

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.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. PCT/US2020/031067	International filing date (day/month/year) 01.05.2020	Priority date (day/month/year) 03.05.2019
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International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61K31/00 A61K39/395 A61K47/06 A61P35/00 A61P35/02 A61K47/68 ADD. A61K39/00

Applicant
SUTRO BIOPHARMA, 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 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 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 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:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Malamoussi, A Telephone No. +49 89 2399-0	
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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 43bis.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 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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

1. Statement

Novelty (N)	Yes: Claims	<u>1-32</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-32</u>
Industrial applicability (IA)	Yes: Claims	<u>1-32</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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

Reference is made to the following documents:

- D1** WO 2014/089335 A2 (AMGEN INC [US]) 12 June 2014 (2014-06-12)
- D2** US 2019/040152 A1 (KINNEER KRISTA [US] ET AL) 7 February 2019 (2019-02-07)
- D3** WO 2015/166073 A1 (MAX DELBRÜCK CT FÜR MOLEKULARE MEDIZIN [DE]) 5 November 2015 (2015-11-05)
- D4** WO 2017/132617 A1 (SUTRO BIOPHARMA INC [US]) 3 August 2017 (2017-08-03) cited in the application
- D5** US 2019/083641 A1 (STAFFORD RYAN [US] ET AL) 21 March 2019 (2019-03-21)

1 Rule 39.1(iv) / 67.1(iv) PCT

Claims 22-32 relate to subject-matter considered by this Authority to be covered by the provisions of **Rule 39.1(iv) / 67.1(iv) PCT**. 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. Patentability, in particular novelty and inventive step, of **claims 22-32** has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

2 Most relevant prior art documents

D1 relates to BCMA antibodies and drug conjugates (ADC) thereof. The human anti-BCMA antibodies bind to human and cynomolgus monkey BCMA (p. 149, I. 10-12, p. 155, table 5). The antibody 2A1 bound to human BCMA expressed on a variety of human myeloma cells (p. 157, I. 6-10). **D1** discloses in example 6 the conjugation of 2A1 to maytansine (DM1) using a non-cleavable linker (SMCC) resulting in an ADC referred to as 2A1-MCC-DM1 (p. 159-161). In

addition, the antibodies 2A1 and 1E1 were conjugated to PEG4-Mal-DM4 (p. 161, l. 10-12). The anti-BCMA ADCs inhibited growth of myeloma cells in a xenograft subcutaneous tumor model (example 9). The ADC were internalized in myeloma cells (p. 180, l. 14-15).

D2 discloses ADCs directed against BCMA conjugated to the pyrrolobenzodiazepine (PDB) payload SG3249 (i.e. tesirine) using site specific conjugation (abstract, [0076]). Antibody 15B2GL bound to human and cynomolgus monkey BCMA (fig. 1). The ADC 15B2GL-SG3249 was able to kill multiple myeloma cell lines (example 4 and fig. 2) and reduce the tumor volume in a H929 xenograft mouse model (example 5 and fig. 4).

D3 describes humanized antibodies against BCMA and teaches ADC comprising maytansinoids (p. 18, l. 11-28, p. 29, l. 3-17). The antibody J22.9-xi binds to human and cynomolgous monkey BCMA with high affinity (p. 43, l. 15-19, fig. 1 and 10).

D4 teaches an anti-CD74 antibody, in which para-azido methyl phenylalanine (pAMF) was incorporated into position F404 (EU numbering) ([00526]). The anti-CD74 IgG was conjugated to a cytotoxic agent, maytansine, using a strained cyclooctyne reagent to yield Conjugate A ([00526]). Conjugate A was able to bind and kill a variety of B-lymphoma, multiple myeloma and leukemia cells (p. 177, table 2, p. 179, table 3). Furthermore, conjugate A inhibited multiple myeloma tumor growth in the bone marrow of xenograft mice (p. 181, [00547]). **D4** teaches that the antibodies comprise one or more non-natural amino acids at one or more positions selected from the group consisting of heavy chain or light chain residues HC-F404, HC-K121, HC-Y180, HC-F241, HC-221, LC-T22, LC-S7, LC-N152, LC-K42, LC-E161, LC-D170, HC-S136, HC-S25, HC-A40, HC-S 119, HC-S190, HC-K222, HC-R19, HC-Y52, or HC-S70 according to the Kabat or Chothia or EU numbering scheme ([0092]).

