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Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO. Includes application details for Sanofi/Genzyme and examination information for Examiner XU, XIAOYUN.

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):

- EOfficePA@mofo.com
PatentDocket@mofo.com
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Office Action Summary

Application No.

16/325,653

Applicant(s)

JIN et al.

Examiner

XIAOYUN R XU, Ph. D.

Art Unit

1797

AIA (FITF) Status

Yes

-- 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 06/17/2021.

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) 1,3,29,31,61-63,89-92,100,128,130,134,136,142 and 150-154 is/are pending in the application.

5a) Of the above claim(s) 3,31,62-63,89-92,100,130,136,142 and 150-154 is/are withdrawn from consideration.

6) Claim(s) _____ is/are allowed.

7) Claim(s) 1,29,61,128 and 134 is/are rejected.

8) Claim(s) _____ 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 02/14/2019 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)

4) Other: _____

Paper No(s)/Mail Date _____

DETAILED ACTION

1. Applicant's election without traverse of group I comprising Claims 1, 29, 61, 128 and 134 in the reply filed on 06/17/2021 is acknowledged. Claims 1, 3, 29, 31, 61-63, 89-92, 100, 128, 130, 134, 136, 142 and 150-154 are pending in the application. Claims 3, 31, 62-63, 89-92, 100, 130, 136, 142 and 150-154 are withdrawn from consideration. Claims 1, 29, 61, 128 and 134 are considered on merits.

Notice of Pre-AIA or AIA Status

2. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Rejections - 35 USC § 102

3. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

5. **Claim(s) 29, 61 and 134** is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated Vliet et al. (Journal of Virological Methods, 2009, IDS) (Vliet).

Regarding claim 29, Vliet teaches a method to determine the serotype of an adeno-associated virus (AAV) particle (abstract) comprising

- a) denaturing the AAV particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured AAV particle to reduction and/or alkylation (page 169, par 5),

c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle (page 169, par 5),

d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS) (page 170, par 2), and

e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle (page 171, par 1);

wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype (Table 2, page 171, par 1).

Regarding claim 61, Vliet teaches a method of determining the serotype of an AAV particle comprising the method of claim 1 combined with a method to determine the serotype of an adeno-associated virus (AAV) particle (abstract) comprising

a) denaturing the AAV particle (boiled for 3 min) (page 169, par 4),

b) subjecting the denatured AAV particle to reduction and/or alkylation (page 169, par 5),

c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle (page 169, par 5),

d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS) (page 170, par 2), and

e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle (page 169, par 6);

wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype (Table 2, page 171, par 1).

Regarding claim 134, Vliet teaches a method to determine the serotype of a viral particle (abstract) comprising

a) denaturing the viral particle (boiled for 3 min) (page 169, par 4),

b) subjecting the denatured viral particle to reduction and/or alkylation (page 169, par 5),

c) subjecting the denatured viral particle to digestion to generate fragments of one or more capsid proteins of the viral particle (page 169, par 5),

d) subjecting the fragments of the one or more capsid proteins to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS) (page 170, par 2), and

e) determining the masses of fragments of the one or more capsid proteins of the viral particle (pae 169, par 6);

wherein the specific combination of masses of fragments of the one or more capsid proteins are indicative of the viral serotype (Table 2, page 171, par 1).

Claim Rejections - 35 USC § 103

6. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

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

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

8. The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating

obviousness or nonobviousness.

9. **Claim 1 and 128** is/are rejected under 35 U.S.C. 103 as being unpatentable over Vliet et al. (Journal of Virological Methods, 2009, IDS) (Vliet) in view of Bark et al. (J. Am. Chem. Soc. 2001, IDS) (Bark).

Regarding claim 1, Vliet teaches a method to determine the serotype of an adeno-associated virus (AAV) particle (abstract) comprising

- a) denaturing the AAV particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured and in-gel digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) (page 169, par 6), and
- c) determining the masses of VP1, VP2 and VP3 of the AAV particle (page 171, par 1);

wherein the specific combination of masses of VP1, VP2 and VP3 are indicative of the AAV serotype (Table 2, page 171, par 1).

Vliet does not specifically teach directly subjecting the denatured AAV particle to liquid chromatography/mass spectrometry (LC/MS). However, Bark teaches directly subjecting the denatured virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis.” (page 1774, par 1); “Two limitations of this method are the time required for adequate proteolysis and the resistance of some proteins to digestion.” (page 1774, par 2). “We have taken advantage of thermal denaturation to generate a facile proteolysis method for identifying proteins.” (page 1774, par 3). At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured AAV particle to liquid chromatography/mass spectrometry (LC/MS), in order to save the time required for adequate proteolysis.

Regarding claim 128, Vliet teaches a method to determine the serotype of a viral particle (abstract) comprising

- a) denaturing the viral particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured and in-gel digested viral particle to liquid chromatography/mass spectrometry (LC/MS) (page 169, par 6), and
- c) determining the masses of one or more capsid proteins of the viral particle (page 171, par 1);

wherein the specific combination of masses of the one or more capsid proteins are indicative of the virus serotype (Table 2, page 171, par 1).

Vliet does not specifically teach directly subjecting the denatured viral particle to liquid chromatography/mass spectrometry (LC/MS). However, Bark teaches directly subjecting the denatured virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis.” (page 1774, par 1); “Two limitations of this method are the time required for adequate proteolysis and the resistance of some proteins to digestion.” (page 1774, par 2). “We have taken advantage of thermal denaturation to generate a facile proteolysis method for identifying proteins.” (page 1774, par 3). At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured viral particle to liquid chromatography/mass spectrometry (LC/MS), in order to save the time required for adequate proteolysis.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to XIAOYUN R XU, Ph. D. whose telephone number is (571)270-5560. The examiner can normally be reached on M-F 8am-5pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Lyle Alexander can be reached on 571-272-1254. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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 <https://ppair-my.uspto.gov/pair/PrivatePair>. 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.

/XIAOYUN R XU, Ph.D./
Primary Examiner, Art Unit 1797

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Xiaoying JIN et al.

Application No.: 16/325,653

Filed: August 14, 2017 (Int'l)

For: METHODS FOR DETECTING AAV

Confirmation No.: 1002

Art Unit: 1797

Examiner: Xiaolin Xu

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION
UNDER 37 C.F.R. 1.111

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

Dear Commissioner:

INTRODUCTORY COMMENTS

This is in response to the non-final Office Action dated July 9, 2021, for which a response was due on October 9, 2021. We hereby petition and submit the fee for a 1-month extension of time, thereby extending the deadline for response to November 9, 2021. Accordingly, this response is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

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

Remarks/Arguments begin on page 10 of this paper.

AMENDMENTS TO THE CLAIMS

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

In the claims:

Claim 1 (currently amended): A method to determine the serotype of an adeno-associated virus (AAV) particle comprising

- a) denaturing the AAV particle,
- b) subjecting the denatured AAV particle to liquid chromatography/mass spectrometry (LC/MS), and
- c) determining the masses of VP1, VP2 and VP3 of the AAV particle;
wherein the specific combination of masses of VP1, VP2 and VP3 are indicative of the AAV serotype,
and wherein the method is performed in the absence of a gel separation step.

Claims 2-28 (canceled)

Claim 29 (currently amended): A method to determine the serotype of an adeno-associated virus (AAV) particle comprising

- a) denaturing the AAV particle,
- b) subjecting the denatured AAV particle to reduction and/or alkylation,
- c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle,
- d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS), and
- e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle;
wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype,
and wherein the method is performed in the absence of a gel separation step.

Claims 30-60 (canceled)

Claim 61 (currently amended): A method of determining the serotype of an AAV particle comprising the method of claim 1 combined with a method to determine the serotype of an adeno-associated virus (AAV) particle comprising

- a) denaturing the AAV particle,
- b) subjecting the denatured AAV particle to reduction and/or alkylation,
- c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle,
- d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS), and
- e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle; wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype,
and wherein the method is performed in the absence of a gel separation step.

Claims 62-127 (canceled)

Claim 128 (currently amended): A method to determine the serotype of a viral particle comprising

- a) denaturing the viral particle,
- b) subjecting the denatured viral particle to liquid chromatography/mass spectrometry (LC/MS), and
- c) determining the masses of one or more capsid proteins of the viral particle; wherein the specific combination of masses of the one or more capsid proteins are indicative of the virus serotype,
and wherein the method is performed in the absence of a gel separation step.

Claims 129-133 (canceled)

Claim 134 (currently amended): A method to determine the serotype of a viral particle comprising

- a) denaturing the viral particle,
 - b) subjecting the denatured viral particle to reduction and/or alkylation,
 - c) subjecting the denatured viral particle to digestion to generate fragments of one or more capsid proteins of the viral particle,
 - d) subjecting the fragments of the one or more capsid proteins to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS), and
 - e) determining the masses of fragments of the one or more capsid proteins of the viral particle;
- wherein the specific combination of masses of fragments of the one or more capsid proteins are indicative of the viral serotype,
and wherein the method is performed in the absence of a gel separation step.

Claims 135-180 (canceled)

Claim 181 (new): The method of claim 1, wherein the calculated masses of VP1, VP2 and VP3 are compared to the theoretical masses of VP1, VP2 and VP3 of one or more AAV serotypes.

Claim 182 (new): The method of claim 1, wherein the AAV particle is denatured with acetic acid, guanidine hydrochloride, and/or an organic solvent.

Claim 183 (new): The method of claim 1, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 184 (new): The method of claim 1, wherein the liquid chromatography is reverse phase chromatography.

Claim 185 (new): The method of claim 184, wherein the reverse phase chromatography is a C4 or C8 reverse chromatography.

Claim 186 (new): The method of claim 1, wherein the liquid chromatography is ultra-performance liquid chromatography (UPLC).

Claim 187 (new): The method of claim 1, wherein the mass spectrometry comprises assisted calibration.

Claim 188 (new): The method of claim 187, wherein sodium iodide is used as a calibrant.

Claim 189 (new): The method of claim 1, wherein the AAV particle is a recombinant AAV (rAAV) particle.

Claim 190 (new): The method of claim 1, wherein the AAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV4 capsid, an AAV5 capsid, an AAV6 capsid, an AAV7 capsid, an AAV8 capsid, an AAVrh8 capsid, an AAV9 capsid, an AAV10 capsid, an AAVrh10 capsid, an AAV11 capsid, an AAV12 capsid, an AAV LK03 capsid, an AAV2R471A capsid, an AAV2/2-7m8 capsid, an AAV DJ capsid, an AAV DJ8 capsid, an AAV2 N587A capsid, an AAV2 E548A capsid, an AAV2 N708A capsid, an AAV V708K capsid, a goat AAV capsid, an AAV1/AAV2 chimeric capsid, a bovine AAV capsid, a mouse AAV capsid rAAV2/HBoV1 (chimeric AAV / human bocavirus virus 1), an AAV2HBKO capsid, an AAVPHP.B capsid or an AAVPHP.eB capsid.

