

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

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/GB2018/051570	International filing date (day/month/year) 08.06.2018	Priority date (day/month/year) 09.06.2017
International Patent Classification (IPC) or both national classification and IPC INV. C07K16/28 C07K14/725 G01N33/574 A61K47/68		
Applicant AUTOLUS LIMITED		

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Nauche, Stéphane Telephone No. +31 70 340-0
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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 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	<u>1-14</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-14</u>
Industrial applicability (IA)	Yes: Claims	<u>1-14</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following document:

D1 WO 2015/132598 A1 (UCL BUSINESS PLC [GB]) 11 September 2015 (2015-09-11)

Summary of the application

The present application relates to an anti-TRBC1 antigen binding domain characterized by the sequences of the variable chains. The CDRs sequences of the variable chains are : (VH CDR1) GYTFT , (VH CDR2) NPYNDDIQS and (VH CDR3) GAGYNFDGAYRFFDF and (VL CDR1) RSSQRLVHSNGNTYL, (VL CDR2) RVSNRFP, (VL CDR3) SQSTHVPYT. The claimed humanized antibodies derive from the murine JOVI antibody

Prior art

D1 relates to a chimeric antigen receptor (CAR) which comprises an antigen-binding domain which selectively binds TCR beta constant region 1 (TRBC1) or TRBC2; cells; such a T cells comprising such a CAR; and the use of such cells for the treatment of a T-cell lymphoma or leukaemia in a subject. D1 claims antibodies with the same CDRs as those of the present application (See claims)

Item V

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

Novelty

D1 discloses the same CDRs as those of the present application. However D1 discloses different variable chains compared to those claimed in claim 1 of the present application. Hence, in light of the subject matter disclosed in D1 the present application meets the requirements of Art.33(1) PCT because the subject matter of claims 1-14 is new in the sense of Art. 33(2) PCT.

Inventive step

The subject-matter of the present application does not meet the requirements of Article 33(1) PCT, because the subject-matter of claims 1-14 does not involve an inventive step in the sense of Article 33(3) PCT.

Document D1 may be considered as the closest prior art. D1 relates to a chimeric antigen receptor (CAR) which comprises an antigen-binding domain which selectively binds TCR beta constant region 1 (TRBC1) or TRBC2; cells; such a T cells comprising such a CAR; and the use of such cells for the treatment of a T-cell lymphoma or leukaemia in a subject. D1 claims antibodies with the same CDRs as those of the present application (See claims).

The results provided in the present application show that the molecules are thermostable (65°C) compared to JOVI, and efficient in cancer therapy (example 5)

Thus, the difference between the subject matter of D1 and the present application consists in further anti -TRBC1 antibodies. There is no striking technical effect associated with this difference.

In the light of the cited prior art, the technical problem to be solved may be considered as the provision of further anti-TRBC1 antibodies.

To solve the technical problem, the current application proposes anti TRBC1 antigen binding domains with the same CDRs as those of D1.

Immunization procedure, selection and production of monoclonal antibodies and engineered derivatives thereof such as chimeric antigen receptors directed against a well-known protein, is considered a routine procedure for any skilled person. It would be apparent to the skilled person that what is disclosed in D1 could be adapted to the purpose of the claimed invention in a straightforward manner, using no more than common general knowledge.

With the knowledge disclosed in D1, the skilled person would arrive at the subject

Certain defects in the international application (form or content)

The subject-matter of claim 12 comprises a method of treatment of the animal body by therapy or surgery, contrary to the requirement of Rule 39.1(iv) PCT. The patentability of such subject-matter 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 said claim has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Concluding remarks

Should the applicant decide to enter the regional phase before the EPO, the applicant is invited to file a new set of claims taking the here above remarks into consideration and the relevant description pages taking in to account the following, when applicable :

The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 123(2) EPC). Further, according to the EPC guidelines, a claim may be limited by inclusion of additional features, provided the resulting combination was originally disclosed and does not relate to an invention which was not search. Additional features from examples are allowed. An undue generalization of an example constitutes added subject-matter not allowable under Article 123(2) EPC. With respect to this experimental results are provided for a few CARs only. The applicant is invited to relate said CARs with the claimed sequences and provide unexpected positive features compared to the prior art.

To meet the requirements of Rule 42(1)(b) EPC, if not already done, D1 should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

It is kindly reminded that a European patent application should be self-contained. Therefore references in the description to prior art documents as "incorporated by reference", are not allowed (see the Guidelines, C-II, 4.19).

The Applicant is minded to replace references to US application numbers by their corresponding publication numbers.

The application should not include subject matter which covers alternatives or equivalents of features of the claims since such alternatives may throw doubt on the extent of protection (GL F-IV, 4.3 iii).

Any passages in the description relating to non-patentable subject-matter (eg methods of treatment as part of the invention) should be deleted or redrafted, if applicable.

The Applicant is minded to delete any reference to "spirit and scope of the application", if applicable.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant should clearly identify the amendments made, irrespective of whether they concern amendments by addition, replacement or deletion, and indicate the passages of the application as filed on which

these amendments are based (See Guidelines H-III, 2.2). If the applicant considers it appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.