

DO/EO WORKSHEET

Patent Application Specialist/ National Stage Division

U.S. Appl. No. 11887679

International Appl. No. PCT/US 2006/013375

Application filed by: ☐ 20 months ☒ 30 months

WIPO PUBLICATION INFORMATION:

Publication No.: WO2006/110689 Publication Language: ☒ English ☐ German ☐ Japanese ☐ Chinese ☐ Korean
☐ French ☐ Spanish ☐ Russian ☐ Other: _____
 Publication Date: 10 19 2006 Not Published: ☐ U.S. only designated ☐ EP request Published: ☐ EP request

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE:

- ☒ International Application (RECORD COPY) ☐ PCT/IB/306
- ☐ Article 19 Amendments ☐ Request form PCT/RO/101
- ☐ PCT/IPEA/409 IPER: ☐ EP ☐ JP ☐ SE ☐ AU ☒ PCT/ISA/210 - Search Report: ☒ EP ☐ JP ☐ SE ☐ AU
☐ US ☐ FR ☐ CN ☐ ES ☐ RU ☐ AT ☐ KR ☐ _____ ☐ US ☐ FR ☐ CN ☐ ES ☐ RU ☐ AT ☐ KR ☐ _____ ☐ NONE
- ☐ Annexes to 409 ☐ Search Report References
- ☒ PCT/ISA/237: ☒ EP ☐ JP ☐ SE ☐ AU ☒ Priority Document (s) No. 2
☐ US ☐ FR ☐ CN ☐ ES ☐ RU ☐ AT ☐ KR ☐ _____ ☐ N/A
☐ PCT/IPEA/409 or PCT/ISA/237 was NOT AVAILABLE at the time of paralegal review ☐ Priority Document was NOT AVAILABLE at the time of paralegal review
- ☒ Other: express

RECEIPTS FROM THE APPLICANT (other than checked above):

- ☒ Basic National Fee (or authorization to charge) 50 ☒ Preliminary Amendment(s) Filed on: _____
☒ Description ☒ Claims ☒ Abstract ☐ Information Disclosure Statement(s) Filed on: _____
☒ Drawing Figure(s) - (# of drwgs. 21) ☐ Assignment Document (forwarded to Assignment Branch) _____
☐ Translation of Article 19 Amendments ☐ Assignee Statement Under 37 CFR 3.73(b) _____
☐ entered ☐ not entered: ☒ Assignee PG Publication Notice _____
☐ not a page for page substitution ☐ Substitution Specification Filed on: _____
☐ replaced by Article 34 Amendment ☐ Verified Small Status Statement _____
- ☐ Annexes to 409 ☐ Oath/ Declaration (executed) _____
☐ entered ☐ not entered: ☐ Oath/ Declaration ☐ unsigned ☐ no citizenship ☐ other _____
☐ not a page for page substitution ☐ DNA Diskette ☒ Sequence Listing CR1FD
☐ no translation ☐ other: _____ ☐ Other: _____
- ☒ Application Data Sheet ☐ Oath/ Declaration (executed) _____
☒ Power of Attorney ☐ Oath/ Declaration ☐ unsigned ☐ no citizenship ☐ other _____
☐ Change of Address ☐ DNA Diskette ☒ Sequence Listing CR1FD

NOTES: ☐ I.A. used as Specification ☐ Other: _____

35 U.S.C. 371 - Receipt of Request (PTO-1390)

mo. 10 day 02 yr. 200 7

Date Acceptable Oath/ Declaration Received

☐ Same as 371 Req. Date; ☐ mo. 10 day 02 yr. 200 7

Date of Completion of requirements under 35 U.S.C. 371

☐ Same as 371 Req. Date; ☐ Same as OATH Date; ☐ mo. 10 day 02 yr. 200 7

Date of Completion of DO/EO 903 - Notification of Acceptance

Date of Completion of DO/EO 905 - Notification of Missing Requirements

Date of Completion of DO/EO 909 - Notification of Abandonment

Date of Completion of DO/EO 916 - Notification of Defective Response

Date of Completion of DO/EO 922 - Notification to Comply w/ Requirements for Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures

Date of Completion of DO/EO 923

**MULTIPLE DEPENDENT CLAIM
FEE CALCULATION SHEET**
(FOR USE WITH FORM PTO-875)

SERIAL NO.