Claim 191 (new): The method of claim 29, wherein the calculated masses of the fragments of VP1, VP2 and/or VP3 are compared to the theoretical masses of fragments of VP1, VP2 and/or VP3 of one or more AAV serotypes.

Claim 192 (new): The method of claim 29, wherein the AAV particle is denatured with acetic acid, guanidine hydrochloride and/or an organic solvent.

Claim 193 (new): The method of claim 29, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 194 (new): The method of claim 1, wherein the liquid chromatography is reverse phase liquid chromatography.

Claim 195 (new): The method of claim 194, wherein the reverse phase chromatography is a C18 reverse chromatography.

Claim 196 (new): The method of claim 29, wherein the reduction is by subjecting the AAV particle to dithiothreitol, beta-mercaptoethanol, or tris(2-carboxyethyl)phosphine (TCEP).

Claim 197 (new): The method of claim 29, wherein the alkylation is by subjecting the AAV particle to iodoacetic acid, iodoacetamide, or 4-vinylpyridine.

Claim 198 (new): The method of claim 1, wherein the digestion is an endopeptidase digestion.

Claim 199 (new): The method of claim 198, wherein the endopeptidase digestion is a trypsin digestion, a LysC digestion, an Asp-N digestion or a Glu-C digestion.

Claim 200 (new): The method of claim 29, wherein the AAV particle is a recombinant AAV (rAAV) particle.

Claim 201 (new): The method of claim 29, wherein the AAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV4 capsid, an AAV5 capsid, an AAV6 capsid,

an AAV7 capsid, an AAV8 capsid, an AAVrh8 capsid, an AAV9 capsid, an AAV10 capsid, an AAVrh10 capsid, an AAV11 capsid, an AAV12 capsid, an AAV LK03 capsid, an AAV2R471A capsid, an AAV2/2-7m8 capsid, an AAV DJ capsid, an AAV DJ8 capsid, an AAV2 N587A capsid, an AAV2 E548A capsid, an AAV2 N708A capsid, an AAV V708K capsid, a goat AAV capsid, an AAV1/AAV2 chimeric capsid, a bovine AAV capsid, a mouse AAV capsid rAAV2/HBoV1 (chimeric AAV / human bocavirus virus 1), an AAV2HBKO capsid, an AAVPHP.B capsid or an AAVPHP.eB capsid.

Claim 202 (new): The method of claim 128, wherein the calculated masses of the one or more capsid proteins are compared to the theoretical masses of the one or more capsid proteins of one or more virus serotypes.

Claim 203 (new): The method of claim 128, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 204 (new): The method of claim 128, wherein the liquid chromatography is reverse phase chromatography.

Claim 205 (new): The method of claim 204, wherein the reverse phase chromatography is a C4 or C8 reverse chromatography.

Claim 206 (new): The method of claim 128, wherein the liquid chromatography is ultra-performance liquid chromatography (UPLC).

Claim 207 (new): The method of claim 128, wherein the mass spectrometry comprises assisted calibration.

Claim 208 (new): The method of claim 207, wherein sodium iodide is used as a calibrant.

Claim 209 (new): The method of claim 128, wherein the viral particle comprises a viral vector encoding a heterologous transgene.

Claim 210 (new): The method of claim 134, wherein the calculated masses of the fragments of the one or more capsid proteins are compared to the theoretical masses of fragments of the one or more capsid proteins of one or more viral serotypes.

Claim 211 (new): The method of claim 134, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 212 (new): The method of claim 134, wherein the liquid chromatography is reverse phase liquid chromatography.

Claim 213 (new): The method of claim 212, wherein the reverse phase chromatography is a C18 reverse chromatography.

Claim 214 (new): The method of claim 134, wherein the reduction is by subjecting the viral particle to dithiothreitol, beta-mercaptoethanol, or tris(2-carboxyethyl)phosphine (TCEP).

Claim 215 (new): The method of claim 134, wherein the alkylation is by subjecting the viral particle to iodoacetic acid, iodoacetamide, or 4-vinylpyridine.

Claim 216 (new): The method of claim 134, wherein the digestion is an endopeptidase digestion.

Claim 217 (new): The method of claim 216, wherein the endopeptidase digestion is a trypsin digestion, a LysC digestion, an Asp-N digestion or a Glu-C digestion.

Claim 218 (new): The method of claim 134, wherein the viral particle comprises a viral vector encoding a heterologous transgene.

REMARKS

Claims 1, 3, 29, 31, 61-63, 89-92, 100, 128, 130, 134, 136, 142, and 150-154 were pending in the present application. Claims 3, 31, 62-63, 89-92, 100, 130, 136, 142, and 150-154 were withdrawn from consideration. By virtue of this response, claims 1, 29, 61, 128, and 134 have been amended, claims 3, 31, 62-63, 89-92, 100, 130, 136, 142, and 150-154 have been canceled, and new claims 181-218 have been added. Accordingly, claims 1, 29, 61, 128, 134, and 181-218 are currently under consideration.

Support for the amended claims may be found throughout the specification. Support for the amendment to claims 1, 29, 61, 128, and 134 may be found, for example, in paragraph [0015]. Support for new claim 181 may be found, for example in original claim 2. Support for new claim 182 may be found, for example in original claim 5. Support for new claim 183 may be found, for example in original claim 6. Support for new claim 184 may be found, for example in original claim 7. Support for new claim 185 may be found, for example in original claim 8. Support for new claim 186 may be found, for example in original claim 17. Support for new claim 187 may be found, for example in original claim 20. Support for new claim 188 may be found, for example in original claim 21. Support for new claim 189 may be found, for example in original claim 23. Support for new claim 190 may be found, for example in original claim 24. Support for new claim 191 may be found, for example in original claim 30. Support for new claim 192 may be found, for example in original claim 39. Support for new claim 193 may be found, for example in original claim 40. Support for new claim 194 may be found, for example in original claim 41. Support for new claim 195 may be found, for example in original claim 42. Support for new claim 196 may be found, for example in original claim 33. Support for new claim 197 may be found, for example in original claim 34. Support for new claim 198 may be found, for example in original claims 35 and 36. Support for new claim 199 may be found, for example in original claim 37. Support for new claim 200 may be found, for example in original claim 55. Support for new claim 201 may be found, for example in original claim 56. Support for new claim 202 may be found, for example in original claim 129. Support for new claim 203 may be found, for example in original claim 132. Support for new claim 204 may be found, for

example in original claim 132. Support for new claim 205 may be found, for example in original claim 8. Support for new claim 206 may be found, for example in original claim 17. Support for new claim 207 may be found, for example in original claim 20. Support for new claim 208 may be found, for example in original claim 21. Support for new claim 209 may be found, for example in original claim 133. Support for new claim 210 may be found, for example in original claim 135. Support for new claim 211 may be found, for example in original claim 138. Support for new claim 212 may be found, for example in original claim 138. Support for new claim 213 may be found, for example in original claim 42. Support for new claim 214 may be found, for example in original claim 33. Support for new claim 215 may be found, for example in original claim 34. Support for new claim 216 may be found, for example in original claims 35 and 36. Support for new claim 217 may be found, for example in original claim 37. Support for new claim 218 may be found, for example in original claim 139. No new matter has been added.

With respect to all claim amendments, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the patent office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application.

Applicant-Initiated Interview Summary

The Applicant and the Applicant's representative, Brian Donahue, thank Examiner Xu for his time and for his assistance during the Applicant-initiated Interview on October 14, 2021. The claimed subject matter in relation to the prior art was discussed. No agreement was reached. In accordance with MPEP 713.04, this response contains a summary of the substance of the interview.

Rejections under 35 U.S.C. § 102

Claims 29, 61 and 134 are rejected under 35 U.S.C. § 102(a)(1) as allegedly being anticipated Vliet *et al.* (*Journal of Virological Methods*, 2009) ("Vliet").

Applicant respectfully notes that claim 61 incorporates the limitations of claim 1, which the Examiner holds to be novel in view of Vliet. Therefore, pending claim 61 is novel in view of Vliet.

Nonetheless, without acquiescing to the Examiner's rejection, and solely for purposes of expediting prosecution, claims 29, 61, and 134 have been amended to recite "wherein the method is performed in the absence of a gel separation step."

Applicant respectfully submits that Vliet neither teaches nor suggests performing the disclosed method of serotype identification of adeno-associated viruses (AAVs) in the absence of a gel separation step. As such, claims 29, 61, and 134 are novel in view of Vliet.

In view of the foregoing, Applicant respectfully requests withdrawal of this § 102 rejection of the claims.

Rejections under 35 U.S.C. § 103

Claims 1 and 128 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Vliet *et al.* (*Journal of Virological Methods*, 2009) ("Vliet") in view of Bark *et al.* (*J. Am. Chem. Soc.* 2001) ("Bark").

Applicant respectfully traverses.

Without acquiescing to the Examiner's rejection, and for purposes of expediting prosecution, claims 1 and 128 have been amended to recite "wherein the method is performed in the absence of a gel separation step."

Applicant respectfully submits that it would not have been obvious to a person of ordinary skill in the art to combine the teachings of Vliet and Bark with a reasonable expectation of success to arrive at the presently claimed invention. Further, there is no teaching, suggestion, or motivation in Vliet and Bark that would have led one of ordinary skill to modify or combine the references to arrive at the presently claimed invention.

First, Vliet discloses that samples of AAV particles “were boiled for 3 min, centrifuged briefly and loaded on a 10% polyacrylamide gel”, after which SDS-PAGE was performed and “AAV bands were cut from the gel”. The reducing, alkylating, and digestion steps were then performed on the cut slices of the gel containing the AAV capsid proteins, prior to elution of the resulting peptide fragments from the gel followed by LC/MS/MS analysis of the eluted fragments. *See* 2.5.1. SDS-PAGE, 2.5.2. In-gel digestion, and 2.5.3. Mass spectrometry. Vliet is completely silent regarding a method to determine the serotype of a viral particle comprising a) denaturing the viral particle, b) subjecting the denatured viral particle to liquid chromatography/mass spectrometry (LC/MS), and c) determining the masses of one or more capsid proteins of the viral particle, *wherein the method is performed in the absence of a gel separation step*, as required by the amended claims.

Further, Vliet teaches away from performing the disclosed method in the absence of a gel separation step. Vliet explains that “The SDS-PAGE gel functions as a separation step for the three overlapping AAV capsid proteins that comprise the virion as well as impurities that may be present in the sample; therefore, samples of varying levels of purity can be analyzed.” *See* 3. Results. Therefore, one of ordinary skill in the art reading Vliet would not have a reasonable expectation of success in performing the disclosed method in the absence of a gel separation step, as required by the claims, since according to Vliet, this would not enable separation of the overlapping AAV capsid proteins and analysis of samples of varying levels of purity.

Bark does not cure the defects of Vliet. Bark is directed to the development of a method for high-temperature proteolytic digestion using a thermotolerant protease (thermolysin) to generate protein fragments for analysis via mass spectrometry. One of the proteins analyzed using the disclosed method is a capsid protein from the HK97 virus. The Examiner alleges that “Bark teaches directly subjecting the denatured virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) (Fig. 1, page 1774, par 4).” *See* Office Action dated July 9, 2021, page 5. Applicant respectfully disagrees.

