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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
PRELIMINARY REPORT ON PATENTABILITY
(CHAPTER I OF THE PATENT COOPERATION
TREATY)

(PCT Rule 44bis.1(c))

To:

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Date of mailing (day/month/year)

02 November 2017 (02.11.2017)

Applicant's or agent's file reference

297/289PCT

IMPORTANT NOTICE

International application No.

PCT/US2016/028605

International filing date (day/month/year)

21 April 2016 (21.04.2016)

Priority date (day/month/year)

21 April 2015 (21.04.2015)

Applicant

NORTH CAROLINA STATE UNIVERSITY

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

DATE RECEIVED: 11/2/17

DOCKET DATES: 11/21/17 - NP

ASSIGNED ATTY: AAT/ALO

FILE NO. 297/289 PCT

DOCKETED BY: REL DATE: 11/3/17

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 297/289PCT	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2016/028605	International filing date (<i>day/month/year</i>) 21 April 2016 (21.04.2016)	Priority date (<i>day/month/year</i>) 21 April 2015 (21.04.2015)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NORTH CAROLINA STATE UNIVERSITY		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	This REPORT consists of a total of 6 sheets, including this cover sheet.																								
In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																									
3.	This report contains indications relating to the following items: <table style="width: 100%;"> <tr> <td style="width: 5%; text-align: center;">☒</td> <td style="width: 25%;">Box No. I</td> <td style="width: 70%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	☒	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
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☐	Box No. VIII	Certain observations on the international application																							
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 24 October 2017 (24.10.2017) Authorized officer Lingfei Bai e-mail: pct.team2@wipo.int
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: Arles A. Taylor, Jr.
.Jenkins, Wilson, Taylor & Hunt, P.A.
Suite 1200, University Tower
3100 Tower Boulevard
Durham, NC 27707
United States of America

Date of mailing
(day/month/year)

15 JUL 2016

Applicant's or agent's file reference
297/289 PCT

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US16/28605

International filing date (day/month/year)

21 April 2016 (21.04.2016)

Priority date (day/month/year)

21 April 2015 (21.04.2015)

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

IPC(8) - A61K 9/50, 9/51, 31/00, 31/04, 38/28, 38/43, 38/44 (2016.01)

CPC - A61K 9/50, 9/5031, 9/5036, 9/51, 31/00, 31/04, 31/417, 38/28, 38/43, 38/44, 38/443

Applicant

NORTH CAROLINA STATE UNIVERSITY

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 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/
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

11 June 2016 (11.06.2016)

Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US16/28605

Box No. 1 Basis of this 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 43*bis*.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 13*ter*.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 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US16/28605

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. 4-13 and 17-33

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 4-13 and 17-33 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 4-13 and 17-33 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ 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 said claims Nos. 4-13 and 17-33

☐ 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.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US16/28605

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

1. Statement

Novelty (N)	Claims	1-2, 3/1-2, 14-15, 16/14-15	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-2, 3/1-2, 14-15, 16/14-15	NO
Industrial applicability (IA)	Claims	1-2, 3/1-2, 14-15, 16/14-15	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-2, 3/1-2, 14 and 16/14 lack an inventive step under PCT Article 33(3) as being obvious over US 2008/0102114 A1 to Koritala, et al. (hereinafter "Koritala") in view of an article entitled "Hypoxia-responsive polymeric nanoparticles for tumor-targeted drug delivery" by Thambi, et al. (hereinafter "Thambi").

As per claim 1, Koritala discloses a composition (a composition; abstract; paragraph [0132]) comprising: (a) an amphiphilic polymeric material (a polymeric particle is a modified chitosan with a hydrophobic agent and a hydrophilic agent; paragraphs [0015], [0030], [0138]), wherein the amphiphilic polymeric material comprises a hydrophilic polymer (the polymeric particle with the hydrophilic polymer; paragraphs [0030], [0041], [0138]); (b) a diabetes treatment agent (a glucose-responsive insulin delivery system for treating diabetes, the particles able to release therapeutic agent; abstract; paragraphs [0029]-[0030]), optionally wherein the diabetes treatment agent is an insulin (insulin; abstract; paragraph [0132]) or a bioactive derivative thereof; and (c) a glucose oxidizing agent (a glucose oxidase; paragraph [0132]). Koritala does not disclose the polymer conjugated to a hypoxia-sensitive hydrophobic group, wherein said hypoxia-sensitive hydrophobic group comprises a hypoxia-sensitive moiety that can be reduced in the presence of a hypoxic environment to form a hydrophilic moiety. However, Thambi discloses the polymer conjugated to a hypoxia-sensitive hydrophobic group (a polymer particle with a hypoxia-sensitive hydrophobic 2-nitroimidazole group; abstract), wherein said hypoxia-sensitive hydrophobic group comprises a hypoxia-sensitive moiety (2-nitroimidazole group = NI; abstract) that can be reduced in the presence of a hypoxic environment to form a hydrophilic moiety (under hypoxic conditions NI is reduced to 2-aminoimidazole as NI is reduced to an amino group (form a hydrophilic moiety); abstract; page 1739, column 2, first paragraph; page 1740, column 1, first paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the composition, as previously disclosed by Koritala, in order to have provided the polymer conjugated to a hypoxia-sensitive hydrophobic group, wherein said hypoxia-sensitive hydrophobic group comprises a hypoxia-sensitive moiety that can be reduced in the presence of a hypoxic environment to form a hydrophilic moiety, as previously disclosed by Thambi, for the benefit of using hypoxia-sensitive material to selectively release a therapeutic agents (Thambi; page 1742, column 2, third paragraph).

