

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 113086-0140	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2019/040654	International filing date (<i>day/month/year</i>) 03 July 2019 (03.07.2019)	Priority date (<i>day/month/year</i>) 04 July 2018 (04.07.2018)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CYTOIMMUNE THERAPEUTICS, INC.		

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 15 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: <table style="width: 100%;"> <tr> <td style="width: 5%; text-align: center;">☒</td> <td style="width: 25%;">Box No. I</td> <td style="width: 70%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	☒	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
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.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).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 05 January 2021 (05.01.2021) Authorized officer Yukari Nakamura e-mail: pct.team7@wipo.int
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: Antoinette F. Konski
Foley & Lardner LLP
3000 K Street NW, Suite 600
Washington, DC 20007

Date of mailing
(day/month/year)

06 DEC 2019

Applicant's or agent's file reference
113086-0140

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US19/40654

International filing date (day/month/year)

03 July 2019 (03.07.2019)

Priority date (day/month/year)

04 July 2018 (04.07.2018)

International Patent Classification (IPC) or both national classification and IPC

IPC - C12N 5/078, 5/0783; C07K 14/705, 14/725, 16/28, 16/32; A61K 39/395 (2019.01)

CPC - C12N 5/0638; C07K 14/705, 16/28, 16/32, 16/2863; A61K 39/0011, 39/395, 39/3955

Applicant

CYTOIMMUNE THERAPEUTICS, LLC

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 43bis.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 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 66.1bis(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/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

20 November 2019 (20.11.2019)

Authorized officer

Shane Thomas

PCT Help Desk

Telephone No. 571-272-4300

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

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Box No. I Basis of this 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(b)).
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:

**WRITTEN OPINION OF THE
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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. 7-9, 12-34, 42-48, 55-70

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. 7-9, 12-34, 42-48, 55-70 are so unclear that no meaningful opinion could be formed (*specify*):

Claims Nos. 7-9, 12-34, 42-48, and 55-70 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. 7-9, 12-34, 42-48, 55-70

- ☐ 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.

**WRITTEN OPINION OF THE
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☒ paid additional fees.
- ☐ paid additional fees under protest and, where applicable, the protest fee.
- ☐ paid additional fees under protest but the applicable protest fee was not paid.
- ☐ not paid additional fees.
2. ☐ 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.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:

****-Please see supplemental page-****

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-2, 3/1-2, 4/3/1-2, 5/4/3/1-2, 6/4/3/1-2, 10-11, 35-40, 41/35-40, 49-54; B7.1

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement			
1. Statement				
Novelty (N)	Claims	4/3/1-2, 5/4/3/1-2, 6/4/3/1-2, 35-40, 41/35-40, 49-54	YES	
	Claims	1-2, 3/1-2, 10-11	NO	
Inventive step (IS)	Claims	35, 37-38, 40, 41/35, 41/37, 41/38, 41/40, 49, 51-52, 54	YES	
	Claims	-***-Please see below-***-	NO	
Industrial applicability (IA)	Claims	-***-Please see below-***-	YES	
	Claims	NONE	NO	
2. Citations and explanations:				
-***-Continued from Box No. V: 1. Statement-***-				
Inventive step (IS): NO: Claims 1-2, 3/1-2, 4/3/1-2, 5/4/3/1-2, 6/4/3/1-2, 10-11, 36, 39, 41/36, 41/39, 50, 53				
Industrial Applicability (IA): YES: Claims 1-2, 3/1-2, 4/3/1-2, 5/4/3/1-2, 6/4/3/1-2, 10-11, 35-40, 41/35-40, 49-54				
-***-Box No. V: 2. Citations and Explanations-***-				
Claims 1-2, 3/1-2, and 10-11 lack novelty under PCT Article 33(2) as being anticipated by WO 2015/142675 A2 (NOVARTIS AG, et al.) (hereinafter "Novartis").				
As per claim 1, Novartis discloses an isolated nucleic acid (an isolated nucleic acid molecule encoding a chimeric antigen receptor; paragraph [005]) or a vector comprising: a. a polynucleotide encoding a chimeric antigen receptor, CAR (an isolated nucleic acid molecule encoding a chimeric antigen receptor; paragraph [005]), comprising: a. an antigen binding domain of an FLT3 antibody (an antigen binding domain against FLT3; paragraph [00365]); b. a hinge domain (an antibody hinge region; paragraph [00457], [00488]); c. a transmembrane domain (the transmembrane domain; paragraph [00488]); d. and an intracellular domain (an intracellular signaling domain; paragraph [00494]); and b. a polynucleotide encoding an antibody or antigen binding fragment thereof comprising an antigen binding domain that recognizes and binds PD-1 (the agent comprises a nucleic acid sequence encoding the PD1 CAR; paragraph [00522]) and/or PD-L1.				
As per claim 2, Novartis discloses the isolated nucleic acid or the vector of claim 1, and Novartis discloses further comprising e. a signaling domain (an intracellular signaling domain; paragraph [00494]).				
As per claims 3/1-2, Novartis discloses the isolated nucleic acid or the vector of claims 1-2, and Novartis further discloses wherein the CAR further comprises an inducible or a constitutively active element (inducible promoters; paragraph [00596]).				
As per claim 10, Novartis discloses the isolated nucleic acid or the vector of claim 1, and Novartis further discloses wherein the CAR comprises: a. an antigen binding domain of a FLT3 antibody (an antigen binding domain against FLT3; paragraph [00365]); b. a CD8 a hinge domain (a CD8 hinge; paragraph [0012]); c. a CD8 a transmembrane domain (a CD8 transmembrane domain; paragraph [0010]); and d. a CD28 costimulatory signaling region (a CD28 costimulatory domain; paragraph [0046]) and/or a 4-1BB costimulatory signaling region.				
As per claim 11, Novartis discloses the isolated nucleic acid or the vector of claim 2, and Novartis further discloses wherein the CAR comprises: a. an antigen binding domain of a FLT3 antibody (an antigen binding domain against FLT3; paragraph [00365]); b. a CD8 a hinge domain (a CD8 hinge; paragraph [0012]); c. a CD8 a transmembrane domain (a CD8 transmembrane domain; paragraph [0010]); d. a CD28 costimulatory signaling region (a CD28 costimulatory domain; paragraph [0046]) and/or a 4-1BB costimulatory signaling region; and e. a CD3 zeta signaling domain (a CD3 zeta signaling domain; paragraph [0046]).				
Claims 36, 39, 41/36, 41/39, 50, and 53 lack novelty under PCT Article 33(2) as being anticipated by US 2016/0331793 A1 (PSIOXUS THERAPEUTICS LIMITED) (hereinafter "Psioxus").				
As per claim 36, Psioxus discloses an antibody comprising a single chain variable fragment sequence, scFv (the expression of a scFv form of anti-human PD-L1 antibody; paragraph [0297]), comprising an amino acid sequence EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHVVWVQAPGKGLEWVAVWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAE DTAVVYCARRHWPGGFDYWGQGLTVTVSAGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASKGVSTSGSYLHWYQQK PGEAPRLLIYLAESYLGVPARFSGSGSGTDFLTITSSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIK or an equivalent thereof (the above sequence of the instant PCT application is 79% identical to SEQ ID NO: 37 of the Psioxus reference (an equivalent thereof intends at least about 70% homology or identity as defined by the instant application; paragraph [0075]); paragraph [0298]).				
-***-Continued Within the Next Supplemental Box-***-				