The method disclosed in Bark is directed to *thermolysin*-mediated proteolysis of proteins, and does not teach performing the method without a protease. Bark attempts to overcome the challenges associated with proteolysis in proteomic techniques by taking advantage of “thermal denaturation to generate a facile proteolysis method for identifying proteins.” Importantly, Bark states that “The key to this method is the use of a thermophilic enzyme, thermolysin, that exhibits optimal activity at elevated temperatures.” *See* page 1774, paragraph 3. Thermolysin is well-known in the art to be a thermostable protease. Nowhere in Bark does it describe directly subjecting denatured viral capsid proteins to LC/MS without first subjecting them to proteolytic digestion with a protease.

The Examiner cites Figure 1 of Bark as teaching directly subjecting the denatured HK97 virus particle to LC/MS. *See* Office Action dated July 9, 2021, page 5. Applicant respectfully notes that Figure 1 shows mass fragments of the HK97 viral capsid, and does not show the mass of an intact, non-fragmented viral capsid protein. The largest panel of Figure 1, with an x-axis ranging from 500 to 4000 m/z, shows a large peak at 1263 m/z. Bark explains that “The 1263 (1263.66) mass peptide fragment appears most rapidly during the digestion process. This corresponds to residues 162-181 or 173-182 in the capsid sequence.” *See* page 1774, paragraph 5, emphasis added. Therefore, the 1263 m/z peak in Figure 1 corresponds to a peptide fragment of the capsid protein resulting from thermolysin digestion, and not the entire, undigested capsid protein. Figure 1 further contains an inset panel showing additional mass fragments, which includes a tilde over the peak at 1263 m/z to show that the peak has been cut off in the inset. The largest mass fragment shown in at 2467 m/z, which is well below the sequence-predicted mass of the intact HK97 gp5 capsid protein (42,243 Da; UniProt P49861). The Figure 1 caption also discusses the rapid thermolysin digestion conditions used to generate the detected fragments. While the Figure 1 caption points out that “Trypsin cleavage showed no significant fragmentation within this time”, Figure 1 does not show a mass chromatograph in which the mass of the unfragmented HK97 gp5 capsid protein can be detected. Therefore, Bark does not disclose that the samples containing the trypsin-treated (unfragmented) capsid protein were subjected to LC/MS, or that the mass of the unfragmented capsid protein was thus determined. In view of the foregoing, Applicant respectfully submits that Bark does not teach or

suggest directly subjecting a viral particle to LC/MS and determining its mass without using a protease.

Further, Applicant respectfully submits that, even if Bark did teach directly subjecting a viral particle to LC/MS without using a protease, with which Applicant respectfully disagrees, one of skill in the art would not look to this teaching to overcome the deficiencies of Vliet to arrive at the claimed invention. HK97 is a phage with only one major capsid protein which interlinks to form the viral capsid. *See* page 1774, paragraphs 5 and 6 of Bark. HK97 stands in stark contrast to AAVs, which have three capsid proteins (VP1, VP2, and VP3) with serotype-dependent sequences and masses. As explained above, Vliet discusses the need for an SDS-PAGE gel for analyzing AAV, which “functions as a separation step for the three overlapping AAV capsid proteins.” *See* 3. Results of Vliet. Therefore, one of ordinary skill in the art reading Bark would not have a reasonable expectation of success in combining the teachings of Vliet and Bark to determine the serotype of an AAV particle, since Bark discloses only a simple phage particle and do provide a means to analyze VP1, VP2, and VP3 in the absence of a gel separation step.

The Examiner alleges that, because Bark discusses the long times required for adequate proteolysis in proteomic techniques, it would have thus been obvious to perform the method without using a protease in order to save the time required for adequate proteolysis. *See* Office Action dated July 9, 2021, page 5. However, as discussed above, the authors of Bark do not teach or suggest bypassing proteolytic digestion and directly subjecting denatured viral particles to LC/MS. Instead, they propose to overcome the aforementioned challenges through the use of a thermotolerant thermolysin capable of rapid proteolytic digestion at high temperatures. Thus, Bark does not teach or suggest directly subjecting denatured viral particles to LC/MS without using a protease.

For at least the reasons above, Applicant respectfully submits that the claims, as amended, are not obvious in view of the teachings of Vliet and Bark. Therefore, Applicant requests that the rejection of claims 1 and 128 be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. **15979-20141.00**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 9, 2021

Respectfully submitted,

Electronic signature: /Brian A. Donahue/

Brian A. Donahue

Registration No.: 58,206

MORRISON & FOERSTER LLP

755 Page Mill Road

Palo Alto, CA 94304-1018

+1 (650) 813-5632



UNITED STATES PATENT AND TRADEMARK OFFICE

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Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO. Includes application details for Sanofi/Genzyme and examination information.

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):

- EOfficePA@mofo.com
PatentDocket@mofo.com
pair_mofo@firsttofile.com

DETAILED ACTION

1. The amendment filed on 11/09/2021 has been entered and fully considered. Claims 1, 3, 29, 31, 61-63, 89-92, 100, 128, 130, 134, 136, 142, 150-154 and 181-218 are pending. Claims 3, 31, 62-63, 89-92, 100, 130, 136, 142 and 150-154 have been withdrawn from consideration. Claims 1, 29, 61, 128, 134 and 181-218 are considered on merits, of which claim 1, 29, 61, 128 and 134 are amended, and Claims 181-218 are newly added.

Response to Amendment

2. In response to amendment, the examiner establish rejection under 35 U.S.C 112(b), and modifies rejection over the prior art established in the previous Office action.

Notice of Pre-AIA or AIA Status

3. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Rejections - 35 USC § 112

4. The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. **Claim 198-199** are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

6. Claim 198 recites the limitation "the digestion" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. **Claim 1, 29, 61, 128 and 134, 181, 183-186, 189-191, 193-206 and 209-218** is/are rejected under 35 U.S.C. 103 as being unpatentable over Vliet et al. (Journal of Virological Methods, 2009, IDS) (Vliet) in view of Bark et al. (J. Am. Chem. Soc. 2001, IDS) (Bark).

Regarding claim 1, Vliet teaches a method to determine the serotype of an adeno-associated virus (AAV) particle (abstract) comprising

- a) denaturing the AAV particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured and in-gel digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) (page 169, par 6), and
- c) determining the masses of VP1, VP2 and VP3 of the AAV particle (page 171, par 1);

wherein the specific combination of masses of VP1, VP2 and VP3 are indicative of the AAV serotype (Table 2, page 171, par 1).

Vliet does not specifically teach wherein the method is performed in the absence of a gel separation step. However, Bark teaches directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis.” (page 1774, par 1); “Two limitations of this method are the time required for adequate proteolysis and the resistance of some proteins to digestion.” (page 1774, par 2). “We have taken advantage of thermal denaturation to generate a facile proteolysis method for identifying proteins.” (page 1774, par 3). At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured and digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for gel separation.

Regarding claim 29, Vliet teaches a method to determine the serotype of an adeno-associated virus (AAV) particle (abstract) comprising

- a) denaturing the AAV particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured AAV particle to reduction and/or alkylation (page 169, par 5),
- c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle (page 169, par 5),
- d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS) (page 170, par 2), and
- e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle (page 171, par 1);

wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype (Table 2, page 171, par 1).

Again, Vliet does not specifically teach wherein the method is performed in the absence of a gel separation step. However, Bark teaches directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis.” (page 1774, par 1); “Two limitations of this method are the time required for adequate proteolysis and the resistance of some proteins to digestion.” (page 1774, par 2). “We have taken advantage of thermal denaturation to generate a facile proteolysis method for identifying proteins.” (page 1774, par 3). At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured and digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for gel separation.

Regarding claim 61, Vliet teaches a method of determining the serotype of an AAV particle comprising the method of claim 1 combined with a method to determine the serotype of an adeno-associated virus (AAV) particle (abstract) comprising

- a) denaturing the AAV particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured AAV particle to reduction and/or alkylation (page 169, par 5),
- c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle (page 169, par 5),
- d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS) (page 169, par 6, page 170, par 2), and
- e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle (page 169, par 6);

wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype (Table 2, page 171, par 1).

Again, Vliet does not specifically teach wherein the method is performed in the absence of a gel separation step. However, Bark teaches directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis.” (page 1774, par 1); “Two limitations of this method are the time required for adequate proteolysis and the resistance of some proteins to digestion.” (page 1774, par 2). “We have taken advantage of thermal denaturation to generate a facile proteolysis method for identifying proteins.” (page 1774, par 3). At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured and digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for gel separation.

Regarding claim 128, Vliet teaches a method to determine the serotype of a viral particle (abstract) comprising

- a) denaturing the viral particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured and in-gel digested viral particle to liquid chromatography/mass spectrometry (LC/MS) (page 169, par 6), and

c) determining the masses of one or more capsid proteins of the viral particle (page 171, par 1);

wherein the specific combination of masses of the one or more capsid proteins are indicative of the virus serotype (Table 2, page 171, par 1).

Again, Vliet does not specifically teach wherein the method is performed in the absence of a gel separation step. However, Bark teaches directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis.” (page 1774, par 1); “Two limitations of this method are the time required for adequate proteolysis and the resistance of some proteins to digestion.” (page 1774, par 2). “We have taken advantage of thermal denaturation to generate a facile proteolysis method for identifying proteins.” (page 1774, par 3). At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured and digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for gel separation.

Regarding claim 134, Vliet teaches a method to determine the serotype of a viral particle (abstract) comprising

- a) denaturing the viral particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured viral particle to reduction and/or alkylation (page 169, par 5),
- c) subjecting the denatured viral particle to digestion to generate fragments of one or more capsid proteins of the viral particle (page 169, par 5),
- d) subjecting the fragments of the one or more capsid proteins to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS) (page 170, par 2), and
- e) determining the masses of fragments of the one or more capsid proteins of the viral particle (pae 169, par 6);

wherein the specific combination of masses of fragments of the one or more capsid proteins are indicative of the viral serotype (Table 2, page 171, par 1).

Again, Vliet does not specifically teach wherein the method is performed in the absence of a gel separation step. However, Bark teaches directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis.” (page 1774, par 1); “Two limitations of this method are the time required for adequate proteolysis and the resistance of some proteins to digestion.” (page 1774, par 2). “We have taken advantage of thermal denaturation to generate a facile proteolysis method for identifying proteins.” (page 1774, par 3). At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured and digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for gel separation.

Regarding claim 181, 191, 202 and 210, Vliet teaches that wherein the calculated masses of VP1, VP2 and VP3 are compared to the theoretical masses of VP 1, VP2 and VP3 of one or more AAV serotypes (Fig. 2, page 168, par 3).

Regarding claim 183, 193, 203 and 211, Vliet teaches that wherein the liquid chromatography is reverse phase liquid chromatography (C18 column), size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography (page 169, par 6).