11887679

FILING DATE

10-02-2007

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1 st AMENDMENT		AFTER 2 nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
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TOTAL IND.	5	↓	5	↓		↓
TOTAL DEP.	27	←	18	←		←
TOTAL CLAIMS	32		23			

	AS FILED		AFTER 1 st AMENDMENT		AFTER 2 nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
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TOTAL IND.		↓		↓		↓
TOTAL DEP.		←		←		←
TOTAL CLAIMS						

U.S. DEPARTMENT of COMMERCE
Patent and Trademark Office

PTO-1360 (REV. 11/04)

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 8, 2004

Application or Docket Number

11887679

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
U.S. NATIONAL STAGE FEES		
ASIC FEE	SMALL ENT. = \$ 150	LARGE ENT. = \$ 300
EXAMINATION FEE	Satisfies PCT Article 33(1)-(4) = \$ 50 / \$ 100	All other situations = \$ 100 / \$ 200
SEARCH FEE	U.S. is ISA = \$ 50 / \$ 100 ALL other countries = \$ 200 / \$ 400	ALL other situations = \$ 250 / \$ 500
REDUCTION FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =
ADDITIONAL CHARGEABLE CLAIMS	23 minus 20 =	3
DEPENDENT CLAIMS	5 minus 3 =	2
MULTIPLE DEPENDENT CLAIM PRESENT ☐		

If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐ OR

OTHER THAN SMALL ENTITY

RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	310
EXAM. FEE			EXAM. FEE	40
SEARCH FEE			SEARCH FEE	410
X \$ 125 =			X \$ 250 =	520
X \$ 25 =		OR	X \$ 50 =	130
X \$ 100 =		OR	X \$ 200 =	420
+ \$ 180 =		OR	+ \$ 360 =	—
TOTAL		OR	TOTAL	2220

CLAIMS AS AMENDED - PART II

	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

SMALL ENTITY OR

OTHER THAN SMALL ENTITY

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X \$ 25 =		OR	X \$ 50 =	
X \$ 100 =		OR	X \$ 200 =	
+ \$ 180 =		OR	+ \$ 360 =	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X \$ 25 =		OR	X \$ 50 =	
X \$ 100 =		OR	X \$ 200 =	
+ \$ 180 =		OR	+ \$ 360 =	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

If the "Highest Number Previously Paid For" IN THIS SPACE is less than '20', enter "20".

If the "Highest Number Previously Paid For" IN THIS SPACE is less than '3', enter "3".

If the "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln No: 11/887,679 Confirmation No.: 5864
Applicant: Vandenberghe et al
Filed: October 2, 2007
Art Unit: 1639
Examiner: Gross, Christopher M.
Customer No.: 00270
Title: METHOD OF INCREASING THE FUNCTION OF AN AAV VECTOR

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT

Sir:

This paper is being filed in response to a non-final Office Action dated August 12, 2013. A Petition to Extend the Period for response for one month from November 12, 2013 to December 12, 2013 is being filed herewith. Kindly amend the application as follows.

Amendments to the Claims are reflected in the listing of claims, which begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, or claims in the application.

Listing of Claims:

1(Currently Amended). A method of increasing the packaging yield, transduction efficiency, and/or gene transfer efficiency of a parental AAV, said method comprising the steps of:

(a) comparing a parental AAV capsid sequence with a library of functional AAV capsid sequences in an alignment, wherein said library comprises ~~functional AAV capsids from at least three different clades and further comprises~~ at least three functional AAV capsids which are at least 85% identical over the full-length of the aligned vp1 sequences and which represent at least three different clades;

(b) identifying at least one singleton in the parental AAV capsid, said singleton being an amino acid residue in a position in the parental AAV capsid which differs from the amino acid in the corresponding position of the aligned functional AAV capsid sequences in the library all of which have the same amino acid residue in that position;

(c) altering the singleton in the parental AAV capsid to the amino acid located in the corresponding position in the functional AAV capsid sequences in the library to provide a modified AAV capsid sequence, and

(d) assessing the modified AAV for increased packaging yield, transduction efficiency, and/or gene transfer efficiency as compared to the parental AAV .