D5 relates to anti-folate receptor antibodies having para-azidomethyl-L-phenylalanine (pAMF) incorporated at the HC F404 site, and being conjugated to a non-cleavable maytansine to form antibody-drug conjugates (ADCs) at a drug-antibody ratio of two (DAR2) having the structure of Conjugate M ([0461]) (conjugate M has identical structure with the conjugate presented in claim 1, see p. 73 of **D5**). **D5** teaches that the conjugate M was conjugated to sites K42/Y180/F404 of the 1848-B10 antibody (VH of 1848 anti-FOLR1 antibody, VL of trastuzumab, see table 5 of **D5**). Furthermore, as an alternative, Y180, F404 conjugation sites were used to conjugate cleavable hemiasterlin to the anti-FOLR1 antibodies ([0466], table 16). To increase the in vivo potency of the

FolR α targeting ADCs, 1848-B 10 antibodies was expressed with 2, 4, or 6 para-azidomethyl-phenylalanine (pAMF) residues incorporated on each antibody and conjugated to non-cleavable maytansine (Conjugate M, Example 10) and cleavable hemiasterlin (Conjugate P, Example 11) to generate ADCs with DAR=2, 4 or 6 (see example 12 and table 14). **D5** concludes that the antibody 1848-B10 HC-Y180/F404 can be used with alternative linker warheads in ADCs targeting FolR α ([0474]).

3 **Novelty (Art. 33(2) PCT)**

The prior art documents at hand do not appear to disclose an antibody conjugate according to the claimed formula, wherein n is from 1 to 4; the antibody comprises a V_H region of SEQ ID NO: 13, and a V_L region of SEQ ID NO: 14; the antibody further comprises a residue of p-azidomethyl-phenylalanine substituting at each of sites HC-F404 and HC-Y180 according to the EU numbering scheme; and each structure within the brackets of the formula is bonded to the antibody at one of the p-azidomethyl-phenylalanine residues, nor its use in therapy or diagnosis.

Therefore, the subject matter of **claims 1-32** appears to be novel (**Art. 33(2) PCT**).

4 **Inventive Step (Art. 33(3) PCT)**

D1 is regarded as being the prior art closest to the subject-matter of **claim 1** and discloses the anti-human BCMA antibody 2A1 and its the conjugation to maytansine (DM1) using a non-cleavable linker (SMCC) resulting in an ADC referred to as 2A1-MCC-DM1 (p. 159-161). In addition, the anti-human BCMA antibodies 2A1 and 1E1 were conjugated to PEG4-Mal-DM4 (p. 161, l. 10-12). The anti-BCMA ADCs inhibited growth of myeloma cells in a xenograft subcutaneous tumor model (example 9). The ADC were internalized in myeloma cells (p. 180, l. 14-15).

Alternatively **D2** or **D3** could represent the closest prior art document for the subject matter of **claim 1**, since each of those documents is concerned with anti-BCMA antibody drug conjugates.

The subject-matter of **claim 1** therefore differs from this known **D1** (or **D2** or **D3**) in that the sequences of the antibody are different and in the type of conjugation to maytansine, and is therefore new.

There does not appear to be a technical effect caused by this difference, since both the prior art antibody drug conjugates and the claimed one bind with high affinity to human and cynomolgous monkey BCMA and can inhibit tumour growth.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative anti-BCMA antibody drug conjugate, which can be used in therapy and diagnosis.

The solution proposed in **claim 1** of the present application cannot be considered as involving an inventive step (**Art. 33(3) PCT**) for the following reasons:

It appears that the two differences to **D1** (or **D2** or **D3**), i.e. sequence of the antibody and type of conjugation, relate to features which are not functionally interdependent, since they do not appear to mutually influence each other to achieve a technical success over and above the sum of their respective individual effects. Therefore, it has to be established whether each set of features is separately obvious in the light of the prior art.

Concerning the first difference to **D1** (or **D2** or **D3**), i.e. the different antibody sequences, no surprising or unexpected effect appears to be associated with the claimed antibody sequences, since both the prior art antibodies and the claimed one bind to human and cynomolgous monkey BCMA with high affinity (see **D1**, p. 155, table 5, **D2**, table 3 and fig. 1, **D3**, p. 43, I. 15-19, fig. 1 and 10 and application: tables on p. 66). Therefore, it appears that the claimed antibody represents an alternative anti-human BCMA antibody.