Regarding claim 184, 194, 204 and 212, Vliet teaches that wherein the liquid chromatography is reverse phase chromatography (page 169, par 6).

Regarding claim 185 and 205, while Vliet teaches that wherein the reverse phase chromatography is a C18 reverse chromatography (page 169, par 6), Vliet does not teach that wherein the reverse phase chromatography is a C4 or C8 reverse chromatography. However, like C18, C4 and C8 are known reverse phase columns. C18 has 18 carbon atoms while C8 has only 8 carbon atoms. C18 has a longer carbon chain, but C8 has a shorter one. C18 has higher retention while C8 has shorter

retention. C18 has higher hydrophobicity, but C8 has a lower hydrophobicity. At time before the filing it would have been obvious to one of ordinary skill in the art to optimize the hydrophobicity of the reverse phase column, by routine experimentation.

Regarding claim 186 and 206, Vliet teaches that wherein the liquid chromatography is ultra- performance liquid chromatography (UPLC) (page 169, par 6).

Regarding claim 189 and 200, Vliet teaches that wherein the AAV particle is a recombinant AAV (rAAV) particle (abstract).

Regarding claim 190 and 201, Vliet teaches that wherein the AAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV4 capsid, an AAV5 capsid, an AAV6 capsid, an AAV7 capsid, an AAV8 capsid, an AAVrh8 capsid, an AAV9 capsid, an AAV10 capsid, an AAVrh10 capsid, an AAV I1 capsid, an AAV 12 capsid, an AAV LK03 capsid, an AAV2R471A capsid, an AAV2/2-7m8 capsid, an AAV DJ capsid, an AAV DJ8 capsid, an AAV2 N587A capsid, an AAV2 E548A capsid, an AAV2 N708A capsid, an AAV V708K capsid, a goat AAV capsid, an AAV1/AAV2 chimeric capsid, a bovine AAV capsid, a mouse AAV capsid rAAV2/HBoVI (chimeric AAV / human bocavirus virus 1), an AAV2HBKO capsid, an AAVPHP.B capsid or an AAVPHP.eB capsid (Fig. 1, page 167, par 2).

Regarding claim 195 and 213, Vliet teaches that wherein the reverse phase chromatography is a C18 reverse chromatography (page 169, par 6).

Regarding claim 196 and 214, Vliet teaches that wherein the reduction is by subjecting the AAV particle to dithiothreitol, beta-mercaptoethanol, or tris(2-arboxyethyl)phosphine (TCEP) (page 169, par 5).

Regarding claim 197 and 215, Vliet teaches that wherein the alkylation is by subjecting the AAV particle to iodoacetic acid, iodoacetamide, or 4-vinylpyridine (page 169, par 5).

Regarding claim 198 and 216, Vliet teaches that wherein the digestion is an endopeptidase digestion (page 169, par 5).

Regarding claim 199 and 217, Vliet teaches that wherein the endopeptidase digestion is a trypsin digestion (page 169, par 5).

Regarding claim 209 and 218, Vliet teaches that wherein the viral particle comprises a viral vector encoding a heterologous transgene (page 167, par 1).

9. **Claim 182, 192** is/are rejected under 35 U.S.C. 103 as being unpatentable over Vliet in view of Bark as applied to claims 1, 29, 61, 128 and 134, 181, 183-186, 189-191, 193-206 and 209-218 above, and further in view of Anderson (US 2014/0017716).

Regarding claim 182 and 192, Vliet does not teach that wherein the AAV particle is denatured with acetic acid, guanidine hydrochloride, and/or an organic solvent. However, Anderson teaches that protein sample is denatured with guanidine hydrochloride, and/or an organic solvent (par 0022)]. At time before the filing, it would have been obvious to one of ordinary skill in the art to select guanidine hydrochloride, and/or an organic solvent for denaturizing the AAV particle, because the selection is based on its suitability for the intended use.

10. **Claim 187-188 and 207-208** is/are rejected under 35 U.S.C. 103 as being unpatentable over Vliet in view of Bark as applied to claims 1, 29, 61, 128 and 134, 181, 183-186, 189-191, 193-206 and 209-218 above, and further in view of Taylor et al. (US 2013/0217789)(Taylor).

Regarding claim 187-188 and 207-208, Vliet does not specifically teach that wherein the mass spectrometry comprises assisted calibration and sodium iodide is used as a calibrant. However, Taylor teaches that the mass spectrometry comprises assisted calibration and sodium iodide is used as a calibrant (par [0125]). At time before the filing it would have been obvious to one of ordinary skill in the art to incorporate assisted calibration in mass spectrometry and use sodium iodide as a calibrant, in order to obtain accurate mass measurement.

Response to Arguments

11. Applicant's arguments filed 11/09/2021 have been fully considered but they are not persuasive.

Applicant argues that "Vliet teaches away from performing the disclosed method in the absence of a gel separation step. Vliet explains that "The SDS-PAGE gel functions as a separation step for the three overlapping AAV capsid proteins that comprise the virion as well as impurities that may be present in the sample; therefore, samples of varying levels of purity can be analyzed." See 3. Results. Therefore, one of ordinary skill in the art reading Vliet would not have a reasonable expectation of

success in performing the disclosed method in the absence of a gel separation step, as required by the claims, since according to Vliet, this would not enable separation of the overlapping AAV capsid proteins and analysis of samples of varying levels of purity..” (remark, page 13, par 2).

This agreement is not persuasive. Vliet teaches the benefit of performing gel separation. However, the benefit of performing gel separation is not teach away for without gel separation, because Vliet teaches that gel separation is a good to have step, instead of a must have step.

Applicant argues that “The method disclosed in Bark is directed to thermolysin-mediated proteolysis of proteins, and does not teach performing the method without a protease. Bark attempts to overcome the challenges associated with proteolysis in proteomic techniques by taking advantage of “thermal denaturation to generate a facile proteolysis method for identifying proteins.” Importantly, Bark states that “The key to this method is the use of a thermophilic enzyme, thermolysin, that exhibits optimal activity at elevated temperatures.” See page 1774, paragraph 3. Thermolysin is well-known in the art to be a thermostable protease. Nowhere in Bark does it describe directly subjecting denatured viral capsid proteins to LC/MS without first subjecting them to proteolytic digestion with a protease.” (remark, page 14, par 1).

This argument is not persuasive. First, performing the method without a protease is not recited in the instant claims. Second, Bark is cited for directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for the gel separation (Fig. 1, page 1774, par 4).

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to XIAOYUN R XU, Ph. D. whose telephone number is (571)270-5560. The examiner can normally be reached on M-F 8am-5pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lyle Alexander can be reached on 571-272-1254. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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 <https://ppair-my.uspto.gov/pair/PrivatePair>. 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.

/XIAOYUN R XU, Ph.D./
Primary Examiner, Art Unit 1797

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Xiaoying JIN et al.

Application No.: 16/325,653

Filed: August 14, 2017 (Int'l)

For: METHODS FOR DETECTING AAV

Confirmation No.: 1002

Art Unit: 1797

Examiner: X. Xu

AMENDMENT AFTER FINAL ACTION UNDER 37 C.F.R. 1.116

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

Dear Commissioner:

INTRODUCTORY COMMENTS

This is in response to the final Office Action dated November 17, 2021, for which a response is due on February 17, 2022. Accordingly, this response is timely filed. This response accompanies a Certification and Request for Consideration under the After Final Consideration Pilot Program 2.0. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

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

Remarks/Arguments begin on page 10 of this paper.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Xiaoying JIN et al.

Application No.: 16/325,653

Filed: August 14, 2017 (Int'l)

For: METHODS FOR DETECTING AAV

Confirmation No.: 1002

Art Unit: 1797

Examiner: X. Xu

AMENDMENT AFTER FINAL ACTION UNDER 37 C.F.R. 1.116

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

Dear Commissioner:

INTRODUCTORY COMMENTS

This is in response to the final Office Action dated November 17, 2021, for which a response is due on February 17, 2022. Accordingly, this response is timely filed. This response accompanies a Certification and Request for Consideration under the After Final Consideration Pilot Program 2.0. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

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

Remarks/Arguments begin on page 10 of this paper.

AMENDMENTS TO THE CLAIMS

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

In the claims:

Claim 1 (currently amended): A method to determine the serotype of an adeno-associated virus (AAV) particle comprising

- a) denaturing the AAV particle,
 - b) directly subjecting the denatured AAV particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis, and
 - c) determining the masses of VP1, VP2 and VP3 of the AAV particle;
- wherein the specific combination of masses of VP1, VP2 and VP3 are indicative of the AAV serotype,
- and wherein the method is performed in the absence of a gel separation step.

Claims 2-28 (canceled)

Claim 29 (previously presented): A method to determine the serotype of an adeno-associated virus (AAV) particle comprising

- a) denaturing the AAV particle,
 - b) subjecting the denatured AAV particle to reduction and/or alkylation,
 - c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle,
 - d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS), and
 - e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle;
- wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype,
- and wherein the method is performed in the absence of a gel separation step.

Claims 30-60 (canceled)

Claim 61 (previously presented): A method of determining the serotype of an AAV particle comprising the method of claim 1 combined with a method to determine the serotype of an adeno-associated virus (AAV) particle comprising

- a) denaturing the AAV particle,
- b) subjecting the denatured AAV particle to reduction and/or alkylation,
- c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle,
- d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS), and
- e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle; wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype, and wherein the method is performed in the absence of a gel separation step.

Claims 62-127 (canceled)

Claim 128 (currently amended): A method to determine the serotype of a viral particle comprising

- a) denaturing the viral particle,
- b) directly subjecting the denatured viral particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis, and
- c) determining the masses of one or more capsid proteins of the viral particle; wherein the specific combination of masses of the one or more capsid proteins are indicative of the virus serotype, and wherein the method is performed in the absence of a gel separation step.

Claims 129-133 (canceled)

Claim 134 (previously presented): A method to determine the serotype of a viral particle comprising

- a) denaturing the viral particle,
 - b) subjecting the denatured viral particle to reduction and/or alkylation,
 - c) subjecting the denatured viral particle to digestion to generate fragments of one or more capsid proteins of the viral particle,
 - d) subjecting the fragments of the one or more capsid proteins to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS), and
 - e) determining the masses of fragments of the one or more capsid proteins of the viral particle;
- wherein the specific combination of masses of fragments of the one or more capsid proteins are indicative of the viral serotype,
- and wherein the method is performed in the absence of a gel separation step.

Claims 135-180 (canceled)

Claim 181 (previously presented): The method of claim 1, wherein the calculated masses of VP1, VP2 and VP3 are compared to the theoretical masses of VP1, VP2 and VP3 of one or more AAV serotypes.

Claim 182 (previously presented): The method of claim 1, wherein the AAV particle is denatured with acetic acid, guanidine hydrochloride, and/or an organic solvent.

Claim 183 (previously presented): The method of claim 1, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 184 (previously presented): The method of claim 1, wherein the liquid chromatography is reverse phase chromatography.

Claim 185 (previously presented): The method of claim 184, wherein the reverse phase chromatography is a C4 or C8 reverse chromatography.

