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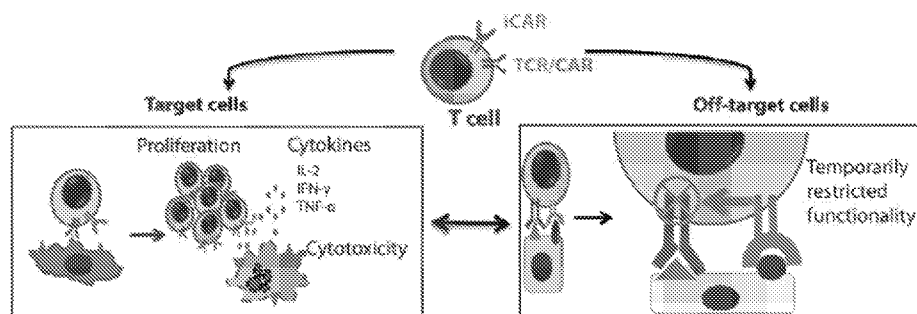
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, 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, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(54) Title: METHODS FOR IDENTIFYING ACTIVATING ANTIGEN RECEPTOR (ACAR)/INHIBITORY CHIMERIC ANTIGEN RECEPTOR (ICAR) PAIRS FOR USE IN CANCER THERAPIES

**Fig. 1**



(57) Abstract: The present invention provides a method for identifying a target pair comprising i) an inhibitory chimeric antigen receptor (iCAR) or a protective chimeric antigen receptor (pCAR) capable of preventing or attenuating undesired activation of an effector immune cell, wherein the iCAR or pCAR target is directed to a target extracellular polymorphic epitope, and ii) an activating chimeric antigen receptor (aCAR), wherein the aCAR is directed to a target non-polymorphic cell surface epitope of a protein, as well as methods of making and use of such pairs in the treatment of cancer.



**(84) Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

**Published:**

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

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30 July 2020 (30.07.2020)

INTERNATIONAL SEARCH REPORT

International application No  
PCT/IB2019/001108

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61K39/00 C12N15/10 C12Q1/6886  
ADD.  
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)  
A61K C07K C12N C12Q  
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)  
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/075612 A1 (RINAT NEUROSCIENCE CORP [US]; COLLECTIS [FR]) 19 May 2016 (2016-05-19) example 3 -----	1-105
X	WO 2016/097231 A2 (COLLECTIS [FR]) 23 June 2016 (2016-06-23) table 3 -----	1-105
X	WO 2015/142314 A1 (SLOAN KETTERING INST CANCER [US]) 24 September 2015 (2015-09-24) cited in the application example 1 -----	1-105
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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  10 March 2020	Date of mailing of the international search report  26/06/2020
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Aslund, Fredrik
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/IB2019/001108

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	V. D. FEDOROV ET AL: "PD-1- and CTLA-4-Based Inhibitory Chimeric Antigen Receptors (iCARs) Divert Off-Target Immunotherapy Responses", SCIENCE TRANSLATIONAL MEDICINE, vol. 5, no. 215, 11 December 2013 (2013-12-11), pages 215ra172-215ra172, XP055210508, ISSN: 1946-6234, DOI: 10.1126/scitranslmed.3006597 figures 1,8	1-105
X	----- WO 2014/145252 A2 (MILONE MICHAEL C [US]; WANG ENXIU [US]) 18 September 2014 (2014-09-18) example 9	1-105
X	----- WO 2018/061012 A1 (GAVISH GALILEE BIO APPL LTD [IL]; IMPACT BIO LTD [IL]) 5 April 2018 (2018-04-05) example 4 -----	1-105

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB2019/001108

## 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:

see additional 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 an 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.:

1-105(partially)

### 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.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-105(partially)

A method of identifying an inhibitory chimeric antigen receptor (iCAR) or protective chimeric antigen receptor (pCAR)/activating chimeric antigen receptor (aCAR) target pair comprising:i) selecting an iCAR or a pCAR capable of preventing or attenuating undesired activation of an effector immune cell, wherein the iCAR or pCAR target is directed to a target extracellular polymorphic epitope from a gene selected from the group consisting of the 598 genes listed in Fig. 22; andii) selecting an aCAR capable of inducing activation of an effector immune cell, wherein the aCAR is directed to a target non-polymorphic cell surface epitope of a protein selected from the group consisting of the 49 target proteins listed Fig. 23;iii) expressing the iCAR or pCAR from step i) and the aCAR from step ii) in a population of cells;iv) subjecting the population of cells to one or more assays, wherein the one or more assays are capable of detecting preventing or attenuating undesired activation of an effector immune cell and/or detecting inducing activation of an effector immune cell: andv) identifying an iCAR or pCAR/aCAR target pair based on the assay results in step iv). Furthermore, a safe effector immune cell expressing an iCAR + aCAR combination as above and a method of treating cancer using a safe effector immune cell. Furthermore, a nucleic acid or vector encoding an iCAR and/or aCAR as above. The above methods and products concern an iCAR targeting ABCA4.

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2-598. claims: 1-105(partially)

A method of identifying an inhibitory chimeric antigen receptor (iCAR) or protective chimeric antigen receptor (pCAR)/activating chimeric antigen receptor (aCAR) target pair comprising:i) selecting an iCAR or a pCAR capable of preventing or attenuating undesired activation of an effector immune cell, wherein the iCAR or pCAR target is directed to a target extracellular polymorphic epitope from a gene selected from the group consisting of the 598 genes listed in Fig. 22; andii) selecting an aCAR capable of inducing activation of an effector immune cell, wherein the aCAR is directed to a target non-polymorphic cell surface epitope of a protein selected from the group consisting of the 49 target proteins listed Fig. 23;iii) expressing the iCAR or pCAR from step i) and the aCAR from step ii) in a population of cells;iv) subjecting the population of cells to one or more assays, wherein the one or more assays are capable of detecting preventing or attenuating undesired activation of an effector immune cell and/or detecting inducing activation of an effector immune cell: andv) identifying an iCAR or pCAR/aCAR target pair based on the

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

assay results in step iv). Furthermore, a safe effector immune cell expressing an iCAR + aCAR combination as above and a method of treating cancer using a safe effector immune cell. Furthermore, a nucleic acid or vector encoding an iCAR and/or aCAR as above. The above methods and products concern an iCAR targeting a gene listed in Fig. 22, said gene not being ABCA4.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No  
PCT/IB2019/001108

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