WRITTEN OPINION OF THE
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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 39 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect in the form or contents thereof: in line 2 of claim 39, there is a parenthesis between SQ of the amino acid sequence which appears to be a typographical error and for the purposes of this opinion has been ignored.

Claim 53 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect in the form or contents thereof: in line 1 of claim 53, there is the text "or 47 45" which appears to be a typographical error and for the purposes of this opinion has been ignored.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Supplemental Box

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

-Continued from Box V: Citations and Explanations-

As per claim 39, Psioxus discloses a bispecific antibody (a full length antibody and bispecific or multi-specific formats; paragraph [0266]) comprising a single chain variable fragment sequence, scFv (the expression of a scFv form of anti-human PD-L1 antibody; paragraph [0297]), comprising an amino acid sequence of:
SQVQLVQSGVEVKKPGASVKVCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPNSNGGTNFNEKFKNRVLTLDSTTTAYMELKSLQ
FDDTAVYYCARRDYRFDMGFYWGQGTITVTVSSGGGGSGGGGGSGGGGSDIQTQSPSSLSASVGDRTITCRASQDVSTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFLTITSSLPEDFATYYCQYLYHPATFGQGTKEIKR and/or
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHVWRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAE
DTAVYYCARRHWPGGFDYWGQGTITVTVSAGGGGGSGGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASKGVSTSGSYLHWYQQK
PGEAPRLIYLASYLESVGPARGSGSGTDFLTITSSLEPEDFAVYYCQHSRDLPLTFGGGKVEIK, or an equivalent of each thereof (the
above sequence of the instant PCT application is 79% identical to SEQ ID NO: 37 of the Psioxus reference (an equivalent thereof intends
at least about 70% homology or identity as defined by the instant application; paragraph [0075]); paragraph [0298]).

As per claims 41/36 and 41/39, Psioxus discloses the antibody of claims 36 and 39, and Psioxus further discloses wherein the antibody is an IgA, an IgD, an IgE, an IgG or an IgM antibody (may be human IgA, IgD, IgE, IgG or IgM domains; paragraph [0282]).

As per claim 50, Psioxus discloses an antigen binding fragment (antibody-binding fragment; paragraph [0030]) comprising an amino acid sequence:
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHVWRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAE
DTAVYYCARRHWPGGFDYWGQGTITVTVSAGGGGGSGGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASKGVSTSGSYLHWYQQK
PGEAPRLIYLASYLESVGPARGSGSGTDFLTITSSLEPEDFAVYYCQHSRDLPLTFGGGKVEIK, or an equivalent of each thereof (the
above sequence of the instant PCT application is 79% identical to SEQ ID NO: 37 of the Psioxus reference (an equivalent thereof intends
at least about 70% homology or identity as defined by the instant application; paragraph [0075]); paragraph [0298]).

As per claim 53, Psioxus discloses a polypeptide (the sequence encoding a protein/polypeptide/peptide; paragraph [0234]) comprising an amino acid sequence of:
QVQLVQSGVEVKKPGASVKVCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPNSNGGTNFNEKFKNRVLTLDSTTTAYMELKSLQF
DDTAVYYCARRDYRFDMGFYWGQGTITVTVSSGGGGSGGGGGSGGGGSDIQTQSPSSLSASVGDRTITCRASQDVSTAVAWYQQK
GKAPKLLIYSASFLYSGVPSRFSGSGSGTDFLTITSSLPEDFATYYCQYLYHPATFGQGTKEIKR or
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHVWRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAE
DTAVYYCARRHWPGGFDYWGQGTITVTVSAGGGGGSGGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASKGVSTSGSYLHWYQQK
PGEAPRLIYLASYLESVGPARGSGSGTDFLTITSSLEPEDFAVYYCQHSRDLPLTFGGGKVEIK, or an equivalent of each thereof
(the above sequence of the instant PCT application is 79% identical to SEQ ID NO: 37 of the Psioxus reference (an equivalent thereof
intends at least about 70% homology or identity as defined by the instant application; paragraph [0075]); paragraph [0298]).

Claims 4/3/1-2, 5/4/3/1-2, and 6/4/3/1-2 lack an inventive step under PCT Article 33(3) as being obvious over Novartis in view of WO 2004/029197 A2 (MAXYGEN, INC., et al.) (hereinafter "Maxygen").

As per claims 4/3/1-2, Novartis discloses the isolated nucleic acid or the vector of claims 3/1-2, but Novartis does not disclose wherein the inducible or the constitutively active element controls the expression of a polynucleotide encoding an immunoregulatory molecule or a cytokine. Maxygen does disclose wherein the inducible or the constitutively active element controls the expression of a polynucleotide encoding an immunoregulatory molecule or a cytokine (expression vector encoding B7-1 and B7-2 polypeptide can be induced by using an inducible on- and off-gene expression system; page 25, line 25; page 173, line 10). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the nucleic acid, as previously disclosed by Novartis, for the integration of wherein the inducible or the constitutively active element controls the expression of a polynucleotide encoding an immunoregulatory molecule or a cytokine, as previously disclosed by Maxygen, as the previous disclosure by Novartis includes immune effector cells, e.g., T cells, NK cells, engineered to express a CAR that binds to a tumor antigen (paragraph [004]), the Maxygen reference discloses expression vector encoding B7-1 and B7-2 polypeptide can be induced by using an inducible on- and off-gene expression system (page 25, line 25; page 173, line 10), and this combination would provide a co-stimulatory molecule that acts in association or conjunction with, or is involved with, another molecule to stimulate or enhance an immune response (page 4, lines 3-5).