Claim 186 (previously presented): The method of claim 1, wherein the liquid chromatography is ultra-performance liquid chromatography (UPLC).

Claim 187 (previously presented): The method of claim 1, wherein the mass spectrometry comprises assisted calibration.

Claim 188 (previously presented): The method of claim 187, wherein sodium iodide is used as a calibrant.

Claim 189 (previously presented): The method of claim 1, wherein the AAV particle is a recombinant AAV (rAAV) particle.

Claim 190 (previously presented): The method of claim 1, wherein the AAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV4 capsid, an AAV5 capsid, an AAV6 capsid, an AAV7 capsid, an AAV8 capsid, an AAVrh8 capsid, an AAV9 capsid, an AAV10 capsid, an AAVrh10 capsid, an AAV11 capsid, an AAV12 capsid, an AAV LK03 capsid, an AAV2R471A capsid, an AAV2/2-7m8 capsid, an AAV DJ capsid, an AAV DJ8 capsid, an AAV2 N587A capsid, an AAV2 E548A capsid, an AAV2 N708A capsid, an AAV V708K capsid, a goat AAV capsid, an AAV1/AAV2 chimeric capsid, a bovine AAV capsid, a mouse AAV capsid rAAV2/HBoV1 (chimeric AAV / human bocavirus virus 1), an AAV2HBKO capsid, an AAVPHP.B capsid or an AAVPHP.eB capsid.

Claim 191 (previously presented): The method of claim 29, wherein the calculated masses of the fragments of VP1, VP2 and/or VP3 are compared to the theoretical masses of fragments of VP1, VP2 and/or VP3 of one or more AAV serotypes.

Claim 192 (previously presented): The method of claim 29, wherein the AAV particle is denatured with acetic acid, guanidine hydrochloride and/or an organic solvent.

Claim 193 (previously presented): The method of claim 29, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 194 (currently amended): The method of claim [[1]]29, wherein the liquid chromatography is reverse phase liquid chromatography.

Claim 195 (previously presented): The method of claim 194, wherein the reverse phase chromatography is a C18 reverse chromatography.

Claim 196 (previously presented): The method of claim 29, wherein the reduction is by subjecting the AAV particle to dithiothreitol, beta-mercaptoethanol, or tris(2-carboxyethyl)phosphine (TCEP).

Claim 197 (previously presented): The method of claim 29, wherein the alkylation is by subjecting the AAV particle to iodoacetic acid, iodoacetamide, or 4-vinylpyridine.

Claim 198 (currently amended): The method of claim [[1]]29, wherein the digestion is an endopeptidase digestion.

Claim 199 (previously presented): The method of claim 198, wherein the endopeptidase digestion is a trypsin digestion, a LysC digestion, an Asp-N digestion or a Glu-C digestion.

Claim 200 (previously presented): The method of claim 29, wherein the AAV particle is a recombinant AAV (rAAV) particle.

Claim 201 (previously presented): The method of claim 29, wherein the AAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV4 capsid, an AAV5 capsid, an AAV6 capsid, an AAV7 capsid, an AAV8 capsid, an AAVrh8 capsid, an AAV9 capsid, an AAV10 capsid, an AAVrh10 capsid, an AAV11 capsid, an AAV12 capsid, an AAV LK03 capsid, an AAV2R471A capsid, an AAV2/2-7m8 capsid, an AAV DJ capsid, an AAV DJ8 capsid, an AAV2 N587A capsid, an AAV2 E548A capsid, an AAV2 N708A capsid, an AAV V708K capsid, a goat AAV capsid, an AAV1/AAV2 chimeric capsid, a bovine AAV capsid, a mouse AAV capsid rAAV2/HBoV1 (chimeric AAV / human bocavirus virus 1), an AAV2HBKO capsid, an AAVPHP.B capsid or an AAVPHP.eB capsid.

Claim 202 (previously presented): The method of claim 128, wherein the calculated masses of the one or more capsid proteins are compared to the theoretical masses of the one or more capsid proteins of one or more virus serotypes.

Claim 203 (previously presented): The method of claim 128, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 204 (previously presented): The method of claim 128, wherein the liquid chromatography is reverse phase chromatography.

Claim 205 (previously presented): The method of claim 204, wherein the reverse phase chromatography is a C4 or C8 reverse chromatography.

Claim 206 (previously presented): The method of claim 128, wherein the liquid chromatography is ultra-performance liquid chromatography (UPLC).

Claim 207 (previously presented): The method of claim 128, wherein the mass spectrometry comprises assisted calibration.

Claim 208 (previously presented): The method of claim 207, wherein sodium iodide is used as a calibrant.

Claim 209 (previously presented): The method of claim 128, wherein the viral particle comprises a viral vector encoding a heterologous transgene.

Claim 210 (previously presented): The method of claim 134, wherein the calculated masses of the fragments of the one or more capsid proteins are compared to the theoretical masses of fragments of the one or more capsid proteins of one or more viral serotypes.

Claim 211 (previously presented): The method of claim 134, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 212 (previously presented): The method of claim 134, wherein the liquid chromatography is reverse phase liquid chromatography.

Claim 213 (previously presented): The method of claim 212, wherein the reverse phase chromatography is a C18 reverse chromatography.

Claim 214 (previously presented): The method of claim 134, wherein the reduction is by subjecting the viral particle to dithiothreitol, beta-mercaptoethanol, or tris(2-carboxyethyl)phosphine (TCEP).

Claim 215 (previously presented): The method of claim 134, wherein the alkylation is by subjecting the viral particle to iodoacetic acid, iodoacetamide, or 4-vinylpyridine.

Claim 216 (previously presented): The method of claim 134, wherein the digestion is an endopeptidase digestion.

Claim 217 (previously presented): The method of claim 216, wherein the endopeptidase digestion is a trypsin digestion, a LysC digestion, an Asp-N digestion or a Glu-C digestion.

Claim 218 (previously presented): The method of claim 134, wherein the viral particle comprises a viral vector encoding a heterologous transgene.

REMARKS

Claims 1, 29, 61, 128, 134, and 181-218 were pending in the present application. By virtue of this response, claims 1, 128, 194, and 198 have been amended. Accordingly, claims 1, 29, 61, 128, 134, and 181-218 are currently under consideration. Support for the amendments to claims 1 and 128 can be found at least in paragraphs [0189], [0192], and [0194] of the specification as filed. Claims 194 and 198 were amended to depend from claim 29. No new matter has been added. Entry of the claim amendments is respectfully requested.

With respect to all claim amendments, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the patent office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application.

Rejections under 35 U.S.C. § 112

Claims 198-199 are rejected under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention. Specifically, the Examiner alleges that there is insufficient antecedent basis for the limitation “the digestion” in line 1 of claim 198.

Without acquiescing to the Examiners rejection, and solely for purposes of expediting prosecution, claim 198 has been amended to depend from claim 29. Claim 29 recites “subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle”. Therefore, claims 198 and 199 as amended have sufficient antecedent basis for the limitation “the digestion”.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

Claims 1, 29, 61, 128, 134, 181, 183-186, 189-191, 193-206 and 209-218 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Vliet *et al.* (*Journal of Virological Methods*, 2009, “Vliet”) in view of Bark *et al.* (*J. Am. Chem. Soc.* 2001, Bark).

Applicant respectfully traverses.

Without acquiescing to the Examiner’s rejection, and solely for purposes of expediting prosecution, claims 1 and 128 have been amended to recite directly subjecting the denatured AAV or viral particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis.

Applicant respectfully submits that it would not have been obvious to a person of ordinary skill in the art to combine the teachings of Vliet and Bark with a reasonable expectation of success to arrive at the presently claimed invention. Further, there is no teaching, suggestion, or motivation in Vliet and Bark that would have led one of ordinary skill to modify or combine the references to arrive at the presently claimed invention.

By virtue of the amendment filed on November 9, 2021, the claims require that the method is carried out in the absence of a gel separation step. The Examiner acknowledges that Vliet does not teach performing the method in the absence of a gel separation, but alleges that Bark teaches performing the method in the absence of a gel separation step in order to save time required for gel separation. *See* the Office Action dated November 17, 2021, hereafter “Office Action”, *e.g.*, page 3. Applicant respectfully disagrees.

Applicant respectfully submits that Bark does not cure the defects of Vliet, because it does not teach performing the method in the absence of a gel separation step. Bark is directed to the development of a method for high-temperature proteolytic digestion using a thermotolerant protease (thermolysin) to generate protein fragments for analysis via mass spectrometry. The Examiner highlights specific passages of Bark: “The ***primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion***, mass spectrometry, and computer-facilitated data analysis” (page 1774, par. 1; emphasis added); “Two ***limitations of this***

method are the time required for adequate proteolysis and the resistance of some proteins to digestion” (page 1774, par. 2; *emphasis added*); and “We have taken advantage of thermal denaturation to generate a facile proteolysis method for identifying proteins” (page 1774, par. 2) *See* the Office Action, *e.g.*, page 3. These passages do not teach that the time required for gel separation is a limitation of proteomic methods; rather, these passages indicate that 2-D gel electrophoresis is a primary technique that is carried out prior to proteolytic digestion. Except for the passage above, Bark is completely silent about gel separation. Instead, Bark describes high-temperature proteolysis methods to reduce the time required for *proteolysis*, which is the limitation identified in the passages cited by the Examiner. In fact, Bark provides no description of how the samples were prepared prior to proteolysis, including whether or not a gel separation step was performed. Since, as Bark points out in paragraph 1 of page 1774, gel separation is carried out prior to proteolysis in proteomics techniques, it is not clear that the various proteins enumerated in paragraph 4 of page 1774 were not separated in a gel separation step prior to digestion. Given that Bark teaches that gel separation is a primary technique carried out prior to proteolytic digestion, one skilled in the art would assume that gel separation was used prior to the analysis. Therefore, Bark neither teaches performing the method in the absence of a gel separation step, nor suggests that proteomics methods could be performed in the absence of a gel separation step in order to save the time required for gel separation.

Further, as discussed in Applicant’s remarks filed on November 9, 2021, Vliet teaches away from performing the disclosed method in the absence of a gel separation step. Vliet explains that “The SDS-PAGE gel functions as a separation step for the three overlapping AAV capsid proteins that comprise the virion as well as impurities that may be present in the sample; therefore, samples of varying levels of purity can be analyzed.” *See* 3. Results. One of ordinary skill in the art reading Vliet would not have a reasonable expectation of success in performing the disclosed method in the absence of a gel separation step, as required by the claims, since according to Vliet, this would not enable separation of the overlapping AAV capsid proteins and analysis of samples of varying levels of purity.