Cancel claim 2.

3 (Original). The method according to claim 1, wherein the library comprises at least two AAV sequences from each clade.

Cancel claim 4.

5 (Original). The method according to claim 1, wherein the library of aligned AAV capsid sequences comprises at least three to 100 AAV sequences.

6 (Original). The method according to claim 1, wherein the library of aligned AAV capsid sequences comprises at least six to 50 AAV sequences.

7 (Original). The method according to claim 6, wherein the library comprises at least 12 AAV sequences.

8 (Original). The method according to claim 1, wherein the parental AAV contains multiple singletons.

9 (Original). The method according to claim 8, wherein the parental AAV contains 2 to 4 singletons.

10 (Original). The method according to claim 8, wherein step (c) is repeated at different singletons.

11 (Previously Presented). The method according to claim 1, wherein the parental AAV is altered by site directed mutagenesis of the codon for the variable amino acid.

12 (Previously Presented). The method according to claim 11, wherein the site directed mutagenesis is performed on the parental AAV carried on a plasmid backbone.

13 (Previously Presented). The method according to claim 1, further comprising the step of utilizing the altered AAV to produce a viral vector having the protein sequence of the altered AAV.

14 (Previously Presented). The method according to claim 13, wherein the AAV vector has increased packaging efficiency as compared to the parental AAV.

15 (Previously Presented). The method according to claim 13, wherein in the AAV vector has increased transduction efficiency as compared to the parental AAV.

16 (Previously Presented). The method according to claim 13, wherein the AAV vector has increased gene transfer efficiency as compared to the parental AAV.

Claims 17 – 25. Cancelled.

26 (Previously Presented). The method according to claim 13, wherein the AAV vector has packaged in the capsid a transgene encoding a gene product under the control of regulatory sequences which direct expression of the product in a host cell.

27 (Currently Amended). A method of increasing the packaging yield, transduction efficiency, and/or gene transfer efficiency of a parental AAV, said method comprising the steps of:

(a) comparing a parental AAV capsid sequence with a library of functional AAV capsid sequences in an alignment, wherein said library comprises at least two functional AAV capsids from each of at least three different clades, and wherein said sequences further comprises functional AAV capsids which are at least 85% identical over the full-length of the aligned vp1 sequences;

(b) identifying at least one singleton in the parental AAV capsid, said singleton being an amino acid residue in a position in the parental AAV capsid which differs from the amino acid in the corresponding position of the aligned functional AAV capsid sequences in the library all of which have the same amino acid residue in that position;

(c) altering the singleton in the parental AAV capsid to the amino acid located in the corresponding position in the functional AAV capsid sequences in the library to provide a modified AAV capsid sequence, and

(d) utilizing the altered AAV to produce a viral vector having the protein sequence of the altered AAV.

28 (Previously Presented). The method according to claim 27, where the alignment comprises four clades.

29 (Previously Presented). The method according to claim 27, wherein the alignment comprises five clades.

30 (Currently Amended). The method according to claim 27, wherein AAV4 ~~and/or AAV5~~ is excluded from the alignment.

31 (New). The method according to claim 27, wherein AAV5 is excluded from the alignment.

REMARKS/ARGUMENTS

Claims 1, 3, 5-16, 26, and 27-30 are pending. New claim 31 is added. This claim is supported on page 6, lines 14 – 16.

No new matter is added by this amendment.

Claims 1, 3, 4-16, and 26-30 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The examiner has indicated that this is a new matter rejection.

While applicants respectfully traverse the examiner's interpretation of the amended claim language, in order to advance prosecution of this application Claims 1 and 27 has been amended to recite language the examiner indicated would be acceptable to overcome this rejection.

The examiner has rejected claim 30 as lacking support. The examiner argues that the specification does not permit both AAV4 and AAV5 to be excluded.

Applicants respectfully disagree.

The passage on page 6, lines 14 – 17 of the specification provides: "In one embodiment, the libraries used in the method of the invention exclude AAV5. In another embodiment, the libraries used in the method of the invention exclude AAV4."

