

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/EP2016/068549	International filing date (day/month/year) 03.08.2016	Priority date (day/month/year) 03.08.2015
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International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 C07K16/30 C07K16/46 A61P35/00

Applicant
ENGMAB AG

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 Brouns, Gaby 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. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

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>1-23</u> |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | <u>1-23</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-23</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

The present application discloses six monoclonal antibodies specifically binding to B cell maturation antigen (BCMA; TNFRSF17), Mab21, Mab22, Mab42, Mab27, Mab33 and Mab39. Bispecific antibodies recognising both BCMA and CD3 ϵ comprising the variable domains of Mab21, Mab22 and Mab42 have been shown to induce T cell mediated killing of BCMA positive cells. For Mab22 and Mab42 *in vitro* killing of patient bone marrow myeloma plasma cells has been demonstrated.

CITED DOCUMENTS

Reference is made to the following documents:

- D1** WO 2014/122144 A1 (ENGMAB AG [CH]) 14 August 2014 (2014-08-14)
- D2** WO 2014/140248 A1 (AMGEN RES MUNICH GMBH [DE]; BOEHRINGER INGELHEIM INT [DE]) 18 September 2014 (2014-09-18)
- D3** CARPENTER R O ET AL: "B-cell Maturation Antigen Is a Promising Target for Adoptive T-cell Therapy of Multiple Myeloma", CLINICAL CANCER RESEARCH, vol. 19, no. 8, 15 April 2013, pages 2048-2060, XP002727959

Re Item IV

Lack of unity of invention

The present application deals with the following problem: How to provide human B cell maturation antigen (BCMA) binding proteins? The solution is to provide antibody heavy and light chain sequences capable of binding to BCMA, optionally present in a bispecific antibody or chimeric antigen receptor (CAR).

The single general concept linking all independent claims that can be identified a priori is: The provision of BCMA binding proteins using proteins comprising a CDR3H defined by SEQ ID NO:17 and a CDR3L defined by SEQ ID NO:20.

However, antibody 83A10 comprising a CDR3H defined by SEQ ID NO:17 and a CDR3L defined by SEQ ID NO:20 already known. **D1** discloses anti-BCMA antibody 83A10 comprising a CDR3H defined by SEQ ID NO:59, and a CDR3L defined by SEQ ID NO:89, which are 100% identical to SEQ ID NO:17 and NO:20, respectively. Bispecific antibodies based on 83A10 also binding CD3 ϵ are foreseen (p.8, §1).

In the light of D1, the above identified single general concept is not novel and inventive and thus cannot be the single general inventive concept as required to establish unity of invention (Rule 13.1 PCT).

It appears that the six defined antigen binding regions in the context CAR and the method of producing monoclonal antibodies may be seen as a separate invention (Rule 13.2 PCT).

Accordingly, the claimed inventions have to be split-up as indicated in the search report:

Inventions 1-3: Subject-matter relating to monoclonal and bispecific antibodies comprising the CDRs of mAb21 (invention 1), mAb22 (invention 2) and mAb 42 (invention 3) respectively (*claims 1-21, all partially*)

Inventions 4-6: Subject-matter relating to monoclonal and bispecific antibodies comprising the CDRs of mAb27 (invention 4), mAb33 (invention 5) and mAb 39 (invention 6) respectively (*claims 1, 4-21, all partially*)

Invention 7: Subject-matter relating to a chimeric antigen receptor comprising one of the six defined antibody domains binding to BCMA (*claim 22, complete*)

Invention 8: Subject-matter relating to a method of producing a monoclonal antibody starting from VH and VL comprising a CDR3H defined by SEQ ID NO:17 and CDR3L defined by SEQ ID NO:20 (*claim 23, complete*)

The search for claimed inventions did not represent a major extra search burden. Therefore all inventions have been searched and examined in the present opinion. Restriction to unitary subject-matter is required in the regional phase.

Re Item V

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

NOVELTY (Article 33(2) PCT)

inventions 1-8

Anti-BCMA antibodies, bispecific antibodies and chimeric antigen receptors comprising the defined CDRs to allow binding to BCMA, and the method for producing a monoclonal antibody as defined in *claims 1-23* appear not to be disclosed in the prior art (**Art. 33(2) PCT**).

INVENTIVE STEP (Article 33(3) PCT)

(i) Inventions 1-6 (monoclonal antibodies)

D1 discloses a panel of anti-BCMA antibodies including 83A10 described above, which is shown to have affinity for BCMA which is largely maintained in presence of the APRIL ligand (fig. 9). From this the subject-matter of the present application differs in that it relate to further anti-BCMA antibodies comprising the defined CDR3H

and CDR3L.

The affinity constants for the six monoclonal antibodies as claimed have been shown in table 4, which are higher than the affinity constant of 83A10 when tested with human BCMA (effect), the relevant antigen in view of the intended therapeutic use.

