PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2018/073253	29.08.2018	29.08.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 C12N5/00

Applicant
OSE IMMUNOTHERAPEUTICS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ 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 Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and 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 usually 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 notifed 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.

Name and mailing address of the ISA:

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Date of completion of this opinion
see form PCT/ISA/210

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ 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 43*bis*.1(a))

3. ☒ 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. ☒ forming part of the international application as filed:

      ☒ 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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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:

   see separate sheet

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 3, 15-18
	No:	Claims	1, 4-14, 19, 20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item I

Basis of the report

Sequences SEQ ID NOs 1-26 from the sequence listing are also included in the basis of this written opinion.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

D1 WO 2017/149394 A1 (OSE IMMUNOTHERAPEUTICS [FR]) 8 September 2017 (2017-09-08)

D2 S. TOUIL ET AL: "Depletion of T regulatory cells through selection of CD127-positive cells results in a population enriched in memory T cells: implications for anti-tumor cell therapy", HAEMATOLOGICA, THE HEMATOLOGY JOURNAL : OFFICIAL ORGAN OF THE EUROPEAN HEMATOLOGY ASSOCIATION, vol. 97, no. 11, 1 November 2012 (2012-11-01), pages 1678-1685, XP055419575

D3 NATALIA MAREK ET AL: "The Time Is Crucial for Ex Vivo Expansion of T Regulatory Cells for Therapy", CELL TRANSPLANTATION, vol. 20, no. 11, 1 November 2011 (2011-11-01), pages 1747-1758, XP55083629

D4 VOLKER SCHIRRMACHER: "Cancer-reactive memory T cells from bone marrow: Spontaneous induction and therapeutic potential (Review)", INTERNATIONAL JOURNAL OF ONCOLOGY, vol. 47, no. 6, 12 October 2015 (2015-10-12), pages 2005-2016, XP055434149

D5 ROBERT F. KUDERNATSCH ET AL: "Human bone marrow contains a subset of quiescent early memory CD8 + T cells characterized by high CD127 expression and efflux capacity : Cellular immune response", EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 44, no. 12, 27 October 2014 (2014-10-27), pages 3532-3542, XP55434147

D6 LIU WEIHONG ET AL: "CD127 expression inversely correlates with FoxP3 and suppressive function of human CD4(+) T reg cells", THE JOURNAL OF EXPERIMENTAL MEDICINE, ROCKEFELLER UNIVERSITY PRESS, US, vol. 203, no. 7, 1 July 2006 (2006-07-01), pages 1701-1711, XP002469608

D7 EP 2 583 980 A1 (EFFIMUNE [FR]; INST NAT SANTE RECH MED [FR]) 24 April 2013 (2013-04-24)

D8 NICOLAS A. GIRALDO ET AL: "Tumor-Infiltrating and Peripheral Blood T-cell Immunophenotypes Predict Early Relapse in Localized Clear Cell Renal Cell Carcinoma", CLINICAL CANCER RESEARCH, vol. 23, no. 15, 1 August 2017 (2017-08-01), pages 4416-4428, XP055420162

D9 EP 2 955 196 A1 (EFFIMUNE [FR]) 16 December 2015 (2015-12-16)

D10 SANDER KELDERMAN ET AL: "Antigen-specific TIL therapy for melanoma: A flexible platform for personalized cancer immunotherapy", EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 46, no. 6, 3 May 2016 (2016-05-03), pages 1351-1360, XP055431343

2 Document D2 already discloses a method for the isolation of effector T cells based on immunomagnetic selection of CD127 positive labelled T cells from leuko-apheresis samples freshly collected from healthy donors, which also means depletion of CD127 negative regulatory T cells. The method disclosed in D1 does not report whether unspecific human polyclonal immunoglobulins were used in the blocking/staining buffer in order to avoid non specific staining of undesired cells with anti-CD127 monoclonal antibody, e.g. via the Fc receptor/Fc portion interaction. However the use of such a saturating step with said unspecific human polyclonal antibodies in any cell-staining methods with monoclonal antibodies, previous to the staining step with the antibody of interest, still in the presence of unspecific polyclonal antibodies, is always performed by the person skilled in the art. Using said methodology of D2 more than 90% of $CD127^-$ regulatory T cells have been eliminated from the $CD127^+$ T cell population. Said population of effector T cells has been prepared in the aim of hematopoietic stem cell transplantation. Moreover, in the absence of evidence to the contrary, the antibody that specifically binds to CD127, used in the methodology of D2 does not interfere with the IL-7