As stated the cited passage, the libraries used in the method of the invention may exclude AAV4. Thus, where the specification refers to "libraries used in the method of the invention" which may exclude AAV5, those libraries which exclude AAV4 are encompassed by the phrase. Similarly, the libraries used in the method of the invention may exclude AAV5. Thus, where the specification refers to "libraries used in the method of the invention" which may exclude AAV4, those libraries which exclude AAV5 are encompassed by the phrase. Nevertheless, in order to advance prosecution, applicants have amended claim 30 to remove the term "and/or" and have added new claim 31.

US Patent Application No. 11/887,679
Response NFOA 08/12/2013
December 12, 2013

Applicants respectfully request reconsideration of the outstanding rejection in view of the arguments presented herein.

The Director is hereby authorized to charge any deficiency in any fees due, or credit any overpayment in any fees, to Deposit Account No. 08-3040.

Respectfully submitted,

HOWSON & HOWSON ^{LLP}
Attorneys for Applicants

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/887,679	10/02/2007	Luk Vandenberghe	UPN-R3895	5864

270 7590 04/07/2014
HOWSON & HOWSON LLP
350 Sentry Parkway
Building 620, Suite 210
Blue Bell, PA 19422

EXAMINER

WEILER, KAREN S

ART UNIT	PAPER NUMBER
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1639

NOTIFICATION DATE	DELIVERY MODE
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04/07/2014

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@howsoniplaw.com
ckodroff@howsoniplaw.com

Office Action Summary	Application No. 11/887,679	Applicant(s) VANDENBERGHE ET AL.	
	Examiner KAREN S. WEILER	Art Unit 1639	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12-12-2013.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1,3,5-16 and 26-31 is/are pending in the application.
5a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 6) ☒ Claim(s) 27-31 is/are allowed.
- 7) ☒ Claim(s) 1, 5, 6, 8-16 and 26 is/are rejected.
- 8) ☒ Claim(s) 3 and 7 is/are objected to.
- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) ☒ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____ | 4) ☐ Other: _____ |

Art Unit: 1639

DETAILED ACTION

Status of Claims

1. Claims 1, 3, 5-16 and 26-31 of the instant application are under examination, under the pre-AIA first to invent provisions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1, 5, 8-16 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bowles et al. (US PGPub 2008/0269149 A1, effective filing date 12-15-2004) in view of Gao et al. (US PGPub 2003/0138772 A1, published 07-24-2003; as cited in the IDS), as evidenced by Vanderberghe et al. (Gene Therapy 16:1416–1428, published 09-03-2009; as cited in the IDS).

With regard to instant **claims 1 and 8-10**, Bowles et al. teach a method of increasing the packaging yield, transduction efficiency, and/or gene transfer efficiency of a parental AAV, said method comprising the steps of:

(a) comparing a parental AAV capsid sequence (e.g. AAV2; e.g. paragraph [0250]) with a library of

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functional AAV capsid sequences in an alignment (e.g. AAV1 and AAV7; e.g. paragraph [0250] and Figure 1);

(b) identifying at least one singleton in the parental AAV capsid, said singleton being an amino acid residue in a position in the parental AAV capsid which differs from the amino acid in the corresponding position of the aligned functional AAV capsid sequences in the library all of which have the same amino acid residue in that position, wherein the parental AAV contains multiple singletons, wherein the parental AAV contains 2-4 singletons (e.g. amino acids shown as residues 556, 558 and 560 of Figure 1B, which are the same in AAV1 and AAV7, but differ from AAV2);

(c) altering the singleton in the parental AAV capsid to the amino acid located in the corresponding position in the functional AAV capsid sequences in the library to provide a modified AAV capsid sequence, wherein step (c) is repeated at different singletons (e.g. the amino acids changed in the triage approach are shown with arrows in Figure 1C; e.g. paragraph [0039]; e.g. key amino acids residues in the AAV capsid proteins were identified that account for enhanced AAV1 transduction for testing in the context of majority AAV2 capsid; e.g. paragraph [0250]), and

(d) assessing the modified AAV for increased packaging yield, transduction efficiency, and/or gene transfer efficiency as compared to the parental AAV (e.g. transduction efficiency; e.g. paragraph [0251]).