As per claims 5/4/3/1-3, Novartis and Maxygen, in combination, disclose the isolated nucleic acid or the vector of claims 4/3/1-2, but Novartis does not disclose wherein the immunoregulatory molecule or cytokine comprises B7.1. Maxygen does disclose wherein the immunoregulatory molecule or cytokine comprises B7.1 (expression vector encoding B7-1 polypeptide; page 25, line 25). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the nucleic acid, as previously disclosed by Novartis, for the integration of wherein the immunoregulatory molecule or cytokine comprises B7.1, as previously disclosed by Maxygen, as the previous disclosure by Novartis includes immune effector cells, e.g., T cells, NK cells, engineered to express a CAR that binds to a tumor antigen (paragraph [004]), the Maxygen reference discloses expression vector encoding B7-1 polypeptide (page 25, line 25), and this combination would provide a co-stimulatory molecule that acts in association or conjunction with, or is involved with, another molecule to stimulate or enhance an immune response (page 4, lines 3-5).

-Continued Within the Next Supplemental Box-

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Supplemental Box

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

-Continued from Previous Supplemental Box-

As per claims 6/4/3/1-2, Novartis and Maxygen, in combination, disclose the isolated nucleic acid or the vector of claims 4/3/1-2, but Novartis does not disclose wherein the immunoregulatory molecule or cytokine comprises IL-12 and/or GM-CSF; and/or IL-12 and/or one or more of IL-2 and low-toxicity IL-2; and/or IL-12 and/or IL-15; and/or IL-12 and/or IL-21; IL-12 and/or B7.1; and/or IL-12 and/or OX40L; and/or IL-12 and/or CD40L; and/or IL-12 and/or GITRL; and/or IL-12 and/or IL-18; and/or one or more of IL-2 and low-toxicity IL-2 and one or more of CCL19, CCL21, and LEC; and/or IL-15 and one or more of CCL 19, CCL21, and LEC; and/or IL-21 and one or more of CCL 19, CCL21, and LEC; and/or GM-CSF and one or more of CCL19, CCL21, and LEC; and/or OX40L and one or more of CCL19, CCL21, and LEC; and/or CD137L and one or more of CCL19, CCL21, and LEC; and/or comprises B7.1 and one or more of CCL19, CCL21, and LEC; and/or CD40L and one or more of CCL19, CCL21, and LEC; and/or GITRL and one or more of CCL 19, CCL21, and LEC. Maxygen does disclose wherein the immunoregulatory molecule or cytokine comprises B7.1 (expression vector encoding B7-1 and B7-2 polypeptide; page 25, line 25). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the nucleic acid, as previously disclosed by Novartis, for the integration of wherein the immunoregulatory molecule or cytokine comprises B7.1, as previously disclosed by Maxygen, as the previous disclosure by Novartis includes immune effector cells, e.g., T cells, NK cells, engineered to express a CAR that binds to a tumor antigen (paragraph [004]), the Maxygen reference discloses expression vector encoding B7-1 polypeptide (page 25, line 25), and this combination would provide a co-stimulatory molecule that acts in association or conjunction with, or is involved with, another molecule to stimulate or enhance an immune response (page 4, lines 3-5).

Claims 35, 37-38, 40, 41/35, 41/37, 41/38, 41/40, 49, 51-52, and 54 meet the criteria set out in PCT Article 33(2)-(3).

Claim 35 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antibody comprising a single chain variable fragment sequence, scFv, comprising an amino acid sequence of
 QQVLVQSGVEVKKPGASVKVCSKASGYTFNYYMYWVRQAPGQGLEWMGGINPSNGGTNFKNEKFKNRVLTLDSTTTAYMELKSLQF
 DDTAVYYCARRDYRFDMGFDYWGQGTITVSSGGGGSGGGSGGGSGGSDIQTQSPSSLSASVGDRTITCRASQDVSTAVAWYQQKPK
 GKAPKLLIYSASFYSGVPSRFSGSGSGTDFLTISLQPEDFATYYCQQYLYHPATFGQGTKVEIKR or an equivalent thereof.

Novartis discloses an antibody comprising a single chain variable fragment sequence, scFv (the antigen binding domain of the first CAR molecule comprises a scFv; paragraph [0057]), comprising an amino acid sequence with some similarity to the sequence provided in claim 35 or an equivalent thereof (the above sequence of the instant PCT application is 11% identical to SEQ ID NO: 39 of the Novartis reference; paragraph [00520]). Novartis does not disclose the amino acid sequence the sequence provided in claim 35 or an equivalent thereof.

WO 2018/045110 A1 (XENCOR, INC.) (hereinafter "Xencor") discloses an antibody comprising a single chain variable fragment sequence, scFv (first antigen binding domain comprising an scFv that binds a first antigen; paragraph [0012]), comprising an amino acid sequence with similarity to the sequence provided in claim 35 or an equivalent thereof (the above sequence of the instant PCT application is 64% identical to SEQ ID NO: 28,620 of the Xencor reference; paragraph [00114]). Xencor does not disclose the amino acid sequence the sequence provided in claim 35. Xencor does not disclose any motivation for selecting SEQ ID NO: 28,620 from the long list of sequences in which it appears.

The publication entitled "Crystal structures of mono- and bi-specific diabodies and reduction of their structural flexibility by introduction of disulfide bridges at the Fv interface" by KIM, JH et al. (hereinafter "Kim") discloses an antibody (recombinant bispecific antibodies; page 1, 2nd paragraph) comprising an amino acid sequence similar to the sequence provided in claim 35 or an equivalent thereof (the above sequence of the instant PCT application is 62% identical to Accession No. 5GS2_D of the Kim reference; Supplemental Data). Kim does not disclose comprising a single chain variable fragment sequence, scFv; and the amino acid sequence the sequence provided in claim 35 or an equivalent thereof.

The publication entitled "Production and characterization of a phage-display recombinant antibody against carrageenans: evidence for the recognition of a secondary structure of carrageenan chains present in red algae tissues" by LINERS, F et al. (hereinafter "Liners") discloses an antibody comprising a single chain variable fragment sequence, scFv (a scFv recombinant antibody; abstract), comprising an amino acid sequence similar to the sequence provided in claim 35 or an equivalent thereof (the above sequence of the instant PCT application is 64% identical to Accession No. AAS77223.1 of the Liners reference; Supplemental Data). Liners does not disclose the amino acid sequence provided in claim 35 or an equivalent thereof.

Novartis, Xencor, Kim, and Liners, either alone or in combination fail to disclose the amino acid sequence provided in claim 35. While Xencor, Kim, and Liners disclose a sequence similar to the sequence as shown in Claim 35, they do not disclose the amino acid sequence provided in claim 35. Thus, it would not have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the amino acid sequence of claim 35 because the references of record fail to disclose all the elements.

Claim 41/35 meet the criteria set out in PCT Article 33(2)-(3), because of their dependence on positive claim 35.

