PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.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/EP2004/014630	International filing date *(day/month/year)* 22.12.2004
Priority date *(day/month/year)* 23.12.2003	
International Patent Classification (IPC) or both national classification and IPC A61K39/39, A61K9/127	
Applicant VECTRON THERAPEUTCIS AG	

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 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
- ☒ 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"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed 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 three 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.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Telephone No. +31 70 340-

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/014630

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, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto 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.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 32

because:

☒ the said international application, or the said claims Nos. 32 for industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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)	Yes:	Claims	10-16
	No:	Claims	1-9,17-33
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	1-31,33
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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

III. Non-establishment of opinion (Continuation)

1 Present claim 32, differs from 30 and 31, in that an adjuvant and/or cytokine is administered prior, simultaneously or after administration of the liposome or liposomal composition. Thus its characterising part consists of a method of treatment, which is considered by this Authority to be covered by the provisions of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V. Reasoned statement (Continuation)

2 CITATIONS

Reference is made to the following documents:

D1: US 2003/224010 A1 (DAVIS HEATHER L ET AL) 4 December 2003 (2003-12-04)

D2: US 2003/161834 A1 (GARCON NATHALIE ET AL) 28 August 2003 (2003-08-28)

D3: WO 03/028656 A (VALIANTE NICHOLAS ; CHIRON CORP (US); O'HAGAN DEREK (US)) 10 April 2003 (2003-04-10)

D4: RICHARDS R L ET AL: "LIPOSOMES LIPID A AND ALUMINUM HYDROXIDE ENHANCE THE IMMUNE RESPONSE TO A SYNTHETIC MALARIA SPOROZOITE ANTIGEN" INFECTION AND IMMUNITY, vol. 56, no. 3, 1988, pages 682-686, XP008034645 ISSN: 0019-9567

D5: GREGORIADIS G: "IMMUNOLOGICAL ADJUVANTS A ROLE FOR LIPOSOMES" IMMUNOLOGY TODAY, vol. 11, no. 3, 1990, pages 89-96, XP000102991 ISSN: 0167-5699

D6: EP-A-0 356 340 (LIPOSOME CO INC) 28 February 1990 (1990-02-28)

D7: FUENTES P ET AL: "Use of gamma-inulin/liposomes/Vitamin E adjuvant

combination in contraceptive vaccines." INTERNATIONAL JOURNAL OF PHARMACEUTICS (KIDLINGTON), vol. 257, no. 1-2, 12 May 2003 (2003-05-12), pages 85-95, XP002294261 ISSN: 0378-5173

3 NOVELTY (Art. 33(2) PCT)

3.1 D1 discloses adjuvant compositions comprising an unmethylated CpG dinucleotide, a non-nucleic acid adjuvant (e.g. alum, MPL), an antigen and a delivery complex e.g. liposome. These combinations result in a synergistic immune response e.g. against tumor, viral, bacterial antigens (see paragraphs 2,6,8,10,20,41,59,67-70,73-86,137) . In view of D1, the subject-matter of claims 1,5-8,17,18,20,22-26,29,30,32,33 is not novel.

3.2 D2 discloses vaccine compositions comprising a saponin and an immunostimulatory oligonucleotide and optionally a lipopolysaccharide adjuvant with a liposome carrier to enhance the adjuvanticity of the adjuvant combination and an viral, bacterial or tumor antigen (see abstract; paragraphs 1,13,22-25,40-43,50,60,74,114,120,172,220). In view of D2, the subject-matter of claims 1-9,17-26,29-31,33 is not novel.

3.3 D3 discloses vaccine compositions comprising double stranded RNA in combination with an antigen delivery system, e.g. liposome, and immunostimulatory molecules e.g. LPS, MPL, immunostimulatory nucleotide sequences. The addition of the delivery system stimulates the immune system. (see abstract; page 3, line 1-29; page 18, line 12-23; page 25, line 18-32; page 44, line 1-23; page 55, line 12 - page 56, line 19; page 59, line 4-16; page 62, line 3 - page 64, line 23). In view of D3, the subject-matter of claims 1,6-8,17-26,29-33 is not novel.

