PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

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/US2016/039796	28.06.2016	29.06.2015

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/48 C07D487/04 C07D519/00 C07K16/28 A61P35/00

Applicant
IMMUNOGEN, INC.

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:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Monami, Amélie Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2016/039796

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:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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	7-76, 78-140
	No:	Claims	1-6, 77, 141-146
Inventive step (IS)	Yes:	Claims	7-76
	No:	Claims	1-6, 77-146
Industrial applicability (IA)	Yes:	Claims	1-146
	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

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

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

1 The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

2 Reference is made to the following documents:

D1 WO 96/14339 A1 (WELLCOME FOUND [GB]; KULL FREDERICK CHARLES JR [US]; FLING MARY ELIZAB) 17 May 1996 (1996-05-17)

D2 STIMMEL J B ET AL: "Site-specific conjugation on serine right-arrow cysteine variant monoclonal antibodies", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 275, no. 39, 29 September 2000 (2000-09-29), pages 30445-30450, XP002714201, ISSN: 0021-9258, DOI: 10.1074/JBC.M001672200 [retrieved on 2000-07-03]

D3 WO 2012/128868 A1 (IMMUNOGEN INC [US]; LI WEI [US]; MILLER MICHAEL [US]; FISHKIN NATHAN [) 27 September 2012 (2012-09-27)

D4 WO 2010/091150 A1 (IMMUNOGEN INC [US]; LI WEI [US]; FISHKIN NATHAN ELLIOTT [US]; ZHAO ROB) 12 August 2010 (2010-08-12)

D5 US 8 557 966 B2 (AB OLGA [US] ET AL) 15 October 2013 (2013-10-15) cited in the application

3 Novelty (Article 33(2) PCT)

3.1 The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 1-6, 77, 141-146 is not new.

3.2 Document D1 discloses conjugates of antibodies having a cysteine residue at the EU/OU numbering position 442 of the heavy chain to radiolabelled chelates having a bromoacetyl or maleimide reactive group. The conjugates

of D1 are for use in the treatment or diagnosis of cancer (D1, examples 1-7; page 7, paragraph 3 - page 10, paragraph 1). The subject-matter of claims 1-6, 77, 141-146 is therefore not novel.

3.3 Document D2 discloses conjugates of antibodies having a cysteine residue at the EU/OU numbering position 442 of the heavy chain to a radiolabelled chelate having a bromoacetyl, iodoacetyl or maleimide reactive group (D2, abstract; page 30447, column 2, paragraph 5 - page 30448, column 1, paragraph 2; page 30450, column 1, paragraph 2). The subject-matter of claims 1-6, 77, 141 is therefore not novel.

4 Inventive step (Article 33(3) PCT)

4.1 The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claims 1-6, 77-146 does not involve an inventive step.

4.2 Being not new, the subject-matter of present claims 1-6, 77, 141-146 cannot be considered as involving an inventive step (Article 33(3) PCT).

4.3 Any of documents D3 or D4 can be regarded as being the prior art closest to the subject-matter of claims 78-140. Both documents disclose pyrrolobenzodiazepine (PBD) dimers comprising a reactive moiety, such as a NHS ester, for conjugation to lysine residues of antibodies (D3, examples 1-32; D4, examples 1-40).

The subject-matter of claims 78-140 therefore differs from these known documents in that the PBD dimers comprise a reactive moiety J_{CB} according to claim 78 or 96, such as a maleimide or a vinyl sulfone, and is therefore new.

The technical effect brought about by this difference is that the PBD dimers are suitable for conjugation to cysteine residues of antibodies.

The problem to be solved by the present invention may therefore be regarded as the provision of PBD dimers for conjugation to cysteine residues of antibodies.

However, maleimide, haloacetyl or vinyl sulfone groups are generally used to conjugate drugs to cysteine residues of antibodies. The skilled person would therefore have designed compounds according to claims 78-140 without exercising inventive skill.

4.4 Any of documents D3 or D5 can be regarded as being the prior art closest to the subject-matter of claims 7-76. D3 discloses conjugates of antibodies to PBD dimers through lysine residues. D5 discloses conjugates of antibodies to maytansinoids through lysine residues.

The subject-matter of claims 7-76 therefore differs from these known documents in that the cytotoxic agent is conjugated to a cysteine residue at the EU/OU numbering position 442 of the heavy chain of the antibody and is therefore new.

The technical effect brought about by this difference is that the conjugation is site-specific.

The problem to be solved by the present invention may therefore be regarded as the provision of site-specific antibody-drug conjugates.

It is generally known to the skilled person that cysteine residues can be engineered in antibodies for subsequent site-specific conjugation to cytotoxic agents. However, the skilled person would not have been prompted to select the position 442 of the heavy chain to introduce said cysteine residue. Claims 7-76 therefore meet the requirements of the PCT with respect to novelty and inventive step.

Re Item VI

Certain documents cited

Patent No	Publication date	Filing date	Priority date
WO2015/196167	23.12.2015	19.06.2015	20.06.2014
WO2015/196089	23.12.2015	19.06.2015	20.06.2014
WO2016/036861	10.03.2016	02.09.2015	02.09.2014

The examination has been carried out assuming that the priority of the application is valid. However, attention is drawn to the fact that the documents which have been cited in the search report as "P" documents may become relevant in the national/ regional examination phase.

Re Item VIII

Certain observations on the international application

1 Present claims 1-33, 76, 77 relate to an extremely large number of possible antibody-cytotoxic agent conjugates. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the conjugates claimed, namely for conjugates comprising a maytansinoid or a pyrrolobenzodiazepine dimer as disclosed on page 75, line 3 - page 80, line 7. Consequently, the claims lack support, and the application lacks disclosure.

2 Claim 96 lacks clarity (Article 6 PCT) because X' in the J_{CB} moeities X'-CR^bR^c-C(=O)- and X'-CR^bR^c-C(=O)-NR^e- is not defined. This has the effect that the person skilled in the art cannot decide clearly which compounds are to be covered by the claim and which are not.