As per claim 2, Koritala and Thambi, in combination, disclose the composition of claim 1, and Koritala further discloses wherein the hydrophilic polymer is biodegradable (the hydrophilic polymer is chitosan (biodegradable); paragraph [0015]).

As per claims 3/1-2, Koritala and Thambi, in combination, disclose the composition of claim 1 or claim 2, and Koritala further discloses wherein the hydrophilic polymer is a polyamino acid, such as polyglutamic acid (optional), a synthetic block copolymer (optional), or a polysaccharide (the hydrophilic polymer is a modified chitosan (a polysaccharide); paragraph [0015]), optionally wherein the hydrophilic polymer is a polysaccharide (the hydrophilic polymer is the modified chitosan (a polysaccharide); paragraph [0015]), further optionally wherein the polysaccharide is a glucosaminoglycan (optional).

As per claim 14, Koritala discloses a vesicle (a nano/microparticle (a vesicle) composition; abstract; paragraphs [0017], [0132]) comprising an amphiphilic polymeric material (a polymeric particle is a modified chitosan with a hydrophobic agent and a hydrophilic agent; paragraphs [0015], [0030], [0138]) comprising a hydrophilic polymer (the polymeric particle with the hydrophilic polymer; paragraphs [0030], [0041], [0138]), and further wherein (i) a diabetes treatment agent (a glucose-responsive insulin delivery system for treating diabetes, the particles able to release therapeutic agent; abstract; paragraphs [0029]-[0030]), optionally an insulin (insulin; abstract; paragraph [0132]) or a bioactive derivative thereof and (ii) a glucose oxidizing agent are contained within said vesicle (the particle comprising a glucose oxidase; paragraph [0132]). Koritala does not disclose the polymer conjugated to a hypoxia-sensitive hydrophobic group, wherein said hypoxia-sensitive hydrophobic group comprises a hypoxia-sensitive moiety that can be reduced in the presence of a hypoxic environment to form a hydrophilic moiety. However, Thambi discloses the polymer conjugated to a hypoxia-sensitive hydrophobic group (a polymer particle with a hypoxia-sensitive hydrophobic 2-nitroimidazole group; abstract), wherein said hypoxia-sensitive hydrophobic group comprises a hypoxia-sensitive moiety (2-nitroimidazole group = NI; abstract) that can be reduced in the presence of a hypoxic environment to form a hydrophilic moiety (under hypoxic conditions NI is reduced to 2-aminoimidazole as NI is reduced to an amino group (form a hydrophilic moiety); abstract; page 1739, column 2, first paragraph; page 1740, column 1, first paragraph). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the composition, as previously disclosed by Koritala, in order to have provided the polymer conjugated to a hypoxia-sensitive hydrophobic group, wherein said hypoxia-sensitive hydrophobic group comprises a hypoxia-sensitive moiety that can be reduced in the presence of a hypoxic environment to form a hydrophilic moiety, as previously disclosed by Thambi, for the benefit of using hypoxia-sensitive material to selectively release a therapeutic agents (Thambi; page 1742, column 2, third paragraph).

-Continued Within the Next Supplemental Box-

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US16/28605

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

-Continued from Box V: Citations and Explanations-

As per claim 16/14, Koritala and Thambi, in combination, disclose the vesicle of claim 14, but Koritala does not disclose wherein the hypoxia-sensitive moiety comprises a nitroimidazole. However, Thambi discloses wherein the hypoxia-sensitive moiety comprises a nitroimidazole (the hypoxia-sensitive hydrophobic group is 2-nitroimidazole group; abstract). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the composition, as previously disclosed by Koritala, in order to have provided wherein the hypoxia-sensitive moiety comprises a nitroimidazole, as previously disclosed by Thambi, for the benefit of using hypoxia-sensitive material to selectively release a therapeutic agents (Thambi; page 1742, column 2, third paragraph).

Claims 15 and 16/15 lack an inventive step under PCT Article 33(3) as being obvious over Koritala in view of Thambi, and further in view of WO 2007/075388 A2 to X-Cell Medical Incorporated (hereinafter "Baumbach").

As per claim 15, Koritala and Thambi, in combination, disclose the vesicle of claim 14, and Koritala further discloses wherein the hydrophilic polymer is a polyamino acid (optional), such as polyglutamic acid, a synthetic block copolymer (optional), or a polysaccharide (the hydrophilic polymer is the modified chitosan (a polysaccharide); paragraph [0015]), optionally wherein the hydrophilic polymer is hyaluronic acid (optional). Koritala does not disclose wherein the polysaccharide is such as a glucosaminoglycan. However, Baumbach discloses wherein the polysaccharide is such as a glucosaminoglycan (a microparticle produced from glycosaminoglycan polymers; page 4, lines 27-30). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the composition, as previously disclosed by Koritala, in order to have provided wherein the polysaccharide is such as a glucosaminoglycan, as previously disclosed by Baumbach, for the benefit of using a highly polar hydrophilic polymer.

As per claim 16/15, Koritala, Thambi, and Baumbach, in combination, disclose the vesicle of claim 15, but Koritala does not disclose wherein the hypoxia-sensitive moiety comprises a nitroimidazole. However, Thambi discloses wherein the hypoxia-sensitive moiety comprises a nitroimidazole (the hypoxia-sensitive hydrophobic group is 2-nitroimidazole group; abstract). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the composition, as previously disclosed by Koritala, in order to have provided wherein the hypoxia-sensitive moiety comprises a nitroimidazole, as previously disclosed by Thambi, for the benefit of using hypoxia-sensitive material to selectively release a therapeutic agents (Thambi; page 1742, column 2, third paragraph).

Claims 1-2, 3/1-2, 14-15, and 16/14-15 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.