

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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

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

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

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2015/054836

International filing date (day/month/year)
09.10.2015

Priority date (day/month/year)
09.10.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/861 C07K14/47 A61K48/00

Applicant
GENVEC, INC.

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 notified 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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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 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/US2015/054836

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>1-15</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-15</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-15</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 V

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

1 Cited documents:

Reference is made to the following documents (D) cited in the International Search Report:

- D1 SHOU JIANYONG ET AL: "Robust generation of new hair cells in the mature mammalian inner ear by adenoviral expression of Hath1",
MOLECULAR AND CELLULAR NEUROSCIENCES, SAN DIEGO, US,
vol. 23, no. 2, 1 June 2003 (2003-06-01), pages 169-179, XP002291286,
ISSN: 1044-7431, DOI: 10.1016/S1044-7431(03)00066-6
- D2 PRAETORIUS MARK ET AL: "Adenovector-mediated hair cell regeneration is affected by promoter type.",
ACTA OTO-LARYNGOLOGICA FEB 2010,
vol. 130, no. 2, February 2010 (2010-02), pages 215-222, XP009187599,
ISSN: 1651-2251
- D3 C SCHLECKER ET AL: "Selective atonal gene delivery improves balance function in a mouse model of vestibular disease",
GENE THERAPY,
vol. 18, no. 9, 7 April 2011 (2011-04-07), pages 884-890, XP055234381,
GB
ISSN: 0969-7128, DOI: 10.1038/gt.2011.33
- D4 Keerthana Devarajan ET AL: "Adenovector-Mediated Gene Delivery to Human Umbilical Cord Mesenchymal Stromal Cells Induces Inner Ear Cell Phenotype",
Cellular reprogramming, 1 February 2013 (2013-02-01), pages 43-54,
XP055234384,
United States
DOI: 10.1089/cell.2011.0097
Retrieved from the Internet:
URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4298749/pdf/cell.2011.0097.pdf>
[retrieved on 2015-12-08]

D5 WO 2004/076626 A2 (GENVEC INC [US]; BROUGH DOUGLAS E [US]) 10
September 2004 (2004-09-10)

D6 US 5 851 806 A (KOVESDI IMRE [US] ET AL) 22 December 1998 (1998-12-22)cited
in the application

2 Novelty (Article 33(2) PCT) and inventive step (Article 33(3) PCT)

2.1 The present application pertains to an adenovirus vector of serotype 5 comprising deletions of the E1, E3 and E4 regions, further comprising an expression cassette in orientation opposite to the orientation of the E1 region and a transcriptionally inert spacer (TIS), whereby the expression cassette comprises a glial fibrillary acidic protein (GFAP) promoter, a nucleic acid encoding a human atonal homolog 1 (Hath-1) protein and an SV40 early polyadenylation sequence, and the TIS is located in the E4 region of the adenoviral genome between the E4 polyadenylation sequence and the E4 promoter.

The above described combination of features is not anticipated or suggested in any of the cited prior art documents, whose disclosure is summarized in the following (please refer to the passages mentioned in the International Search Report):

D1 (Shou et al) discloses a human adenovirus type 5 with deletion of the E1 and E3 regions and a cassette for expressing Hath-1 under control of the CMV promoter.

D2 (Praetorius et al) discloses that an adenoviral vector design including a tissue-selective promoter (GFAP) driving atoh1 (Hath1) with an E1/E3/E4 deleted vector is likely to have both safety and efficacy advantages.

Document D3 (Schlecker et al) discloses an adenovirus vector of serotype 28 carrying in its deleted E1 region a GFAP promoter-driven expression cassette for Atoh1 (Hath1) with SV40 polyadenylation signal. The orientation of the cassette is not apparent.

D4 (Devarajan et al) discloses adenovirus type 5 vectors deleted in E1, E3 and E4 and carrying a GFAP-Atoh1 cassette in the E1 region. The orientation of the expression cassette is unknown.

D5 provides a method of changing the sensory perception of an animal, whereby the method comprises administering to the inner ear an adenoviral expression vector comprising a nucleic acid sequence encoding an atonal-associated factor, more particularly *Hath1*. The adenoviral genome is deficient in the E1, E3 and E4 region and comprises a spacer in the E4 region.

D6 discloses the use of a spacer, preferably in the deleted E4 region, in adenoviruses carrying multiple deletions in order to sufficiently separate the retained L5 fiber region from the right-side ITR.

3 Industrial applicability (Article 33(4) PCT)

All claims appear to comply with the requirements of Article 33(4) PCT.

4 Reservation concerning the patentability of medical use claims

Claims 12-15 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 (Article 53(c) EPC) , but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Re Item VII

Certain defects in the international application

1 Certain defects

- 1.1 A patent specification should, regarding the essential features of the invention, be self-contained, that is, capable of being understood without reference to any other document. If matter in the document referred to is essential to satisfy the requirements of Article 5, this matter should be incorporated into the description (PCT Guidelines II 4.26), otherwise the expressions "incorporated by reference" throughout the description should be removed from the application.

Re Item VIII

Certain observations on the international application

- 1 Objections under Article 6 PCT:
 - 1.1 The technical feature of a "transcriptionally inert spacer (TIS)" is deemed to lack clarity under Article 6 PCT as it is purely functional without revealing its exact nature. It should be replaced by the embodiment of dependent claim 9.

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