PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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PCT

INVITATION TO PAY ADDITIONAL FEES
AND, WHERE APPLICABLE, PROTEST FEE

(PCT Article 17(3)(a) and Rules 40.1 and 40.2(e))

Date of mailing (day/month/year) 28 MAR 2016
PAYMENT DUE within ONE MONTH from
the above date of mailing

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)
Applicant ALECTOR LLC

1. This International Searching Authority
   (i) considers that there are 3+ (number of) inventions claimed in the international application covered
      by the claims indicated below/on an extra sheet:
      ----see extra sheet----

   (ii) therefore considers that the international application does not comply with the requirement of unity of invention
      (Rules 13.1, 13.2 and 13.3) for the reasons indicated below/on an extra sheet:
      ----see extra sheet----

   (iii)☐ has carried out a partial international search (see Annex) ☑ will establish the international search report
         on those parts of the international application which relate to the invention first mentioned in claims Nos.:
         1-6, 9-10 limited to amino acid residues 29-112 of SEQ ID NO: 1

   (iv) will establish the international search report on the other parts of the international application only if, and to the extent
        to which, additional fees are paid.

2. Consequently, the applicant is hereby invited to pay, within the time limit indicated above, additional fees in the amount
   indicated below:
   $2080 × 2+ number of additional inventions = $4180+ (See Item 2 of annex)
   total amount of additional fees/currency

3. The applicant is informed that, according to Rule 40.2(c), the payment of any additional fees may be made under protest,
   that is, a reasoned statement to the effect that the international application complies with the requirement of unity of invention
   or that the amount of the required additional fees is excessive, where applicable, subject to the payment of a protest fee.
   Where the applicant pays additional fees under protest, the applicant is hereby invited, within the time limit indicated above,
   to pay a protest fee (Rule 40.2(e)) in the amount of ___________________________ (amount/currency)
   Where the applicant has not, within the time limit indicated above, paid the required protest fee, the protest will be considered
   not to have been made and the International Searching Authority will so declare.

4. ☑ Claim(s) Nos. 13-49, 55-66, 69-93, 95, 96, 100, 102 have been found to be unsearchable under
   Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the ISA/US
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Form PCT/ISA/206 (April 2005)
Item 2 (continued). For International Applications filed on or after 01 January 2014, Applicant is reminded that the search fee per additional invention indicated in item 2 is the undiscounted fee per additional invention. An Applicant may pay the search fee per additional invention fee reduced by 50% (small entity assertion) or 75% (micro entity certification), as appropriate. See 37 CFR 1.27 and 1.29.

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.

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) will 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).

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 II+ 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 comprises SEQ ID NOs: 120, 138, 153, 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-human 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).

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.

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:

Special Technical Features

Group I+ includes the special technical feature of an isolated TREM2 antibody exhibiting agonistic or antagonistic activities, not required by Groups II+, III.

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.

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.

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.

---------see next sheet for continuation---------
Continued from prior sheet:

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 Groups II+ 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 skill 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 [0009]), TREM-2: SEQ ID NO:2, 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, Labeutrie, France) received an initial subcutaneous injection of 100 g purified huTREM-2-IgM in Freund's complete adjuvant (FCA) behind the neck ?. One of the anti-TREM-2 antibodies was designated as 29E3 mAb (IgG2a;X).

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 miRNA-34a' by Zhao et al. (hereinafter 'Zhao') (Neuroreport. 2013 April 17; 24(6): 3187323, 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.

Continuation of Section 4:

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).