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B82Y 5/00 (2011.01) A61P 35/00 (2006.01)
C07K 16/28 (2006.01)

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PCT/US2015/054295

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English

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English

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62/206,772	18 August 2015 (18.08.2015)	US

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55905 (US).

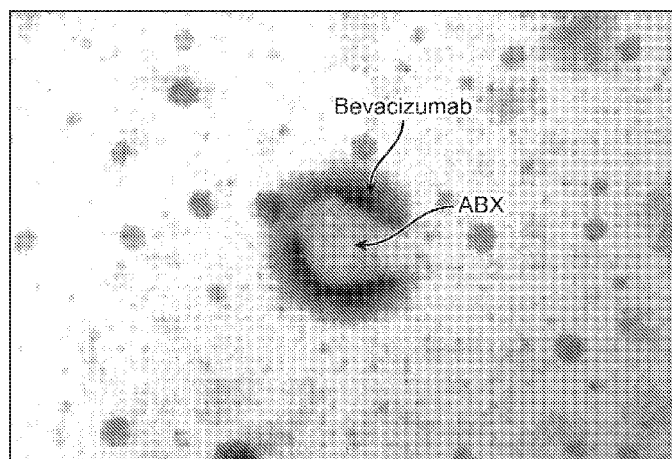
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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

[Continued on next page]

(54) Title: CARRIER-ANTIBODY COMPOSITIONS AND METHODS OF MAKING AND USING THE SAME

Electron Microscopy of AB160 labeled with gold anti-human IgG



Abraxane-avastin_2
Abraxane-avastin complex
JEOL1400
X150000

200 nm
80 kV
10/1/2013
BQ

(57) Abstract: Described herein are com-
positions of antibodies and carrier proteins
and methods of making and using the same,
in particular, as a cancer therapeutic. Also
described are lyophilized compositions of
antibodies and carrier proteins and methods
of making and using the same, in particular,
as a cancer therapeutic.

FIG. 1B



(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 113301.68686WO	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCTUS2015/054295	International filing date (<i>day/month/year</i>) 06.10.2015	Priority date (<i>day/month/year</i>) 06.10.2014	
International Patent Classification (IPC) or national classification and IPC INV. C07K16/22			
Applicant MAYO FOUNDATION FOR MEDICAL			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (<i>sent to the applicant and to the International Bureau</i>) a total of <u>19</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ 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 Article 35(2) 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			
Date of submission of the demand 08.08.2016		Date of completion of this report 13.10.2016	
Name and mailing address of the international preliminary examining authority:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016		Authorized officer Covone-van Hees, M Telephone No. +31 70 340-4416 	

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Present application discloses the production of nanoparticles composition comprising a complex formed by albumin-paclitaxel (Abraxane) and bevacizumab or rituximab or trastuzumab or cisplatin to deliver the paclitaxel to the tumour site. The elements of the nanoparticles are bound by non-covalent bonds. By disaggregation, the paclitaxel remains bound to the antibody.

1 Novelty (Art.33(2) PCT)

- 1.1 WO2014055415 (**D1**) discloses the production of nanoparticles comprising a complex of Abraxane/bevacizumab (ex.1; pg.45 l.16-pg.47 l.4; ex.11), Abraxane/cisplatin (ex.5), Abraxane/ trastuzumab or rituxan (ex.6,12,13) of sizes between 100 to 900 nm (pg.3 l.26-29). Stability in vitro and in serum has been tested (ex.4,7,14,17). The complex Abraxane/bevacizumab has been used to inhibit cancer cell proliferation in vitro and in vivo of melanoma (ex. 10,19).
- 1.2 WO2014123612 (**D3**) suggest the use of Abraxane (not in a complex with bevacizumab) in either dry formulation or suspended (para.198), suitable for parenteral administration (para.220).
- 1.3 None of the available prior art documents discloses the lyophilized composition referred to in claim 1. Remaining claims are all dependent on claim 1 or refer back to it.
- 1.4 Claims 1,2,8-13,22-24,46,47,82,83 are novel (Art.33(2) PCT).

2 Inventive Step (Art.33(3) PCT)

- 2.1 D1 is considered to represent the most relevant state of the art, from which the subject-matter of claim 1 differs in that the nanoparticle composition is lyophilized and maintains the non-covalent interaction among the proteins after reconstitution.
- 2.2 The effect of the difference is a composition which is easy to preserve and transport.
- 2.3 The problem to be solved by the present invention may be therefore seen in the provision of an improved nanoparticle composition.

- 2.4 The solution, as in claim 1, is not obvious and inventive over the prior art. Neither D1 alone or in combination with D3 suggest that a complex of proteins i.e. an antibody and a carrier protein that have non-covalent structural interaction between the first and second proteins before lyophilization is maintained upon reconstitution after lyophilization. The subject-matter of claim 1 is therefore inventive. Remaining claims are all dependent on claim 1 or refer back to it and comprise therefore all the distinguishing features of claim 1 and as such are also inventive (Art.33(3) PCT).

Re Item VII

Certain defects in the international application

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

Re Item VIII

Certain observations on the international application

- 2.6 The definition of the carrier protein and the type of interaction among proteins e.g. non-covalent or hydrophobic, may be necessary to fully define the invention.

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2015/054295

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ 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 (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-72 as originally filed

Claims, Numbers

1, 2, 8-13, 22-24, 46, filed with telefax on 08-08-2016
47, 82, 83

Drawings, Sheets

1/44-44/44 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☒ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☒ the claims, Nos. 3-7, 14-21, 25-45, 48-81
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2015/054295

6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 23.09.2016 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1, 2, 8-13, 22-24, 46, 47, 82, 83</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1, 2, 8-13, 22-24, 46, 47, 82, 83</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1, 2, 8-13, 22-24, 46, 47, 82, 83</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

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

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (PCT Rule 71.1)

To:

REA, Teresa Stanek
CROWELL & MORING LLP
1001 Pennsylvania Avenue
N.W., Washington, D.C. 20004-2595
ETATS-UNIS D'AMERIQUE

Date of mailing
(day/month/year)

