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)*	16 April 2020 (16-04-2020)
Applicant's or agent's file reference 48885-724601	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2019/001307	13 December 2019 (13-12-2019)	14 December 2018 (14-12-2018)

International Patent Classification (IPC) or both national classification and IPC
IPC: ***C07K 16/18*** (2006.01), ***A61K 39/395*** (2006.01), ***A61P 35/00*** (2006.01), ***C07K 16/46*** (2006.01), ***C12N 15/13*** (2006.01), ***C12N 5/10*** (2006.01), ***C12P 21/08*** (2006.01).

Applicant
NORTHERN BIOLOGICS INC.

1. This opinion contains indications relating to the following items:

- [x] 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
- [x] 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
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [x] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will 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/CA	Date of completion of this opinion	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	08 April 2020 (08-04-2020)	Mostapha Bayaa (819) 639-7743

Box No I **Basis of this 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(b))

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 in 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)	Claims 1-66	YES
	Claims None	NO
Inventive step (IS)	Claims 1-66	YES
	Claims None	NO
Industrial applicability (IA)	Claims 1-66	YES
	Claims None	NO

2. Citations and explanations:

Reference is made to the following document:

D1: ORECCHIA P et al. Identification of a novel cell binding site of periostin involved in tumour growth. Eur J Cancer. 2011 Sep;47(14):2221-9. doi: 10.1016/j.ejca.2011.04.026. Epub 2011 May 24.

D1 is the closest prior art and it discloses a periostin (POSTN) specific monoclonal antibody (mAb OC-20) that specifically binds the second FAS1 domain (FAS1-2, also known as FAS2). Moreover, this antibody significantly inhibits tumour growth and angiogenesis.

The present alleged invention is directed to a specific anti-POSTN antibody, NB0828, and variants thereof wherein these antibodies comprise CDRs as set forth in SEQ ID NOS: 1-12 and/or the variable heavy and light chain as set forth in SEQ ID Nos: 13 and 14, respectively. These antibodies specifically bind the FAS2 domain, more specifically the amino acids N276, R284, E288, L287, V295 and K302 of present SEQ ID NO: 15. Moreover, use of said antibodies in treatment of cancer is disclosed.

Novelty and Inventive Step:

Claims 1-66 appear to be novel and inventive and therefore comply with PCT Articles 33(2) and 33(3). Document D1 is considered to represent the closest prior art. Document D1 discloses a POSTN specific monoclonal antibody (mAb OC-20) that specifically binds the FAS2, and uses thereof in inhibiting tumour growth. However, none of the cited documents discloses the antibodies of the present application having specific CDRs and variable regions recited in the present claims, nor would these antibodies be obvious to the skilled artisan. Claims 1-66 are therefore novel and inventive.

Industrial Applicability:

The subject matter of claims 1-66 is considered to be industrially applicable and thus complies with the requirements of PCT Article 33(4).

Methods of Medical Treatment:

Claims 43, 45, 46, 49, 51, 53, 55 and 57 relate to a subject matter considered to be a method of medical treatment. Of note, some jurisdictions, such as Canada, do not recognize the patentability of claims to methods of medical treatment; they may, however, permit claims directed to a product, particularly substances or compositions, as well as claims directed to the contemplated medical use of said product.

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:

Claims 2, 6, 7, 14, 15, 19, 20, 31, 32 and dependent claims thereon do not comply with PCT Article 6. These claims are not fully supported by the description. With respect to antibodies characterized by variations in the CDRs and/or the variable domains, the claims are not adequately disclosed by the present description. The present application only discloses antibodies comprising specific CDRs and VL and VH regions. It is well established in the art that the formation of an intact antigen binding site as well as the maintenance of the antigen binding specificity and affinity critically depends on the amino acid sequence and conformations of each of the CDRs of the light and heavy chain. It is further expected that all CDRs in the proper order and in the context of the framework sequences which maintain their required conformation, are required to produce a polypeptide having functional antigen binding sites and are essential for the functional properties of the antibody. Accordingly, it is unlikely that all the antibodies encompassed by the present claims have the required function and thus solve the problem of the present invention.

Claims 10, 14 and 15 do not comply with PCT Article 6 due to a lack of clarity. The expression “at least about” is ambiguous. Said expression attempts to define the contemplated value in both an absolute and approximate manner simultaneously.