PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

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

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

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2018/073643	03.09.2018	01.09.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/85 A61K48/00 C12N5/079

Applicant
THE PROVOST, FELLOWS AND SCHOLARS OF THE...

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

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step 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 notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 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:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Kools, Patrick Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2018/073643

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 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:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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

1. Statement

Novelty (N)	Yes:	Claims	1-22, 24-57
	No:	Claims	23
Inventive step (IS)	Yes:	Claims	24-37
	No:	Claims	1-23, 38-57
Industrial applicability (IA)	Yes:	Claims	1-57
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

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

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

For the assessment of the present claims 38-47 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Reference is made to the following documents:

D1 ELDER G A ET AL: "Novel DNA binding proteins participate in the regulation of human neurofilament H gene expression", MOLECULAR BRAIN RESEARCH, ELSEVIER SCIENCE BV, AMSTERDAM, NL, vol. 15, no. 1-2, 1 September 1992 (1992-09-01), pages 85-98, XP024331773, ISSN: 0169-328X, DOI: 10.1016/0169-328X(92)90155-5

D2 MICHAEL L SCHWARTZ ET AL: "Brain-specific Enhancement of the Mouse Neurofilament Heavy Gene Promoter in vitro", J BIOL CHEM., vol. 269, no. 18, 1 January 1994 (1994-01-01), pages 13444-13450, XP055520822, ISSN: 1552-2466

D3 WO 2017/093566 A1 (UNIV PIERRE ET MARIE CURIE [FR]; INSERM (INSTITUT NAT DE LA SANTÉ ET) 8 June 2017 (2017-06-08)

D4 Chan Y Kim ET AL: "Gene expression profile of the adult human retinal ganglion cell layer", Molecular vision, 22 December 2006 (2006-12-22), pages 1640-8, XP055520855, US, Retrieved from the Internet: URL:http://www.molvis.org/molvis/v12/a188/v12a188-kim.pdf [retrieved on 2018-11-02] cited in the application

D5 KILLIAN S. HANLON ET AL: "A Novel Retinal Ganglion Cell Promoter for Utility in AAV Vectors", FRONTIERS IN NEUROSCIENCE, vol. 11, 21 September 2017 (2017-09-21), XP055520701, DOI: 10.3389/fnins.2017.00521

Novelty, Article 33(2) PCT

D1 discloses the identification of the human Neurofilament heavy gene promoter. Figure 1 provides a sequence which overlaps almost completely with present Seq ID No 1, it further has three nucleotide alterations. This sequence is considered as a functional variant of Seq ID No 1. In view of the extensive overlap and the almost identity in sequence it is believed to act as a nucleic acid molecule with promoter activity. It is considered to meet all requirements of claim 23. Novelty objections are raised accordingly.

D2 discloses the identification of the murine promoter and a 0.6kb DNA fragment which is used in other publications (see e.g. Zhang et al., 2000, cited in the ISR) as the Neurofilament heavy gene promoter. The exact sequences could be deduced from sequences in the database. However, this in depth analysis was not considered useful in the presence of D1.

Inventive step, Article 33(3) PCT

In the description the applicant discloses the method followed to identify the present promoter sequences as specific for retinal ganglion cells. Although the method followed is not a standard one, it appears that identifying a retinal Ganglion Cell specific promoter with high expression has been the end goal.

The description further discloses that one specific fragment (region A) is considered to have a very strong and specific in vivo expression. Adding region F reduced the expression level, further by using a spacer/stuffer mimicking the spacing in the original genomic sequence the expression was notably reduced (page 61, lines 25-31). Based on this observation it appears that the many proposed combinations do not necessarily result in a high and specific expression. At least data for this is lacking.

In view of the disclosure of the promoter sequence of the human Neurofilament H gene (and the functional fragment wording) it is considered that D1 would in an obvious manner teach the skilled person to use said sequence to make expression cassettes (claim 48), vectors comprising said cassette (claims 50-52) and cells comprising said nucleic acid, cassette or vector (claim 54). As a result objections are raised against said claims.