signaling pathway (cf. D2 abstract, p. 1679 left-hand column second full paragraph - fourth full paragraph and right-hand column second and third full paragraphs, p. 1680 left-hand column first and second full paragraphs, right-hand column last full paragraph, paragraph bridging p. 1681 to p. 1682 - p. 1683 left-hand column first full paragraph, p. 1684 left-hand column first full paragraph - right-hand column first full paragraph and Fig. 1-4). Hence the disclosure of document D2 appears to anticipate the subject-matter of present claims 1, 4-14, 19 and 20 contrary to the requirements of Articles 33(1) and 33(2) PCT.

3 A similar objection as to lack of novelty of the subject-matter of claims 1, 4-14, 19 and 20 applies *mutatis mutandis* in view of the disclosure of document D3 (cf. D3 abstract, p. 1748 paragraph bridging the left- to the right-hand column - right-hand column first full paragraph, Fig. 1, 4, 5 and 6). Hence document D3 appears therefore to anticipate the novelty of claims 1, 4-14, 19 and 20 contrary to the requirements of Articles 33(1) and 33(2) PCT.

4 None of the prior-art documents at hand discloses the subject-matters of claims 2-3 and 15-18. Claims 2-3 and 15-18 appear therefore to be novel and to meet the requirements of Article 33(2) PCT.

5 However, the subject-matters of claims 2-3 and 15-18 do not appear to be based on an inventive concept and claims 2-3 and 15-18 therefore are considered to fail to the requirements of Articles 33(1) and 33(3) PCT, the reasons being as follows:

5.1 Document D2 can be considered to represent the closest prior art document for the subject-matter of claims 2-3 which differs from the teaching of D2 by the fact that the magnetic immunoselection of CD127 positive T cell is performed in presence of a distinct anti-CD127 monoclonal antibody. However the instant application is mute as regards a technical effect due to said difference. Indeed no comparative data are therein provided that would allow the present instance to ascertain whether a surprising or unexpected effect has been arrived at.

5.2 Hence in view of D2 the objective technical problem to be solved by the subject-matter of claims 2 or 3 can be seen in the provision of an alternative method for the magnetic immunoselection of CD127 positive cells.

5.3 The solution proposed in the claim, i.e. the use of said alternative anti-CD127 monoclonal antibody cannot however be considered as inventive because the generation of further alternative monoclonal antibodies specifically binding to

CD127 is a matter of the skilled person's routine experimentation and the choice of said particular monoclonal antibodies as those listed in the claims is arbitrary since, in the absence of evidence to the contrary, said choice is not associated with any particular technical effect other than the well known possibility to use those in the method of immuno-magnetic selection of CD127 positive cells. Hence the subject-matter of claims 2 and 3 would not be considered inventive and claims 2 and 3 would not be considered to meet the requirements of Articles 33(1) and 33(3) PCT.

5.4 In view of the teaching of document D2 that already reports the positive selection of a pool of CD127 positive memory T cells able to give rise to a reinforced capacity of said cells to respond to pathogenic antigens (cf. D2 the paragraph bridging p. 1681 to p. 1682 and discussion), together with the general knowledge provided by D4 and D5 (cf. D4 (abstract, p. 2 paragraph bridging the left- to the right-hand column - p. 3 left-hand column line 6, p. 4 left-hand column first full paragraph - p. 6 left-hand column line 5, p. 7 right-hand column second full paragraph - p. 9 left-hand column first full paragraph, D5 abstract, p. 3536 right-hand column first full paragraph - p. 3540 left-hand column line 3), the use of said positively selected CD127 expressing T cell in the treatment of hematologic malignancies (claim 15), cancer including solid tumors (claim 16) and chronic diseases (claim 17) appears to be an obvious option the person skilled in the art would select without the need of inventive skills contrary to the requirements of Articles 33(1) and 33(3) PCT.

5.5 Moreover, in the absence of experimental data proving that a surprising or unexpected effect has been arrived at or that a yet unforeseeable objective technical problem has been solved in the art, the combination of said CD127 positive sorted effective T cell population with a further therapeutic agent cannot be considered inventive. Hence the subject-matter of claim 18 would not be considered to fulfill the requirements of Articles 33(1) and 33(3) PCT.

