

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/IB2015/053365	International filing date (day/month/year) 08.05.2015	Priority date (day/month/year) 08.05.2014
International Patent Classification (IPC) or both national classification and IPC INV. A61K39/245 A61K39/12		
Applicant REDVAX 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 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:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Chapman, Rob Telephone No. +49 89 2399-0
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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>3-25, 27-30, 32-35, 38-41</u>
	No: Claims	<u>1, 2, 26, 31, 36, 37, 42</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-42</u>
Industrial applicability (IA)	Yes: Claims	<u>1-42</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

Re Item V

Reference is made to the following documents:

- D1 D. C. FREED ET AL: "Pentameric complex of viral glycoprotein H is the primary target for potent neutralization by a human cytomegalovirus vaccine",
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES,
vol. 110, no. 51, 2 December 2013 (2013-12-02), pages E4997-E5005,
XP055137188,
ISSN: 0027-8424, DOI: 10.1073/pnas.1316517110
- D2 F. WUSSOW ET AL: "A Vaccine Based on the Rhesus Cytomegalovirus UL128 Complex Induces Broadly Neutralizing Antibodies in Rhesus Macaques",
JOURNAL OF VIROLOGY,
vol. 87, no. 3, 14 November 2012 (2012-11-14), pages 1322-1332,
XP055137191,
ISSN: 0022-538X, DOI: 10.1128/JVI.01669-12
- D3 WO 2012/051211 A2 (NOVARTIS AG [CH]; LILJA ANDERS [US]; LOOMIS REBECCA [US]; FRANTI MICHA) 19 April 2012 (2012-04-19)
- D4 WO 2014/005959 A1 (NOVARTIS AG [CH]) 9 January 2014 (2014-01-09)
- D5 WO 2012/106377 A2 (UNIV PENNSYLVANIA [US]; WEINER DAVID B [US]; SHEDLOCK DEVON J [US]) 9 August 2012 (2012-08-09)
- D6 TANG X C ET AL: "Baculovirus-Produced Influenza Virus-like Particles in Mammalian Cells Protect Mice from Lethal Influenza Challenge",
VIRAL IMMUNOLOGY, MARY ANN LIEBERT, INC., NEW YORK, US,
vol. 24, no. 4, 10 August 2011 (2011-08-10), pages 311-319,
XP002711212,
ISSN: 0882-8245, DOI: 10.1089/VIM.2011.0016
- D7 TONG-MING FU ET AL: "Progress on pursuit of human cytomegalovirus vaccines for prevention of congenital infection and disease",
VACCINE,

vol. 32, no. 22, 1 May 2014 (2014-05-01), pages 2525-2533,
XP055137184,
ISSN: 0264-410X, DOI: 10.1016/j.vaccine.2014.03.057

- D8 MACAGNO ANNALISA ET AL: "Isolation of Human Monoclonal Antibodies That Potently Neutralize Human Cytomegalovirus Infection by Targeting Different Epitopes on the gH/gL/UL128-131A Complex", JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US,
vol. 84, no. 2, 15 January 2010 (2010-01-15), pages 1005-1013,
XP009129527,
ISSN: 0022-538X, DOI: 10.1128/JVI.01809-09
- D9 Biotechnet: "The Vaccine-Factory in the Box - from vision to reality",
, 11 July 2013 (2013-07-11), XP055137200,
Swissinnovate
Retrieved from the Internet:
URL:[http://www.swissinnovate.org/content.cfm?
nav=4&content=11&command=details&id=20527](http://www.swissinnovate.org/content.cfm?nav=4&content=11&command=details&id=20527)
[retrieved on 2014-08-28]
- D10 RYCKMAN BRENT J ET AL: "Characterization of the human cytomegalovirus gH/gL/UL128-131 complex that mediates entry into epithelial and endothelial cells",
JOURNAL OF VIROLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, US,
vol. 82, no. 1, 1 January 2008 (2008-01-01), pages 60-70,
XP002519851,
ISSN: 1098-5514, DOI: 10.1128/JVI.01910-07
[retrieved on 2007-10-17]
- D11 WO 2014/068001 A1 (REDBIOTEC AG [CH]) 8 May 2014 (2014-05-08)

1 Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 2, 26, 31, 36, 37 and 42 is not new in the sense of Article 33(2) PCT.

1.1 Document D1 discloses:

1. A HCMV vaccine expressing a pentameric complex of gH, gL, UL 128, UL130, and UL131. This vaccine, as opposed to AD169 virus, which cannot form the pentameric complex, generated neutralizing antibodies to CMV (p.E4998, §1-2).
2. A pharmaceutical composition comprising recombinant pentameric gH complex constructed from the Towne strain with gH truncated of its cytoplasmic and transmembrane domains. The secreted complex was expressed in a baculovirus culturing system and assembled using Redbiotec's rePax technology (p.E5003, §3; see D9 and D11 for background).

D1 thus anticipates the subject-matter of at least claims 1, 2, 26, 31, 36, 37 and 42.

2 Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-42 does not involve an inventive step in the sense of Article 33(3) PCT.

2.1 The document D1 is regarded as being the closest prior art to the subject-matter of claim 22, and discloses (the references in parentheses applying to this document):

1. A HCMV vaccine expressing a pentameric complex of gH, gL, UL 128, UL130, and UL131. This vaccine, as opposed to AD169 virus, which cannot form the pentameric complex, generated neutralizing antibodies to CMV (p.E4998, §1-2).
2. A pharmaceutical composition comprising recombinant pentameric gH complex constructed from the Towne strain with gH truncated of its cytoplasmic and transmembrane domains. The secreted complex was expressed in a baculovirus culturing system and assembled using Redbiotec's rePax technology (p.E5003, §3; see D9 and D11 for background).

The subject-matter of claim 22 therefore differs from this known D1 in that a method of production is claimed, comprising utilising a baculovirus system.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative method for the production of a pentameric gH complex of CMV gH, gL, UL 128, UL130, and UL131.

The solution proposed in claim 22 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons

The use of baculovirus systems to produce a pentameric gH complex of gH, gL, UL 128, UL130, and UL131 is known from D1. The skilled person with a knowledge of D1 would therefore find it obvious to use a baculovirus system to produce such a complex.

- 2.2 Dependent claims 2-21, 23-25, 27-30, 32-35 and 37-41 do not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step.

Re Item VIII

3 Clarity and disclosure

The following claims are not clear and/or lack sufficient disclosure.

- 3.1 Claim 1 attempts to define a product by the process to obtain it. In the absence of technical features that enable said product to be distinguished from existing products, or those derived by other methods, a product is not necessarily rendered novel merely by the fact that it is produced by a means of a new process.
- 3.2 Although claims 26, 31 and 42 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.
- 3.3 The application does not disclose methods of using baculoviruses as a vaccine vector, resulting in a lack of support and sufficiency of disclosure.
- 3.4 The Applicant is further warned that a lack of unity objection could have been raised in relation to claims 1-23 and 36-42, since the unifying feature 'a pentameric complex of CMV gH, gL, UL 128, UL130, and UL131 is known

from D1-D5. Methods for producing such a complex using a baculovirus, and the expression of such proteins by other viral vectors per se, or their use of such vectors or their isolated protein products in vaccines thus constitute individual, separate inventions.