PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant’s or agent’s file reference
73502200440

FOR FURTHER ACTION

See item 4 below

International application No.
PCT/US2015/044396

International filing date (day/month/year)
08 August 2015 (08.08.2015)

Priority date (day/month/year)
08 August 2014 (08.08.2014)

International Patent Classification (8th edition unless older edition indicated)
See relevant information in Form PCT/ISA/237

Applicant
ALECTOR LLC

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒ Box No. I Basis of the report
☐ Box No. II Priority
☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒ Box No. IV Lack of unity of invention
☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐ Box No. VI Certain documents cited
☐ Box No. VII Certain defects in the international application
☐ Box No. VIII Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 84bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

Date of issuance of this report
14 February 2017 (14.02.2017)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer
Kihwan Moon

Facsimile No. +41 22 338 82 70
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Form PCT/IB/373 (January 2004)
**PATENT COOPERATION TREATY**

From the  
INTERNATIONAL SEARCHING AUTHORITY

To: JIE ZHOU  
MORRISON & FOERSTER LLP  
425 MARKET STREET  
SAN FRANCISCO, CA 94105-2482

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PCT  
WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43bis.1)

**Date of mailing**  
**03 JUN 2016**

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**FOR FURTHER ACTION**  
See paragraph 2 below

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**Applicant's or agent's file reference**  
735022000440

**International application No.**  
PCT/US 15/44396

**International filing date (day/month/year)**  
08 August 2015 (08.08.2015)

**Priority date (day/month/year)**  
08 August 2014 (08.08.2014)

**International Patent Classification (IPC) or both national classification and IPC**  
IPC(8) - C12N 5/07, C12P 21/06, C07H 21/04 (2016.01)  
CPC - A61K 38/00

**Applicant**  
ALECTOR LLC

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1. **This opinion contains indications relative to the following items:**

- [x] Box No. I  Basis of the opinion
- [x] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [x] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority (“IPEA”) except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

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**Name and mailing address of the ISA/US**  
Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450  
Facsimile No. 571-273-8300

**Date of completion of this opinion**  
10 May 2016 (10.05.2016)

**Authorized officer:**  
Lee W. Young  
PCT Helpdesk: 571-292-4300  
PCT OSP: 571-292-7774

Form PCT/ISA/237 (cover sheet) (January 2015)
1. With regard to the language, this opinion has been established on the basis of:
   - [X] the international application in the language in which it was filed.
   - [ ] a translation of the international application into ________ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. [ ] This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a)).

3. [X] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of a sequence listing:
   a. [X] forming part of the international application as filed:
      - [X] in the form of an Annex C/ST.25 text file.
      - [ ] on paper or in the form of an image file.
   b. [ ] furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:
      - [ ] in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
      - [ ] on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

4. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:
The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.
☒ claims Nos. 13-49, 55-66, 69-93, 95, 96, 100, 102

because:

☐ the said international application, or the said claims Nos. __________________________________________ relate to the following subject matter which does not require an international search (specify):

☒ the description, claims or drawings (indicate particular elements below) or said claims Nos. see below are so unclear that no meaningful opinion could be formed (specify):

Claims 13-49, 55-66, 69-93, 95, 96, 100, 102 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. __________________________________________ are so inadequately supported by the description that no meaningful opinion could be formed (specify):

☒ no international search report has been established for said claims Nos. 13-49, 55-66, 69-93, 95, 96, 100, 102