Bowles et al. teach instant **claims 11 and 12**, wherein the parental AAV is altered by site directed mutagenesis of the codon for the variable amino acid, wherein the site directed mutagenesis is performed on the parental AAV carried on a plasmid backbone (e.g. paragraph [0245]).

Bowles et al. teach instant **claim 13**, further comprising the step of utilizing the altered AAV to produce a viral vector having the protein sequence of the altered AAV (e.g. paragraph [0246]).

Bowles et al. teach instant **claims 14-16**, wherein the AAV vector has increased packaging efficiency as compared to the parental AAV, wherein the AAV vector has increased transduction efficiency as compared to the parental AAV, wherein the AAV vector has increased gene transfer efficiency as compared to the parental AAV (i.e. properties that are considered inherent to the modified viruses). It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe

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inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Bowles et al. teach instant **claim 26**, wherein the AAV vector has packaged in the capsid a transgene encoding a gene product under the control of regulatory sequences which direct expression of the product in a host cell (e.g. injection of the infected animals with a luciferan substrate enabled detection of viral expression in the transduced muscle cells, as illustrated in Figures 2, 4-6 and 12, which implicitly teaches a reporter transgene under control of regulatory sequences active in muscle; e.g. paragraph [0247]).

However, the library taught by Bowles et al. has only two members of at least 85% identity and which belong to 2 clades (i.e. AV1 and AAV7) instead of at least 3 members of at least 85% identity belonging to at least 3 clades, as per instant claim 1.

Gao et al. (2003) teach instant **claim 1**, in part, wherein said library comprises at least three functional AAV capsids which are at least 85% identical over the full-length of the aligned vp1 sequences and which represent at least three different clades (e.g. the additional library members of rh.10 (clone 44.2) and rh.2 (clone 43.1); e.g. working example 9 and Table 8 at paragraph [0253]). As evidenced by Vanderberghe et al. (Supplementary Table S1), AAV1, AAV2 and rh.10 represent 3 clades (A, D and E, respectively) and exhibit at least 85% sequence identity.

Gao et al. (2003) teach instant **claim 5**, wherein the library of aligned AAV capsid sequences comprises at least three to 100 AAV sequences (e.g. four AAV sequences: AAV1, AAV7, rh.2 and rh.10; e.g. working example 9 and Table 8 at paragraph [0253]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the applicant's invention to combine the method of Bowles et al. for generating chimeric AAV to transfer a desirable property (muscle tropism) between serotypes, with library members of Gao et al. (2003) having said desirable property, thus obtaining the applicant's invention. Gao et al. (2003) teach that new AAV isolates rh.10 and rh.2 have high tropism for muscle tissue, comparable to that of AAV1 (e.g. Table 8). One would have been motivated to so combine the inventions in order to increase the size of the library,

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which would allow better discrimination of amino acid differences that do or do not correlate with the property of muscle tropism. Thus, a larger library of members having the trait of muscle tropism better guides the selection of amino acids to alter in the parental AAV2 virus. One of ordinary skill in the art would have had a reasonable expectation of success in so combining the inventions since the nucleotide sequences of the library members are known, and publicly available alignment programs such as ClustalW are well-suited for multiple sequence alignment, and routinely used by the skilled artisan..

3. Claims 1, 5, 6, 8-16 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bowles et al. (US PGPub 2008/0269149 A1, effective filing date 12-15-2004) in view of Gao et al. (US PGPub 2003/0138772 A1, published 07-24-2003; as cited in the IDS), as applied to claims 1, 5, 8-16 and 26, and in further view of Gao et al. (Journal of Virology 78(12):6381-6388, published June 2004; of record), as evidenced by Vanderberghe et al. (Gene Therapy 16:1416–1428, published 09-03-2009; as cited in the IDS).

The teachings of Bowles et al. in view of Gao et al. (2003) are described above.

Bowles et al. in view of Gao et al. (2003) do not teach at least six library sequences, as per instant claim 6.

