

PATENT COOPERATION TREATY

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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/US2022/014812

International filing date (day/month/year)
02.02.2022

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International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/09 A61K39/385 A61K39/39 A61P11/00 A61P31/04 A61P37/04

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

Authorized Officer

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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>3-20</u>
	No: Claims	<u>1, 2, 21, 22</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-22</u>
Industrial applicability (IA)	Yes: Claims	<u>1-22</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

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

and / or

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

see form 210

Item V

V.1 Reference is made to the following documents:

- D1 ARADOTTIR PIND A A ET AL: "Adjuvants Enhance the Induction of Germinal Center and Antibody Secreting Cells in Spleen and Their Persistence in Bone Marrow of Neonatal Mice", FRONTIERS IN IMMUNOLOGY, vol. 10, 1 January 2019 (2019-01-01), page 2214, XP055911943
- D2 LEROUX-ROELS G ET AL: "A randomized, observer-blind Phase Ib study to identify formulations and vaccine schedules of a trivalent Group B Streptococcus vaccine for use in non-pregnant and pregnant women", VACCINE, vol. 34, no. 15, 05 March 2016 (2016-03-05), pages 1786-1791, XP029463429
- D3 EP 3 919 076 A1 (MAX PLANCK GESELLSCHAFT [DE]) 8 December 2021 (2021-12-08) (Pdoc)
- D4 OTT G ET AL: "A cationic sub-micron emulsion (MF59/DOTAP) is an effective delivery system for DNA vaccines", JOURNAL OF CONTROLLED RELEASE, vol. 79, no. 1-3, 19 February 2002 (2002-02-19), pages 1-5, XP004340908
- D5 E A THORYK ET AL: "Co-Administration of Lipid Nanoparticles and Sub-Unit Vaccine Antigens Is Required for Increase in Antigen-Specific Immune Responses in Mice", VACCINES, vol. 4, no. 4, 6 December 2016 (2016-12-06), page 47, XP55407769

V.2 Novelty (Article 33(2) PCT)

V.2.1 Prior art documents

Document D1 describes the vaccination with a pneumococcal conjugate vaccine Pnc1-TT in combination with MF59 showing significantly enhanced GC formation and FDC maturation in neonatal mice (abstract, p. 3 left-hand col. 3rd paragraph). One dose of MF59 comprises 1.175 mg sorbitan trioleate (SPAN-85), 1.175 mg polysorbate 80 and 9.75 mg squalene (+sodium citrate and citric acid).

Document D2 describes a study using a trivalent Group B Streptococcus vaccine comprising CRM197-glycoconjugate and MF59 adjuvant (abstract).

Intermediate document D3 describes a vaccine comprising a glycoconjugate (pneumococcal oligosaccharide + CRM197) and the adjuvant MF59 (paragraphs [322]-[325], Table 1, paragraphs [348], [354]-[358]).

Document D4 describes a cationic nanoemulsion (CNE) comprising MF59 and DOTAP used in the field of DNA vaccines (see entire document).

Document D5 describes lipid nanoparticles (LNP) comprising the cationic lipid (13Z, 16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine, DSPC, cholesterol and PEG2000-DMG. Said LNP is used as adjuvant in a vaccine comprising HBsAg or OVA. Said LNPs boost B-cell and T cell responses to sub-unit vaccine antigens in mice (abstract, p. 2 6th paragraph - p. 3 1st paragraph).

V.2.2 With respect to claims 1, 2, 21, and 22

The disclosure of D1 is novelty destroying for the subject-matter of claims 1, 2, 21 and 22. Therefore, claims 1, 2, 21 and 22 do not meet the requirements of Article 33(2) PCT.

V.2.3 With respect to claims 3-20

None of the cited prior art documents describes the subject-matter of claims 3-20. Therefore, the subject-matter of claims 3-20 is considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 3 and 5

The subject-matter of claims 3 and 5 differs from the closest prior art document D1 in that the vaccine comprises a cationic lipid.

A technical effect based on said difference is shown in the application only for the specific cationic lipid (13Z, 16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine. No such effect is shown for cationic lipids in general.

The technical problem to be solved may be regarded as providing a composition comprising an alternative adjuvant.

Cationic lipids are known in the field of adjuvants, also in combination with MF59 (see D4 and D5).

Therefore, a skilled person searching for alternative adjuvants would combine the vaccine described in D1 with a cationic lipid thereby arriving at the subject-matter of claims 3 and 5.

V.3.3 With respect to claim 4

The subject-matter of claim 4 differs from the closest prior art document D1 in that the cationic lipid (13Z,16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine is used in combination with MF59.

The technical effect based on said difference is an equal immunogenicity, induction of OPA and survival rate in mice (see Figures 5, 7 and 9 of the application).

The technical problem to be solved may be regarded as providing an alternative vaccine composition.

The skilled person searching for an alternative vaccine composition certainly knows that cationic lipids may be introduced in a vaccine wherein the cationic lipid (13Z,16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine is known to be beneficial in the context of subunit vaccines (see D5). It appears to be obvious for the skilled person to use said cationic lipid in combination with the vaccine composition described in D1.

The mere provision of an alternative can only be regarded as demonstrating inventive step when the alternative provides some sort of technical advantage, otherwise the specific choice is merely an arbitrary selection of one among a number of equally viable known alternatives.

Therefore, the subject-matter of claim 4 is not considered inventive in the sense of Article 33(3) PCT.

V.3.4 With respect to claims 6, and 8-17

The subject-matter of claims 6 and 8-17 differs from D1 in that the vaccine comprises multiple serotypes of capsular polysaccharides of *S. pneumoniae*.

The technical effect based on this difference is the induction of immune responses against multiple pneumococcal serotypes.

The technical problem to be solved may be regarded as a vaccine capable of inducing immune responses against multiple pneumococcal serotypes.

It appears to be obvious for the skilled person to add the serotypes mentioned in claims 6, 8-17. Hence the subject-matter of claims 6 and 8-17 is not considered inventive in the sense of Article 33(3) PCT.

V.3.5 With respect to claim 7

The subject-matter of claim 7 differs from the closest prior art D1 in that the carrier is CRM197 instead of TT.

The technical effect based on this difference is not apparent, since comparative data are missing.

The technical problem to be solved may be regarded as providing a vaccine comprising PS-conjugates conjugated to an alternative carrier protein.

The carrier CRM197 is widely known in the field of *S. pneumoniae* conjugates and the skilled person consider to replace TT by CRM197 as an alternative carrier protein.

Therefore, the subject-matter of claim 7 does not meet the requirements of Article 33(3) PCT.

V.3.6 With respect to claims 18-20

The subject-matter of claims 18-20 is not considered inventive since the replacement of PS80 by PS20 and the use of histidine and NaCl are considered obvious alternatives the skilled person would choose without an inventive action. Therefore, claims 18-20 do not meet the requirements of Article 33(3) PCT.

V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-22

The subject-matter of claims 1-22 appears to be susceptible of industrial application.

V.5 Further remarks

V.5.1 With respect to claims 21 and 22

The subject-matter of claims 21 and 22 is considered to be a method of treatment by therapy of the human or animal body.

For the assessment of the present claims 21 and 22 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. 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 21 and 22 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Item VI

VI.1 With respect to document D3

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited document D3 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the document D3 could be relevant to the question of novelty.