13.10.2016

Applicant's or agent's file reference
113301.68686WO

IMPORTANT NOTIFICATION

International application No.
PCT/US2015/054295

International filing date (day/month/year)
06.10.2015

Priority date (day/month/year)
06.10.2014

Applicant
MAYO FOUNDATION FOR MEDICAL

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Authorized Officer

Rodríguez Nóvoa, M

Tel. +31 70 340-2591



The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA <u>EP</u>	Date of receipt of DEMAND <u>08-08-2016</u>
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
Applicant's or agent's file reference 113301.68686WO	
International application No. PCT/US2015/054295	International filing date (day/month/year) 6 October 2015 (06-10-2015)
(Earliest) Priority date (day/month/year) 6 October 2014 (06-10-2014)	
Title of invention CARRIER-ANTIBODY COMPOSITIONS AND METHODS OF MAKING AND USING THE SAME	
Box No. II APPLICANT(S)	
Name and address: (family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH 200 First Street SW Rochester, Minnesota 55905 United States of America	
Telephone No.	
Facsimile No.	
Applicant's registration No. with the Office	
E-mail authorization: Marking one of the check-boxes below authorizes the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send notifications issued in respect of this international application if those offices are willing to do so. ☐ as advance copies followed by paper notifications; or ☐ exclusively in electronic form (no paper notifications will be sent). E-mail address: _____	
State (that is, country) of nationality: US	State (that is, country) of residence: US
Name and address: (family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) MARKOVIC, Svetomir N. c/o MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH 200 First Street SW Rochester, Minnesota 55905 United States of America	
Canceled ex-officio by IPEA/EP	
State (that is, country) of nationality: US	State (that is, country) of residence: US
☒ Further applicants are indicated on a continuation sheet.	

Sheet No. 2

International application No.
PCT/US2015/054295

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

** (Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
NIEVALA, Wendy K.
c/o MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH
200 First Street SW
Rochester, Minnesota 55905
United States of America

**

Cancelled ex-officio by IPEA/EP

State (that is, country) of nationality:
USState (that is, country) of residence:
US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 3

International application No.
PCT/US2015/054295**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The following person is ☒ agent ☐ common representative
 and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☒ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: (Family name followed by given name; for a legal entity, full official designation.
 The address must include postal code and name of country.)

Teresa Stanek Rea
 Crowell & Moring LLP
 1001 Pennsylvania Ave., NW
 Washington, DC 20004
 United States of America

Telephone No.

202-264-2500

Facsimile No.

202-628-8844

Agent's registration No. with the Office

30,427

E-mail authorization: Marking one of the check-boxes below authorizes the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send notifications issued in respect of this international application if those offices are willing to do so.

☒ as advance copies followed by paper notifications; or ☐ exclusively in electronic form (no paper notifications will be sent).
 E-mail address: edocket@crowell.com

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION**Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

- the description ☒ as originally filed, or
☐ as amended under Article 34
 the sequence listing (if any) ☐ as originally filed, or
☐ as amended under Article 34:
☐ in the form of an Annex C/ST.25 text file
☐ on paper or in the form of an image file

- the claims ☐ as originally filed, or
☐ as amended under Article 19, and/or
☒ as amended under Article 34

- the drawings (if any) ☒ as originally filed, or
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.
 3. ☐ Where the IPEA wishes to start the international preliminary examination at the same time as the international search in accordance with Rule 69.1(b), the applicant requests the IPEA to postpone the start of the international preliminary examination until the expiration of the applicable time limit under Rule 69.1(d).
 4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

- ☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Sheet No. 4

International application No.
PCT/US2015/054295**Box No. VI CHECK LIST**

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | | |
|---|---|-------|--------|
| 1. translation of international application | : | _____ | sheets |
| 2. amendments under Article 34 | : | 9 | sheets |
| 3. letter accompanying the amendments under Article 34 (Rule 66.8) | : | 12 | sheets |
| 4. copy (or, where required, translation) of amendments under Article 19 | : | _____ | sheets |
| 5. copy of the letter accompanying the amendments under Article 19 (Rules 46.5(b) and 53.9) | : | _____ | sheets |
| 6. copy (or, where applicable, translation) of any statement under Article 19 (Rule 62.1(ii)) | : | _____ | sheets |
| 7. other (specify) Substitute Sheets and References | : | 99 | sheets |

For International Preliminary Examining Authority use only

received not received

- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ sequence listing in the form of an Annex C/ST.25 text file |
| 2. ☐ original separate power of attorney | 6. ☐ other (specify): _____ |
| 3. ☐ original general power of attorney | _____ |
| 4. ☒ copy of general power of attorney; reference number, if any: 113301.68686WO | _____ |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

/Mary Anne Schofield/

Mary Anne Schofield Reg. No. 36,669
for Teresa Stanek Rea, Reg. No. 30,427
Date: August 8, 2016

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND: 08-08-2016

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☒ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
☒ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rules 82 or 82quater.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.
7. ☒ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rules 82 or 82quater.

For International Bureau use only

Demand received from IPEA on:

Sheet No. ...4

International application No.
PCT/US2015/054295**Box No. VI CHECK LIST**

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | | |
|---|---|-------|--------|
| 1. translation of international application | : | _____ | sheets |
| 2. amendments under Article 34 | : | 9 | sheets |
| 3. letter accompanying the amendments under Article 34 (Rule 66.8) | : | 12 | sheets |
| 4. copy (or, where required, translation) of amendments under Article 19 | : | _____ | sheets |
| 5. copy of the letter accompanying the amendments under Article 19 (Rules 46.5(b) and 53.9) | : | _____ | sheets |
| 6. copy (or, where applicable, translation) of any statement under Article 19 (Rule 62.1(ii)) | : | _____ | sheets |
| 7. other (specify) Substitute Sheets and References | : | 99 | sheets |

For International Preliminary Examining Authority use only

received not received

☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ sequence listing in the form of an Annex C/ST.25 text file |
| 2. ☐ original separate power of attorney | 6. ☐ other (specify): _____ |
| 3. ☐ original general power of attorney | _____ |
| 4. ☒ copy of general power of attorney; reference number, if any: 113301.68686WO | _____ |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Mary Anne Schofield
Mary Anne Schofield Reg. No. 36,669
for Teresa Stanek Rea, Reg. No. 30,427
Date: August 8, 2016

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND: 08-08-2016

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☒ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☒ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rules 82 or 82quater.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.

7. ☒ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.

8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rules 82 or 82quater.