The Examiner alleges that Vliet does not teach away from performing the method in the absence of a gel separation step, because it allegedly teaches that “gel separation is a good to

have step, instead of a must have step.” *See* Office Action, page 10. Applicant respectfully disagrees. Nowhere in Vliet does it teach or suggest that a gel separation step prior to digestion is optional, or that the method would be successful if carried out in the absence of a gel separation step. Rather, the references cited by the Examiner identify gel separation as a standard step in proteomic methods. *See* 3. Results of Vliet and page 1774, paragraph 1 of Bark. The fact that gel separation is a standard step is also emphasized in paragraph [0174] of the specification as filed, which states that “Conventionally, a Gel-LC/MS method (SDS-PAGE, in-gel tryptic digestion and LC/MS/MS) was used in characterization of VPs”. Applicant respectfully submits that the Examiner has not identified a cited reference that teaches or suggests that gel separation prior to digestion is optional in existing proteomic methods, or that such methods could be successfully executed without a gel separation step, prior to the priority date of the present application.

For at least the above reasons, claims 1, 29, 128, and 134, and all claims depending therefrom, are not obvious over Vliet and Bark.

With respect to claims 1 and 29, one of skill in the art would not look to the teachings of Bark to overcome the deficiencies of Vliet to arrive at method of determining the serotype of an AAV particle. HK97 is a phage with only one major capsid protein which interlinks to form the viral capsid. *See* page 1774, paragraphs 5 and 6 of Bark. HK97 stands in stark contrast to AAVs, which have three capsid proteins (VP1, VP2, and VP3) with serotype-dependent sequences and masses. As explained above, Vliet discusses the need for an SDS-PAGE gel for analyzing AAV, which “functions as a separation step for the three overlapping AAV capsid proteins.” *See* 3. Results of Vliet. Therefore, one of ordinary skill in the art reading Vliet and Bark would not have a reasonable expectation of success in combining the teachings thereof to determine the serotype of an AAV particle, since Bark discloses only a simple phage particle and do provide a means to analyze VP1, VP2, and VP3 in the absence of a gel separation step. For at least these reasons, claims 1 and 129, and all claims depending therefrom, are not obvious over Vliet and Bark.

With respect to claims 1 and 128, by virtue of the amendment filed herewith, claims 1 and 128 require that the method comprises directly subjecting the denatured AAV or viral particle to liquid chromatography/mass spectrometry (LC/MS) *intact protein analysis*. As discussed in Applicant's remarks filed on November 9, 2021, neither Vliet nor Bark teaches or suggests directly subjecting a denatured AAV or viral particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis, *i.e.*, without using a protease. For at least this reason, claims 1 and 128 as amended, and all claims depending therefrom, are not obvious over Vliet and Bark.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of the claims over Vliet and Bark.

Claims 182, 192 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Vliet in view of Bark as applied to claims 1, 29, 61, 128 and 134, 181, 183-186, 189-191, 193-206 and 209-218 above, and further in view of Anderson *et al.* (US 2014/0017716, "Anderson").

As discussed above, claims 1 and 29 and their dependents, including claims 182 and 192, are not obvious over Vliet and Bark. Anderson does not cure the defects of Vliet and Bark. Anderson is completely silent regarding determining the serotype of an viral particle in the absence of a gel separation step, and does not teach or suggest directly subjecting a denatured viral particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis. For at least these reasons, claims 182 and 192 are not obvious over Vliet, Bark, and Anderson.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of the claims over Vliet, Bark and Anderson.

Claims 187-188 and 207-208 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Vliet in view of Bark as applied to claims 1, 29, 61, 128 and 134, 181, 183-186, 189-191, 193-206 and 209-218 above, and further in view of Taylor *et al.* (US 2013/0217789, "Taylor").

As discussed above, claim 1 and its dependents, including claims 187 and 188, are not obvious over Vliet and Bark. Taylor is completely silent regarding determining the serotype of a viral particle in the absence of a gel separation step, and does not teach or suggest directly subjecting a denatured viral particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis. For at least these reasons, claims 187 and 188 are not obvious over Vliet, Bark, and Taylor.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of the claims over Vliet, Bark and Taylor.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. **15979-20141.00**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: February 17, 2022

Respectfully submitted,

Electronic signature: /Brian A. Donahue/

Brian A. Donahue

Registration No.: 58,206

MORRISON & FOERSTER LLP

755 Page Mill Road

Palo Alto, CA 94304-1018

+1 (650) 813-5632



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Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO. Includes application details for Sanofi/Genzyme and examination information.

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):

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DETAILED ACTION

1. The amendment and RCE filed on 03/10/2022 has been entered and fully considered. Claims 1, 29, 61, 128, 134, and 181-218 are pending, of which claims 1 and 128 are amended.

Response to Amendment

2. In response to amendment, the examiner withdraws rejection to claim 1 and 128 as well as dependent claims. and maintains rejection to claim 29, 61 and 134 as well as dependent claims over the prior art established in the previous Office action.

Notice of Pre-AIA or AIA Status

3. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Rejections - 35 USC § 103

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. **Claim 29, 61, 134, 191, 193, 196-197, 200-201 and 210-218** is/are rejected under 35 U.S.C. 103 as being unpatentable over Vliet et al. (Journal of Virological Methods, 2009, IDS) (Vliet) in view of Bark et al. (J. Am. Chem. Soc. 2001, IDS) (Bark).

Regarding claim 29, Vliet teaches a method to determine the serotype of an adeno-associated virus (AAV) particle (abstract) comprising

- a) denaturing the AAV particle (boiled for 3 min) (page 169, par 4),
 - b) subjecting the denatured AAV particle to reduction and/or alkylation (page 169, par 5),
 - c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle (page 169, par 5),
 - d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS) (page 170, par 2),
- and

e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle (page 171, par 1);

wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype (Table 2, page 171, par 1).

Again, Vliet does not specifically teach wherein the method is performed in the absence of a gel separation step. However, Bark teaches directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis. Masses for proteolytic fragments of the target protein generated by enzymatic degradation can be measured directly with high accuracy (± 0.005 Da for a 1000 Da peptide). Alternatively, liquid chromatography tandem mass spectrometry can be used to analyze the protein digest fragments” (page 1774, par 1). Here Bark teaches that alternatively, one can directly subject the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step. At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured and digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for gel separation.

Regarding claim 61, Vliet teaches a method of determining the serotype of an AAV particle comprising the method of claim 1 combined with a method to determine the serotype of an adeno-associated virus (AAV) particle (abstract) comprising

- a) denaturing the AAV particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured AAV particle to reduction and/or alkylation (page 169, par 5),
- c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle (page 169, par 5),
- d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS) (page 169, par 6, page 170, par 2), and

e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle (page 169, par 6);

wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype (Table 2, page 171, par 1).

Again, Vliet does not specifically teach wherein the method is performed in the absence of a gel separation step. However, Bark teaches directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis. Masses for proteolytic fragments of the target protein generated by enzymatic degradation can be measured directly with high accuracy (± 0.005 Da for a 1000 Da peptide). Alternatively, liquid chromatography tandem mass spectrometry can be used to analyze the protein digest fragments” (page 1774, par 1). Here Bark teaches that alternatively, one can directly subject the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step. At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured and digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for gel separation.

Regarding claim 134, Vliet teaches a method to determine the serotype of a viral particle (abstract) comprising

- a) denaturing the viral particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured viral particle to reduction and/or alkylation (page 169, par 5),
- c) subjecting the denatured viral particle to digestion to generate fragments of one or more capsid proteins of the viral particle (page 169, par 5),
- d) subjecting the fragments of the one or more capsid proteins to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS) (page 170, par 2), and

e) determining the masses of fragments of the one or more capsid proteins of the viral particle (page 169, par 6);

wherein the specific combination of masses of fragments of the one or more capsid proteins are indicative of the viral serotype (Table 2, page 171, par 1).

Again, Vliet does not specifically teach wherein the method is performed in the absence of a gel separation step. However, Bark teaches directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis. Masses for proteolytic fragments of the target protein generated by enzymatic degradation can be measured directly with high accuracy (± 0.005 Da for a 1000 Da peptide). Alternatively, liquid chromatography tandem mass spectrometry can be used to analyze the protein digest fragments” (page 1774, par 1). Here Bark teaches that alternatively, one can directly subject the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step. At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured and digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for gel separation.

Regarding claim 191 and 210, Vliet teaches that wherein the calculated masses of VP1, VP2 and VP3 are compared to the theoretical masses of VP 1, VP2 and VP3 of one or more AAV serotypes (Fig. 2, page 168, par 3).

Regarding claim 193 and 211, Vliet teaches that wherein the liquid chromatography is reverse phase liquid chromatography (C18 column), size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography (page 169, par 6).

Regarding claim 200, Vliet teaches that wherein the AAV particle is a recombinant AAV (rAAV) particle (abstract).

Regarding claim 201, Vliet teaches that wherein the AAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV4 capsid, an AAV5 capsid, an

AAV6 capsid, an AAV7 capsid, an AAV8 capsid, an AAVrh8 capsid, an AAV9 capsid, an AAV10 capsid, an AAVrh10 capsid, an AAV I1 capsid, an AAV 12 capsid, an AAV LK03 capsid, an AAV2R471A capsid, an AAV2/2-7m8 capsid, an AAV DJ capsid, an AAV DJ8 capsid, an AAV2 N587A capsid, an AAV2 E548A capsid, an AAV2 N708A capsid, an AAV V708K capsid, a goat AAV capsid, an AAV1/AAV2 chimeric capsid, a bovine AAV capsid, a mouse AAV capsid rAAV2/HBoVI (chimeric AAV / human bocavirus virus 1), an AAV2HBKO capsid, an AAVPHP.B capsid or an AAVPHP.eB capsid (Fig. 1, page 167, par 2).

Regarding claim 212, Vliet teaches that wherein the liquid chromatography is reverse phase chromatography (page 169, par 6).

Regarding claim 213, Vliet teaches that wherein the reverse phase chromatography is a C18 reverse chromatography (page 169, par 6).

Regarding claim 196 and 214, Vliet teaches that wherein the reduction is by subjecting the AAV particle to dithiothreitol, beta-mercaptoethanol, or tris(2-arboxyethyl)phosphine (TCEP) (page 169, par 5).

Regarding claim 197 and 215, Vliet teaches that wherein the alkylation is by subjecting the AAV particle to iodoacetic acid, iodoacetamide, or 4-vinylpyridine (page 169, par 5).

Regarding claim 216, Vliet teaches that wherein the digestion is an endopeptidase digestion (page 169, par 5).

Regarding claim 217, Vliet teaches that wherein the endopeptidase digestion is a trypsin digestion (page 169, par 5).

Regarding claim 218, Vliet teaches that wherein the viral particle comprises a viral vector encoding a heterologous transgene (page 167, par 1).

6. **Claim 192** is/are rejected under 35 U.S.C. 103 as being unpatentable over Vliet in view of Bark as applied to claims 29, 61, 134, 191, 193, 196-197, 200-201 and 210-218 above, and further in view of Anderson (US 2014/0017716).

Regarding claim 192, Vliet does not teach that wherein the AAV particle is denatured with acetic acid, guanidine hydrochloride, and/or an organic solvent. However, Anderson teaches that protein sample is denatured with guanidine hydrochloride, and/or an organic solvent (par 0022)]. At time before the filing, it would

have been obvious to one of ordinary skill in the art to select guanidine hydrochloride, and/or an organic solvent for denaturing the AAV particle, because the selection is based on its suitability for the intended use.

