

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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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/EP2020/062802

International filing date (day/month/year)
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International Patent Classification (IPC) or both national classification and IPC
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Applicant
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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>1-7, 13-19, 21-27</u>
	No: Claims	<u>8-12, 20</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-27</u>
Industrial applicability (IA)	Yes: Claims	<u>1-27</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

Re Item V

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

Reference is made to the following documents:

- D1** **NAOYA YAMASHITA ET AL:** "Anti-Semaphorin 3A neutralization monoclonal antibody prevents sepsis development in lipopolysaccharide-treated mice", INTERNATIONAL IMMUNOLOGY, vol. 27, no. 9, 7 April 2015 (2015-04-07), pages 459-466, XP055280232, ISSN: 0953-8178, DOI: 10.1093/intimm/dxv014
- D2** **EP 2 955 195 A1** (UNIV YOKOHAMA CITY [JP]; CHIOME BIOSCIENCE INC [JP]) 16 December 2015 (2015-12-16)
- D3** **EP 3 385 281 A1** (SAMSUNG LIFE PUBLIC WELFARE FOUNDATION [KR]; PANGEN BIOTECH INC [KR]) 10 October 2018 (2018-10-10)
- D4** **WO 2014/127479 A1** (RSEM LTD PARTNERSHIP [CA]) 28 August 2014 (2014-08-28)
- D5** **SHIRVAN ANAT ET AL:** "Anti-semaphorin 3A antibodies rescue retinal ganglion cells from cell death following optic nerve axotomy", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 51, 20 December 2002 (2002-12-20), pages 49799-49807, XP002483825, ISSN: 0021-9258, DOI: 10.1074/JBC.M204793200 [retrieved on 2002-10-09]
- D6** **HAYNES SHEK HEI YUAN ET AL:** "A mechanism for semaphorin-induced apoptosis: DNA damage of endothelial and myogenic cells in primary cultures from skeletal muscle", ONCOTARGET, vol. 9, no. 32, 27 April 2018 (2018-04-27), XP055633014, United States ISSN: 1949-2553, DOI: 10.18632/oncotarget.25200
- D7** **PAOLO GIACOBINI ET AL:** "Brain Endothelial Cells Control Fertility through Ovarian-Steroid-Dependent Release of Semaphorin 3A", PLOS BIOLOGY, vol. 12, no. 3, 11 March 2014 (2014-03-11), page e1001808, XP055633040, DOI: 10.1371/journal.pbio.1001808
- D8** **WO 2013/005603 A1** (PUBLIC UNIV CORP YOKOHAMA CITY [JP]; TANAKA JUNMI [JP] ET AL.) 10 January 2013 (2013-01-10)

Remark

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 10-19** has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

1 Most relevant prior art documents

D1 discloses the humanized anti-human Sema3A antibody 4-2 that neutralized the Sema3A actions with high affinity (K_D of 200pM) (p. 460, left col., paragraph 4-right col., paragraph 1, p. 463, left col., paragraph 2, p. 463, right col., paragraph 1). Antibody 4-2 inhibited the binding of Sema3A to the receptor NRP1 (p. 463, right col., paragraph 2). The antibody increased the survival rate in LPS-induced sepsis mouse mode (fig. 4).

D2 teaches humanized anti-Sema3 antibodies and their use in the treatment of Alzheimer's disease and inflammatory immune diseases (abstract, p. 16, example 2). The antibodies bind human and mouse Sema3A with high affinity and show low IC50 values (p. 21, table 6 and p. 22, example 7).

D3 discloses anti-human Sema3A scFv antibodies, in particular F11, A08 and C10 (p. 8-9, example 1, p. 9-10, paragraph [0123]). The antibodies were shown to inhibit cell growth and cell migration (p. 13, example 4).

D4 relates to the inhibition of Sema3A in the prevention and treatment of ocular hyperpermeability and macular edema (abstract, paragraph [003]) and discloses that intravitreal neutralization of Sema3A (by gene silencing) reduces retinal vascular permeability in the diabetic retina (example 7). **D4** concludes that neutralization of Sema3A in the diabetic retina is an effective strategy to reduce vasogenic edema (paragraph [0126]). **D4** teaches the use of neutralizing anti-Sema3A antibodies (paragraph [065]).