For International Bureau use only

Demand received from IPEA on:

Application No. PCT/US15/54295
Attorney Docket No.: 113301.68686WO
Article 34 Amended Claims

APPENDIX A
Marked-Up Version of Claims
Insertions – Underlined
Deletions – Stricken through

1. (Currently Amended) A lyophilized ~~nanoparticle~~ composition comprising nanoparticle complexes having an outer surface, wherein each of the nanoparticle complexes comprises

a. a carrier protein,

b. between about 100 to about 1000 antibodies having an Fc portion and an antigen-binding portion, and

c. ~~optionally~~ at least one therapeutic agent,

said nanoparticle complexes being lyophilized, and wherein the antibodies are arranged on an outside surface of the nanoparticles, and further wherein upon reconstitution with an aqueous solution, antigen-binding portions of the antibodies retain their association with remain arranged on the outside outer surface of the nanoparticle complexes, provided that said lyophilized composition is stable at about 20°C to about 25°C for at least 3 months, and further wherein the nanoparticle complexes are remain capable of binding to a predetermined epitope the antigen in vivo.

2. (Currently Amended) The lyophilized nanoparticle composition of claim 1, wherein each of the nanoparticle complexes comprises between about 400 and about 800 antibodies.

3. (Canceled)

4. (Canceled).

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5. (Canceled)

6. (Canceled)

7. (Canceled)

8. (Currently Amended) The lyophilized ~~nanoparticle~~ composition of any one of the above claims, wherein the at least one therapeutic agent is located inside the nanoparticle, arranged on the outside surface of the nanoparticle, or both.

9. (Currently Amended) The lyophilized ~~nanoparticle~~ composition of any one of the above claims, wherein the antibodies are selected from the group consisting of adotrastuzumab emtansine, alantuzumab, bevacizumab, cetuximab, denosumab, dinutuximab, ipilimumab, nivolumab, obinutuzumab, ofatumumab, panitumumab, pembrolizumab, pertuzumab, rituximab, and trastuzumab

10. (Currently Amended) The lyophilized ~~nanoparticle~~ composition of any one of the above claims, wherein the at least one therapeutic agent is selected from the group consisting of abiraterone, bendamustine, bortezomib, carboplatin, cabazitaxel, cisplatin, chlorambucil, dasatinib, docetaxel, doxorubicin, epirubicin, erlotinib, etoposide, everolimus, gefitinib, idarubicin, imatinib, hydroxyurea, imatinib, lapatinib, leuprorclin, melphalan, methotrexate, mitoxantrone, nedaplatin, nilotinib, oxaliplatin, paclitaxel, pazopanib, pemetrexed, picoplatin, romidepsin, satraplatin, sorafenib, vemurafenib, sunitinib, teniposide, triplatin, vinblastine, vinorelbine, vincristine, and cyclophosphamide.

11. (Currently Amended) The lyophilized ~~nanoparticle~~ composition of any one of the above claims, wherein the carrier protein is selected from the group consisting of albumin, gelatin, elastin, gliadin, legumin, zein, a soy protein, a milk protein, and a whey protein.

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12. (Currently Amended) The lyophilized ~~nanoparticle~~ composition of any one of the above claims wherein the albumin carrier protein is ~~human serum~~ albumin.

13. (Currently Amended) The lyophilized ~~nanoparticle~~ composition any one of the above claims, wherein the antibodies arrange into a substantially single layer of antibodies on all or part of the outer surface of the nanoparticle complexes.

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. (Canceled)

18. (Canceled)

19. (Canceled)

20. (Canceled)

21. (Canceled)

22. (Currently Amended) A lyophilized ~~nanoparticle~~ composition of claim 1, ~~comprising nanoparticle having an outer surface~~, wherein each of the nanoparticle complexes comprises:

a. an albumin-bound paclitaxel core and

b. an amount of bevacizumab arranged on ~~a~~ the outer surface of the albumin-bound paclitaxel core such that the binding portion of the antibody is directed outward from ~~that the~~ the

Application No. PCT/US15/54295
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Article 34 Amended Claims

outer surface, wherein the antibodies retain their association with the outer surface of the nanoparticle upon reconstitution with an aqueous solution, ~~provided that said lyophilized composition is stable at about 20 °C to about 25 °C for at least 3 months~~ and the reconstituted nanoparticle complexes are capable of binding to VEGF *in vivo*, ~~and further wherein the average reconstituted nanoparticle size is from greater than 800 nm to about 3.5 µm.~~

23. (Currently Amended) The lyophilized nanoparticle composition of claim 21 ~~22~~, wherein the weight ratio of albumin-bound paclitaxel to bevacizumab is between about 5:1 to about 1:1.

24. (Currently Amended) The lyophilized nanoparticle composition of claim 23, wherein the weight ratio of albumin-bound paclitaxel to bevacizumab is about 10:4.

25. (Canceled)

26. (Canceled)

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Canceled)

31. (Canceled)

32. (Canceled)

33. (Canceled)

Application No. PCT/US15/54295
Attorney Docket No.: 113301.68686WO
Article 34 Amended Claims

34. (Canceled)

35. (Canceled)

36. (Canceled)

37. (Canceled)

38. (Canceled)

39. (Canceled)

40. (Canceled)

41. (Canceled)

42. (Canceled)

43. (Canceled)

44. (Canceled)

45. (Canceled)

46. (Currently Amended) [[A]] ~~The nanoparticle~~ lyophilized composition of
claim 1 comprising nanoparticles wherein each of the nanoparticle complexes comprises:

a. a carrier protein,

b. between about 400 to about 800 antibodies having an Fc portion and an antigen-
binding portion, and

c. ~~optionally~~ at least one therapeutic agent that is not paclitaxel,

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said nanoparticle complexes being lyophilized, and wherein upon reconstitution with an aqueous solution antigen-binding portions of the antibodies are remain arranged on a the outer surface of the nanoparticle complexes such that the antigen-binding portions of the antibodies ~~γ is~~ are directed outward from that the outer surface and wherein the nanoparticle complexes are remain capable of binding to a predetermined epitope the antigen in vivo.

47. (Currently Amended) ~~[[A]] nanoparticle~~ The lyophilized composition of claim 1 comprising nanoparticles wherein each of the nanoparticle complexes comprises:

- a. a carrier protein that is not albumin,
- b. between about 400 to about 800 antibodies having an Fc portion and an antigen-binding portion, and
- c. ~~optionally~~ at least one therapeutic agent,

said nanoparticle complexes being lyophilized, and wherein upon reconstitution with an aqueous solution antigen-binding portions of the antibodies are remain arranged on a the outer surface of the nanoparticle complexes such that the antigen-binding portions of the antibodies are γ is-directed outward from that the outer surface and wherein the nanoparticle complexes are remain capable of binding to a predetermined epitope the antigen in vivo.

