The present invention provides markers, marker signatures and molecular targets that correlate with dysfunction or activation of immune cells. The present markers, marker signatures and molecular targets provide for new ways to evaluate and modulate immune responses. Therapeutic methods are also provided to treat a patient in need thereof who would benefit from a modulated immune response.
ISSN: 0021-9738, DOI: 10.1172/JCI46102
Abstract
page 2354, left-hand column, paragraph 2-
page 2356, left-hand column, paragraph 1
page 2359, left-hand column, paragraph 2
page 2358, left-hand column, last paragraph
Figure 5

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

"*" 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
"*A" document member of the same patent family

Date of the actual completion of the international search
31 January 2018

Date of mailing of the international search report
03/04/2018

Authorized officer
Ul brecht, Matthias
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<td>I. Tirosh et al.: &quot;Dissecting the multilayer ecosystem of metastatic melanoma by single-cell RNA-seq&quot;, SCI ENCE, vol. 352, no. 6282, 8 April 2016 (2016-04-08), pages 189-196, XP055306751, ISSN: 0036-8075, DOI: 10.1126/science.aad0501 abstract page 195, middle column, paragraph 3 - page 196, left-hand column, paragraph 2 figure 5</td>
<td>1-18, 36-50, 52-86</td>
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<td>X</td>
<td>M. Giordano et al.: &quot;Molecular profiling of CD8+ T cells in autochthonous melanoma identifies Mafr as driver of exhaustion&quot;, EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 34, no. 15, 2 July 2015 (2015-07-02), pages 2042-2058, XP055220471, DE ISSN: 0261-4189, DOI: 10.15252/embj.201490786 abstract page 2043, right-hand column, paragraph 1 page 2054, right-hand column, paragraph 3 table 1 figure 5 page 2055, left-hand column, last paragraph - right-hand column, paragraph 1</td>
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<td>SINGER MEROMIT ET AL: &quot;A Distinct Gene Module for Dysfunction Uncoupled from Activation in Tumor-Infiltrating T Cells&quot;. CELL, CELL PRESS, AMSTERDAM, NL, vol. 166, no. 6, 8 September 2016 (2016-09-08), page 1500, XP029718849, ISSN: 0092-8674, DOI: 10.1016/J.CELL.2016.08.052 the whole document</td>
<td>1-18, 36-50, 52-86</td>
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**INTERNATIONAL SEARCH REPORT**

**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.:

   1-18, 49, 50, 85, 86(completely); 36-48, 52-84(partly)

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

1. claims: 1-18, 49, 50, 85, 86 (completely) ; 36-48, 52-84 (partially)

A method as defined in claims 1, 6, 7, 8, 11 and 17, respectively; an isolated immune cell as defined in claim 14; a population of immune cells as defined in claim 15; a composition or pharmaceutical composition as defined in claim 16; a method as defined in claims 36 and 37, but limited to the immune cell as defined in claims 1-16; a kit as defined in claim 46, but limited to means for detecting the signature referred to in claims 1-5; an isolated immune cell as defined in claim 49; a population of immune cells as defined in claim 67, a method as defined in claim 68 a composition as defined in claim 73, the isolated immune cell or population for use in therapy or specific therapy as defined in claims 74 and 75 respectively, a method of treatment as defined in claims 78 and 82, but each of claims 67, 68, 73-75, 78 and 82 limited to immune cells as defined in claim 49 or claims 52-66 dependent thereon or a population of these immune cells, as applicable; a medical use as defined in claim 85.

2. claims: 19-35, 51, 87, 88 (completely) ; 36-48, 52-84 (partially)

A method as defined in claims 19, 23, 24, 25 and 28, respectively; an isolated immune cell as defined in claim 31; a population of immune cells as defined in claim 32; a composition or pharmaceutical composition as defined in claim 33; a method as defined in claim 34; a method as defined in claims 36 and 37, but limited to the immune cell as defined in claims 19-34; a kit as defined in claim 46, but limited to means for detecting the signature referred to in claims 19-22; an isolated immune cell as defined in claim 51; a population of immune cells as defined in claim 67, a method as defined in claim 68 a composition as defined in claim 73, the isolated immune cell or population for use in therapy or specific therapy as defined in claims 74 and 75 respectively, a method of treatment as defined in claims 78 and 82, but each of claims 67, 68, 73-75, 78 and 82 limited to immune cells as defined in claim 51 or claims 52-66 dependent thereon or a population of these immune cells, as applicable; a medical use as defined in claim 87.
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