D5 teaches neutralizing polyclonal and monoclonal anti-Sema3A antibodies directed against peptide Pep1A, a peptide corresponding to amino acids 363-380 from chick Sema3A (p. 49800, right col., paragraph 4-p. 49801, left col., paragraph 1). **D5** discloses that damage to the optic nerve induces retrograde degeneration and apoptosis of the retinal ganglion cell (RGC) bodies (abstract). The application of function-blocking anti-Sema3A antibodies in rats following optic nerve injury, protected the RGC (p. 49806, left col., paragraph 3).

D6 discloses the commercially available neutralizing anti-Sema3A antibody AB9604 (fig. 3, p. 22626, right col., paragraph 4).

D7 teaches the commercially available neutralizing anti-human Sema3A antibody MAB-1250 (p. 15, left col., paragraph 4).

2 Novelty (Art. 33(2) PCT)

- 2.1 **Claim 8** aims at providing an anti-Sema3A antibody that binds to at least one amino acid residue within amino acid regions 370-382 of human Sema3A as set forth in SEQ ID No 22. **Claim 9** specifies that the antibody binds to SEQ ID No 21.

There are numerous antibodies disclosed in the prior art as binding Sema3A, as already discussed for **D1** to **D7**. The applicant has not demonstrated that said antibodies do not bind at least one amino acid within the claimed region of human Sema3A as set forth in SEQ ID No 22 or do not bind SEQ ID No 21 at all. In the absence of any such evidence, the novelty of **claims 8-9** cannot be acknowledged.

Since the antibodies of the any of **D1** to **D5** are used in therapy, the subject matter of claims **10-12** (see also point 4.3) and **20**, when dependent on claims 8-9, is not novel (**Art. 33(2) PCT**).

- 2.2 The prior art documents at hand do not appear to disclose an anti-Sema3A antibody or an antigen binding fragment thereof comprising the recited 6 CDRs, nor its use in therapy. Therefore, **claims 1-7, 13-19** and **21-27** appear to be novel (**Art. 33(2) PCT**).

3 Inventive Step (Ar. 33(3) PCT)

- 3.1 **D1** might be considered to represent the closest prior art document for the subject matter of **claim 1**. Alternatively, any one of **D2, D3, or D5** (each independently) might represent the closest prior art document.
- 3.2 The subject matter of **claim 1** differs from **D1** (or any of **D2, D3, or D5**) in that the antibody comprises particular CDR sequences.
- 3.3 It is noted that the antibody as defined in present **claim 1** does not have the technical features of the corresponding antibody shown in the examples (i.e. clone I), e.g. high affinity, since said features are not inherent to antibodies only defined by their CDRs. It is known in the art that the affinity and neutralization

- activity of an antibody depends on both the CDRs and the framework sequences and that binding to a particular epitope does not imply any particular affinity or neutralization/blocking potency.
- 3.4 The objective technical problem may thus be regarded as the provision of an alternative anti-Sema3 antibody.
- 3.5 The procedure to obtain, screen and produce monoclonal antibodies specifically recognizing well known proteins such as Sema3A, is considered routine procedure for the skilled artisan. Therefore, the production of monoclonal antibodies directed against Sema3A is considered to represent a routine procedure (see for example **D1-D3** or **D5**) and, in the absence of evidence to the contrary, the antibodies as defined in the claims do not solve a previously unforeseeable technical problem and do not lead to an unexpected and surprising technical effect.
- 3.6 It is considered that the presence of a prior art antibody and the common knowledge which guides the skilled person to produce similar ones, having similar functional properties, is in general sufficient to deny inventive step, in spite of noticeable structural differences at CDR level and/or framework or constant region level. It is true that structure can support inventive step however, different CDR sequences are usually not enough to acknowledge inventive step unless the differences give rise to an unexpected technical effect.
- 3.7 Therefore, the subject matter of **claims 1-7** does not involve an inventive step in view of **D1** or any of **D2, D3** or **D5**. (**Art. 33(3) PCT**).
- 3.8 It might be possible to recognise inventive step for the antibodies for which a technical effect has been shown, provided the applicant can show that this technical effect cannot be observed with the antibody of the closest prior art and is, therefore, surprising.
- 3.9 The same reasoning applies to **claims 23-27**, which do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step since these additional features appear conventional and do not result in any unexpected technical effect (**Art. 33(3) PCT**).
- 3.10 Relating to the medical use **claims 13-19** and **21-22**:
- 3.11 **D4** might be considered to represent the closest prior art document for the subject matter of **claims 13-19** and **21-22**.