Allowable Subject Matter

7. **Claim 1, 128, 181-190, 194-195, 198-199 and 202-209** are allowed.

8. The following is an examiner's statement of reasons for allowance: neither Vliet nor Bark teaches or fairly suggests directly subjecting a denatured AAV or viral particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis, i.e., without using a protease.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Response to Arguments

9. Applicant's arguments filed 02/17/2022 have been fully considered but they are not persuasive to some rejections.

Applicant argues that "Applicant respectfully submits that Bark does not cure the defects of Vliet, because it does not teach performing the method in the absence of a gel separation step. Bark is directed to the development of a method for high-temperature proteolytic digestion using a thermotolerant protease (thermolysin) to generate protein fragments for analysis via mass spectrometry. The Examiner highlights specific passages of Bark: "The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis" (page 1774, par. 1; emphasis added); "Two limitations of this method are the time required for adequate proteolysis and the resistance of some proteins to digestion" (page 1774, par. 2; emphasis added), and "We have taken advantage of thermal denaturation to generate a facile proteolysis method for identifying proteins" (page 1774, par. 2) See the Office Action, e.g., page 3. These passages do not teach that the time required for gel separation is a limitation of

proteomic methods; rather, these passages indicate that 2-D gel electrophoresis is a primary technique that is carried out prior to proteolytic digestion. Except for the passage above, Bark is completely silent about gel separation. Instead, Bark describes high-temperature proteolysis methods to reduce the time required for proteolysis, which is the limitation identified in the passages cited by the Examiner. In fact, Bark provides no description of how the samples were prepared prior to proteolysis, including whether or not a gel separation step was performed. Since, as Bark points out in paragraph 1 of page 1774, gel separation is carried out prior to proteolysis in proteomics techniques, it is not clear that the various proteins enumerated in paragraph 4 of page 1774 were not separated in a gel separation step prior to digestion. Given that Bark teaches that gel separation is a primary technique carried out prior to proteolytic digestion, one skilled in the art would assume that gel separation was used prior to the analysis. Therefore, Bark neither teaches performing the method in the absence of a gel separation step, nor suggests that proteomics methods could be performed in the absence of a gel separation step in order to save the time required for gel separation.” (remark, page 11-12).

Examiner respectfully disagrees. Bark teaches directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis. Masses for proteolytic fragments of the target protein generated by enzymatic degradation can be measured directly with high accuracy (± 0.005 Da for a 1000 Da peptide). Alternatively, liquid chromatography tandem mass spectrometry can be used to analyze the protein digest fragments” (page 1774, par 1). Here Bark teaches that alternatively, one can directly subject the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step. At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured and digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for gel separation.

Applicant argues that “Vliet teaches away from performing the disclosed method in the absence of a gel separation step. Vliet explains that “The SDS-PAGE gel functions as a separation step for the three overlapping AAV capsid proteins that comprise the virion as well as impurities that may be present in the sample; therefore, samples of varying levels of purity can be analyzed.” See 3. Results. Therefore, one of ordinary skill in the art reading Vliet would not have a reasonable expectation of success in performing the disclosed method in the absence of a gel separation step, as required by the claims, since according to Vliet, this would not enable separation of the overlapping AAV capsid proteins and analysis of samples of varying levels of purity.” (remark, page 12, par 2).

This agreement is not persuasive. Vliet teaches the benefit of performing gel separation. However, the benefit of performing gel separation is not teach away for without gel separation, because Vliet teaches that gel separation is a good to have step, instead of a must have step.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to XIAOYUN R XU, Ph. D. whose telephone number is (571)270-5560. The examiner can normally be reached on M-F 8am-5pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Lyle Alexander can be reached on 571-272-1254. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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 <https://ppair->

my.uspto.gov/pair/PrivatePair. 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.

/XIAOYUN R XU, Ph.D./
Primary Examiner, Art Unit 1797

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Xiaoying JIN et al.

Application No.: 16/325,653

Filed: August 14, 2017 (Int'l)

For: METHODS FOR DETECTING AAV

Confirmation No.: 1002

Art Unit: 1797

Examiner: X. Xu

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION
UNDER 37 C.F.R. 1.111

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

Dear Commissioner:

INTRODUCTORY COMMENTS

This is in response to the non-final Office Action dated April 28, 2022, for which a response was due on July 28, 2022. We hereby petition and submit the fee for a three-month extension of time, thereby extending the deadline for response to October 28, 2022.

Accordingly, this response is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

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

Remarks/Arguments begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

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

In the claims:

Claim 1 (previously presented): A method to determine the serotype of an adeno-associated virus (AAV) particle comprising

- a) denaturing the AAV particle,
 - b) directly subjecting the denatured AAV particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis, and
 - c) determining the masses of VP1, VP2 and VP3 of the AAV particle;
- wherein the specific combination of masses of VP1, VP2 and VP3 are indicative of the AAV serotype,
- and wherein the method is performed in the absence of a gel separation step.

Claims 2-60 (canceled)

Claim 61 (previously presented): A method of determining the serotype of an AAV particle comprising the method of claim 1 combined with a method to determine the serotype of an adeno-associated virus (AAV) particle comprising

- a) denaturing the AAV particle,
 - b) subjecting the denatured AAV particle to reduction and/or alkylation,
 - c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle,
 - d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS), and
 - e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle;
- wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype,
- and wherein the method is performed in the absence of a gel separation step.

Claims 62-127 (canceled)

Claim 128 (previously presented): A method to determine the serotype of a viral particle comprising

- a) denaturing the viral particle,
 - b) directly subjecting the denatured viral particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis, and
 - c) determining the masses of one or more capsid proteins of the viral particle;
- wherein the specific combination of masses of the one or more capsid proteins are indicative of the virus serotype,
and wherein the method is performed in the absence of a gel separation step.

Claims 129-180 (canceled)

Claim 181 (previously presented): The method of claim 1, wherein the calculated masses of VP1, VP2 and VP3 are compared to the theoretical masses of VP1, VP2 and VP3 of one or more AAV serotypes.

Claim 182 (previously presented): The method of claim 1, wherein the AAV particle is denatured with acetic acid, guanidine hydrochloride, and/or an organic solvent.

Claim 183 (previously presented): The method of claim 1, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 184 (previously presented): The method of claim 1, wherein the liquid chromatography is reverse phase chromatography.

Claim 185 (previously presented): The method of claim 184, wherein the reverse phase chromatography is a C4 or C8 reverse chromatography.

Claim 186 (previously presented): The method of claim 1, wherein the liquid chromatography is ultra-performance liquid chromatography (UPLC).

Claim 187 (previously presented): The method of claim 1, wherein the mass spectrometry comprises assisted calibration.

Claim 188 (previously presented): The method of claim 187, wherein sodium iodide is used as a calibrant.

Claim 189 (previously presented): The method of claim 1, wherein the AAV particle is a recombinant AAV (rAAV) particle.

Claim 190 (previously presented): The method of claim 1, wherein the AAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV4 capsid, an AAV5 capsid, an AAV6 capsid, an AAV7 capsid, an AAV8 capsid, an AAVrh8 capsid, an AAV9 capsid, an AAV10 capsid, an AAVrh10 capsid, an AAV11 capsid, an AAV12 capsid, an AAV LK03 capsid, an AAV2R471A capsid, an AAV2/2-7m8 capsid, an AAV DJ capsid, an AAV DJ8 capsid, an AAV2 N587A capsid, an AAV2 E548A capsid, an AAV2 N708A capsid, an AAV V708K capsid, a goat AAV capsid, an AAV1/AAV2 chimeric capsid, a bovine AAV capsid, a mouse AAV capsid rAAV2/HBoV1 (chimeric AAV / human bocavirus virus 1), an AAV2HBKO capsid, an AAVPHP.B capsid or an AAVPHP.eB capsid.

Claim 191-201 (canceled)

Claim 202 (previously presented): The method of claim 128, wherein the calculated masses of the one or more capsid proteins are compared to the theoretical masses of the one or more capsid proteins of one or more virus serotypes.

Claim 203 (previously presented): The method of claim 128, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 204 (previously presented): The method of claim 128, wherein the liquid chromatography is reverse phase chromatography.

Claim 205 (previously presented): The method of claim 204, wherein the reverse phase chromatography is a C4 or C8 reverse chromatography.

Claim 206 (previously presented): The method of claim 128, wherein the liquid chromatography is ultra-performance liquid chromatography (UPLC).

Claim 207 (previously presented): The method of claim 128, wherein the mass spectrometry comprises assisted calibration.

Claim 208 (previously presented): The method of claim 207, wherein sodium iodide is used as a calibrant.

Claim 209 (previously presented): The method of claim 128, wherein the viral particle comprises a viral vector encoding a heterologous transgene.

Claim 210-218 (canceled)

REMARKS

Claims 1, 29, 61, 128, 134, and 181-217 were pending in the present application. By virtue of this response, claims 29, 134, 191-201, and 210-218 have been canceled. Accordingly, following entry of this amendment, claims 1, 61, 128, 181-190, and 202-209 will be under consideration. No new matter has been added. Entry of the claim amendments is respectfully requested.

With respect to all claim amendments, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the patent office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application.

Rejections under 35 U.S.C. §103

Claims 29, 61, 134, 191, 193, 196-197, 200-201 and 210-218 are rejected under 35 U.S.C. 103 as allegedly being unpatentable over Vliet et al. (Journal of Virological Methods, 2009, IDS) (Vliet) in view of Bark et al. (J. Am. Chem. Soc. 2001, IDS) (Bark).

Applicant traverses the rejection and its supporting remarks. However, without acquiescing to the Examiner's rejection, and solely to expedite prosecution, claims 29, 134, 191, 193, 196-197, 200-201 and 210-218 have been canceled without prejudice, thus rendering the rejection of said claims moot.

Applicant respectfully submits that claim 61 depends from claim 1, and therefore incorporates all of the limitations of, claim 1, which was not rejected as allegedly obvious over Vliet and Bark. Therefore, claim 61 is not obvious over Vliet and Bark. Applicant respectfully requests withdrawal of claim 61 as allegedly obvious over Vliet and Bark.

Claim 192 is rejected under 35 U.S.C. 103 as allegedly being unpatentable over Vliet in view of Bark as applied to claims 29, 61, 134, 191, 193, 196-197, 200-201 and 210-218 above, and further in view of Anderson (US 2014/0017716).

Applicant traverses the rejection and its supporting remarks. However, without acquiescing to the Examiner's rejection, and solely to expedite prosecution, claim 192 has been canceled without prejudice, thus rendering the rejection moot.

Allowed Claims

Applicant thanks the Examiner for acknowledging that 1, 128, 181-190, and 202-209 are patentable.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. **15979-20141.00**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 27, 2022

Respectfully submitted,

Electronic signature: /Sarah E. Bloch/

Sarah Bloch

Registration No.: 79,763

MORRISON & FOERSTER LLP

755 Page Mill Road

Palo Alto, CA 94304-1018

+1 (650) 813-4046



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Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO. Includes application details for Xiaoying JIN and examination information for Examiner XU, XIAOYUN.

