

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2019/039893

International filing date (day/month/year)
28.06.2019

Priority date (day/month/year)
29.06.2018

International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/864 C12N9/64 A61K48/00

Applicant
RESEARCH INSTITUTE AT NATIONWIDE CHILDREN'S...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>2-10, 14, 20-22, 26-28, 32-34</u>
	No: Claims	<u>1, 11-13, 15-19, 23-25, 29-31, 35, 36</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-36</u>
Industrial applicability (IA)	Yes: Claims	<u>1-36</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re item V

Reference is made to the following documents:

- D1 US 2016/058890 A1 (BUJ BELLO ANA MARIA [FR] ET AL) 3 March 2016 (2016-03-03)
- D2 ROUDAUT CARINNE ET AL: "Restriction of Calpain3 Expression to the Skeletal Muscle Prevents Cardiac Toxicity and Corrects Pathology in a Murine Model of Limb-Girdle Muscular Dystrophy", 3 September 2013 (2013-09-03), CIRCULATION, VOL. 128, NR. 10, PAGE(S) 1094-1104, XP002794062, ISSN: 0009-7322(print)
- D3 DAN WANG ET AL: "The potential of adeno-associated viral vectors for gene delivery to muscle tissue", EXPERT OPINION ON DRUG DELIVERY, vol. 11, no. 3, 1 March 2014 (2014-03-01), pages 345-364, XP055232689, GB ISSN: 1742-5247, DOI: 10.1517/17425247.2014.871258
- D4 RICHARD I ET AL: "MUTATIONS IN THE PROTEOLYTIC ENZYME CALPAIN 3 CAUSE LIMB-GIRDLE MUSCULAR DYSTROPHY TYPE 2A", CELL, ELSEVIER, AMSTERDAM, NL, vol. 81, no. 1, 7 April 1995 (1995-04-07), pages 27-40, XP002010548, ISSN: 0092-8674, DOI: 10.1016/0092-8674(95)90368-2
- D5 WO 2017/180976 A1 (RES INST AT NATIONWIDE CHILDREN'S HOSPITAL [US]) 19 October 2017 (2017-10-19)
- D6 LOUISE R. RODINO-KLAPAC ET AL: "Micro-dystrophin and follistatin co-delivery restores muscle function in aged DMD model", HUMAN MOLECULAR GENETICS, vol. 22, no. 24, 1 January 2013 (2013-01-01), pages 4929-4937, XP055478537, gb ISSN: 0964-6906, DOI: 10.1093/hmg/ddt342
- D7 WO 2017/087395 A1 (RES INST AT NATIONWIDE CHILDREN'S HOSPITAL [US]) 26 May 2017 (2017-05-26)

If not stated otherwise, the passages already cited in the search report are referred to.

Novelty (Article 33(2) PCT)

Documents D1-D3 disclose a recombinant adeno-associated virus 9 (rAAV9) vector comprising a first ITR, a muscle-specific promoter, a nucleotide sequence encoding the calpain 3 protein and a second ITR. This recombinant AAV is used for treating Limb-Girdle Muscular Dystrophy 2A (LGMD2A) by administering the AAV by intravenous injection. Moreover, documents D1 and D3 indicates that the promoter is an MCK promoter. Furthermore, Document D2 teaches the use of AAV2-ITR sequences.

In view of D1-D3, **claims 1, 11-13, 15-19, 23-25, 29-31, 35 and 36** lack novelty.

Inventive step (Article 33(3) PCT)

The nucleotide sequence of the Calpain 3 coding cDNA is well known in the art (see for instance D4).

Moreover, the use the tMCK promoter to drive the expression of a transgene in the gene therapy of limb-girdle muscular dystrophy is trivial (see for instance D5).

Furthermore, the use of the serotype AAV rh74 for transducing muscular cells is also well known in the art as shown in D6 and D7.

Therefore, the embodiments set forth in claims 2-10, 14, 20-22, 26-28, 32-34 are merely some of the several straightforward possibilities which the skilled person would select, in accordance with circumstances, without requiring any inventive skill. Indeed, the features of said claims merely cover embodiments that fall into the range of the conventional for the skilled person (in particular in view of D4-D7) and none of said features appears to be associated with a technical effect that would go beyond the effect the skilled person would immediately associate with it.

Therefore, **claims 2-10, 14, 20-22, 26-28, 32-34** are not inventive (Article 33(3) PCT).

Further remarks

Claims 19-24 relate to a subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.

The attention of the Applicant is drawn to the fact that no unified criteria exist in PCT for assessment of patentable inventions. The EPO, for example, considers that claims 19-24 as far as they concern a method of treatment relate to a subject-matter considered to be covered by the provisions of Article 53(c) EPC. Consequently, in an eventual subsequent examination in regional phase, this invention would not be considered as being patentable.

Re item VIII

Claims 20-22, 26-28, 32-34 merely attempt to define the claimed subject-matter by the result to be achieved and only amounts to claiming the underlying technical problem which is not allowable. In that respect, **claims 20-22, 26-28, 32-34** do not satisfy the criteria of Article 6 PCT.