- 3.12 **D4** relates to the inhibition of Sema3A in the prevention and treatment of ocular hyperpermeability and macular edema (abstract, paragraph [003]) and discloses that intravitreal neutralization of Sema3A (by gene silencing) reduces retinal vascular permeability in the diabetic retina (example 7). **D4** concludes that neutralization of Sema3A in the diabetic retina is an effective strategy to reduce vasogenic edema (paragraph [0126]). **D4** teaches the use of neutralizing anti-Sema3A antibodies.

The subject matter of **claims 13-19** and **21-22** differs from **D4** in the provision of antibody, which is then used in the treatment of the listed diseases.

Starting from the disclosure of **D4**, the skilled person would be aware of the neutralizing anti-Sema3A antibodies of any of **D1-D3**, or **D5** and would use such antibodies to neutralize Sema3A in order to treat the diseases, suing the teachings of **D4**, without being inventive.

Consequently, no inventive step can be acknowledged for the subject matter of **claims 13-19** and **21-22** (**Art. 33(3) PCT**).

Re Item VIII

4 Certain observations on the international application

- 4.1 **Claims 1** and **3** encompass antibodies that have the 3 CDRs of the VL and the 3 CDRs of the VH in all possible configurations, since the information put in brackets is entirely optional. Importantly the application lacks support for any antibodies comprising these CDRs in all possible configurations (**Art. 6 PCT**).
- 4.2 Similarly, claims 3-4 lack support, since the application appears to disclose only particular combinations of VH/VL sequences.
- 4.3 **Claims 11-12** aim at defining an anti-Sema3A antibody for inhibiting the vasorepressive effect of Sema3A or for improving revascularization of the retina. A claim for a substance or composition for a particular use should be construed as meaning a substance or composition which is in fact suitable for the stated use. Medical uses must follow a strict format: "Substance X for use in the prevention or treatment of disease Y". The present claims do not conform to this format and can be construed as covering antibodies which are suitable for the stated use. Since the claim fails to identify the specific therapeutic indication for the antibody the feature "for inhibiting the vasorepressive effect of Sema3A (in claim 11) or improving revascularization of the retina (in claim 12) remains de facto purely illustrative and does not limit the scope of the claim to that specific application. Furthermore, the terms "for inhibiting the vasorepressive

- effect of Sema3A (in claim 11) or improving revascularization of the retina (in claim 12) does not necessarily relate to use in a method of treatment since they could refer to an in-vitro method. Consequently, the subject-matter of **claims 11-12** is anticipated if said antibody is known in the prior art.
- 4.4 In addition, **claims 11-12** do not comply with the requirements of **Art. 6 PCT**, since the therapeutic application is functionally defined by a mechanism of action (i.e. inhibiting the vasorepressive effect of Sema3A or improving revascularization of the retina) which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease). However, in a medical use claim the disease to be treated must be clearly defined.
- 4.5 **Claim 13** aims at providing a medical use of the claimed antibody, wherein the antibody is used for the treatment or prevention of an eye disease.
- D8** discloses a method for preventing and / or treating allergic inflammation in the conjunctiva, comprising administering to a subject a pharmaceutically effective amount of semaphorin 3A (abstract).
- D8** casts serious doubts, substantiated by verifiable facts, on the subject matter of **claim 13**, since it discloses that Sema3A, and not an antibody that inhibits its activity, can prevent conjunctivitis in the eye, thus being in clear contradiction with the subject matter of **claims 13 (Art. 5 PCT)**.
- 4.6 **Claims 20-22** are unclear and the dependency doubtful, since they refer to the antibodies of **claim 1**, and medical use **claims 10-19**, wherein the antibody is administered e.g. by a parenteral or intravitreal route. A suitable formulation for dependent claims may read: Substance X for use according to claim # characterised in that/wherein ... (other features).
- 4.7 In a later European regional phase objections might be raised against any expression within the description such as "...incorporated by reference..." (e.g. paragraph [0184]) as the regional patent law requires that the application is self-contained.