

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/EP2020/062526

International filing date (day/month/year)
06.05.2020

Priority date (day/month/year)
10.05.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/12 C07K14/005

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 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:



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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	
	No: Claims	<u>1-28</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-28</u>
Industrial applicability (IA)	Yes: Claims	<u>1-28</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

Reference is made to the following documents:

- D1 US 2019/046634 A1 (VAN SANTEN VICKY L [US] ET AL) 14 February 2019 (2019-02-14)
- D2 US 8 828 407 B2 (BRITTON PAUL [GB]; BICKERTON ERICA [GB] ET AL.) 9 September 2014 (2014-09-09)
- D3 WO 2014/177873 A1 (PIRBRIGHT INST [GB]) 6 November 2014 (2014-11-06)
- D4 WO 2004/092360 A2 (CHIRON CORP [US]; RAPPUOLI RINO [IT] ET AL.) 28 October 2004 (2004-10-28)
- D5 WO 86/05806 A1 (NAT RES DEV [GB]) 9 October 1986 (1986-10-09)

Note

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy.

Methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods practiced on the human or animal body are subject matter on which an Authority is not required to carry out international search or preliminary examination. Search and preliminary examination are, however, conducted for surgical, therapeutic or diagnostic instruments or apparatus **for use** in such methods. Search and preliminary examination are also conducted for products, particularly substances or compositions **for use** in these methods of treatment or diagnosis.

With respect to the subject matter of the present claims 26-28 the attention of the Applicant is drawn to the fact that the EPO considers that the whole set of claims, as far as they concern methods of treatment/diagnosis that may be practised on the human or animal body, are examined by the IPEA as indicated above, but relate to subject matter considered by the Examining Division at the EPO to be covered by the provision of Article 53c EPC.

Consequently, in a subsequent examination in the regional phase, these inventions would not be considered as patentable.

Item V

D1 discloses IBV spike protein having the 267C mutation in the S1 protein which is 82-99% identical to the spike proteins of the present SEQ ID NOs: 2-8, 76, 77 (see e.g. D1, SEQ ID 57 and claims 1-21). In addition, D1 discloses a recombinant viral nucleic acid that may function as a vector for the immunogenic IBV S1 protein by virtue of the recombinant viral nucleic acid containing foreign DNA or RNA. The recombinant viral nucleic acid, packaged in a virus may be introduced into a vaccinee by standard methods for vaccination with live vaccines. A live vaccine of the invention can be administered at, for example, about 10^4 to 10^8 viruses/dose, or $10^{6.5}$ to $10^{9.5}$ pfu/dose. Actual dosages of such a vaccine can be readily determined by one of ordinary skill in the field of vaccine technology (see e.g. [0080]).

Therefore, D1 is novelty destroying for the present claims 1-22, 24-28 (Article 33(2) PCT).

D2 discloses that cell tropism of coronaviruses is determined by the S2 protein, and that substitution of the S2 protein with all or part of another coronavirus can alter (extend or reduce) the cell tropism of the virus, depending on the cell tropism of the virus from which the S2 protein was derived. The S1 protein disclosed in D2 has the 267C mutation and is 82-96% identical to the spike proteins of the present SEQ ID NOs: 2-8, 76 and 77 (see e.g. SEQ ID NO 1 and claims 1-21). Moreover, D2 discloses

- (i) a method for treating and/or preventing a disease in a subject which comprises the step of administering a vaccine according to the sixth aspect of the invention to the subject;
- (ii) a vaccine according to the sixth aspect of the invention for treating and/or preventing a disease in a subject;
- (iii) the use of a viral particle according to the fourth aspect of the invention in the manufacture of a vaccine for treating and/or preventing a disease in a subject.
- (iv) a method for producing a vaccine according to the sixth aspect of the invention, which comprises the step of infecting Vero cells with a viral particle according to the fourth aspect of the invention;
- (v) a method for altering the cell tropism of a coronavirus which comprises the step of substitution of at least a part of the S2 protein with the S2 protein, or corresponding part thereof, from a different strain; and
- (vi) a cell culture comprising a cell or a population of cells according to the fifth aspect of the invention.

The extended cell tropism conferred on the virus disclosed in D2 by the presence of the chimeric gene means that virus stock for vaccine production can be produced by growing on cell lines, rather than embryonated eggs or primary cells.

The use of cell lines such as Vero cell has many advantages:

- (i) it has been previously validated for growth of viruses and diagnostic purposes;
- (ii) the cells (and therefore virus) can be grown in suspension, rather than flat beds; and
- (iii) it is possible to achieve consistent yields.

Consequently, the present claims 1-28 are not new over D2 (Article 33(2) PCT).

D3 discloses an infectious bronchitis virus (IBV) spike protein (S protein) which is based on an S protein from an IBV strain with restricted tissue tropism, but which comprises the sequence XBBXB in the part of the S2 protein corresponding to residues 686 to 691 of the sequence given as SEQ ID No. 2 and which has the 267C substitution such that an IBV virus comprising the S protein has extended tissue tropism (see e.g. SEQ ID NO: 1 and claims 1-18).

Therefore, the present claims 1-28 are not novel over D3 (Article 33(2) PCT).

D4 discloses proteins of SEQ ID NOs: 6072 and 9909 which contain the 267C substitution and have 82-96% sequence identity to the present SEQ ID NOs: 2-8. Therefore, at least the product claims 1-22 of the present application are not novel (Article 33(2) PCT).

D5 discloses a DNA molecule which codes for an IBV spike-protein polypeptide comprising (consisting of or including) the S1 or S2 polypeptide. Such DNA is conveniently referred to as "spike DNA" for brevity. It includes DNA coding for the spike protein precursor. Preferably there is at least 80%, more preferably at least 90%, amino acid sequence homology between the sequence coded for and the amino acid sequence of the corresponding polypeptide of the IBV Beaudette, M41 or 6/82 strain. D5 includes specifically a DNA molecule which codes substantially only for any of (1) the spike protein precursor, (2) the S1 signal plus the S1 polypeptide, (3) the S1 polypeptide and (4) the S1 plus the S2 polypeptides, wherein the S1 267C mutation is present (see e.g.). Therefore, the subject matter of at least the product claims 1-22 is not new (Article 33(2) PCT).

Item VIII

The term "fragment thereof" used in claims 1-16, 18-19, 23 and 24 is open for interpretation and renders the subject matter of all the claims 1-28 unclear (Article 6 PCT).

The present claims 1-6 do not recite any sequence to which the position of amino acid 267 could be assigned. Therefore, claims 1-6 and 8-28 are unclear (Article 6 PCT).

The expressions "introduced by a mutation" used in the language of claim 4 and "comprising a mutation" in claim 2 solely indicate a product-by-process feature which is insufficient in establishing the novelty of the claimed product over the same product known from the prior art. Such expressions render the subject matter for which protection is sought unclear (Article 6 PCT).

Rule 13.1 PCT

Since the subject matter of the present claims 1-28 is not new, an issue under Rule 13.1 PCT arises as regards the lack of novel, unifying inventive concept. Consequently, the applicant should expect an objection as to the lack of unity, should the present application enter the examination phase before the EPO.