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**WRITTEN OPINION OF THE
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Claim 37 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antibody comprising a single chain variable fragment sequence, scFv, encoded by the nucleotide sequence comprising a nucleic acid sequence
CAGGTCCAATTGGTACAGAGCGGCGTCAAGTAAAGAAGCCTGGAGCCAGCGTTAAAGTTTCTTGCAAGGCTTCAGGATATACTTTTCT
ACTAACTACTATATGTACTGGGTACGGCAGGCTCCAGGGCAAGGGTTGGAGTGGATGGGAGGGATCAATCCTTCTAACGGCGGCAC
TAACTTTAACGAAAAATTTAAAAATAGGGTGACCCTCACAACCTGACTCAAGTACGACTACAGCATACATGGAACCTCAAATCTCTCCAAT
TCGATGACACGGCTGTCTATTATTGCGCGAGAAGAGACTATCGCTTCGATATGGGGTTTGATTATTGGGGGCAAGGTACTACGGTTA
CCGTACAGCTCCGGGGGTGGCGGCTCCGGCGGCGGTGGGTGAGGTGGAGGAGGGTCTGACATTCAGATGACGCAATCCCCAAGCT
CTCTGTCCGCGTCAGTGGGCGACCGAGTTACAATCACATGCCGCGCTTCTCAAGATGTGTCAACCGCTGTGCGCTGGTACCAACAGA
AGCCTGGGAAGGGCCCTAAGCTTCTCATCTACTACGCTTCTTTCTGTACTCAGGGGTACCGTCTAGATTCTCAGGATCCGGTAGTG
GGACGGACTTCACATTGACCATAAGTTCCTTGACGCTGAGGATTTGCTACATATTATTGCCAACAGTACCTTTACCATCCTGCCAC
TTTTGCCAGGGTACTAAGGTCGAGATCAAACGG, or an equivalent thereof.

Novartis discloses an antibody comprising a single chain variable fragment sequence, scFv (the antigen binding domain of the first CAR molecule comprises a scFv; paragraph [0057]). Novartis does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence as shown in claim 37, or an equivalent thereof.

US 2009/0170159 A1 (BOBROWICZ, P et al.) (hereinafter "Bobrowicz") discloses an antibody (antibody sequences; paragraph [0090]), encoded by the nucleotide sequence comprising a nucleic acid sequence similar to the sequence provided in claim 37, or an equivalent thereof (residues 406-701 of the above sequence of the instant PCT application are 58% identical to residues 1-317 of SEQ ID NO: 7 of the Bobrowicz reference for an overall similarity of 41%; paragraph [0031]). Bobrowicz does not disclose comprising a single chain variable fragment sequence, scFv; and encoded by the nucleotide sequence comprising a nucleic acid sequence provided in claim 37, or an equivalent thereof.

US 2012/0003695 A1 (DAVIDSON, RC et al.) (hereinafter "Davidson") discloses an antibody (antibody; paragraph [0209]), comprising a single chain variable fragment sequence, scFv (single chain Fv; paragraph [0039]); encoded by the nucleotide sequence comprising a nucleic acid sequence similar to the sequence provided in claim 37, or an equivalent thereof (residues 406-722 of the above sequence of the instant PCT application are 58% identical to residues 1-317 of SEQ ID NO: 69 of the Davidson reference for an overall similarity of 43%; paragraph [0209]). Davidson does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence provided in claim 37.

US 2014/0294834 A1 (MERRIMACK PHARMACEUTICALS, INC.) (hereinafter "Merrimack") discloses an antibody comprising a single chain variable fragment sequence, scFv (single chain Fvs; paragraph [0162]), encoded by the nucleotide sequence comprising a nucleic acid sequence similar to the sequence provided in claim 37, or an equivalent thereof (residues 503-728 of the above sequence of the instant PCT application are 58% identical to residues 116-341 of SEQ ID NO: 230 of the Merrimack reference for an overall similarity of 18%; paragraph [0092]). Merrimack does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence provided in claim 37.

Claim 41/37 meets the criteria set out in PCT Article 33(2)-(3), because of their dependence on positive claim 37.

Novartis, Bobrowicz, Davidson, and Merrimack, either alone or in combination fail to disclose the sequence as shown in Claim 37. While Novartis & Merrimack disclose a single chain variable fragment sequence and a sequence similar to the sequence as shown in claim 37, they do not disclose the sequence provided in claim 37. Thus, it would not have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the nucleotide sequence of claim 37 because the references of record fail to disclose all the elements.

Claim 38 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antibody comprising a single chain variable fragment sequence, scFv, encoded by the nucleotide sequence:
GAAGTTCAAGTTGGTCAAGTCAAGGAGGCGCTGGTGCAACCGGGGCTCACTCCGGTTGTCTGTGCTGCTTCAGGATTTACGTT
TTCTGACTCATGGATACATTGGGTGCGCCAAGCCCCGGGCAAGGGGCTGGAATGGGTGGCCTGGATCTCTCCGTATGGGGGTTCCA
CCTACTATGCTGATTCAAGTAAAGGACGGTTCACTATAAGCGCGGATACAAGTAAGAATACTGCCTATCTTCAAATGAATTCTTTCGCG
GCCGAGGATACAGCGGTATATTATTGCGCTAGACGACATTGGCCAGGGGGCTTTGACTATTGGGGGCAAGGTACTCTTGTGACCGT
TAGTGCGGGAGGTGGTGGCAGCGGTGGAGGCGGCTCCGGGGGTGGTGGTTCAGAAATTGCTGACTCAATCCCCCTGCCACATTG
AGTTTGAGCCCAGGAGAGAGCAACTCTGTCTATGCCGGGCGTCAAAAGGTGTCAAGTACGTACGGCTACTCCTATCTTCAATTGGTAT
CAGCAGAAACCGGGAGAAGCGCCGCGCTTCTCATATACCTGGCTAGTTACCTTGAGAGTGGCGTCCCGGGCCGGTTAGTGGGAG
TGGGTCTGGGACTGATTTTACGCTGACAATCAGCAGTCTTGAGCCAGAGGACTTCGCGGTTTACTATTGCCAACATTACGCGGATTTG
CCCCTCACCTTCGGCGGTGGAACGAAGTTGAAATAAAA, or an equivalent thereof.

Novartis discloses an antibody comprising a single chain variable fragment sequence, scFv (the antigen binding domain of the first CAR molecule comprises a scFv; paragraph [0057]). Novartis does not disclose encoded by the nucleotide sequence provided in claim 38, or an equivalent thereof.

