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)*	2 June 2020 (02-06-2020)
Applicant's or agent's file reference 08945437WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2020/050321	11 March 2020 (11-03-2020)	12 March 2019 (12-03-2019)

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

Applicant
UNIVERSITY HEALTH NETWORK

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	25 May 2020 (25-05-2020)	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 1-77	YES
	Claims None	NO
Inventive step (IS)	Claims 1-77	YES
	Claims None	NO
Industrial applicability (IA)	Claims 1-77	YES
	Claims None	NO

2. Citations and explanations:

Reference is made to the following document:

D1 : WATANABE R et al. Emerging Roles of Tumor Necrosis Factor-Stimulated Gene-6 in the Pathophysiology and Treatment of Atherosclerosis. Int J Mol Sci. 2018 Feb 5;19(2):465. doi: 10.3390/ijms19020465.

D1 is the closest prior art and it discloses the use of TSG-6 in the diagnosis and treatment of atherosclerotic cardiovascular diseases. D1 also discloses exogenous TSG-6 infusion and endogenous TSG-6 attenuation with a neutralizing antibody retards and accelerates, respectively, the development of aortic atherosclerotic lesions in ApoE-deficient mice.

The present application is directed to 13 specific TSG-6 binding antibodies, wherein these antibodies are defined by their variable regions or CDRs as set forth in present claims 1 and 2, respectively. Moreover, encoding nucleic acids, expression vectors, host cells and therapeutic methods thereof are disclosed.

Novelty and Inventive Step:

Claims 1-77 are novel and therefore comply with PCT Article 33(2). Document D1 is considered to represent the closest prior art. Document D1 discloses a TSG-6 neutralizing antibody and uses thereof in attenuating endogenous TSG-6, which results in accelerated development of aortic atherosclerotic lesions. However, none of the cited documents discloses the antibodies recited in present claims 1 and 2, nor any other therapeutic TSG-6 specific antibodies that can be used in the methods recited therein. Claims 1-77 are therefore novel.

Industrial Applicability:

The subject matter of claims 1-77 is considered to be industrially applicable and thus complies with the requirements of PCT Article 33(4).

Methods of Medical Treatment:

Claims 14-41 and 54-77 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:

Claim 1 does not comply with PCT Article 6. The claim shall be clear and concise. After element g) in claim 1, there appears to be a clerical error that labels the next element as "8)" which is confusing. Said element should be labelled as "h)" while the elements following that should be relabelled accordingly.

Claims 3, 4 and 8 do not comply with PCT Article 6. The claims shall be clear and concise. The claims should refer to preceding claims by number.

Claims 13-17, 25, 29, 38, 53-56, 64 and 68 do not comply with PCT Article 6. The claims shall be clear and concise. Improper reference to preceding claims causes ambiguity. Specifically, the expressions “antibody according to any one of claims 1-8” and “antibody according to any one of claims 42-48” are inaccurate and confusing. Claims 8 and 48 are directed to a nucleic acid composition, and not to an antibody *per se*.

Claims 14-41 and 54-77 do not comply with PCT Article 6. The claims shall be clear and concise. It is unclear how the exact same antibodies can simultaneously serve as both an agonist and an antagonist of TSG-6, i.e. opposite functions, (see claims 15 and 16).

Claims 14, 16, 38-41 and 54 do not comply with PCT Article 6. These claims are not fully supported by the description. All the antibodies disclosed appear to inhibit TSG-6 binding to HA, i.e. TSG-6 antagonists. As such, the contemplated use of the recited antibodies as TSG-6 agonists is not adequately disclosed in the present application.

Claims 18, 19, 26, 27, 31, 35, 36, 37, 40, 57, 58, 65, 66, 70, 74 and 74 do not comply with PCT Article 6. The claims shall be clear and concise. The use of relative terms without a point of reference causes ambiguity. Specifically, the terms “high”, “increased” and “low” have no universal meaning to the skilled artisan, thus rendering the scope of the claims unclear.