Gao et al. 2004 teach instant **claim 6**, wherein the library of aligned AAV capsid sequences comprises at least six to 50 AAV sequences (e.g. AAV sequences Cy5, rh.20, rh.8 and AAV9, in addition to AAV1, AAV7, rh.2 and rh.10; e.g. p. 6386, Figure 4). As evidenced by Vanderberghe et al. (Supplementary Table S1), AAV1, AAV2, rh.10 and rh.8 represent at least 3 clades (A, D, E and unnamed) and exhibit at least 85% sequence identity.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the applicant's invention to combine the method of Bowles et al. in view of Gao et al. (2003) for generating chimeric AAV to transfer a desirable property (muscle tropism) between serotypes, with library members of Gao et al. (2004) having said desirable property, thus obtaining the applicant's invention. Gao et al. (2004) teach that AAV isolates Cy5, rh.20, rh.8 and AAV9 have high tropism for muscle tissue, similar to that of AAV1 and AAV7 (e.g. p. 6386, Figure 4). One would have been motivated to so combine the

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inventions in order to increase the size of the library of AAV serotypes exhibiting high muscle tropism, which would allow better discrimination of amino acid differences that do or do not correlate with this property. Thus, a larger library of members having the trait of muscle tropism better guides the selection of amino acids to alter in the parental AAV2 virus. One of ordinary skill in the art would have had a reasonable expectation of success in so combining the inventions since the nucleotide sequences of the library members are known, and publicly available alignment programs such as ClustalW are well-suited for multiple sequence alignment, and routinely used by the skilled artisan.

Response to Arguments

4. RE: 35 U.S.C. § 112 rejection of claims 1, 3, 5-16 and 26-30

This rejection is withdrawn in view of the Applicant's claim amendments.

Allowable Subject Matter

5. Claims 27-31 are allowed.
6. Claims 3, 7 and 27-31 are free of the prior art. Claims 3 and 7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

7. Claims 1, 5, 6, 8-16 and 26 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAREN S. WEILER whose telephone number is (571)270-5322. The examiner can normally be reached on Monday through Friday, 7:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on (571)272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/K. S. W./
Examiner, Art Unit 1639

/Tracy Vivlemore/
Primary Examiner, Art Unit 1674

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln No: 11/887,679 Confirmation No.: 5864
Applicant: Vandenberghe et al
Filed: October 2, 2007
Art Unit: 1639
Examiner: Gross, Christopher M.
Customer No.: 00270
Title: METHOD OF INCREASING THE FUNCTION OF AN AAV VECTOR

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT

Sir:

This paper is being filed in response to a final Office Action dated April 7, 2014. A Petition to Extend the Period for response for two months from July 7, 2014 to September 7, 2014 is being filed herewith. Kindly amend the application as follows.

Amendments to the Claims are reflected in the listing of claims, which begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, or claims in the application.

Listing of Claims:

Claim 1. Cancel.

Claim 2. Cancelled.

Claim 3 (Currently Amended). ~~The method according to claim 1~~ A method of increasing the packaging yield, transduction efficiency, and/or gene transfer efficiency of a parental AAV, said method comprising the steps of:

(a) comparing a parental AAV capsid sequence with a library of functional AAV capsid sequences in an alignment, wherein said library comprises at least three functional AAV capsids which are at least 85% identical over the full-length of the aligned vp1 sequences and which represent at least three different clades, wherein the library comprises at least two AAV sequences from each clade;

(b) identifying at least one singleton in the parental AAV capsid, said singleton being an amino acid residue in a position in the parental AAV capsid which differs from the amino acid in the corresponding position of the aligned functional AAV capsid sequences in the library all of which have the same amino acid residue in that position;

(c) altering the singleton in the parental AAV capsid to the amino acid located in the corresponding position in the functional AAV capsid sequences in the library to provide a modified AAV capsid sequence, and

(d) assessing the modified AAV for increased packaging yield, transduction efficiency, and/or gene transfer efficiency as compared to the parental AAV,

Claim 4. Cancelled.

Claims 5 - 6. Cancel.