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**WRITTEN OPINION OF THE
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US 2013/0259923 A1 (MODERNA THERAPEUTICS) (hereinafter "Moderna") discloses an antibody comprising a single chain variable fragment sequence, scFv (single chain Fv; paragraph [0857]), encoded by a nucleotide sequence with some sequence similarity to the nucleotide sequence provided in claim 38, or an equivalent thereof (residues 13-288 of the above sequence of the instant PCT application are 51% identical to residues 85-360 of SEQ ID NO: 15,975 of the Moderna reference for an overall similarity of 19%; claim 2). Moderna does not disclose encoded by the nucleotide sequence provided in claim 38, or an equivalent thereof. Moderna does not disclose any motivation for selecting SEQ ID NO: 15,975 from the long list of sequences in which it appears.

Xencor discloses an antibody comprising a single chain variable fragment sequence, scFv (first antigen binding domain comprising an scFv that binds a first antigen; paragraph [0012]). Xencor does not disclose encoded by the nucleotide sequence: the nucleotide sequence provided in claim 38, or an equivalent thereof.

Merrimack discloses an antibody comprising a single chain variable fragment sequence, scFv (single chain Fvs; paragraph [0162]). Merrimack does not disclose encoded by the nucleotide sequence provided in claim 38, or an equivalent thereof.

Novartis, Moderna, Xencor, and Merrimack, either alone or in combination fail to disclose the nucleotide sequence provided in claim 38. While Novartis, Moderna, Xencor, and Merrimack disclose an antibody comprising a single chain variable fragment sequence, scFv, they do not disclose the nucleotide sequence provided in claim 38. Thus, it would not have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the nucleotide sequence of claim 38 because the references of record fail to disclose all the elements.

Claim 41/38 meets the criteria set out in PCT Article 33(2)-(3), because of their dependence on positive claim 38.

Claim 40 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a bispecific antibody comprising a single chain variable fragment sequence, scFv encoded by the nucleotide sequence comprising a nucleic acid sequence: CAGGTCCAATTGGTACAGAGCGGCGTGAAGTAAAGAAAGCCTGGAGCCAGCGTTAAAGTTTCTTGCAAGGCTTCAGGATATACCTTTC ACTAACTACTATATGTACTGGGTACGGCAGGCTCCAGGGCAAGGGTTGGAGTGGATGGGAGGGATCAATCCTTCTAACGGCGGCAC TAACCTTAACGAAAAATTTAAAAATAGGGTGACCCTCACAACCTGACTCAAGTACGACTACAGCATACATGGAAGCTCAATCTCTCCAAT TCGATGACACGGCTGTCTATTATTGCGCGAGAAGAGACTATCGCTTCGATATGGGGTTTGATTATTGGGGCAAGGTACTACGGTTA CCGTCAGCTCCGGGGGTGGCGGCTCCGGCGGCGGTGGGTGAGGTGGAGGAGGGTCTGACATTCAGATGACGCAATCCCCAAGCT CTCTGTCCGCGCTCAGTGGGCGACCGAGTTACAATCACATGCCGCGCTTCTCAAGATGTGTCAACCGCTGTGCGCTGGTACCAACAG AAGCCTGGGAAGGCCCTAAGCTTCTCATCTACTCAGCTTCTTTCTGTACTCAGGGTACCCTCTAGATTTCTCAGGATCCGGTAGT GGGACGGACTTCACATTGACCATAAGTTCTTGCAGCTGAGGATTTCGCTACATATTATTGCCAACAGTACCTTTACCATCCTGCCA CTTTTGCCAGGGTACTAAGGTCGAGATCAAACGG and/or GAAGTTCAAGTTGGTTCGAGTCAGGAGGAGGCCCTGGTGCAACCCGGGGGCTCACTCCGGTTGTCTGTGCTGCTTCAAGATTACGTT TTCTGACTCATGGATACATTGGGTGCGCCAAGCCCCGGGCAAGGGGCTGGAATGGGTGGCCTGGATCTCTCCGTATGGGGGTTCGA CCTACTATGCTGATTCAGTAAAGGACGGTTCACTATAAGCGCGGATACAAGTAAGAATACTGCCTATCTTCAAATGAATTCCTTTCGC GCGAGGATACAGCGGTATATTATTCGCTAGACGACATTGGCCAGGGGCTTTGACTATTGGGGGCAAGGGTACTCTTGTGACCGT TAGTGCGGGAGGTTGGTGGCAGCGGTGGAGCGGCTCCGGGGGTGGTGGTTTCAGAAATTGCTCCTGACTCAATCCCCTGCCACATTG AGTTTGAGCCAGGAGAGAGAGCAACTCTGTCATGCCGGGCGTCAAAGGTGTGACGTACGTACGGCTACTCCTATCTTCATTGGTAT CAGCAGAAACCGGGAGAGCGCCGCGCTTCTCATATACCTGGCTAGTTACCTTGAGAGTGGCGTCCCGGCCCGGTTTGTAGTGGGAG TGGGTCTGGGACTGATTTACGCTGACAATCAGCAGTCTTGAGCCAGAGGACTTCGCGGTTTACTATTGCCAACATTACGCGGATT GCCCTCACCTTCGGCGGTGGAAACGAAGTTGAAATAAAA or an equivalent of thereof.

Davidson discloses a bispecific antibody (bispecific antibodies; paragraph [0036]) comprising a single chain variable fragment sequence, scFv (single chain Fv; paragraph [0039]), encoded by a nucleotide sequence comprising a nucleic acid sequence similar to the first sequence provided in claim 40 and/or an equivalent of thereof (residues 406-722 of the above sequence of the instant PCT application are 58% identical to residues 1-317 of SEQ ID NO: 69 of the Davidson reference for an overall similarity of 43%; paragraph [0209]). Davidson does not disclose a nucleotide sequence comprising the nucleotide sequences provided in claim 40 or an equivalent of thereof.

Merrimack discloses a bispecific antibody (bispecific antibodies; paragraph [0162]) comprising a single chain variable fragment sequence, scFv (single chain Fvs; paragraph [0162]), encoded by a nucleotide sequence comprising a nucleic acid sequence similar to the first sequence provided in claim 40 or an equivalent of thereof (residues 503-728 of the above sequence of the instant PCT application are 58% identical to residues 116-341 of SEQ ID NO: 230 of the Merrimack reference for an overall similarity of 18%; paragraph [0092]). Merrimack does not disclose a nucleotide sequence comprising the nucleic acid sequences provided in claim 40 or an equivalent of thereof.

