

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/EP2019/056197	International filing date (day/month/year) 12.03.2019	Priority date (day/month/year) 12.03.2018
International Patent Classification (IPC) or both national classification and IPC INV. C07K16/10 C07K16/28 C07K16/30 A61K47/68		
Applicant GENMAB A/S		

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 Loubradou, Gabriel 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. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-133(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for the whole application or for said claims Nos. 1-133(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details

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. 1-133(partially)

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>1-133(partially)</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-133(partially)</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-133(partially)</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item IV

Lack of unity of invention

1 This Authority considers that the application does not meet the requirements of unity of invention and that there are 5 inventions.

1.1 As explained below, the following separate inventions or groups of inventions are not so linked as to form a single general inventive concept:

1. claims: 1-133(partially)

Subject-matter of claims 1 to 133 wherein the antibody has CDR sequences according to claim 52 (a) (f) or (g).

2. claims: 1-133(partially)

Subject-matter of claims 1 to 133 wherein the antibody has CDR sequences according to claim 52 (b).

3. claims: 1-133(partially)

Subject-matter of claims 1 to 133 wherein the antibody has CDR sequences according to claim 52 (c).

4. claims: 1-133(partially)

Subject-matter of claims 1 to 133 wherein the antibody has CDR sequences according to claim 52 (d).

5. claims: 1-133(partially)

Subject-matter of claims 1 to 133 wherein the antibody has CDR sequences according to claim 52 (e).

1.2 The reasons, for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

- 1.2.1 The common matter linking together the antibodies of the present five inventions are antibodies having human CDRs, binding to human 5T4 and having the technical feature of claim 1. Some of the inventions also share the technical feature of corresponding to antibodies binding to cynomolgus monkey 5T4.

This common matter does not comprise a single general inventive concept, based on same or corresponding special technical features, because it lacks novelty and/or inventive step:

- human antibodies binding to human and optionally cynomolgus monkey 5T4 are known in the art:
 - D1 discloses a fully human antibody and affinity optimised derivatives thereof binding to human and cynomolgus monkey 5T4 (see D1: Examples 1 to 3; Figures 3 to 10). In absence of evidence to the contrary, it is also considered that the antibodies of D1 have the technical feature of claim 1 of the present application (i.e. that the antibodies of D1 are able to block binding to 5T4 of an antibody comprising a variable heavy chain (VH) region comprising the sequence set forth in SEQ ID NO: 5, and a variable light chain (VL) region comprising the sequence set forth in SEQ ID NO: 9 [059]). In this respect, it is noted that this technical feature corresponds to an unusual parameter and that the burden of proof lies with the applicant. In view of this reasoning, the antibodies of D1 anticipate the common matter shared by inventions 1 to 5. For the sake of completeness only, it is further noted that in absence of evidence that any particular technical problem is solved by antibodies having the technical feature of claim 1, the provision of antibodies having such a technical feature cannot involve an inventive step (selecting the corresponding antibodies is considered to represent an arbitrary selection). In particular, the antibodies do not inherently have the properties of the antibody 059 of the examples both quantitatively (e.g. a particular affinity for a given target) and qualitatively (e.g. the ability to be internalised or to cross-react with 5T4 from other species). Therefore, if the antibodies of present claim 1 would not be anticipated by the the antibodies of D1, they would in any case not involve an inventive step over the antibodies of D1 because they would correspond to arbitrary selected alternatives to the antibodies of D1.

- D2 discloses four fully human antibodies binding to human and cynomolgus monkey 5T4 (see D2: Examples 1 to 4). In absence of evidence to the contrary, it is also considered that at least some of the antibodies of D2 have the technical feature of claim 1 of the present application. In this case, the antibodies of D2 anticipate the common matter shared by inventions 1 to 5. It is also noted that following the same reasoning as for D1, if the antibodies of present claim 1 would not be anticipated by the the antibodies of D2, they would in any case not involve an inventive step over the antibodies of D2 because they would correspond to arbitrary selected alternatives to the antibodies of D2.

- D3 discloses two fully human antibodies binding to human 5T4 (see D3: Example 1). The same reasoning as for D1 and D2 applies *mutatis mutandis* and D3 is considered to anticipate the common matter shared by inventions 1 to 5.