48. (Canceled)

49. (Canceled)

50. (Canceled)

51. (Canceled)

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Article 34 Amended Claims

- 52. (Canceled)
- 53. (Canceled)
- 54. (Canceled)
- 55. (Canceled)
- 56. (Canceled)
- 57. (Canceled)
- 58. (Canceled)
- 59. (Canceled)
- 60. (Canceled)
- 61. (Canceled)
- 62. (Canceled)
- 63. (Canceled)
- 64. (Canceled)
- 65. (Canceled)
- 66. (Canceled)
- 67. (Canceled)
- 68. (Canceled)

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Article 34 Amended Claims

69. (Canceled)

70. (Canceled)

71. (Canceled)

72. (Canceled)

73. (Canceled)

74. (Canceled).

75. (Canceled)

76. (Canceled)

77. (Canceled)

78. (Canceled)

79. (Canceled)

80. (Canceled)

81. (Canceled).

82. (New) The lyophilized composition of claim 12, wherein the albumin is human serum albumin.

83. (New) The lyophilized composition of claim 1, wherein each of the nanoparticle complexes comprises,

a. albumin,

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b. between about 100 to about 1000 bevacizumab antibodies, each having a hydrophobic Fc portion and an VEGF-binding portion, wherein the VEGF-binding portion is arranged on the outside outer surface of the complexes and

c. paclitaxel,

said nanoparticle complexes being lyophilized, and wherein upon reconstitution with an aqueous solution, the VEGF-binding portions of the antibodies remain arranged on the outside outer surface of the nanoparticle complexes, and remain capable of binding to VEGF *in vivo* and the Fc portions are associated with said albumin; and further wherein said complexes have an average size from about 130nm to about 800nm.

SUBSTITUTE SHEET

1. A lyophilized composition comprising nanoparticle complexes having an outer surface, wherein each of the nanoparticle complexes comprises

a. a carrier protein,

b. between about 100 to about 1000 antibodies having an Fc portion and an antigen-binding portion, and

c. at least one therapeutic agent,

said nanoparticle complexes being lyophilized, and wherein upon reconstitution with an aqueous solution, antigen-binding portions of the antibodies remain arranged on the outer surface of the nanoparticle complexes, and further wherein the nanoparticle complexes remain capable of binding to the antigen *in vivo*.

2. The lyophilized nanoparticle composition of claim 1, wherein each of the nanoparticle complexes comprises between about 400 and about 800 antibodies.

3. (Canceled)

4. (Canceled).

5. (Canceled)

6. (Canceled)

7. (Canceled)

8. The lyophilized composition of any one of the above claims, wherein the at least one therapeutic agent is located inside the nanoparticle, arranged on the outer surface of the nanoparticle complexes, or both.

9. The lyophilized composition of any one of the above claims, wherein the antibodies are selected from the group consisting of ado-trastuzumab emtansine, alemtuzumab, bevacizumab, cetuximab, denosumab, dinutuximab, ipilimumab, nivolumab,

SUBSTITUTE SHEET

obinutuzumab, ofatumumab, panitumumab, pembrolizumab, pertuzumab, rituximab, and trastuzumab

10. The lyophilized composition of any one of the above claims, wherein the at least one therapeutic agent is selected from the group consisting of abiraterone, bendamustine, bortezomib, carboplatin, cabazitaxel, cisplatin, chlorambucil, dasatinib, docetaxel, doxorubicin, epirubicin, erlotinib, ctoposide, everolimus, gefitinib, idarubicin, imatinib, hydroxyurea, imatinib, lapatinib, leuprorelin, melphalan, methotrexate, mitoxantrone, nedaplatin, nilotinib, oxaliplatin, paclitaxel, pazopanib, pemetrexed, picoplatin, romidepsin, satraplatin, sorafenib, vemurafenib, sunitinib, teniposide, triplatin, vinblastine, vinorelbine, vincristine, and cyclophosphamide.

11. The lyophilized composition of any one of the above claims, wherein the carrier protein is selected from the group consisting of albumin gelatin, elastin, gliadin, legumin, zein, a soy protein, a milk protein, and a whey protein.

12. The lyophilized composition of any one of the above claims wherein the carrier protein is albumin.

13. The lyophilized composition any one of the above claims, wherein the antibodies arrange into a substantially single layer of antibodies on all or part of the outer surface of the nanoparticle complexes.

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. (Canceled)

18. (Canceled)

19. (Canceled)

SUBSTITUTE SHEET

20. (Canceled)

21. (Canceled)

22. A lyophilized composition of claim 1, wherein each of the nanoparticle complexes comprises:

- a. an albumin-bound paclitaxel core and
- b. an amount of bevacizumab arranged on the outer surface of the albumin-bound paclitaxel core such that the binding portion of the antibody is directed outward from the outer surface, wherein the antibodies retain their association with the outer surface of the nanoparticle upon reconstitution with an aqueous solution, and the reconstituted nanoparticle complexes are capable of binding to VEGF *in vivo*.

23. The lyophilized composition of claim 21, wherein the weight ratio of albumin-bound paclitaxel to bevacizumab is between about 5: 1 to about 1: 1.

24. The lyophilized composition of claim 23, wherein the weight ratio of albumin-bound paclitaxel to bevacizumab is about 10:4.

25. (Canceled)

26. (Canceled)

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Canceled)

31. (Canceled)

32. (Canceled)

33. (Canceled)

34. (Canceled)

SUBSTITUTE SHEET

35. (Canceled)

36. (Canceled)

37. (Canceled)

38. (Canceled)

39. (Canceled)

40. (Canceled)

41. (Canceled)

42. (Canceled)

43. (Canceled)

44. (Canceled)

45. (Canceled)

46. The lyophilized composition of claim 1 wherein each of the nanoparticle complexes comprises:

- a. a carrier protein,
- b. between about 400 to about 800 antibodies having an Fc portion and an antigen-binding portion, and
- c. at least one therapeutic agent that is not paclitaxel,

said nanoparticle complexes being lyophilized, and wherein upon reconstitution with an aqueous solution antigen-binding portions of the antibodies remain arranged on the outer surface of the nanoparticle complexes such that the antigen-binding portions of the antibodies are directed outward from the outer surface and wherein the nanoparticle complexes remain capable of binding to the antigen *in vivo*.