Moderna discloses a bispecific antibody (bispecific antibodies; paragraph [0101]) comprising a single chain variable fragment sequence, scFv (single chain Fv; paragraph [0857]), encoded by a nucleotide sequence comprising a nucleic acid sequence similar to: the second sequence provided in claim 40 or an equivalent of thereof (residues 13-288 of the above sequence of the instant PCT application are 51% identical to residues 85-360 of SEQ ID NO: 15,975 of the Moderna reference for an overall similarity of 19%; claim 2). Moderna does not disclose a nucleotide sequence comprising a nucleic acid sequence provided in claim 40 or an equivalent of thereof.

Novartis discloses a bispecific antibody (a bispecific antibody; paragraph [00250]) comprising a single chain variable fragment sequence, scFv (the antigen binding domain of the first CAR molecule comprises a scFv; paragraph [0057]). Novartis does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence: the sequences provided in claim 40 or an equivalent of thereof.

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Davidson, Merrimack, Moderna, and Novartis, either alone or in combination fail to disclose the nucleic acid sequences provided in claim 40 or an equivalent of thereof. While Davidson, Merrimack, Moderna, and Novartis disclose a bispecific antibody, they do not disclose the nucleic acid sequences provided in claim 40. Thus, it would not have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the nucleotide sequences of claim 40 because the references of record fail to disclose all the elements.

Claim 41/40 meets the criteria set out in PCT Article 33(2)-(3), because of their dependence on positive claim 40.

Claim 49 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antigen binding fragment comprising an amino acid sequence:

QVQLVQSGVEVKKPGASVKVCKASGYFTFTNYYMYWVRQAPGQGLEWMGINPSNGGTNFKNEFKNRVLTLDSSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTITVTVSSGGGGSGGGSGGGGGSDIQTQSPSSLSASVGDRTITCRASQDVSTAVAWYQQKPKGKAPKLLIYSASFLYSGVPSRFSGSGSGDFTLTISLQPEDFATYYCYQLYHPATFGQGTKVEIKR or an equivalent of each thereof.

Novartis discloses an antigen binding fragment (antigen binding domain; paragraph [0249]) comprising an amino acid sequence similar to the sequence provided in claim 49 or an equivalent of each thereof (the above sequence of the instant PCT application is 11% identical to SEQ ID NO: 39 of the Novartis reference; paragraph [00520]). Novartis does not disclose comprising an amino acid sequence provided in claim 49 or an equivalent of each thereof.

Xencor discloses an antigen binding fragment (antigen binding domain; paragraph [00153]) comprising an amino acid sequence similar to the sequence provided in claim 49 or an equivalent of each thereof (the above sequence of the instant PCT application is 64% identical to SEQ ID NO: 28,620 of the Xencor reference; paragraph [00114]). Xencor does not disclose an amino acid sequence as provided in claim 49 or an equivalent of each thereof.

Kim discloses an antigen binding fragment (the antigen- binding domains; page 1, 2nd paragraph) comprising an amino acid sequence similar to the sequence provided in claim 49 or an equivalent of each thereof (the above sequence of the instant PCT application is 62% identical to Accession No. 5GS2_D of the Kim reference; Supplemental Data). Kim does not disclose comprising an amino acid sequence provided in claim 49 or an equivalent of each thereof.

Liners discloses an antigen binding fragment (the antigen binding portions of antibodies; page 2, 2nd column, 2nd paragraph) comprising an amino acid sequence similar to the sequence provided in claim 49 or an equivalent of each thereof (the above sequence of the instant PCT application is 64% identical to Accession No. AAS77223.1 of the Liners reference; Supplemental Data). Liners does not disclose an amino acid sequence provided in claim 49 or an equivalent of each thereof.

Novartis, Xencor, Kim, and Liners, either alone or in combination fail to disclose the sequence provided in claim 49. While Novartis, Xencor, Kim, and Liners disclose an antigen binding fragment, they do not disclose the sequence provided in claim 49 or an equivalent of each thereof. Thus, it would not have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the amino acid sequence of claim 49 because the references of record fail to disclose all the elements.

Claim 51 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antigen binding fragment encoded by the nucleotide sequence comprising a nucleic acid sequence:

CAGGTCCAATTGGTACAGAGCGGCGTCAAGTAAGAAAGCCTGGAGCCAGCGTTAAAGTTTCTTGCAAGGCTTCAGGATATACTTTCCAGGTGACACGCGCTGTCTATTATTGCGCGAGAGAAGACTATCGCTTCGATATGGGGTTTGATTATTGGGGGCAAGGTACTACGGTTACCGTCAGCTCCGGGGGTGGCGGCTCCGGCGGCGGTGGGTCAAGTGGAGGAGGGTCTGACATTACAGTACGCAATCCCCAAGCTCTCTGTCCGCGTCAGTGGGCGACCGAGTTACAATCACATGCCGCGCTTCTCAAGATGTGTCAACCGCTGTGCGCTGGTACCAACAGAACGCTGGGAAGGCCCTAAGCTTCTCATCTACTACGCTTCTTTCTGTACTCAGGGGTACCGTCTAGATTCTCAGGATCCGGTAGTGGGACGGACTTCACATTGACCATAAGTTCCTTGCAGCCTGAGGATTTCGCTACATATTATTGCCAACAGTACCTTTACCATCCTGCCACTTTTGGCCAGGGTACTAAGTTCGAGATCAAACGG or an equivalent of each thereof.

Novartis discloses an antigen binding fragment (antigen binding domain; paragraph [0249]). Novartis does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence as shown in claim 51 or an equivalent of each thereof.

Bobrowicz discloses an antigen binding fragment (antibody; paragraph [0094]) encoded by the nucleotide sequence comprising a nucleic acid sequence similar to the nucleic acid sequence as shown in claim 51 or an equivalent of each thereof (residues 406-701 of the above sequence of the instant PCT application are 58% identical to residues 1-317 of SEQ ID NO: 7 of the Bobrowicz reference for an overall similarity of 41%; paragraph [00031]). Bobrowicz does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence as shown in claim 51 or an equivalent of each thereof.

Davidson discloses an antigen binding fragment (fragment antigen binding; paragraph [0037]) encoded by the nucleotide sequence comprising a nucleic acid sequence similar to the nucleic acid sequence as shown in claim 51 or an equivalent of each thereof (residues 406-722 of the above sequence of the instant PCT application are 58% identical to residues 1-317 of SEQ ID NO: 69 of the Davidson reference for an overall similarity of 43%; paragraph [0209]). Davidson does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence as shown in claim 51 or an equivalent of each thereof.

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Merrimack discloses an antigen binding fragment (antigen-binding portion; paragraph [0162]) encoded by the nucleotide sequence comprising a nucleic acid sequence similar to the nucleic acid sequence as shown in claim 51 or an equivalent of each thereof (residues 503-728 of the above sequence of the instant PCT application are 58% identical to residues 116-341 of SEQ ID NO: 230 of the Merrimack reference for an overall similarity of 18%; paragraph [0092]). Merrimack does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence as shown in claim 51 or an equivalent of each thereof.