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☒ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it, or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☒ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it, or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☒ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.
<table>
<thead>
<tr>
<th>Box No. IV</th>
<th>Lack of unity of invention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:</td>
</tr>
<tr>
<td></td>
<td>☐ paid additional fees.</td>
</tr>
<tr>
<td></td>
<td>☐ paid additional fees under protest and, where applicable, the protest fee.</td>
</tr>
<tr>
<td></td>
<td>☒ paid additional fees under protest but the applicable protest fee was not paid.</td>
</tr>
<tr>
<td></td>
<td>☒ not paid additional fees.</td>
</tr>
<tr>
<td>2.</td>
<td>☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.</td>
</tr>
<tr>
<td>3.</td>
<td>☒ This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is</td>
</tr>
<tr>
<td></td>
<td>☒ not complied with for the following reasons:</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Group I*: Claims 1-12, directed to an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody induces or inhibit one or more TREM2 activities; and wherein the isolated antibody binds to one or more amino acid residues within amino acid residues of SEQ ID NO: 1. Group I* will be searched upon payment of additional fees. The isolated antibody that binds to a TREM2 protein may be searched, for example, to the extent that the epitope encompasses the amino acid residues 29-112 of SEQ ID NO: 1 for an additional fee and election as such. It is believed that claims 1-6, 9-10 read on this exemplary invention. Additional TREM2 antibodies will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected antibodies. Failure to clearly identify how any paid additional invention fees are to be applied to the group(s) result in only the first claimed invention to be searched. Another exemplary election would be that the epitope encompasses the amino acid residues 139-146 of SEQ ID NO: 1 (claims 1-4, 7, 8, 11, 12).</td>
</tr>
<tr>
<td></td>
<td>Group II*: Claims 50-54, 67-68, directed to an isolated anti-human TREM2 antibody, wherein the isolated antibody comprises a heavy chain variable domain and a light chain variable domain. Group III* will be searched upon payment of additional fees. The isolated anti-human TREM2 antibody may be searched, for example, to the extent that the HVR-H1, -H2, -H3 comprise SEQ ID NOs: 3, 25, 50, respectively, and the HVR-L1, -L2, -L3 comprise SEQ ID NUs: 120, 139, 154, respectively; for an additional fee and election as such. It is believed that claims 50-54, 67-68 read on this exemplary invention. Additional anti-humom TREM2 antibodies will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected antibodies. 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. Another exemplary election would be wherein the HVR-H1, -H2, -H3 comprise SEQ ID NOs: 4, 26, 51, respectively; and the HVR-L1, -L2, -L3 comprises SEQ ID NOs: 121, 139, 154, respectively (claims 50-54, 67-68).</td>
</tr>
<tr>
<td></td>
<td>Group III: claims 94, 97-99, 101, drawn to a method of preventing, or treating an individual having a disease with a TREM2 antibody, and a method of modulating innate immune cell survival with a TREM2 antibody.</td>
</tr>
<tr>
<td></td>
<td>The inventions listed as Groups I*, II*, and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:</td>
</tr>
<tr>
<td></td>
<td>Special Technical Features</td>
</tr>
<tr>
<td></td>
<td>Group I* includes the special technical feature of an isolated TREM2 antibody exhibiting agonistic or antagonistic activities, not required by Groups II*, III.</td>
</tr>
<tr>
<td></td>
<td>Group I* includes the special technical feature of an isolated TREM2 antibody binds to an epitope defined by specific amino acid residues of SEQ ID NO: 1, not required by Groups II*, III.</td>
</tr>
<tr>
<td></td>
<td>Group II* includes the special technical feature of an isolated anti-human TREM2 antibody comprising heavy chain and light chain CDRs having specific amino acid sequences, not required by Groups I*, III.</td>
</tr>
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<td></td>
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<tr>
<td>4.</td>
<td>☐ Consequencly, this opinion has been established in respect of the following parts of the international application:</td>
</tr>
<tr>
<td></td>
<td>☒ the parts relating to claims Nos. 1-6, 9-10 limited to 20-112 of SEQ ID NO: 1</td>
</tr>
</tbody>
</table>

Form PCT/ISA/237 (Box No. IV) (January 2015)
## Written Opinion of the International Searching Authority

<table>
<thead>
<tr>
<th>Box No. V</th>
<th>Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</th>
</tr>
</thead>
</table>

### 1. Suitement

**Novelty (N)**
- Claims 2, 3/2, 4-6, 9-10: **YES**
- Claims 1, 3/1: **NO**

**Inventive step (IS)**
- Claims: **NONE**
- Claims 1-6, 9-10: **NO**

**Industrial applicability (IA)**
- Claims: **NONE**

### 2. Citations and explanations:

Claims 1 and 3/1 lack novelty under PCT Article 33(2) as being anticipated by US 2013/0150559 A1 (Novo Nordisk A/S) (hereinafter 'Novo Nordisk').

Regarding claim 1, Novo Nordisk teaches an isolated antibody that binds to a TREM2 antibody, wherein the isolated antibody induces one or more TREM2 activities, and wherein the isolated antibody promotes survival of one or more innate immune cells (para [0313], a chimeric gene encoding the human TREM-2 extracellular domain). For the production of anti-TREM2 mAb, 6-week-old BALB/c mice (Tffla -Credo, Labrosos, France) received an initial subcutaneous injection of 100 g purified huTREM-2-lgM in Freund's complete adjuvant (FCA) behind the neck. One of the anti-TREM-2 antibodies was designated as 29E3 mAb (IgG1K); [0367], Monocyte-derived DCs stimulated with ...F(ab')2 29E3 for various time periods showed resistance to apoptosis (Fig. 34) and the prolonged survival of these cells seems to be mediated by an Erk-dependent pathway (Fig. 35).)

