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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2018/071232	06.08.2018	07.08.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/31 B01D15/38 B01J20/289

Applicant
NAVIGO PROTEINS GMBH

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 notifed 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 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 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-15
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

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

and / or

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

see form 210

Re Item V

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

1 **Cited documents:**

Reference is made to the following documents (D) cited in the International Search Report:

D1 WO 2017/009421 A1 (SCIL PROTEINS GMBH [DE]) 19 January 2017 (2017-01-19)

D2 WO 2016/079033 A1 (GE HEALTHCARE BIOPROCESS R&D AB [SE]) 26 May 2016 (2016-05-26)

D3 WO 2015/005859 A1 (GE HEALTHCARE BIO SCIENCES AB [SE]) 15 January 2015 (2015-01-15)

D4 EP 2 690 173 A1 (KANEKA CORP [JP]) 29 January 2014 (2014-01-29)

2 **Novelty (Article 33(2) PCT) and inventive step (Article 33(3) PCT)**

2.1 Documents **D1-D4** all pertain to Ig binding proteins derived from Staphylococcus aureus protein A and having increased alkaline stability by means of mutagenesis of given positions in the protein A domains. None of them discloses the mutation of the claimed positions in the helix 3 of a protein A domain to a cysteine residue. All claims fulfill therefore the criterion of novelty (Article 33(2) PCT).

2.2 Any of documents D1 to D4, e.g. D1 which pertains to the improvement of the alkaline stability of proteins binding immunoglobulins, can be considered to be the closest prior art.
SEQ ID No: 79 and 81 of the present application (having no Cys residues) differ from SEQ ID No: 28 and 27 disclosed in D1 only by having one additional N-terminal amino acid. SEQ ID No: 27 and 28 are disclosed as Ig binding domains with increased alkaline stability.

The difference between the present claims and the Ig binding proteins of D1 is a cysteine residue in at least one of positions 40,42,43,46,47,49,50,51,53 or 54 corresponding to SEQ ID No: 2.

As no direct comparison is possible, the objective problem to be solved may be formulated as the provision of alternative Ig binding proteins with increased alkaline stability.

None of documents D1-D4 suggest the mutation of the claimed positions in the helix 3 of a protein A domain to a cysteine residue but rather teach away, e.g. D4 stating that "*amino acids with a side chain having a functional group that is reactive in a coupling reaction for immobilization, such as cysteine (Cys), which has a thiol group (-SH) in the side chain, are not suited for the substitutions*" (D4, paragraph 0043).

The application, however, shows that Fc binding proteins having cysteine residues at the claimed positions have increased alkaline stability (ex. 9, Figures 3 + 4).

An inventive step may thus be acknowledged (Article 33(3) PCT).

3 **Industrial applicability (Article 33(4) PCT)**

All claims appear to comply with the requirements of Article 33(4) PCT.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2018029157	15/02/2018	07/08/2017	11/08/2016

This international application has a filing date corresponding to the priority date of the present application and claims the priority date of 11 Aug. 2016 which is anterior to the priority date of the present application.

It discloses a Fc-binding protein (SEQ ID No: 54) having a cysteine at position 43 which is identical to the item "cs14 43C" of SEQ ID No: 17 of the present application. It also discloses a Fc-binding protein (SEQ ID No: 53) having a cysteine at position 46 which is identical to the item "cs27 46C" of SEQ ID No: 22 of the present application.

The Fc-binding protein of SEQ ID No: 54 of D1 has more than 89.5% identity with SEQ ID No: 2, 7 or 8 of the present application, consequently claims 1-6 are potentially affected. D5 also discloses the embodiments of dep. claims 7-12 of the present application, the coupling to an affinity separation matrix (solid support, present claim 13) and the use and method of claims 14 and 15, respectively (please refer to the passages mentioned in the International Search Report).