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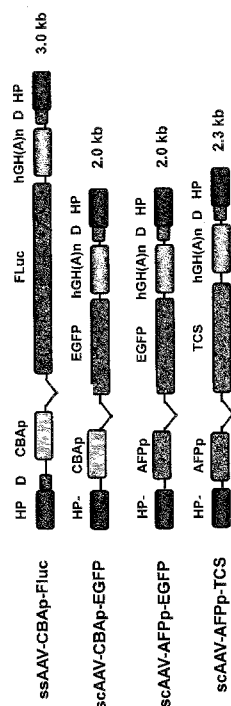
(71) Applicant: UNIVERSITY OF FLORIDA RESEARCH
FOUNDATION, INC. [—/US]; 223 Grinter Hall, Gaines-
ville, Florida 32611 (US).(72) Inventors: SRIVASTAVA, Arun; 3823 SW 92nd Drive,
Gainesville, Florida 32608 (US). ZHONG, Li; 404 Sarg-
ent Road, Boxborough, Massachusetts 01719 (US). ZO-
LOTUKHIN, Sergei; 1122 Sw 96, Gainesville, Florida32607 (US). ASLANIDI, George V.; 2411 NW 69th Ter-
race, Gainesville, Florida 32626 (US). AGBAND-
JE-MCKENNA, Mavis; 10202 SW 17th Place, Gaines-
ville, Florida 32607 (US). VAN VLIET, Kim M.; 8124
SW 57th Place, Gainesville, Florida 32608 (US).(74) Agents: WALLER, Patrick, R.H. et al.; Wolf, Greenfield
& Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210-
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DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM,
ZW.

[Continued on next page]

(54) Title: CAPSID-MODIFIED, RAAV3 VECTOR COMPOSITIONS AND USES IN GENE THERAPY OF HUMAN LIVER
CANCER

(57) Abstract: Disclosed are next-generation multi-mutated capsid protein-modified rAAV expression vectors, as well as infectious virions, compositions, and pharmaceutical formulations that include them. Also disclosed are methods of preparing and using these high transduction efficiency vector constructs in a variety of therapeutic applications including, inter alia, as delivery agents for the treatment or amelioration of one or more diseases or abnormal conditions in an affected mammal using in vivo and/or ex situ viral vector-based gene therapy protocols. Also disclosed are large-scale production methods for the multi-mutated, capsid-modified rAAV expression vectors, viral particles, and infectious virions, as well as use of the disclosed compositions in the manufacture of medicaments for use in a variety of in vitro and/or in vivo therapeutic methodologies.

FIG. 40A





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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 information concerning one or more priority claims considered void (Rule 26bis.2(d))
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/039015

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12N15/864 A61K48/00 A61K49/00
ADD.

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)
C12N

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

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

EPO-Internal, MEDLINE, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	B CHENG ET AL: "Development of optimized AAV3 serotype vectors: mechanism of high-efficiency transduction of human liver cancer cells", GENE THERAPY, vol. 19, no. 4, 21 July 2011 (2011-07-21), pages 375-384, XP055085860, ISSN: 0969-7128, DOI: 10.1038/gt.2011.105 Introduction page 378 table 1 Materials and Methods, paragraph 2; figures 5, 6 -----	1-33



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

"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

22 September 2014

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Sitch, David

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/039015

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.:
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 additional 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 an 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.:

1-33(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-33(partially)

An rAAV3 vector comprising a modified capsid protein that comprises a non-tyrosine residue at one or more of Y252, Y272, Y444, Y701, Y705 and Y731 of the wild type AAV3 capsid protein set forth in SEQ ID NO:3, combinations thereof; related compounds (nucleic acids, cells, compositions etc.) and uses.

2. claims: 1-33(partially)

An rAAV3 vector comprising a modified capsid protein that comprises a non-serine residue at one or more of S459 or S663 of the wild type AAV3 capsid protein set forth in SEQ ID NO:3, combinations thereof insofar as not covered by invention 1; related compounds(nucleic acids, cells, compositions etc.) and uses.

3. claims: 1, 2, 4-33(all partially)

An rAAV3 vector comprising a modified capsid protein that comprises a non-tyrosine residue at one or more of T251 or T492 of the wild type AAV3 capsid protein set forth in SEQ ID NO:3, combinations thereof insofar as not covered by inventions 1 and 2; related compounds (nucleic acids, cells, compositions etc.) and uses.

4. claims: 1, 2, 4-33(all partially)

An rAAV3 vector comprising a modified capsid protein that comprises a non-tyrosine residue at one or more of K528, K533 or K545 of the wild type AAV3 capsid protein set forth in SEQ ID NO:3, combinations thereof insofar as not covered by inventions 1, 2 and 3; related compounds (nucleic acids, cells, compositions etc.) and uses.