Regarding claim 3/1, Novo Nordisk teaches the isolated antibody of claim 1, wherein the one or more innate immune cells are dendritic cells (para 0367), monocyte-derived DCs.

Claims 2 and 3/2 lack an inventive step under PCT Article 33(3) as being obvious over Novo Nordisk.

Regarding claim 2, Novo Nordisk teaches an isolated antibody that binds to a TREM2 antibody, wherein the isolated antibody induces one or more TREM2 activities, and wherein the isolated antibody promotes survival of one or more innate immune cells (para [0313], a chimeric gene encoding the human TREM-2 extracellular domain). For the production of anti-TREM2 mAb, 6-week-old BALB/c mice (Tffla -Credo, Labrosos, France) received an initial subcutaneous injection of 100 g purified huTREM-2-lgM in Freund's complete adjuvant (FCA) behind the neck. One of the anti-TREM-2 antibodies was designated as 29E3 mAb (IgG1K); [0367], Monocyte-derived DCs stimulated with ...F(ab')2 29E3 for various time periods showed resistance to apoptosis (Fig. 34) and the prolonged survival of these cells seems to be mediated by an Erk-dependent pathway (Fig. 35).)

Novo Nordisk further teaches an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody inhibits one or more TREM2 activities (para [0032], methods for modulating the activity of a polypeptide of the invention comprising contacting a cell with an agent that modulates (e.g., inhibits or stimulates) the activity or expression of a polypeptide of the invention, ... such a modulating agent is an antibody that is specific for a polypeptide of the invention), but does not specifically teach wherein the isolated antagonist antibody decreases survival of one or more innate immune cells. However, since agonistic TREM2 antibody prolongs the survival of innate immune cells as taught by Novo Nordisk (para [0367]), one of ordinary skill in the art would have recognized that the antagonistic TREM2 antibody would have decreased survival of innate immune cells and it would have been obvious for one of ordinary skill to confirm by routine experimentation.

Regarding claim 3/2, Novo Nordisk teaches the isolated antibody of claim 2, wherein the one or more innate immune cells are dendritic cells (para [0367], monocyte-derived DCs).

Claims 4-6, 9, 10 lack an inventive step under PCT Article 33(3) as being obvious over the article entitled 'Regulation of TREM2 expression by an NF-kB-sensitive miRNA-34a' by Zhao et al. (hereinafter 'Zhao'), in view of Novo Nordisk.

Regarding claim 4, Zhao teaches an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody binds to one or more amino acids within amino acid residues selected from the group consisting of: i. amino acid residues 29-112 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 29-112 of SEQ ID NO: 1 (pg 3, para 3, anti-human TREM2 antibody B3 (sc-373828)) (NOTE, TREM-2 (B-3) is a mouse monoclonal antibody raised against amino acids 1-160 mapping at the N-terminus of TREM-2 of human origin according to the data sheet of sc-373828 published by SANTA CRUZ BIOTECHNOLOGY, INC. (hereinafter 'sc-373828'), Zhao does not specifically teach SEQ ID NO: 1. However, SEQ ID NO: 1 is well known to one of ordinary skill in the art, for example, Novo Nordisk teaches SEQ ID NO: 1 (para [0011]). The TREM-2 is a transmembrane glycoprotein having the amino acid sequence of SEQ ID NO:4). As SEQ ID NO: 1 is known, one of ordinary skill in the art would have identified amino acid residues 29-112 of TREM2 as referred in sc-373828.

---continued in Supplemental Box---
Supplemental Box

In the space in any of the preceding boxes is not sufficient.

Continuation of:
Box NO. IV. Lack of unity of invention

Group III includes the special technical feature of a method of treating a disease and modulate innate immune cell survival, not required by Groups I+, II+.

Another special technical feature of the inventions listed as Group I+ is the specific epitopes defined by specific amino acid residues of SEQ ID NO: 1, recited therein. Each of the inventions of Group I+ requires a unique epitope amino acid sequence not required by the other inventions. In addition, SEQ ID NO: 1 is taught by US 2013/0150559 A1 to Colonna et al. (hereinafter 'Colonna') (para [0049], Fig. 1. TREM 2 (SEQ ID NO: 4) is 100% match to SEQ ID NO: 1 of Instant invention).