Novartis, Bobrowicz, Davidson, and Merrimack, either alone or in combination fail to disclose the sequence as shown in claim 51. While Novartis, Bobrowicz, Davidson, and Merrimack disclose an antigen binding fragment, they do not disclose the sequence as shown in claim 51. Thus, it would not have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the nucleotide sequence of claim 51 because the references of record fail to disclose all the elements.

Claim 52 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antigen binding fragment encoded by the nucleotide sequence comprising a nucleic acid sequence:

GAAGTTTCAGTTGGTTCGAGTCAGGAGGAGGCCTGGTGCAACCCGGGGGCTCACTCCGGTTGTCCTGTGCTGCTTCAGGATTTACGTTTCTGACTCATGGATACATTGGGTGCGCCAAGCCCCGGGCAAGGGGCTGGAATGGGTGGCCTGGATCTCTCCGTATGGGGGTTCCACCTACTATGCTGATTACAGTAAAGGACGGTTCCTATAAGCGCGGATACAAGTAAGAATACTGCCTATCTTCAAATGAATTCCTTCCGCGGAGGATACAGCGGTATATTATGCGCTAGACGACATTGGCCAGGGGGCTTTGACTATTGGGGGACAGGGTACTCTTGTGACCGTTAGTGCGGGAGGTGGTGGCAGCGGTGGAGCGGCTCCGGGGGTGGTGGTTCAGAAATTGCTCTGACTCAATCCCCTGCCACATTGAGTTTGAGCCAGGAGAGAGAGCAACTCTGTCTATGCCGGGCGTCAAAGGTGTCAGTACGTCAGGCTACTCCTATCTTCATTGGTATCAGCAGAAACCGGGAGAGCGCCGCGCCTTCTCATATACCTGGCTAGTTACCTTGAGAGTGGCGTCCCGGCCCGGTTTGTAGTGGGATGCGGCTCTGGGACTGATTTTACGCTGACAATCAGCAGTCTTGAGCCAGAGGACTTCGCGGTTTACTATTGCCAACATTCACGCGATTGCCCCCTACCTTCGGCGGTGGAACGAAGGTTGAAATAAAA or an equivalent of each thereof.

Novartis discloses an antigen binding fragment (antigen binding domain; paragraph [0249]). Novartis does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence as shown in claim 52 or an equivalent of each thereof.

Moderna discloses an antigen binding fragment (examples of antibody fragments include Fab, Fab', F(ab')₂ and Fv fragments; paragraph [0103]) encoded by the nucleotide sequence comprising a nucleic acid sequence similar to the nucleic acid sequence as shown in claim 52 or an equivalent of each thereof (residues 13-288 of the above sequence of the instant PCT application are 51% identical to residues 85-360 of SEQ ID NO: 15,975 of the Moderna reference for an overall similarity of 19%; claim 2). Moderna does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence as shown in claim 52 or an equivalent of each thereof. Moderna does not disclose any motivation for selecting SEQ ID NO: 15,975 from the long list of sequences in which it appears.

Xencor discloses an antigen binding fragment (antigen binding domain; paragraph [00153]). Xencor does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence as shown in claim 52 or an equivalent of each thereof.

Merrimack discloses an antigen binding fragment (antigen-binding portion; paragraph [0162]). Merrimack does not disclose encoded by the nucleotide sequence comprising a nucleic acid sequence as shown in claim 52 or an equivalent of each thereof.

Novartis, Moderna, Xencor, and Merrimack, either alone or in combination fail to disclose the nucleotide sequence as shown in Claim 52. While Novartis, Moderna, Xencor, and Merrimack disclose an antigen binding fragment, they do not disclose the nucleotide sequence as shown in Claim 52. Thus, it would not have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented the nucleotide sequence of claim 52 because the references of record fail to disclose all the elements.

Claim 54 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an isolated nucleic acid comprising a nucleic acid sequence of:

CAGGTCCAATTGGTACAGAGCGGCTCGAAGTAAAGAAGCCTGGAGCCAGCGTTAAAGTTTCTTGCAAGGCTTCAGGATATACTTTTCTAACTACTATATGTAAGTGGGTACGGCAGGCTCCAGGGCAAGGGTTGGAGTGGATGGGAGGGATCAATCCTTCTAACGGCGGCACTAACCTTTAACGAAAAATTTAAAAATAGGGTGACCCTCACACTGACTCAAGTACGACTACAGCATACATGGAACTCAAATCTCTCCAATTCGATGACACCGGTGTCTATTATTGCGCGAGAGAGACTATCGCTTCGATATGGGGTTTGATTATTGGGGGCAAGGTACTACGGTTACCGTCAGCTCCGGGGGTGGCGGCTCCGGCGCGGTGGGTGAGGTGGAGGAGGGTCTGACATTAGATGACGCAATCCCCAAGCTCTCTGTCCGCGTCAGTGGGCGACCGAGTTACAATCACATGCCGCGCTTCTCAAGATGTGTCAACCGCTGTCCGCTGGTACCAACAGAAGCCTGGGAAGGCCCTAAGCTTCTCATCTACTAGCTTCTTTTCTGTACTCAGGGGTACCGCTAGATTCTCAGGATCCGGTAGTGGGACGGAATTCACATTGACCATAAGTTCTTGCAGCGCTGAGGATTCTCGTACATATTATGGCAACAGTACCTTTACCATCCTGCCACTTTTGGCCAGGGTACTAAGGTGCGAGATCAAACGG or
GAAGTTTCAGTTGGTTCGAGTCAGGAGGAGGCCTGGTGCAACCCGGGGGCTCACTCCGGTTGTCCTGTGCTGCTTCAGGATTTACGTTTCTGACTCATGGATACATTGGGTGCGCCAAGCCCCGGGCAAGGGGCTGGAATGGGTGGCCTGGATCTCTCCGTATGGGGGTTCCACCTACTATGCTGATTACAGTAAAGGACGGTTCCTATAAGCGCGGATACAAGTAAGAATACTGCCTATCTTCAAATGAATTCCTTCCGCGGAGGATACAGCGGTATATTATGCGCTAGACGACATTGGCCAGGGGGCTTTGACTATTGGGGGACAGGGTACTCTTGTGACCGTTAGTGCGGGAGGTGGTGGCAGCGGTGGAGCGGCTCCGGGGGTGGTGGTTCAGAAATTGCTCTGACTCAATCCCCTGCCACATTGAGTTTGAGCCAGGAGAGAGAGCAACTCTGTCTATGCCGGGCGTCAAAGGTGTCAGTACGTCAGGCTACTCCTATCTTCATTGGTATCAGCAGAAACCGGGAGAGCGCCGCGCCTTCTCATATACCTGGCTAGTTACCTTGAGAGTGGCGTCCCGGCCCGGTTTGTAGTGGGAGTGGGTCTGGGACTGATTTTACGCTGACAATCAGCAGTCTTGAGCCAGAGGACTTCGCGGTTTACTATTGCCAACATTCACGCGATTGCCCCCTACCTTCGCGGTGGAACGAAGGTTGAAATAAAA or an of each thereof.