6 In claim 1 the expression "*moderate affinity for CD127*" is a relative expression and leaves the skilled reader in doubt as regards the exact claimed scope contrary to the requirements of Article 6 PCT.

6.1 Also in independent claim 1 the further characteristic defined in functional term by the expression "*in particular wherein the antibody specifically binding to CD127 does not interfere with the IL-7 signalling pathway*" is vague (Article 6 PCT) and considered to be insufficiently disclosed in the application as originally filed because said application is mute as regards the exact structural characteristic features an anti-CD127 monoclonal antibody should possess in order to fulfill said

requirements. Hence the scope of independent claim 1 is unclear contrary to the requirements of Article 6 PCT and a person skilled in the art wishing to repeat its subject-matter would be faced with undue burden/experimentation contrary to the requirements of Article 5 PCT.

7 The subject-matter of claim 8 is unclear contrary to the requirements of Article 6 PCT because claim 8 tends to further define the cell population obtained by the method of claims 1-7, however claim 8 fails to give an indication of the further steps the method should encompass or the origin of the cells that appear compulsory in order to attain the cell population suitable for the purposes the claim recites, i.e. a preparation of hematopoietic stem cells suitable for transplantation (HSCT) or T cells suitable for adoptive therapy, including tumor-infiltrating cells (TILs) and/or genetically modified cancer-specific T cells such as Chimeric-Antigen Receptor T cells (CART). The lack of clarity is such that a person skilled in the art wishing to repeat said claimed subject-matter would be faced to undue burden/experimentation. Hence claim 8 appears also insufficiently disclosed in the application as originally filed contrary to the requirements of Article 5 PCT.

8 Claim 11 corresponds to a product-by-process claim without however a limited purpose, it is furthermore unclear what are the essential structural characteristic features that distinguishes the product of claim 11 from the CD127 positive selected effector T cells already known from D2 and D3 (Article 6 PCT). Its subject-matter lacks therefore novelty (Articles 33(1) and 33(2) PCT).

9 An identical objection arises also to claims 12 and 13 which are considered unclear (Article 6 PCT), since their respective subject-matter corresponds to product-by-process, however the process to which said claims relate, does not give to the person skilled in the art any hint as regards how the particular claimed cell preparation can be obtained, in particular what are steps the method should encompass or what should be the origin of the cells, that would allow the provision of the cell preparations for the specific purposes recited in the claims (see also point 7 herein above). The lack of clarity is such that a person skilled in the art wishing to repeat said claimed subject-matter would be faced to undue burden/experimentation. Hence claims 12 and 13 are also insufficiently disclosed in the application as originally filed contrary to the requirements of Article 5 PCT.

10 Claims 18 and 19 lack clarity because their category are method claims that use further method claims, it would however appear that the goal of the methods of claims 1-8 is identical to that further defined within the wording of claims 18 or 19, i.e. "*for the preparation of a composition comprising treated human cells depleted of Treg cells*". Hence it ensues that the aims of the methods of claims 1-8 and 18 and 19 are unclear since they leave the skilled reader in doubt as to their respective intended scope of protection contrary to the requirements of Article 6 PCT. Moreover, neither the method to which said claims relate, nor the wording of claims 18 and 19 themselves, give to the person skilled in the art any hint as regards how the particular claimed cell preparation can be obtained, in particular what are steps the method should encompass or what should be the origin of the cells, that would allow the provision of the cell preparations for the specific purposes recited in the claims (see also point 7 herein above). The lack of clarity is such that a person skilled in the art wishing to repeat said claimed subject-matter would be faced to undue burden/experimentation. Hence claims 12 and 13 are also insufficiently disclosed in the application as originally filed contrary to the requirements of Article 5 PCT.

Re Item VI

Certain documents cited

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A- 2017/149394	08.09.2017	28.02.2017	29.02.2016

Document D1 (WO-A- 2017/149394) cited in the international search report is not considered to be part of the prior art for the purposes of Articles 33(2) and (3) PCT. However, should the present application enter the national or regional phase, and depending on the validity of the presently claimed priority, the above document could become relevant to the question of novelty [and inventive step].