Another special technical feature of the inventions listed as Group II+ is the specific heavy chain and light chain CDR sequences, recited therein. Each of the inventions of Group II+ requires a specific combination of specific heavy chain and light chain CDR sequences not required by the other inventions.

Common Technical Features

The inventions of Groups I+, II+, and III share the technical feature of an isolated antibody that binds to a TREM2 protein.

The inventions of Group I+ share the common technical feature of claims 1 and 2.

The inventions of Group II+ share the common technical feature of claim 50.

The inventions of Groups I+ and III share the technical feature of modulating innate immune cell survival with a TREM2 antibody.

However, these shared technical features do not represent a contribution over prior art in view of Colonna. Colonna teaches [instant claims 1-2] an isolated TREM2 antibody, wherein the isolated antibody induces one or more TREM2 activities, and wherein the isolated antibody promotes survival of one or more innate immune cells (para [0367]). Monocyte-derived DCs stimulated with ... F(ab')2 29E3 for various time periods showed resistance to apoptosis (Fig. 34) and the prolonged survival of these cells seem to be mediated by an Erk-dependent pathway (Fig. 35). Colonna further teaches an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody inhibits one or more TREM2 activities (para [0032]), methods for modulating the activity of a polypeptide of the invention comprising contacting a cell with an agent that modulates (e.g., inhibits or stimulates) the activity or expression of a polypeptide of the invention ... such a modulating agent is an antibody that is specific for a polypeptide of the invention), but does not specifically teach wherein the isolated antagonistic antibody decreases survival of one or more innate immune cells. However, since agonistic TREM2 antibody prolongs the survival of innate immune cells as taught by Colonna (para [0367]), one of ordinary skill in the art would have recognized that the antagonistic TREM2 antibody would have decreased survival of innate immune cells and it would have been obvious for one of ordinary to confirm by routine experimentation.

Colonna further teaches [instant claim 50] an isolated anti-human TREM2 antibody, wherein the isolated antibody comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises: CDR H1, H2, H3 and wherein the light chain variable domain comprises: CDR L1, L2, L3 (para [0204]), HscM2: ScU JU NO2, expressed on human myeloid cells; [0029], antibodies that specifically bind a polypeptide ... containing either a VL or VH domain or even a complementary determining region (CDR) that specifically binds to a polypeptide of the invention; [0313], a chimeric gene encoding the human TREM-2 extracellular domain ... For the production of anti-TREM2 mAb, 6-week-old BALB/c mice (Iffa-Credo, Labeul, France) received an initial subcutaneous injection of 100 g purified huTREM-2-IGH in Freund's complete adjuvant (FCA) behind the neck ... One of the anti-TREM-2 antibodies was designated as 29F3 mAb (IgG1,K)).

The inventions of Group I+ further share the common technical feature of claim 4 wherein said isolated antibody binds to one or more amino acids of TREM2 protein (SEQ ID NO: 1). The article entitled 'Regulation of TREM2 expression by an NF-κB-sensitive mRNA-34a' by Zhao et al. (hereinafter 'Zhao') (Neuroreport. 2013 April 17; 24(6): 316.323. Author Manuscript) teaches anti-human TREM2 antibody B3 (sc-373828) (pg 3, para 3), wherein said isolated antibody binds to one or more amino acids of TREM2 protein (NOTE, TREM-2 (B-3) is a mouse monoclonal antibody raised against amino acids 1-160 mapping at the N-terminus of TREM-2 of human origin according to the data sheet of sc-373828 published by SANTA CRUZ BIOTECHNOLOGY, INC (hereinafter 'sc-373828') [retrieved on 17 March 2016 from http://datasheets.scbt.com/sc-373828.pdf]).

As said technical features were known in the art at the time of the invention, these cannot be considered special technical feature that would otherwise unify the groups.

Groups I+, II+, and III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.
Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V2. Citations and explanation

Regarding claims 5-6, 9-10, Zhao, in view of Novo Nordisk, teaches an isolated antibody that binds to a TREM2 protein, wherein the isolated antibody binds to one or more amino acids within amino acid residues 29-112 of SEQ ID NO: 1 (pg 3, para 3, anti-human TREM2 antibody B3 (sc-373823)), but does not specifically teach that said anti-TREM2 antibody binds to one or more amino acid residues 43-50 or 49-57 of SEQ ID NO: 1. It would have been obvious to one of ordinary skill in the art, in a routine experimentation, to have mapped the specific amino acid residues in TREM2 protein that are responsible for contacting anti-TREM2 antibody, with high probability of success.

Claims 1-6, 9, 10 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.