- Non-human antibodies binding to human and cynomolgus monkey 5T4 are known in the art and the provision of human antibodies having the corresponding properties is not considered to involve an inventive step because the provision of human antibodies is well known in the art as exemplified in D1 to D3 (see above). Therefore, the common matter shared by inventions 1 to 5 is also considered to lack an inventive step in view of the antibodies disclosed in D4, D5 and D6 (see D4 to D6: the examples).

- 1.2.2 The technical feature, representing the difference between inventions 1 to 5 is the sequences of the antibodies. The sequences are not related and do not allow to solve a particular technical problem not solved by the antibodies of the prior art. Therefore, the matter differing between inventions 1 to 5 does not comprise a single general inventive concept, based on same or corresponding special technical features.

The inventions are based on claim 52 because none of the aspects disclosed in claims 1 to 51 appear to be patentable due to one or more of the following reasons:

- the claims lack novelty over any of D1 to D6 and/or inventive step following *mutatis mutandis* the reasoning applying to claim 1 as discussed above;

- the claims merely define the antibodies by the goal to be achieved without providing the essential technical features allowing to achieve this goal leading to an objection under Article 6 PCT;
- structural definitions of antibodies are used which do not at least define the 6 CDRs of the antibody leading to a lack of essential technical feature (Article 6 PCT);
- the claims lack sufficiency as far as far as they refer to antibodies having particular functional properties without providing a method allowing to obtain them without undue burden (Article 5 PCT).

In a more general way, it is noted that the antibodies of claim 52 correspond to the only new antibodies capable of binding to 5T4 concretely disclosed in the context of the present application.

It is noted that the first invention groups 3 different antibodies (059, 207 and 226). This grouping is based on the ability of the corresponding antibodies to have a good binding to human, cynomolgus monkey and chicken 5T4.

- 1.2.3 In view of the above reasoning, the claims comprise neither the same, nor corresponding special technical features, so the technical relationship between the subject matter of the claims required by Rule 13.2 PCT is lacking and the claims are not so linked as to form a single general inventive concept as required by Rule 13.1 PCT.

Consequently the application does not meet the requirement for unity of invention and correspond to 5 separate inventions.

Re Item V

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

Invention 1 : *claims: 1-133(partially)*

Subject-matter of claims 1 to 133 wherein the antibody has CDR sequences according to claim 52 (a) (f) or (g).

- 2 The claims below are only assessed as far as they belong to invention 1 (i.e. as far as they refer to an antibody having the CDR sequences according to claim 52 (a) (f) or (g)).

3 As far as they belong to invention 1, claims 1 to 133 are considered to be novel since none of the prior art documents disclose an antibody having the corresponding structural limitations.

4 As far as they belong to invention 1, claims 1 to 133 are considered to involve an inventive step.

The antibodies having the CDR sequences according to claim 52 (a) (f) or (g) correspond to antibodies having the 6 CDRs of the antibodies 059, 207 and 226 of the examples. These antibodies bind with comparable affinity to chicken, cynomolgus and human 5T4 (see the present application: Tables 1 and 2; Figure 3). The binding specificity of an antibody is considered to be mediated by its CDRs. Therefore, the same binding specificity is expected for the antibodies of claim 52 (a) (f) or (g).

As already discussed above, most of the antibodies of the prior art bind to human and cynomolgus monkey 5T4 but the cross-reactivity with 5T4 from more distant species such as chicken 5T4 has not been determined. The antibodies of the cited prior art, if this aspect is tested, do not show or show poor binding to mouse or rat 5T4 except for one of the antibodies of D6 which binds to rat 5T4 and one of the antibodies of D7 which binds to mouse 5T4 (see D1: Tables 5 and 6 on page 119; D2: page 74, lines 17 and 18; D4: Table 15; D6: Table 2; D7: Table 8). The level of amino acid sequence identity with the extracellular domain of human 5T4 is above 95% for cynomolgus monkey 5T4, about 80% for mouse or rat 5T4 and only around 60% for chicken 5T4.

Therefore, in absence of particular guidance in this respect, the skilled person would not have had a sufficient expectation of success that antibodies binding human, cynomolgus monkey and chicken 5T4 extracellular domain could be obtained.

5 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 (or the corresponding method, see present claims 127 to 129), 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 123 to 126 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.