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Bobrowicz discloses an isolated nucleic acid (providing a nucleic acid encoding a protein; paragraph [0023]) comprising a nucleic acid sequence of similar to the first sequence provided in claim 54 or an of each thereof (residues 406-701 of the above sequence of the instant PCT application are 58% identical to residues 1-317 of SEQ ID NO: 7 of the Bobrowicz reference for an overall similarity of 41%; paragraph [0031]). Bobrowicz does not disclose either nucleic acid sequence provided in claim 54.

Davidson discloses an isolated nucleic acid (nucleic acid molecules encoding the heterologous protein; paragraph [0020]) comprising a nucleic acid sequence of similar to the first sequence provided in claim 54 (residues 406-722 of the above sequence of the instant PCT application are 58% identical to residues 1-317 of SEQ ID NO: 69 of the Davidson reference for an overall similarity of 43%; paragraph [0209]). Davidson does not disclose either nucleic acid sequence provided in claim 54.

Moderna discloses an isolated nucleic acid (an isolated polynucleotide; claim 1) comprising a nucleic acid sequence of similar to: the second sequence provided in claim 54 or an of each thereof (residues 13-288 of the above sequence of the instant PCT application are 51% identical to residues 85-360 of SEQ ID NO: 15,975 of the Moderna reference for an overall similarity of 19%; claim 2). Moderna does not disclose either nucleic acid sequence provided in claim 54.

Novartis discloses an isolated nucleic acid (an isolated nucleic acid molecule; paragraph [005]). Novartis does not disclose comprising either nucleic acid sequence provided in claim 54.

Bobrowicz, Davidson, Moderna, and Novartis, either alone or in combination fail to disclose the nucleic acid sequences as shown in claim 54. While Bobrowicz, Davidson, Moderna, and Novartis disclose an isolated nucleic acid, they do not disclose the nucleic acid sequences as shown in claim 54. Thus, it would not have been obvious to a person of ordinary skill in the art, at the time of invention, to have implemented either of the nucleic acid sequences of claim 54 because the references of record fail to disclose all the elements.

Claims 1-2, 3/1-2, 10-11, 4/3/1-2, 5/4/3/1-2, 6/4/3/1-2, 35-40, 41/35-40, and 49-54 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

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-Continued from Box No. IV: Lack of unity of invention-

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.

Groups I+, Claims 1-6, 10-11 and B7.1 (immunoregulatory molecule) are directed toward an isolated nucleic acid or a vector comprising:
a. a polynucleotide encoding a chimeric antigen receptor (CAR) comprising: (a) an antigen binding domain of an FLT3 antibody; (b) a hinge domain; (c) a transmembrane domain; (d) and an intracellular domain; and b. a polynucleotide encoding an antibody or antigen binding fragment thereof comprising an antigen binding domain that recognizes and binds PD-1 and/or PD-L1.

The isolated nucleic acid or a vector will be searched to the extent that it encompasses an immunoregulatory molecule comprising B7.1 (first exemplary immunoregulatory molecule). Applicant is invited to elect additional immunoregulatory molecule(s) and/or cytokine(s), and available as an option within at least one searchable claim, to be searched. Additional immunoregulatory molecule(s) and/or cytokine(s) will be searched upon the payment of additional fees. It is believed that claims 1-3, 4-6 (each in-part) and 10-11 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass B7.1 (immunoregulatory molecule). Applicants must specify the claims that encompass any additionally elected immunoregulatory molecule(s) and/or cytokine(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. 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/examined. An exemplary election would be CCL19 (immunoregulatory molecule).

Group II, Claims 35-41 and 49-54 are directed toward anti-PD-1 and anti-PD-L1 antibodies and bi-specific antibodies.

The inventions listed as Groups I+ and II 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: the special technical features of Groups I+ include a chimeric antigen receptor (CAR) comprising: (a) an antigen binding domain of an FLT3 antibody; (b) a hinge domain; (c) a transmembrane domain; (d) and an intracellular domain, not present in any of Groups II; the special technical features of Groups II include SEQ ID NOs 13 and 15, not present in any of Groups I+.

Groups I+ and II+ share the technical features including: anti-PD-1 and anti-PD-L1 antibodies.

However, these shared technical features are previously disclosed by WO 2015/142675 A2 (NOVARTIS AG, et al.) (hereinafter 'Novartis').

Novartis discloses anti-PD-1 and anti-PD-L1 antibodies (paragraphs [0046], [0073]).

No technical features are shared between the immunoregulatory molecule(s) and/or cytokine(s) of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features including: an isolated nucleic acid or a vector comprising:
a. a polynucleotide encoding a chimeric antigen receptor (CAR) comprising: (a) an antigen binding domain of an FLT3 antibody; (b) a hinge domain; (c) a transmembrane domain; (d) and an intracellular domain; and b. a polynucleotide encoding an antibody or antigen binding fragment thereof comprising an antigen binding domain that recognizes and binds PD-1 and/or PD-L1; these shared technical features are previously disclosed by Novartis, as above.

Novartis discloses an isolated nucleic acid (paragraph [005]) or a vector comprising: a. a polynucleotide encoding a chimeric antigen receptor (CAR) (comprising: a. a polynucleotide encoding a chimeric antigen receptor (CAR); paragraph [005]) comprising: (a) an antigen binding domain of an FLT3 antibody ((a) an antigen binding domain of an FLT3 antibody; paragraph [005]); (b) a hinge domain (paragraph [0012]); (c) a transmembrane domain (paragraph [005]); (d) and an intracellular domain (paragraph [005]). Novartis further discloses b. a polynucleotide encoding an antibody or antigen binding fragment thereof comprising an antigen binding domain that recognizes and binds PD-1 and/or PD-L1 (CAR-expressing immune effector cell can further express another agent including a PD-1 and/or PD-L1 inhibitory molecule (a polynucleotide encoding an antibody or antigen binding fragment thereof comprising an antigen binding domain that recognizes and binds PD-1 and/or PD-L1); paragraphs [0046], [0073]).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Novartis reference, unity of invention is lacking.