7 (Currently Amended). ~~The method according to claim 6~~ A method of increasing the packaging yield, transduction efficiency, and/or gene transfer efficiency of a parental AAV, said method comprising the steps of:

(a) comparing a parental AAV capsid sequence with a library of functional AAV capsid sequences in an alignment, wherein said library comprises at least three functional AAV capsids which are at least 85% identical over the full-length of the aligned vp1 sequences and which represent at least three different clades, wherein the library comprises at least 12 AAV sequences;

(b) identifying at least one singleton in the parental AAV capsid, said singleton being an amino acid residue in a position in the parental AAV capsid which differs from the amino acid in the corresponding position of the aligned functional AAV capsid sequences in the library all of which have the same amino acid residue in that position;

(c) altering the singleton in the parental AAV capsid to the amino acid located in the corresponding position in the functional AAV capsid sequences in the library to provide a modified AAV capsid sequence, and

(d) assessing the modified AAV for increased packaging yield, transduction efficiency, and/or gene transfer efficiency as compared to the parental AAV.

8 (Currently Amended). The method according to claim 3 ~~4~~, wherein the parental AAV contains multiple singletons.

9 (Currently Amended). The method according to claim 8, wherein the parental AAV contains 2 to 4 singletons.

10 (Currently Amended). The method according to claim 8, wherein step (c) is repeated at different singletons.

11 (Currently Amended). The method according to claim ~~3~~ 4, wherein the parental AAV is altered by site directed mutagenesis of the codon for the variable amino acid.

12 (Currently Amended). The method according to claim 11, wherein the site directed mutagenesis is performed on the parental AAV carried on a plasmid backbone.

Cancel claims 13 - 16.

Claims 17 – 25. Cancelled.

26 (Currently Amended). The method according to claim ~~27~~ 13, wherein the AAV viral vector of (d) has packaged in the capsid a transgene encoding a gene product under the control of regulatory sequences which direct expression of the product in a host cell.

27(Previously Presented). A method of increasing the packaging yield, transduction efficiency, and/or gene transfer efficiency of a parental AAV, said method comprising the steps of:

(a) comparing a parental AAV capsid sequence with a library of functional AAV capsid sequences in an alignment, wherein said library comprises at least two functional AAV capsids from each of at least three different clades, and wherein said sequences are at least 85% identical over the full-length of the aligned vp1 sequences;

(b) identifying at least one singleton in the parental AAV capsid, said singleton being an amino acid residue in a position in the parental AAV capsid which differs from the amino acid in the corresponding position of the aligned functional AAV capsid sequences in the library all of which have the same amino acid residue in that position;

(c) altering the singleton in the parental AAV capsid to the amino acid located in the corresponding position in the functional AAV capsid sequences in the library to provide a modified AAV capsid sequence, and

(d) utilizing the altered AAV to produce a viral vector having the protein sequence of the altered AAV.

28 (Previously Presented). The method according to claim 27, where the alignment comprises four clades.

29 (Previously Presented). The method according to claim 27, wherein the alignment comprises five clades.

30 (Previously Presented). The method according to claim 27, wherein AAV4 is excluded from the alignment.

31 (Previously Presented). The method according to claim 27, wherein AAV5 is excluded from the alignment.

REMARKS/ARGUMENTS

Claims 3, 7 - 12 and 26-31 are pending. Claims 1, 5, 6, and 14 - 16 are cancelled herein. Claims 2, 4 and 13 were previously cancelled.

Claims 27 - 31 have been indicated to be allowable. Claim 26 is rewritten to depend from claim 27 and is believed to now be in condition for allowance.

Claims 3 and 7 have been rewritten in independent form, in accordance with the statement that these claims would be allowable if so rewritten. Claims 8 - 12 have been rewritten to depend from claim 3. These claims should now be in allowable form, since they now depend from an allowable claim.

No new matter is added by this amendment.

The rejection of claims 1, 5, 8-16 and 26 is rendered moot by this amendment. However, applicants respectfully traverse this rejection, but have cancelled claims 1 and 5 in order to advance prosecution of this application.

The Director is hereby authorized to charge any deficiency in any fees due, or credit any overpayment in any fees, to Deposit Account No. 08-3040.

Respectfully submitted,

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