

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.
PCT/GB2015/050643

International filing date (day/month/year)
05.03.2015

Priority date (day/month/year)
05.03.2014

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/395 A61K47/48 C07K16/28 C07K14/725

Applicant
UCL BUSINESS PLC

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 notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 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>1-19</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-19</u>
Industrial applicability (IA)	Yes: Claims	<u>1-19</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

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

and / or

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

see form 210

Reference is made to the following documents:

- D1 WO 03/093318 A1 (GENPAT77 PHARMACOGENETICS AG [DE]; UTKU NALAN [DE])
13 November 2003 (2003-11-13)
- D2 WO 2013/074916 A1 (UNIV TEXAS [US]) 23 May 2013 (2013-05-23)
- D3 BERGER, C. L. ET AL.: "The growth of cutaneous T-cell lymphoma is stimulated by
immature dendritic cells",
BLOOD,
vol. 99, 2002, pages 2829-2939,
- D4 VINEY, J. L. ET AL.: "Generation of monoclonal antibodies...",
HYBRIDOMA,
vol. 11, 1992, pages 701-713,

Abstract of the disclosure

Based on the fact that the present application determined that the antibody named "JOVI-1" is able to discriminate cells based on specific expression of TRBC1 (T cell receptor beta constant region 1) or TRBC2 (T cell receptor beta constant region 2), the present application claims the JOVI-1 scFv cloned into CAR (chimeric antigen receptors formats), characterised by their CDRs. The resulting CAR are used in cancer therapy and diagnostics.

Prior art

D1 discloses bispecific molecules characterized by having at least a first binding domain which binds T-cell immune response cDNA 7 (TIRC7) and a second binding domain which binds T cell receptor (TCR), in particular TCR beta chain (see examples 1,2; claims 1-7). D1 further discloses compositions comprising said bispecific molecules and their use for the diagnosis and the treatment of diseases, e.g. cancer (See claims 11-14).

D2 relates to methods and compositions for immunotherapy employing a modified T cell comprising disrupted T cell receptor comprising a chimeric antigen receptor. In some embodiments, there is provided universal T cells (consisting of the alpha/beta chains –See paragraphs 68, 75-78) engineered to express an antigen-specific chimeric antigen receptor (CAR) . The compositions are used i.a in cancer therapy. (See examples 4, 5, claims 1-36)

Item V :

Assessment of novelty, inventive step and industrial applicability with respect to the subject-matter of Invention

Method of treatment:

Claims 13-15 relate to a subject-matter considered by this Authority to be covered by the provision 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 recognize 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 in a first or further medical treatment.

Novelty (Art. 33(2) PCT)

None of the prior art describes CARs that comprise antigen binding domains that specifically bind to the T cell receptor beta constant region 1 or 2. Therefore the subject-matter of claims 1-19 appear new in view of the prior art cited.

Inventive step (Art. 33 (3) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-19 does not involve an inventive step in the sense of Article 33(3) PCT.

In general, It is recalled that the 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. Document D1 may be considered as the closest prior art. D1 describes the making of bispecific antibodies containing TCR beta antigen binding domains and their uses in therapy. (see examples 1,2; claims 1-7). D1 further discloses compositions comprising said bispecific molecules and their use for the diagnosis and the treatment of diseases, e.g. cancer (See claims 11-14). However D1 does not characterize the antigen binding domains by their sequences.

The difference between the subject matter of D1 and the present application consists in incorporating the antigen binding parts, characterized by their CDRs /variable sequences, into a chimeric antigen receptor.

In the light of the cited prior art, the technical problem to be solved may be considered as the provision as further constructs containing TRBC antigen binding sites.

According to the inventors, it is possible to deplete malignant T-cells in a subject, without affecting a significant proportion of healthy T cells using the TRBC specific CARs. The solution consists in the production of TRBC specific CARs from known antibodies (Jovi).

Obtaining the production of recombinant complete antibody or single domain or CAR from monoclonal antibodies such as those described in the present application is also regarded as part of the conventional procedures used by persons skilled in the art. The production of CARs are explained for instance in D2. Further, As disclosed in the present application, the antigen recognition domain is usually an scFv.

With the knowledge disclosed in D1 and D2, the skilled person would arrive at the subject matter of the present claims 1-19 without exercising any inventive skill.