SUBSTITUTE SHEET

47. The lyophilized composition of claim 1 wherein each of the nanoparticle complexes comprises:

- a. a carrier protein that is not albumin,
 - b. between about 400 to about 800 antibodies having an Fc portion and an antigen-binding portion, and
 - c. at least one therapeutic agent,
- said nanoparticle complexes being lyophilized, and wherein upon reconstitution with an aqueous solution antigen-binding portions of the antibodies remain arranged on the outer surface of the nanoparticle complexes such that the antigen-binding portions of the antibodies are directed outward from the outer surface and wherein the nanoparticle complexes remain capable of binding to the antigen *in vivo*.

- 48. (Canceled)
- 49. (Canceled)
- 50. (Canceled)
- 51. (Canceled)
- 52. (Canceled)
- 53. (Canceled)
- 54. (Canceled)
- 55. (Canceled)
- 56. (Canceled)
- 57. (Canceled)
- 58. (Canceled)
- 59. (Canceled)
- 60. (Canceled)

SUBSTITUTE SHEET

61. (Canceled)

62. (Canceled)

63. (Canceled)

64. (Canceled)

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68. (Canceled)

69. (Canceled)

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72. (Canceled)

73. (Canceled)

74. (Canceled).

75. (Canceled)

76. (Canceled)

77. (Canceled)

78. (Canceled)

79. (Canceled)

80. (Canceled)

81. (Canceled).

82. (New) The lyophilized composition of claim 12, wherein the albumin is

human serum albumin.

SUBSTITUTE SHEET

83. (New) The lyophilized composition of claim 1, wherein each of the nanoparticle complexes comprises,

- a. albumin,
- b. between about 100 to about 1000 bevacizumab antibodies, each having a hydrophobic Fc portion and an VEGF-binding portion, wherein the VEGF-binding portion is arranged on the outside outer surface of the complexes and
- c. paclitaxel,

said nanoparticle complexes being lyophilized, and wherein upon reconstitution with an aqueous solution, VEGF-binding portions of the antibodies remain arranged on the outside outer surface of the nanoparticle complexes, and remain capable of binding to VEGF in vivo and the Fc portions are associated with said albumin, and further wherein said complexes have an average size from about 130nm to about 800nm.

IN THE EUROPEAN PATENT OFFICE

International Application of: MAYO FOUNDATION FOR MEDICAL EDUCATION
AND RESEARCH

International Application No.: PCT/US2015/054295

International Filing Date: 06 October 2015 (06.10.2015)

Title: CARRIER-ANTIBODY COMPOSITIONS AND METHODS
OF MAKING AND USING THE SAME

European Patent Office
P.B. 5818 Panentlaan 2
NL-2280 HV Rijswijk
Switzerland

VIA FACSIMILE 011 31 70 340 3016

Attn: OSTWINKEL, Nathalie
Attn: COVONE-VAN HEES, M.

**LETTER RE ARTICLE 34 CLAIM AMENDMENTS AND
RESPONSE TO WRITTEN OPINION**

Dear Sirs:

In response to the Written Opinion dated January 25, 2016, Applicant submits the following remarks and amendments to the claims under Article 34. Attached are Substitute Sheets pages 73 to 79 to replace claims pages 73-83 of the application as filed.

Claims 1, 2, 8-13, 22-24, 46, 47, 82 and 83 are pending.

The present submission is made in association with a PCT Chapter II Demand.

Application No.: PCT/US2015/054295
 Attorney Docket No.: 113301.68686WO

Claims Amendments

Applicants have amended the claims for consistency and to more clearly define the invention. As amended all the claims require a chemotherapeutic.

Exemplary support for the amendments to independent claims 1, 46, and 47 and for new claims 82 and 83 is set forth in the table below:

Amended claim	Exemplary Support in Specification
Claim 1 (Amended)	
A lyophilized composition comprising nanoparticle <u>complexes having an outer surface</u> , wherein each of the nanoparticle <u>complexes</u> comprises	Original Claim 1 and paragraph [0155]
a. a carrier protein,	Unchanged from original claim 1
b. between about 100 to about 1000 antibodies <u>having an Fc portion and an antigen-binding portion</u> , and	Paragraph [0127]
c. at least one chemotherapeutic agent,	Original claim 10, paragraph [0033]
said nanoparticle complexes being lyophilized, and	Paragraph [0042]
wherein upon reconstitution with an aqueous solution, the antigen-binding portion of the antibodies <u>remain arranged on the outer surface</u> of the nanoparticle complexes, and further wherein the nanoparticle <u>complexes remain</u> capable of binding to <u>the antigen in vivo</u> .	Paragraphs [0015] and [0023] and [0106]
Claim 46	
<u>The lyophilized composition of claim 1</u> wherein each of the nanoparticle <u>complexes</u> comprises:	Original Claim 46 and paragraph [0155]
a. a carrier protein,	Unchanged from original

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	claim 46
b. between about 400 to about 800 antibodies <u>having an Fc portion and an antigen-binding portion</u> , and	Paragraph [0127]
c. at least one therapeutic agent that is not paclitaxel,	Deleted "optionally" from, "optionally at least one therapeutic agent that is not paclitaxel."
<u>said nanoparticle complexes being lyophilized, and wherein upon reconstitution with an aqueous solution antigen-binding portions of the antibodies remain arranged on the outer surface of the nanoparticle complexes such that the antigen-binding portions of the antibodies are directed outward from the outer surface and wherein the nanoparticle complexes remain capable of binding to the antigen in vivo.</u>	
Claim 47 (Amended)	
<u>The lyophilized composition of claim 1 wherein each of the nanoparticle complexes comprises:</u>	Original Claim 47 and paragraph [0155]
a. a carrier protein that is not albumin	Unchanged from original claim 47
b. between about 400 to about 800 antibodies <u>having an Fc portion and an antigen-binding portion</u> , and	Paragraph [0127]
c. at least one therapeutic agent,	Deleted "optionally" from, "optionally at least one therapeutic agent."
<u>said nanoparticle complexes being lyophilized, and wherein upon reconstitution with an aqueous solution antigen-binding portions of the antibodies remain arranged on the outer surface of the nanoparticle complexes such that the antigen-binding portions of the</u>	Paragraphs [0015] and [0023] and [0106]