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):

- EOfficePA@mofo.com
PatentDocket@mofo.com
pair_mofo@firsttofile.com

DETAILED ACTION

1. The amendment filed on 10/27/2022 has been entered and fully considered. Claim 29, 134, 191-201 and 210-218 are canceled. Claims 1, 61, 128, 181-190 and 202-209 are pending.

Response to Amendment

2. In response to amendment, the examiner maintains rejection to claim 61 over the prior art established in the previous Office action.

Notice of Pre-AIA or AIA Status

3. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Rejections - 35 USC § 103

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. **Claim 61** is/are rejected under 35 U.S.C. 103 as being unpatentable over Vliet et al. (Journal of Virological Methods, 2009, IDS) (Vliet) in view of Bark et al. (J. Am. Chem. Soc. 2001, IDS) (Bark).

Regarding claim 61, Vliet teaches a method of determining the serotype of an AAV particle comprising the method of claim 1 combined with a method to determine the serotype of an adeno-associated virus (AAV) particle (abstract) comprising

- a) denaturing the AAV particle (boiled for 3 min) (page 169, par 4),
- b) subjecting the denatured AAV particle to reduction and/or alkylation (page 169, par 5),
- c) subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/or VP3 of the AAV particle (page 169, par 5),
- d) subjecting the fragments of VP1, VP2 and/or VP3 to liquid chromatography/mass spectrometry-mass spectrometry (LC/MS/MS) (page 169, par 6, page 170, par 2), and

e) determining the masses of fragments of VP1, VP2 and VP3 of the AAV particle (page 169, par 6);

wherein the specific combination of masses of fragments of VP1, VP2 and VP3 are indicative of the AAV serotype (Table 2, page 171, par 1).

Vliet does not specifically teach wherein the method is performed in the absence of a gel separation step. However, Bark teaches directly subjecting the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step (Fig. 1, page 1774, par 4). Bark teaches that “The primary techniques for proteomic analysis consist of 2-D gel electrophoresis followed by proteolytic digestion, mass spectrometry, and computer-facilitated data analysis. Masses for proteolytic fragments of the target protein generated by enzymatic degradation can be measured directly with high accuracy (± 0.005 Da for a 1000 Da peptide). Alternatively, liquid chromatography tandem mass spectrometry can be used to analyze the protein digest fragments” (page 1774, par 1). Here Bark teaches that alternatively, one can directly subject the denatured and digested virus particle (HK97) to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step. At time before the filing, it would have been obvious to one of ordinary skill in the art to directly subjecting the denatured and digested AAV particle to liquid chromatography/mass spectrometry (LC/MS) without a gel separation step, in order to save time that is required for gel separation.

While claim 61 comprises limitations of claim 1, claim 61 overwrites claim 1’s limitation of “directly subjecting the denatured AAV particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis” by adding limitation “subjecting the denatured AAV particle to digestion generate fragments of VP1, VP2 and/or VP3 of the AAV particle”. Thus, claim 61 is not allowable.

Allowable Subject Matter

6. **Claim 1, 128, 181-190 and 202-209** are allowed.
7. The following is an examiner’s statement of reasons for allowance: neither Vliet nor Bark teaches or fairly suggests directly subjecting a denatured AAV or viral particle

to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis, i.e., without using a protease.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Response to Arguments

8. Applicant's arguments filed 10/27/2022 have been fully considered but they are not persuasive to claim 61 rejections.

Applicant submits that "claim 61 depends from claim 1, and therefore incorporates all of the limitations of, claim 1, which was not rejected as allegedly obvious over Vliet and Bark. Therefore, claim 61 is not obvious over Vliet and Bark. Applicant respectfully requests withdrawal of claim 61 as allegedly obvious over Vliet and Bark." (remark, page 6, par 5).

This argument is not persuasive. As has been discussed in Allowable Subject Matter above, claim 1 is allowable because neither Vliet nor Bark teaches or fairly suggests "directly subjecting a denatured AAV or viral particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis", i.e., without using a protease. While claim 61 comprises limitations of claim 1, claim 61 overwrites claim 1's limitation of "directly subjecting the denatured AAV particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis" by adding a limitation "subjecting the denatured AAV particle to digestion generate fragments of VP1, VP2 and/or VP3 of the AAV particle". Thus, claim 61 is not allowable.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to XIAOYUN R XU, Ph. D. whose telephone number is (571)270-5560. The examiner can normally be reached on M-F 8am-5pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lyle Alexander can be reached on 571-272-1254. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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 <https://ppair-my.uspto.gov/pair/PrivatePair>. 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.

/XIAOYUN R XU, Ph.D./
Primary Examiner, Art Unit 1797

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Xiaoying JIN et al.

Application No.: 16/325,653

Filed: August 14, 2017 (Int'l)

For: METHODS FOR DETECTING AAV

Confirmation No.: 1002

Art Unit: 1797

Examiner: X. Xu

AMENDMENT AFTER FINAL ACTION UNDER 37 C.F.R. 1.116

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

Dear Commissioner:

INTRODUCTORY COMMENTS

This is in response to the final Office Action dated November 8, 2022, for which a response is due on February 8, 2023. Accordingly, this response is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

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

Remarks/Arguments begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

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

In the claims:

Claim 1 (previously presented): A method to determine the serotype of an adeno-associated virus (AAV) particle comprising

- a) denaturing the AAV particle,
 - b) directly subjecting the denatured AAV particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis, and
 - c) determining the masses of VP1, VP2 and VP3 of the AAV particle;
- wherein the specific combination of masses of VP1, VP2 and VP3 are indicative of the AAV serotype,
- and wherein the method is performed in the absence of a gel separation step.

Claims 2-127 (canceled)

Claim 128 (previously presented): A method to determine the serotype of a viral particle comprising

- a) denaturing the viral particle,
 - b) directly subjecting the denatured viral particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis, and
 - c) determining the masses of one or more capsid proteins of the viral particle;
- wherein the specific combination of masses of the one or more capsid proteins are indicative of the virus serotype,
- and wherein the method is performed in the absence of a gel separation step.

Claims 129-180 (canceled)

Claim 181 (previously presented): The method of claim 1, wherein the calculated masses of VP1, VP2 and VP3 are compared to the theoretical masses of VP1, VP2 and VP3 of one or more AAV serotypes.

Claim 182 (previously presented): The method of claim 1, wherein the AAV particle is denatured with acetic acid, guanidine hydrochloride, and/or an organic solvent.

Claim 183 (previously presented): The method of claim 1, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 184 (previously presented): The method of claim 1, wherein the liquid chromatography is reverse phase chromatography.

Claim 185 (previously presented): The method of claim 184, wherein the reverse phase chromatography is a C4 or C8 reverse chromatography.

Claim 186 (previously presented): The method of claim 1, wherein the liquid chromatography is ultra-performance liquid chromatography (UPLC).

Claim 187 (previously presented): The method of claim 1, wherein the mass spectrometry comprises assisted calibration.

Claim 188 (previously presented): The method of claim 187, wherein sodium iodide is used as a calibrant.

Claim 189 (previously presented): The method of claim 1, wherein the AAV particle is a recombinant AAV (rAAV) particle.

Claim 190 (previously presented): The method of claim 1, wherein the AAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV4 capsid, an AAV5 capsid, an AAV6 capsid, an AAV7 capsid, an AAV8 capsid, an AAVrh8 capsid, an AAV9 capsid, an AAV10 capsid, an AAVrh10 capsid, an AAV11 capsid, an AAV12 capsid, an AAV LK03 capsid, an AAV2R471A capsid, an AAV2/2-7m8 capsid, an AAV DJ capsid, an AAV DJ8 capsid, an AAV2 N587A capsid, an AAV2 E548A capsid, an AAV2 N708A capsid, an AAV V708K capsid, a goat AAV capsid, an AAV1/AAV2 chimeric capsid, a bovine AAV capsid, a mouse AAV capsid rAAV2/HBoV1 (chimeric AAV / human bocavirus virus 1), an AAV2HBKO capsid, an AAVPHP.B capsid or an AAVPHP.eB capsid.

Claims 191-201 (canceled)

Claim 202 (previously presented): The method of claim 128, wherein the calculated masses of the one or more capsid proteins are compared to the theoretical masses of the one or more capsid proteins of one or more virus serotypes.

Claim 203 (previously presented): The method of claim 128, wherein the liquid chromatography is reverse phase liquid chromatography, size exclusion chromatography, hydrophilic interaction liquid chromatography, or cation exchange chromatography.

Claim 204 (previously presented): The method of claim 128, wherein the liquid chromatography is reverse phase chromatography.

Claim 205 (previously presented): The method of claim 204, wherein the reverse phase chromatography is a C4 or C8 reverse chromatography.

Claim 206 (previously presented): The method of claim 128, wherein the liquid chromatography is ultra-performance liquid chromatography (UPLC).

Claim 207 (previously presented): The method of claim 128, wherein the mass spectrometry comprises assisted calibration.

Claim 208 (previously presented): The method of claim 207, wherein sodium iodide is used as a calibrant.

Claim 209 (previously presented): The method of claim 128, wherein the viral particle comprises a viral vector encoding a heterologous transgene.

Claims 210-218 (canceled)

REMARKS

Claims 1, 61, 128, 181-190 and 202-209 were pending in the present application. By virtue of this response, claim 61 has been cancelled. Accordingly, following entry of this amendment, claims 1, 128, 181-190 and 202-209 will be under consideration. No new matter has been added. Applicant respectfully requests entry of the claim amendments as the number of claims is not increased and the amendments place the claims in condition for allowance.

With respect to all claim amendments, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the patent office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application.

Rejections under 35 U.S.C. § 103

Claim 61 is rejected under 35 U.S.C. 103 as allegedly being unpatentable over Vliet et al. (Journal of Virological Methods, 2009, IDS; hereafter “Vliet”) in view of Bark et al. (J. Am. Chem. Soc. 2001, IDS; hereafter “Bark”). Claim 61 incorporates the limitations of claim 1, which the Examiner acknowledges is not obvious over Vliet and Bark. However, the Examiner alleges that claim 61 “overwrites” claim 1’s limitation of directly subjecting the denatured AAV particle to liquid chromatography/mass spectrometry (LC/MS) intact protein analysis by adding the limitation “subjecting the denatured AAV particle to digestion to generate fragments of VP1, VP2 and/of VP3 of the AAV particle.”

Applicant respectfully disagrees. However, without acquiescing to the Examiner’s rejection, and solely to expedite prosecution, claim 61 has been canceled without prejudice, thus rendering the rejection moot.

Allowed Claims

Applicant thanks the Examiner for acknowledging that claims 1, 128, 181-190, and 202-209 are patentable.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. **15979-20141.00**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: February 3, 2023

Respectfully submitted,

Electronic signature: /Seth Snyder/
Seth Snyder

Registration No.: 60,243
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, CA 94304-1018
+1 (650) 813-4046