 2830; page 6, 3rd paragraph to page 7, 3rd paragraph; DOI: 10.1038/ncomms3830	32-33, 68-69
A	(FOLETTA, VC et al.) Transcriptional regulation in the immune system: all roads lead to AP-1. Journal of Leukocyte Biology. February 1998, Vol. 63, No. 2; pages 139-152; DOI: 10.1002/jlb.63.2.139	1-3, 5-12, 14-16, 20-25, 30-35, 39-41, 58-69

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US18/65801

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+, 1-3, 5, 6 (in-part), 7-11, 12 (in-part), 14-16, 20-22, 23 (in-part), 24 (in-part), 25, 30-35, 39, 40 (in-part), 41 (in-part), 58, 59, 60 (in-part), 61 (in-part), 62, 63, 64 (in-part), 65 (in-part), and 66-69; a CD19 tumor antigen-specific T cell receptor (recombinant receptor); c-Fos (AP-1 transcription factor); JunB (AP-1 inhibitory complex member) and a tumor or cancer (disease or condition)

- 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.

-***-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 1-69, a CD19 tumor antigen-specific T cell receptor (recombinant receptor); c-Fos (AP-1 transcription factor); JunB (AP-1 inhibitory complex member) and a tumor or cancer (disease or condition) are directed toward compositions and methods related to T cells modified to contain elevated levels of one or more AP-1 transcription factors.

The compositions and methods will be searched to the extent they encompass a CD19-specific T cell receptor (first exemplary recombinant receptor); c-Fos (first exemplary AP-1 transcription factor); JunB (first exemplary AP-1 inhibitory complex member), and a tumor or cancer (first exemplary disease or condition). Applicant is invited to elect additional recombinant receptor(s), with specified binding partner for each, and/or additional AP-1 transcription factor(s), and/or AP-1 inhibitory complex member(s), and/or disease(s) or condition(s), to be searched. Additional recombinant receptor(s), and/or AP-1 transcription factor(s), and/or AP-1 inhibitory complex member(s) and/or disease(s) or condition(s) will be searched upon the payment of additional fees. It is believed that claims 1-3, 5, 6 (in-part), 7-11, 12 (in-part), 14-16, 20-22, 23 (in-part), 24 (in-part), 25, 30-35, 39, 40 (in-part), 41 (in-part), 58, 59, 60 (in-part), 61 (in-part), 62, 63, 64 (in-part), 65 (in-part), and 66-69 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a CD19-specific T cell receptor (recombinant receptor); c-Fos (AP-1 transcription factor); JunB (AP-1 inhibitory complex member), and a tumor or cancer (disease or condition). Applicants must specify the claims that encompass any additionally elected recombinant receptor(s), and/or AP-1 transcription factor(s), and/or AP-1 inhibitory complex member(s) and/or disease(s) or condition(s). 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/examined. An exemplary election would be a CD-19 specific chimeric antigen receptor (recombinant receptor).

No technical features are shared between the recombinant receptors and/or AP-1 transcription factors and/or inhibitory complex members and/or diseases or conditions of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features including: a composition comprising isolated T cells modified to overexpress and/or contain elevated levels of one or more AP-1 transcription factors; a method of treating a disease or pathologic condition in a subject comprising administering to the subject having the disease or pathologic condition an effective amount of the composition; a composition comprising isolated T cells modified to reduce and/or eliminate expression and/or activity of one or more AP-1 inhibitory complex members; and a method of treating a disease or condition in a patient comprising administering to the patient having the disease or condition an effective amount of the composition; these shared technical features are previously disclosed by WO 2016/179283 A1 to Fate Therapeutics, Inc. (hereinafter 'Fate') in view of US 2008/0139475 A1 (RONAI).

Fate discloses a composition comprising isolated T cells (a composition comprising isolated T cells; paragraphs [0005], [0022]) modified to contain elevated levels of one or more AP-1 transcription factors (treated (modified) to contain elevated levels of FOS and JUN (one or more AP-1 transcription factors); paragraph [0161]); a method of treating a disease or pathologic condition in a subject (a method of treating a disease or pathologic condition in a subject; paragraphs [0023], [0024], [0097]), comprising administering to the subject having the disease or pathologic condition an effective amount of the composition (comprising administering to the subject having the disease or pathologic condition an effective amount of the composition; paragraphs [0023], [0097]).

Fate does not disclose a composition comprising isolated T cells modified to reduce and/or eliminate expression and/or activity of one or more AP-1 inhibitory complex members; and a method of treating a disease or condition in a patient comprising administering to the patient having the disease or condition an effective amount of the composition.

Ronai discloses therapies for cancer (therapies for cancer; abstract), including an inhibitory ATF2 N-terminal fragment (including an inhibitory ATF2 N-terminal fragment; abstract; paragraph [0008]), or inhibitory RNA (or inhibitory RNA; paragraph [0049]) which inhibits the activity of ATF2 (which inhibits the activity of ATF2; paragraphs [0008]) or expression of ATF2 (or expression of ATF2; paragraph [0049]).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Fate to have included the use of an inhibitor of one or more AP-1 inhibitory complex members, including an inhibitor of ATF2 or ATF2 expression, as disclosed by Ronai, in order to complement or augment the effects of increasing the expression of the AP-1 transcription factors FOS and JUN, as disclosed by Fate, in order to provide cells with enhanced efficacy in the treatment of cancer.

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 Fate and Ronai references, unity of invention is lacking.