The set of claims in fact relate to two different subjects, the promoter per se (independent claim 23) and the medical use of a specified promoter (claim 1). In view of the differences it might be necessary to develop two different problem and solution approaches.

With respect to claims 23-34 (35-37 are unclear) the state of the art has already disclosed the neurofilament heavy gene promoter and the most effective parts of it (see D1). The difference over the promoter sequence in D1 is the presence of further regions next to region A.

The technical effect of this difference is somewhat obscure. As mentioned on page 61 lines 25-31 adding domain F and the combination with a stuffer element resulted in a reduction of promoter activity. There is also no technical data comparing the promoter region identified in D1 with the region A. As a result the problem to be solved is considered to be the provision of alternative Neurofilament H gene promoter sequences. The skilled person starting from D1 is provided with a basic promoter element in figure 1. He could and would by standard and routine experimentation identify further elements in the promoter region to establish all controlling elements. This would be part of a standard analysis of promoter regions. The presence of an inventive step is denied for such subject-matter.

With respect to claims 1-22 the analysis of inventiveness has to start with subject-matter involving a promoter in the treatment of ocular disease.

D3 discloses expression cassettes comprising a promoter which has activity in the Retinal Ganglion Cells. The difference with the subject-matter of claim 1 is the totally different nucleic acid sequence. the technical effect of said difference has not been determined. Therefore, the problem to be solved is defined as the provision of a further promoter expressed in RGC's.

The solution to said problem, part of the defined promoter of Neurofilament heavy chain is not considered inventive. The skilled person starting from D3 will look in the literature for possible other known genes having a relative high and specific expression in RGC's. In doing so he will identify D4 which discloses genes highly expressed in RGC's (see table 2). Having this knowledge, the identification of the promoters is a matter of routine for the skilled person. The present solution is a simple selection from said list in which the Neurofilament heavy gene takes the third position. This position is an incentive to identify the promoter of said gene as one of the first. Late positions in said list might have been seen as forming a counter-incentive, but not position three. Therefore, the subject-matter of independent claim 1 is seen a an obvious selection of a promoter from a list as an alternative to the promoter of D3.

In the dependent claims several combinations are made to yes or no inclusion of further conserved sequences. The effect of these inclusions is not clear. A reduction in expression has even been reported. As a result there are no features which could help in providing a positive inventive step assessment.

Industrial applicability, Article 33(4) PCT

The application finds its use in the treatment of ocular diseases.

Re Item VI

The cited PX document (D5) is the scientific disclosure of the present application. It was published shortly after the priority filing of the present application. Said document can only become relevant for novelty and/or inventive step when the claimed priority rights are not valid. It is presently assumed that said priority rights are validly claimed.

Re Item VIII

Certain observations on the international application

Claim 1 is considered to be directed to a medical use restricted nucleic acid comprising at least Seq ID No 1 or functional variant thereof. All other features mentioned are entirely optional. The term "functional variants thereof" can refer to any promoter sequence which can be useful in the treatment of ocular diseases. This interpretation will be used for all claims. As a result novelty objections could have been raised.However, simple amendments would overcome said objections.

Claim 1 mentions several optional sequences, a quick check revealed that said sequences are a mix from human and mouse sequences. Moreover Seq ID No 6 and 7 are respectively 5 and 13 nucleotides. It is also noted that for any region other then conserved regions A (Seq ID No 1), D (Seq ID No 2) and F (Seq ID No 3) there is no supportive data. Nor is there supportive data for many of the specific combinations of domains mentioned in the dependent claims.

Claim 23 uses the expressions "no more than three" and "no more than four" as a result certain long sequences in the prior art will be excluded from the scope of the claim. Moreover, it also means that none of these domains would also be OK.

Claims 35-37 refer to the "for use according to claim 33 or 34". However, said latter claims do not contain any use term. The claimed subject-matter is therefore unclear defined.