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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
06 January 2022 (06.01.2022)

(54) Title: ADENO-ASSOCIATED VIRUS VIRIONS WITH VARIANT CAPSIDS AND METHODS OF USE THEREOF

FIG. 1A

AAV1

MAADGYDWDNSGRWWDKGAKKANKDDGRGVGYKYGNGDKGVNAADAAAHDKAYDKAGDNYRYNHADARDTSGGNGRAVAKKRVGVGAKTAGKKRVSDS
SSGGKTGAKKRNGTGDSSVDGATAAVGTTMASGGGAMADNNGADGVGNASGNWHCDSTWGDRVTTSTRTWATYNNHYKSSASTGASNDNHYGYSTWGY
DNRHCHSRDWRNNNWGRKRNKNVKVTTNDGVTTANNTSTVVSDSYYVGSAHGCADVMYGYTNNGSAVGRSSYCYSMRTGNNTSYTVHSSYAHSSDRMN
DYYYNRTNSGSANKDSRGSAGMSVKNWGCYRRVSKTKTDNNNSNTWTGASKYNNGRSNGTAMASHKDDDKMSGVMGKSAGASNTADNVMTDKATNVAT
RGTVAVNSSSTDATGDVHAMGAGMVWDRDVYGWAKHTDGHHSMGGGKNKNTVANASATKASTYSTGVSVWKNSKRWNVYTSNYAKSANVDTVDNNGYT
RGTRYTR* (SEQ ID NO:58)

(57) Abstract: The present disclosure provides recombinant adeno-associated virus (AAV) virions comprising: a) a variant capsid protein; and b) a heterologous nucleic acid comprising one or more nucleotide sequences encoding one or more heterologous gene products. The rAAV virions are useful for delivery of gene products to a retinal cell. The present disclosure provides methods of delivering a gene product to a retinal cell in an individual.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/34624

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 35/76, A61P 27/02, C12N 15/86 (2021.01)

CPC - A61K 35/761, C12N 2750/14122, A01K 67/0275, A61K 48/0025, C12N 2750/14145

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/0164106 A1 (SCHAFFER et al.) 28 June 2012 (28.06.2012) abstract, para [0064]	1, 4/1, 6, 50, 52/50
A	US 2019/0255192 A1 (4D MOLECULAR THERAPEUTICS INC.) 22 August 2019 (22.08.2019) abstract, para [0193], [0225], SEQ ID NO: 34	1, 4/1, 6, 50, 52/50

☐ 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
"D" document cited by the applicant in the international application
"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	Date of mailing of the international search report
5 November 2021	NOV 26 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out 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).

2. ☐ 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.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/34624

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 10-49, 55-63
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

---------- see extra sheet ----------

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 4/1, 6, 50 and 52/50 limited to SEQ ID NO: 1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/34624

Continuation of Box No. III, Observations where unity of invention is lacking:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-9 and 50-54 directed to a recombinant adeno-associated virus (rAAV) virion comprising:
a) a variant adeno-associated virus (AAV) capsid protein, wherein the variant AAV capsid protein comprises an insertion of a heterologous peptide, wherein the variant capsid protein confers increased infectivity of a retinal cell and
b) a heterologous nucleic acid comprising nucleotide sequences encoding one or more heterologous gene products.
The rAAV virion will be searched to the extent that the heterologous peptide comprises the 10 amino acid sequence (LAHQDTTKNS) set forth in SEQ ID NO: 1. It is believed that claims 1, 4 (in part), 6, 50 and 52 (in part), limited to said rAAV virion encompass this first named invention, and thus these claims will be searched without fee to the extent that the rAAV virion capsid protein comprises SEQ ID NO: 1. Additional rAAV virions will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected rAAV virions. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be an rAAV virion comprising the 10 amino acid sequence (LALGETTRAA) set forth in SEQ ID NO: 2 (claims 2, 4 (in part), 7, 51 and 52 (in part)). Another exemplary election would be an rAAV virion comprising the 7 amino acid sequence (LGETTRA) set forth in SEQ ID NO: 32 (claims 2, 8 and 54).

The inventions listed as Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

No technical features are shared between the heterologous peptide amino acid sequences of Group I+, accordingly, these groups lack unity a priori.

Additionally, even if the inventions listed as Group I+ were considered to share technical features, these shared technical features are previously disclosed by the prior art, as further discussed below.

Common Technical Features

The inventions of Group I+ share the technical feature of a rAAV virion comprising a variant capsid protein confers increased infectivity of a retinal cell and a heterologous nucleic acid comprising a heterologous gene product. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is taught by US 2012/0164106 A1 to University of California (hereinafter 'CAL').

CAL teaches said rAAV virion comprising a variant capsid protein confers increased infectivity of a retinal cell (abstract "The present disclosure provides adeno-associated virus (AAV) virions with altered capsid protein, where the AAV virions exhibit greater infectivity of retinal cells compared to wild-type AAV.") and a heterologous nucleic acid comprising a heterologous gene product (abstract "The present disclosure further provides methods of delivering a gene product to a retinal cell in an individual, and methods of treating ocular diseases", para [0064] "A subject rAAV virion comprises a heterologous nucleic acid comprising a nucleotide sequence encoding a heterologous gene product, e.g., a nucleic acid gene product or a polypeptide gene product").

As the technical feature was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions.

Group I+ therefore lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.