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antibodies are directed outward from the outer surface and wherein the nanoparticle complexes remain capable of binding to the antigen <i>in vivo</i> .	
Claim 82 New)	
The lyophilized composition of claim 12 wherein the albumin is human serum albumin.	Paragraph [0036]
Claim 83 (New)	
The lyophilized composition of claim 1, wherein each of the nanoparticle complexes comprises,	
a. albumin,	Paragraphs [0025],
b. between about 100 to about 1000 bevacizumab antibodies, each having a hydrophobic Fc portion and an VEGF-binding portion, wherein the VEGF-binding portion is arranged on the outside outer surface of the complexes and	
c. paclitaxel,	
said nanoparticle complexes being lyophilized, and wherein upon reconstitution with an aqueous solution, the VEGF-binding portion of the antibodies remain arranged on the outside outer surface of the nanoparticle complexes, and remain capable of binding to VEGF in vivo and the Fc portions are associated with said albumin; and	
further wherein said complexes have an average size from about 130nm to about 800nm.	Original claim 5 and Paragraph [0140]

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Applicants have amended claims 2, 8, 9, 10, 11, 12, 13, 22, 23 and 24 to refer to the lyophilized composition to be consistent with claims 1, 46 and 47. Support for this amendment is found e.g. paragraph [0155].

Applicants have amended claims 22 to depend on claim 1 as suggested in the Opinion and deleted reference to particle size. Claims 46 and 47 are also amended to depend on claim 1.

Applicants have added claim 82 to specify the albumin is human serum albumin. Support for this claim is found, e.g., in paragraph [0036]

Applicants have added claim 83 to encompass an embodiment of this invention. Support for this claim is found, e.g., in paragraphs [0025] and [0140].

Applicants have canceled claims 3-7, 14-21, 25-46, and 48-81 without prejudice. Applicant reserves the right to pursue the canceled claims during examination in each of the national phase countries.

A marked up version of the claims showing the amendments in each claim is attached (Appendix A). Added text in the amended claims is underlined; deleted text is stricken through.

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Attorney Docket No.: 113301.68686WO

REMARKS

Reconsideration of the objections raised in the Written Opinion is requested based on the following remarks.

The Claimed Invention

The currently claimed invention is directed to stable lyophilized protein-protein nanoparticle "complexes".¹ These complexes are individual particles, each particle containing an antibody, e.g., bevacizumab, rituximab or trastuzumab, a carrier protein, e.g., albumin, and the chemotherapeutic agent, e.g. paclitaxel, and each particle having a defined size. These complexes are in contrast to a formulation where the components are merely intermixed and do not comprise a unitary particle (i.e., an individual particle comprising multiple components). And just as the complexes are in contrast to a formulation where the components are merely intermixed, the lyophilized complexes are in contrast to the formulation where lyophilized components are merely intermixed.

Further, the complexes have a "structural motif" -an interaction between the carrier protein, e.g., albumin, and the antibody such that antigen-binding portions of the antibodies are arranged on the outside of the complex, and antibody-binding domains of the antibodies remain capable of binding to the target antigen *in vivo*. The structural motif thus provides biological activity and directional capacity to the complexes. In particular, the currently claimed invention is directed to the discovery that the lyophilized complexes retain biological efficacy and the ability to bind to the target antigen upon reconstitution. Such stability allows

¹ The carrier protein, e.g., albumin is the first protein whereas the antibody, e.g., the bevacizumab monoclonal antibody, is the second protein. Claim 1 recites that the reconstituted complexes have antigen binding portions of the antibodies arranged on the outer surface and the complexes retain the ability to bind the target antigen upon reconstitution, as demonstrated in the Examples and Figures, thereby indicating that the complexes are stable.

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for regeneration of an injectable composition with pharmacological properties substantially similar to those of the freshly-made composition (non-lyophilized).

In particular, the lyophilized composition retains its antibody-specific targeting capability upon reconstitution, which evidences that the binding portion of the antibody is retained on the surface of the nanoparticles. Retention of antibody binding specificity of the antibody in the complex after reconstitution is a recited element of the claimed composition, and it provides directional guidance by targeting the nanoparticle complex to target antigen, e.g., complexes having bevacizumab as the antibody retain the ability of the antibody to bind VEGF, which is overexpressed in tumors that are treatable with bevacizumab. While the art has described protein-protein complexes previously, including those that are powders, the art did not disclose solid lyophilized compositions. See, for example, WO 2012/154861 (submitted herewith) and WO 2014/055415 (D1 cited in the Written Opinion).

Lyophilization is well known to adversely impact protein structures even when the protein is a homogenous composition of a single protein. See, for example, Shan-Yang Lin, AIMS Biophysics, 2(4): 695-723 (2015)²; Paul Matejtschuk, Cryopreservation and Freeze

² This document recites the following:

"Generally, most peptides or globular proteins are marginally stable under physiological conditions because the free energy released when the protein folds into its native conformation is relatively small (approximately -5--10 kcal/mol-l). However, protein molecules are both structurally complex and chemically reactive, which results in their susceptibility to physical and chemical instability. When subjected to various environmental stresses, such as temperature, storage time, agitation, freeze-thaw cycles, and lyophilization, peptides or protein drugs can become chemically and/or physically unstable. Chemical instability refers to the formation or destruction of covalent bonds within a peptide or protein molecule. These changes alter the protein's primary structure and affect its higher-level structure. The common causes of chemical instability are hydrolysis, deamidation, isomerization, racemization, oxidation, disulfide exchange, dimerization, α -elimination, and Maillard reaction and those of physical instabilities include denaturation, aggregation, precipitation, or adsorption to surfaces.

Unfortunately, the lyophilization process generates both freezing and drying stresses, which can denature proteins to various degrees. An optimal added excipient may preserve the native structure and the biological activity of the protein drug. Lee and Lin directly studied conformational changes in excipient-free salmon calcitonin ("sCT") that were induced by lyophilization. Obviously, the second-derivative IR spectrum of the (Continued...)

