

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/US2020/026686	International filing date (day/month/year) 03.04.2020	Priority date (day/month/year) 05.04.2019	
International Patent Classification (IPC) or both national classification and IPC INV. C07K16/30 A61K39/395 A61P35/00 C07K16/28			
Applicant TENEOBIO, 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 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 Siaterli, Maria Telephone No. +31 70 340-0 

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. 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>1-60</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-60</u>
Industrial applicability (IA)	Yes: Claims	<u>1-60</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

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

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. Patentability, in particular novelty and inventive step, of claims 50-52,60 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.
- 2 Reference is made to the following documents:

D1: WO 2017/122019 A1

D2: WO 2016/187594 A1

D3: Hassani et al: "Construction of a chimeric antigen receptor bearing a nanobody against prostate a specific membrane antigen in prostate cancer", Journal of Cellular Biochemistry, vol. 120, no. 6, 2019-01-22, pages 10787-10795, XP055696932, ISSN: 0730-2312, DOI: 10.1002/jcb.28370

D4: WO 2019/012260 A1

D5: Zare et al: "Production of nanobodies against prostate-specific membrane antigen (PSMA) recognizing LnCaP cells", International Journal of Biological Markers, vol. 29, no. 2, 2014-01-01, pages 169-179, XP055353599, IT ISSN: 0393-6155, DOI: 10.5301/jbm.5000063
- 2.1 **D1** describes immunoconjugates comprising an anti PSMA VHH and biparatopic formats thereof (claims 8-88, example 13)
- 2.2 **D2** describes trispecific molecules containing a PSMA targeting single domain antibody and anti-CD3E scFv, and anti-albumin single domain antibody (example 13, § 143).
- 2.3 **D3** describes anti PSMA VHH (named NBPII) used to construct CAR T cells against PSMA (whole document). Degranulation of NBPII-CAR T cells in response to PSMA-positive target cell (§ 3.6)
- 2.4 **D4** describes anti PSMA VHH (claims 1-29, whole document). Biparatopic anti PSMA VHH were also produced (example 8, table 24b). They showed cytotoxicity against PSMA expressing human cell lines (table 32, example 13)

- 2.5 **D5** describes production of nanobodies against prostate-specific membrane antigen (PSMA) recognizing LnCaP cells. The high specificity and affinity of this nanobody suggests its possible application as an effective tool in the diagnosis and treatment of prostate cancer (whole document).

3 NOVELTY

No available prior art document discloses anti PSMA VHH with the claimed sequences. Thus, the present application meets the criteria of Article 33(1) PCT, because the subject-matter of claim 1-60 is new in the sense of Article 33(2) PCT.

4 INVENTIVE STEP

- 4.1 Any of D1-D5 is regarded as being the prior art closest to the subject-matter of claims 1-60, and all disclose anti PSMA VHH.
- 4.2 The subject-matter of claims 1-60 therefore differs from the prior art in the sequence of the anti PSMA VHH.
- 4.3 There is no particular effect associated with the difference. A particular effect may be considered to be associated with the specific VHH (bispecific or biparatopic or bispecific and biparatopic) actually shown to kill tumor cells.
- 4.4 The problem to be solved by the present invention may therefore be regarded as the provision of alternative anti PSMA VHH.
- 4.5 The solution proposed in the claims of the present application cannot be considered to involve an inventive step (Article 33(3) PCT). The skilled person starting from the disclosure of any of D1-D5 and confronted to the problem of providing additional antibodies would use the common techniques of molecular and cellular biology to generate and characterize further antibodies without applying any inventive skill. The specific VHH represent arbitrary selections. Bispecific forms binding also to CD3 and biparatopic constructs were also disclosed and therefore the claimed bispecific or biparatopic constructs also represent arbitrary selections.
- 4.6 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-60 does not involve an inventive step in the sense of Article 33(3) PCT.

Re Item VII

Certain defects in the international application

- 1.1 It is not sufficient to characterise an antibody with one of the CDR sequences since a single domain antibody is structurally made two heavy chains and it needs at least 3 CDRs to confer antigen binding specificity. Unless the contrary is shown it is considered that a CDR is neither equivalent to an antibody, nor sufficient to define the specificity of an antibody. Moreover claim 1 relates to mix and match of CDR's originating from different antibodies. There is no support that combining CDR's of different antibodies which also recognize different epitopes will allow antigen recognition. Since claims 1-8 do not clearly define the structure of the antibodies, they do not meet the requirements following from Article 6 PCT. Support and disclosure is found only for the combinations of the CDR's specifically disclosed in the application.
- 1.2 Although claims 1, 13 ,14, 15,18,20-25, 36-40 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.