3.4 D4 discloses a vaccine composition comprising alum adsorbed liposomes containing lipid A and a synthetic malaria sporozoite antigen (see abstract; page 682, column 2, last paragraph - page 683, column 1, paragraph 1; page 684, column 1, paragraph 2 - column 2, paragraph 3; page 685, column 2). In view of D4, the subject-matter of claims 1,5-9,17,23-25,30,33 is not novel.

3.5 D5 discusses liposomal immunological adjuvants and states that the immunity to antigens can be drastically improved in some cases through the administration of liposomes together with other adjuvants. This synergism of adjuvants can be effected by co-entrapment of adjuvant together with antigen in the same vesicles, entrapment of adjuvant and antigen in separate vesicle populations which are mixed before injection or by simple addition of adjuvant to antigen containing liposomes. D5 also discloses the use of a targeting moiety attached to the liposome. (see page 89, column 2, paragraph 2; page 91, column 2, paragraph 1; page 92, column 1, last paragraph - page 94, column 1, paragraph 1). In view of D5, the subject-matter of claims 1-9, 17-27, 29-33 is not novel.

3.6 D7 discloses the method for producing a liposome of claim 28 (see page 87, column 2, paragraph 3). In view of D7, claim 28 is not novel.

3.7 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1-9,17-33 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

4 INVENTIVE STEP (Art. 33(3) PCT)

4.1 Dependent claims 10-16 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step because the use of liposomes comprising cholesterol and a lipid selected from the group consisting of phosphatidylserine, phosphatidylglycerol and phosphatidic acid and another lipid is disclosed in D6 (see abstract; page 3, line 50-58; page 4, line 14; claims 1,2,5) and determining the molar lipid composition of the liposome would be obvious for the skilled person.

4.2 The present application does therefore not satisfy the criterion set forth in Article 33(3) PCT and the subject-matter of claims 10-16 does not involve an inventive step (Rule 65(1)(2) PCT).

VII. Certain defects (Continuation)

5.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D1 - D6 is not mentioned in the description, nor are these documents identified therein.

5.2 If amendments are filed, it should be by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate. Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

5.3 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

5.4 The applicant is requested to note that in accordance with Rule 66.4 (a) PCT the issuance of an additional Written Opinion (WO) is facultative. Moreover, as the final action in the PCT procedure is an International **Preliminary** Examination Report (IPER) and not a decision, a violation of the right to be heard cannot exist. The applicant can not therefore rely on obtaining a second WO before the IPER is issued and is requested to answer this first WO in a complete manner.

VIII. Certain Observations (Continuation)

6.1 The abbreviations CH and PE (see claim 11 and 12) should be explained in the claims to fulfill the requirements of Art. 6 PCT.

6.2 The term "essentially" used in claim 16 is vague and indefinite and as such renders

the scope of the claims unclear; accordingly, the claims require amendment to remove this defect (Art. 6 PCT).

6.3 Claims 19,20,21,22,23,26,33 comprise optional features (see the expression "in particular") which are considered to have no limiting effect on the scope of the claims and are regarded to be entirely optional. Therefore, to fulfill the requirements of Art. 6 PCT optional features should be avoided.

6.4 The term "fragments and derivatives" used in claim 19 is vague and indefinite and as such renders the scope of the claim unclear; accordingly, the claim requires amendment to remove this defect (Art. 6 PCT).

6.5 The term "optionally" should be removed from claim 28. The invention is directed to a composition comprising two adjuvants from which at least one adjuvant is included in a liposome. Since claim 28 is directed to the method of producing the liposome of the compositions of claims 1-27, the liposome has to include at least one adjuvant and the presence of the adjuvant cannot be optional.