The problem to be solved may be seen as how to provide anti-BCMA antibodies comprising the defined CDR3H and CDR3L regions with higher affinity.

The solution as claimed lacks inventive step: affinity maturation of known antibodies is considered routine practice for the skilled person and cannot constitute an unexpected property. High affinity anti-BCMA antibodies are for instance known from **D2**, tables 2 and 3 in exp. E5. In conclusion, subject-matter relating to Mab21, Mab22, Mab42, Mab27, 33 and 39 *per se* (*claims 1-3 and 17-21*) lacks inventive step (**Art. 33(3) PCT**).

(ii) inventions 1-6 (bispecific antibodies)

Various T cell bispecific (TCB) anti-BCMA / anti-CD3 ϵ antibodies are known from **D2**. Said TCB antibodies have been tested for T cell mediated killing of BCMA expressing target cells L363 (D2, exp. A12; exp. E12) and H929 (D2, exp. A13; exp. E13). The EC50 value for redirected killing of H929 cells is in the similar range as shown in table 12 of the application. *In vivo* anti-tumor efficacy has been shown (D2, exp. A19; exp. E19).

From this the subject-matter relating to the bispecific anti-BCMA / anti-CD3 TCB antibodies differs in the amino acids forming the six CDR regions. For Mab27, Mab33 and Mab39 no TCB have been produced, therefore no effect may be evaluated. For Mab21, Mab22 and Mab42, T cell mediated killing of L363 and H929 cells has been shown, with EC50 values in the same range or lower.

The problem to be solved may therefore be seen as how to provide further / improved bispecific anti-BCMA / anti-CD3 TCB antibodies.

The solution of *claims 4-21* when relating to Mab27, Mab33 and Mab33 lacks inventive step being arbitrary alternatives to the TCB of D2, for which no unexpected property has been shown (**Art. 33(3) PCT**).

Subject-matter relating to TCB derived from Mab21, mab22 and Mab42 lacks inventive step, since the skilled person is always looking to improve a known product, using routine methods. In view of D2, the affinity and T cell mediated killing are the most relevant parameters for the TCB antibodies. It would be obvious for the skilled person to select a known anti-BCMA antibody (D1, table 5) for improvement.

Knob-in-hole technology, as well as CH1- kappa crossover are standard practise in the field of producing bispecific antibodies (D1, exp.3), and 2+1 bispecific antibodies are shown in fig.3, described on p.14, l.19-23 of D1. Said features cannot render the claimed subject-matter inventive (**Art. 33(3) PCT**).

The prior art does not seem to suggest the bispecific anti-BCMA / anti-CD3 TCB antibodies of *claims 9-11* when restricted to Mab21, Mab22 and Mab42, however, the application does not demonstrate any technical effect for the specific charge alterations, therefore no inventive step may be acknowledged (**Art. 33(3) PCT**).

Invention 7

BCMA-specific CAR are known from D3. From this the subject-matter of invention 7 / claim 22 differs in that different anti-BCMA heavy and light chain CDRs are used. No CAR according to the claim has been produced, nor compared to the BCMA CAR of D3, therefore no effect may be attributed to the distinguishing technical feature. The problem to be solved may thus be seen as how to provide a further BCMA specific CAR. Absent a demonstrated technical effect, the selection of further CDR regions can only be seen as arbitrary, devoid of inventive step (**Art. 33(3) PCT**).

Invention 8

Affinity maturation of known antibodies (such as 83A10), using phage display and selection on the particular antigen, is well known from the prior art (D2, p.29, § 1). No effect has been demonstrated for the specific characteristic measured in claim 23, nor has it been indicated how said feature differs from other ways of measuring the desired characteristics of monoclonal antibodies. Absent any demonstrated technical effect, no inventive step may be acknowledged (**Art. 33(3) PCT**).

Re Item VIII

Certain observations on the international application

The application makes it credible that bispecific anti-BCMA / anti-CD3 ϵ antibodies comprising the antigen recognition portion of Mab21, Mab22 and M42 are suitable for use in treatment of multiple myeloma (claim 21). It may be plausible that said bispecific antibodies may also be used in plasma cell disorders, which are of unknown etiology and are characterized by the disproportionate proliferation of one clone (claim 20).

Treatment of systemic lupus erythematosus has not been made credible by the present application (claim 21)(**Art. 5 and 6 PCT**).

Therapeutic application using all six monospecific antibodies, and using bispecific antibodies derived from Mab27, Mab33 and Mab39 encompassed by claims 20 and 21 is not disclosed and supported (**Art. 5 and 6 PCT**).

The scope of claim 23 is unclear, it refers to a method of generating a monoclonal antibody, but the end product of the claimed method is a bispecific antibody (**Art. 6 PCT**).