It is considered that the presence of a prior art antibody and the common knowledge which guides the skilled person to produce similar ones, having similar functional properties, is in general sufficient to deny inventive step, in spite of noticeable structural differences at CDR level and/or framework or constant region level.

Concerning the second difference to **D1** (or **D2** or **D3**), the different type of conjugation to the same drug maytansine, it appears that said difference provides for the same technical effect as in **D1** (or **D2** or **D3**), i.e. the effective conjugation of the antibody to maytansine. The claimed type of conjugation, via p-azidomethyl-phenylalanine substituted sites HC-F404 and HC-Y180, is known in the art and used for different antibody drug conjugates, as shown in **D5** (see above). **D5** teaches that the conjugation via HC-Y180/F404 can be used with alternative linker warheads in ADCs. Moreover, **D4** teaches the use of the substituted F404 site for conjugation of a toxin and furthermore discloses

positions, e.g. Y180, where further substitutions can be made. Therefore, it appears that the skilled person would contemplate to use this type of linkage to provide an alternative anti-human BCMA ADC, without being inventive.

Consequently, the subject matter of **claim 1** does not appear to involve an inventive step in view of **D1** (or **D2** or **D3**) and **D5** or **D4** (**Art. 33(3) PCT**).

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent **claims 22** and **23**, which therefore are also considered not inventive. **D1** (or **D2** or **D3**) already discloses the use of the anti-human BCMA maytansine conjugates in the treatment of cancer. The use of the antibody drug conjugate in diagnosis does also not appear to be inventive, since the skilled person would use the antibody targeting BCMA in diagnostic methods using common general knowledge, according his needs.

Dependent claims do not contain any features which, in combination with the features of **claim 1**, meet the requirements of the PCT in respect of inventive step, since the claimed features do not appear to provide for any apparent surprising or unexpected effect in view of **D1** (or **D2** or **D3**) and **D5** or **D4**, and common general knowledge. Therefore, **claims 2-21** and **24-32** do not appear to involve an inventive step (**Art. 33(3) PCT**).

Re Item VIII

5 Certain observations on the international application

- 5.1 **Claims 1**, and **12-14** are unclear as they refer to an antibody comprising VH and VL sequences and wherein two defined positions in the constant domain are replaced by para-azidomethyl-phenylalanine (pAMF) residues (**Art. 6 PCT**). However, the antibody of **claim 1** does not necessarily comprise a constant domain (see also claim 6, which explicitly claims an antibody that comprises at least one constant region domain). **Claims 12-14**, for instance, teach that the antibody conjugate of **claim 1** can be an antibody fragment, thus lacking a constant domain.
- 5.2 Moreover, **claim 6** provides for an antibody comprising at least one constant region domain, which can be e.g. only a CH1 region. The claim encompasses thus also antibodies lacking the CH3 domain, where F404 is located. Therefore, for similar reasons as provided under point 5.1, the subject matter of **claim 6** is unclear (**Art. 6 PCT**).

- 5.3 It appears that the claimed VH sequence is human and the VL sequence is derived from trastuzumab and is humanized. **Claim 10**, which defines that the antibody is humanized or human is therefore unclear (**Art. 6 PCT**).
- 5.4 It appears that the mutations at the claimed positions according to EU numbering represent positions in antibodies having IgG1 constant domain. Since **claim 9** claims that the antibody can be IgA, IgD, IgE or IgM which differ in the respective sequences, it is unclear to which position **claim 1** refers to.
- 5.5 It is unclear how an antibody drug conjugate which promotes the killing of tumor cells should be used in a method of in vivo diagnosis (**Art. 6 PCT**).
- 5.6 Contrary to the requirements of **Rule 5.1(a)(ii), PCT**, the relevant background art disclosed in **D1-D3, D5** is not mentioned/discussed in the description, nor are these documents identified therein (Guidelines 4.05).
- 5.7 In a later European regional phase objections might be raised against any expression within the description such as "...incorporated by reference..." (e.g. on page 1) as the regional patent law requires that the application is self-contained.
- 5.8 The vague statements in the description on page 96 imply that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (**Art. 6 PCT**) when used to interpret them.