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Drying Protocols, Volume 368 of the series Methods in Molecular Biology, pp 59-72 (enclosed). The art recognizes that lyophilization results in significant stress upon a protein. Denaturation of a protein can occur due to numerous factors, including high salt concentrations, and can result in irreversible protein aggregation. Matejtschuk, page 60. Further, "a multimeric protein with multiple domains ... will pose a far more demanding challenge to achieve successful lyophilization" than a single-chain protein. Matejtschuk, page 60.

Significantly, the claimed invention does not deal with a single protein structure, such as the antibody alone or the albumin alone, but rather with protein-protein complexes that have a structural interaction between the first and second proteins before lyophilization that is maintained upon reconstitution after lyophilization. Nothing in the prior art regarding such nanoparticle complexes having protein-protein complexation suggests that the interactions between the proteins that result in the structural interaction and biological activity of the complexes can withstand the environmental stresses associated with lyophilization.

Indeed, the lyophilized complexes of the current claims are counter-intuitive. First, human serum albumin does not complex with natural (endogenously produced) antibodies. This suggests that any complexation between antibodies and human serum albumin is likely to be weak, as the differences between natural antibodies and monoclonal antibodies are

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intentionally quite minimal.³ The weak binding affinity to the albumin is evidenced by the fact that these complexes are not stable in plasma or when stored overnight.⁴

Second, the structural motif of the claimed composition requires that the antibody binding portions of the complexes must retain antigen-specific binding after reconstitution and still retain complexation with the carrier protein, e.g., albumin. The cited art does not provide any examples of lyophilized protein-protein complexes. Indeed, one skilled in the art could readily contemplate that lyophilization would lead to an aggregation of the particles, without the recited characteristics. It is also possible that lyophilization would result in the binding portion(s) of the antibody being engulfed by the albumin. It is also possible that the antibody would become completely dissociated from the albumin, thereby eliminating the directional capacity imparted to the complexes. In any of these scenarios, such structural change would render the albumin particle incapable of binding to the target antigen. Retention of the binding specificity of the reconstituted complexes is necessary, as the complexes contain the chemotherapeutic agent, which is guided to the antigen by the binding portion of antibody. Given the likely weak nature of the binding, retention of the structural motif of the complexes during lyophilization is, at best, uncertain.

The lyophilized compositions of the claims include the following claim elements (among others):

- nanoparticle complexes comprising:
 - a carrier protein

³ Bevacizumab is a humanized monoclonal antibody. See, e.g., Avastin (bevacizumab) Prescribing Information.

⁴ See Applicants' specification Table 3, page 56; and WO 2014/055415 page 27, line 30 to page 28, line 4.

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- antibodies and
- at least one chemotherapeutic agent;
- said nanoparticle complexes being lyophilized;
- wherein upon reconstitution with an aqueous solution:
 - antigen-binding portions of the antibodies remain arranged on the outer surface of the complexes (retaining the structural motif between the proteins); and the complexes remain capable of binding to the target antigen *in vivo* (retaining biological and therapeutic activity).

A composition comprising such lyophilized complexes is a recited element of the claims, as is the recitation that the lyophilized composition retains its structural motif upon reconstitution, while also retaining its biological and therapeutic properties.

Novelty

The Opinion cites WO 2014/055415 (D1) for disclosing the production of nanoparticles comprising a complex of Abraxane®/bevacizumab (ex. 1; pg. 45 line 16-pg. 47 line 4; ex. 11), Abraxane/cisplatin (ex. 5), Abraxane/trastuzumab or rituxan (ex. 6, 12, 13) of sizes between 100 to 900 nm (pg. 3 lines 26-29). The Opinion states that the stability *in vitro* and in serum has been tested (ex. 4, 7, 14, 17). However, Applicants submit that D1 does not disclose each and every limitation in the current claims and therefore does not anticipate the invention as claimed.

As noted above, the current claims are directed to a lyophilized composition of a protein-protein nanoparticle complex where the first protein is a carrier protein, e.g., albumin, and the second protein is an antibody, e.g., bevacizumab. The claims have been amended to stress that the composition comprises complexes having surface antibody integration, such

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Attorney Docket No.: 113301.68686WO

that binding portions are exposed on the surface both before lyophilization and upon reconstitution after lyophilization, as evidenced by antigen binding capacity.

D1 fails to disclose lyophilized complexes. D1 Example 1, page 45, line 16 to page 47, line 4 and Example 11 cited in the Opinion, only disclose bevacizumab (Avastin®) with a lyophilized starting material (i.e. lyophilized taxane and human serum albumin (e.g., Abraxane®)). Example 1 states, “they [Avastin® vials] are not frozen or shaken.” D1 does not disclose the mixture of Abraxane® and Avastin® is lyophilized. D1 therefore does not anticipate the lyophilized composition of the present claims.

Applicants request the rejection be withdrawn.

Inventive Step

The Opinion acknowledges that D1 does not teach a lyophilized nanoparticle composition but cites WO 2014/123612 (D3) for suggesting the use of Abraxane® (not in a complex with bevacizumab) in either dry formulation or suspended (para. 198). The Opinion states that a skilled person, looking for alternative formulations, would consider lyophilization. For at least the reasons set forth above, one of skill in the art would not consider lyophilization as an alternate formulation — the skilled artisan would not expect complexes of antibodies, a protein, e.g. albumin, and a chemotherapeutic to survive the rigors of lyophilization and retain their antigen binding activity. The claimed invention does not deal with a single protein structure, such as, e.g., the antibody alone or albumin alone, but rather with protein-protein complexes that have a structural interaction between the first and second proteins before lyophilization that is maintained upon reconstitution after lyophilization. Nothing in the combination of D3 with D1 suggests that the interactions between the proteins that result in the structural interaction and biological activity of the

Application No.: PCT/US2015/054295
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complexes can withstand the environmental stresses associated with lyophilization. At least
for the foregoing reasons the claims all have inventive step as well as novelty.

Applicants request the rejection be withdrawn.

Respectfully submitted,

/Mary Anne Schofield/
Mary Anne Schofield, Reg. No. 36,669

Dated: August 8, 2016

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 111393-0160	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2015/054295	International filing date (<i>day/month/year</i>) 6 October 2015 (06-10-2015)	(Earliest) Priority Date (<i>day/month/year</i>) 6 October 2014 (06-10-2014)
Applicant MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out 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))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1b

- ☒ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention

b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/054295

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/22 B82Y5/00 C07K16/28 C07K16/32 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K B82Y

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/055415 A1 (MAYO FOUNDATION [US]) 10 April 2014 (2014-04-10) examples page 46, line 16 - page 47, line 4 page 3, lines 26-29 ----- -/--	1-81



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 January 2016

Date of mailing of the international search report

25/01/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Covone-van Hees, M

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2015/054295

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Mayo Clinic: "Paclitaxel Albumin-Stabilized Nanoparticle Formulation and Bevacizumab in Treating Patients With Stage IV Melanoma That Cannot Be Removed by Surgery - Full Text View - ClinicalTrials.gov", 19 December 2013 (2013-12-19), pages 1-4, XP055238879, Retrieved from the Internet: URL: https://clinicaltrials.gov/ct2/show/NC_T02020707?term=targeted+nanoparticle+therapy+for+advanced+melanoma&rank=1 [retrieved on 2016-01-06] the whole document	1-81
A	WO 2014/123612 A1 (ABRAXIS BIOSCIENCE LLC [US]) 14 August 2014 (2014-08-14) examples 5,6	1-81
A	US 2010/112077 A1 (DESAI NEIL P [US] ET AL) 6 May 2010 (2010-05-06) examples	1-81

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/054295

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014055415 A1	10-04-2014	AU 2013327638 A1 EP 2903610 A1 US 2015246122 A1 WO 2014055415 A1	30-04-2015 12-08-2015 03-09-2015 10-04-2014
WO 2014123612 A1	14-08-2014	CA 2900668 A1 CN 105120859 A EP 2953622 A1 IL 240388 A KR 20150119177 A WO 2014123612 A1	14-08-2014 02-12-2015 16-12-2015 24-09-2015 23-10-2015 14-08-2014
US 2010112077 A1	06-05-2010	NONE	

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/US2015/054295	International filing date (day/month/year) 06.10.2015	Priority date (day/month/year) 06.10.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07K16/22 B82Y5/00 C07K16/28 C07K16/32 A61P35/00		
Applicant MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH		

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Covone-van Hees, M Telephone No. +31 70 340-0
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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. 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. 1, 46, 47(all partially)

because:

☒ the said international application, or the said claims Nos. 1, 46, 47(all partially) relate to the following subject matter which does not require an international search (*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 (*specify*):

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

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13~~ter~~.1(a) or (b).

☒ See Supplemental Box for further details

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>2-45(completely); 1(partially)</u>
	No: Claims	<u>48-81(completely); 46, 47(partially)</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>2-45, 48-81(completely); 1, 46, 47(partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>2-45, 48-81(completely); 1, 46, 47(partially)</u>
	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

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 1,46 and 47 relate to a nanoparticle composition comprising a carrier protein, antibodies and optionally, a therapeutic agent. The expression "optionally" is not limiting the scope of the claim and therefore the feature "therapeutic agent" has to be disregarded in the assessment of novelty and inventive step. However, the therapeutic agent is an essential feature of the invention, since the purpose of the invention is the targeted delivery of said therapeutic agent. In the absence of this feature i.e. the therapeutic agent, the claims cover subject-matter which is neither supported nor disclosed in the application. In addition, this feature is essential to solve the problem posed by the application, namely the provision of means for the targeted deliver of therapeutic agents.

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1,46,47 (PCT Guidelines 9.19 and 9.23).

The search of claims 1,46,47 was restricted to nanoparticles comprising the therapeutic agent.

The search for the related methods have been also restricted accordingly.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Present application discloses the production of nanoparticles composition comprising a complex formed by albumin-paclitaxel (Abraxane) and bevacizumab or rituximab or trastuzumab or cisplatin to deliver the paclitaxel to the tumour site. The elements of the nanoparticles are bound by non-covalent bonds. By disaggregation, the paclitaxel remains bound to the antibody.

- 1 Claims 38-46,71-81 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. 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.

2 Novelty (Art.33(2) PCT)

- 2.1 WO2014055415 (**D1**) discloses the production of nanoparticles comprising a complex of Abraxane/bevacizumb (ex.1; pg.45 l.16-pg.47 l.4; ex.11), Abraxane/cisplatin (ex.5), Abraxane/ trastuzumab or rituxan (ex.6,12,13) of sizes between 100 to 900 nm (pg.3 l.26-29). Stability in vitro and in serum has been tested (ex.4,7,14,17). The complex Abraxane/bevacizumab has been used to inhibit cancer cell proliferation in vitro and in vivo of melanoma (ex. 10,19). D1 anticipates the subject-matter of claims 46-81 which is therefore not novel (Art.33(2) PCT).
- 2.2 The clinical trial (**D2**) shows the treatment of melanoma with abraxane/ bevacizumab complex. However this document does not give any technical details on the nanoparticle composition and does not detail the process to produce said nanoparticles. This document is therefore not detrimental to the novelty of claims 1-81.

3 Inventive Step (Art.33(3) PCT)

- 3.1 D1 is considered to represent the most relevant state of the art, from which the subject-matter of claim 1 differs in that the nanoparticle composition is lyophilized. The effect of the difference is a composition which is easy to preserve and transport.
- 3.2 The problem to be solved by the present invention may therefore be regarded as the provision of an alternative nanoparticle composition.
- 3.3 The solution proposed in claim 1 of the present application cannot be considered to involve an inventive step (Article 33(3) PCT). The process of lyophilization is a standard process in the medical field to improve preservation and transportation of medicaments. WO2014123612 (**D3**) for example suggest the use of Abraxane (not in a complex with bevacizumab) in either dry formulation or suspended (para.198), suitable for parenteral administration (para.220). The skilled person therefore, looking for alternative formulations, would consider the lyophilization, without inventive skills and with reasonable expectation of success.
- 3.4 The same arguments cited for claim 1 are valid, mutatis mutandis, for claims 21 and 22 of the application.
- 3.5 Claims 2-20,23-45 are also not inventive (Art.33(3) PCT), since they are mainly standard methods and products in this technical field, which do not appear to lead to any surprising effects or advantages.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

Certain observations on the international application

- 4 Claims 22 and 23 comprise all the features of claim 1 and should be redrafted as dependent from it.
- 5 Although claims 65 and 68 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.
- 6 It is clear from the examples that the therapeutic agent is essential to the definition of the invention. Since independent claims 1, 46, 47 do not contain this feature they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.