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|--------------------------------------------------------------------------------------------------------------|-------------|----------------------|------------------------------------|------------------|
| APPLICATION NO.                                                                                              | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.                | CONFIRMATION NO. |
| 13/750,768                                                                                                   | 01/25/2013  | Doug Amorese         | 25115-755.201                      | 1162             |
| 12754 7590 07/15/2015<br>Wilson Sonsini Goodrich & Rosati/NUGEN<br>650 Page Mill Road<br>Palo Alto, CA 94304 |             |                      | EXAMINER<br>BERTAGNA, ANGELA MARIE |                  |
|                                                                                                              |             |                      | ART UNIT                           | PAPER NUMBER     |
|                                                                                                              |             |                      | 1637                               |                  |
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|                                                                                                              |             |                      | 07/15/2015                         | ELECTRONIC       |

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

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

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

patentdocket@wsgr.com

|                              |                                       |                                       |                                                  |
|------------------------------|---------------------------------------|---------------------------------------|--------------------------------------------------|
| <b>Office Action Summary</b> | <b>Application No.</b><br>13/750,768  | <b>Applicant(s)</b><br>AMORESE ET AL. |                                                  |
|                              | <b>Examiner</b><br>Angela M. Bertagna | <b>Art Unit</b><br>1637               | <b>AIA (First Inventor to File) Status</b><br>No |

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

**Period for Reply**

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

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

**Status**

1) ☒ Responsive to communication(s) filed on 3/16/15.  
☐ 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) 1-3,6,9,10,14,40-42,45-49 and 51-62 is/are pending in the application.  
5a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

6) ☐ Claim(s) \_\_\_\_\_ is/are allowed.

7) ☒ Claim(s) 1-3,6,9,10,14,40-42,45-49 and 51-62 is/are rejected.

8) ☒ Claim(s) 55 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](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

**Application Papers**

10) ☐ The specification is objected to by the Examiner.

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

**Priority under 35 U.S.C. § 119**

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

**Certified copies:**

a) ☐ All    b) ☐ Some\*\*    c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)  
Paper No(s)/Mail Date \_\_\_\_\_.

3) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.

4) ☐ Other: \_\_\_\_\_.

## DETAILED ACTION

### *Notice of Pre-AIA or AIA Status*

1. The present application is being examined under the pre-AIA first to invent provisions.

### *Continued Examination Under 37 CFR 1.114*

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 21, 2015 has been entered.

Claims 1-3, 6, 9, 10, 14, 40-42, 45-49, and 51-62 are pending and under examination.

### *Response to Arguments*

3. Applicant's arguments filed on January 21, 2015 have been fully considered.

**Rejection of claims 1-3, 6, 9, 11, 14, and 51-53 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Borodina**

Applicant's arguments on pages 7-8 have been fully considered. Applicant argues that Borodina fails to teach steps (c) and (e) of claim 1. This argument was persuasive. The rejection has been withdrawn. The rejection has also been withdrawn because Borodina fails to teach step (b) of claim 1. The reference does not disclose ligation of the first adaptor to the nucleic acid fragments. Instead, the first adaptor is ligated to the cDNA generated from the RNA fragments (see the reproduction of Figure 5.1 of Borodina on page 8 of Applicant's arguments).

**Rejection of claims 10, 54, and 55 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Borodina in view of Vaidyanathan**

Applicant argues that the rejection should be withdrawn because Vaidyanathan fails to remedy the deficiencies of Borodina with respect to claim 1 (page 12). This argument was persuasive. The rejection has been withdrawn.

**Rejection of claims 40-42, 45-49, and 52 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Costa in view of Kurn**

Applicant argues that the references fail to teach or suggest step (b) of claim 40 (pages 9-12). This argument was persuasive. The rejection has been withdrawn.

***Double Patenting***

4. Applicant is advised that should claim 45 be found allowable, claim 48 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

***Claim Objections***

5. Claim 55 is objected to because “comprise” should be replaced with “comprises”.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of 35 U.S.C. 112(d):

Art Unit: 1637

(d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), fourth paragraph:

Subject to the [fifth paragraph of 35 U.S.C. 112 (pre-AIA)], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

Claims 53 and 59 are rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.

Claim 53 depends from claim 1 and states that the first adaptor sequence is ligated to a 5' end of the nucleic acid fragments. This recitation is not further limiting because steps (c)-(e) of claim 1 already require ligation of the first adaptor to a 5' end of the nucleic acid fragments.

Claim 59 is not further limiting for the same reason.

Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

### ***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of pre-AIA 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 –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 6, 9, 10, 14, 40-42, 45-49, 51-54, and 57-62 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Jones et al. (US 2003/0232348 A1).

Regarding claims 1, 14, and 53, Jones teaches a method for enriching for a nucleic acid sequence of interest in a sample that comprises the following steps (see Figure 3 and paragraph 94; see also Example 1 on page 14, paragraphs 129-132):

(a) fragmenting nucleic acids in the sample, wherein the nucleic acid fragments comprise the sequence of interest (paragraphs 94 and 129);

(b) ligating a first adaptor to a 5' end of the nucleic acid fragments (Figure 3 and paragraphs 94 and 129);

(c) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the nucleic acid fragments comprising the ligated first adaptor, wherein the oligonucleotides comprise a 3' portion that is complementary to the nucleic acid sequence of interest and a 5' portion comprising a second adaptor sequence (Figure 3, paragraph 94, and paragraph 129);

(d) extending said annealed oligonucleotides using a DNA polymerase to obtain extension products comprising sequence complementary to the ligated first adaptor, sequence complementary to the nucleic acid of interest, and the second adaptor (Figure 3, paragraph 94, and paragraph 129); and

(e) amplifying the extension products using a primer that anneals to the complement of the first adaptor sequence and a primer that anneals to the complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest (Figure 3 and paragraphs 130-131).

Regarding claim 2, Jones teaches that the method further comprises sequencing the enriched nucleic acid sequence of interest (paragraph 132).

Regarding claim 3, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 129). The reference also teaches that the nucleic acid sequence of interest may comprise cDNA or RNA (paragraph 47).

Regarding claims 6 and 52, Jones teaches that the nucleic acid fragments are double-stranded and that method comprises denaturing the nucleic acid fragments before the step of annealing the oligonucleotides (step (c) above), thereby generating single-stranded nucleic acid fragments comprising the first adaptor sequence and the nucleic acid sequence of interest (Figure 3 and paragraph 129).

Regarding claim 9, Jones teaches that the first and second adaptor sequence are distinct (Figure 3, paragraph 94, and paragraphs 129-131, where the A2-A3 adaptor ligated to the fragments is distinct from the A1 adaptor contained in the capture probe oligonucleotide).

Regarding claims 10 and 54, Jones teaches that the second adaptor sequence may comprise a barcode sequence (paragraphs 71-72) and also that the first adaptor may include a restriction site (paragraph 56).

Regarding claim 51, in the method of Jones the oligonucleotides comprise a 3' portion that is complementary to a different nucleic acid sequence of interest in the nucleic acid fragments and a 5' portion comprising the second adapter sequence (paragraph 129; see also Figure 3).

Regarding claims 57-61, Jones teaches that the first adaptor sequence is in a long strand of a partial duplex adaptor comprising a long strand and a short strand, the long strand is ligated

to a 5' end of the nucleic acid fragments, and the short strand is ligated to a 3' end of the nucleic acid fragments (see Figure 3 and paragraph 94).

Regarding claim 62, Jones teaches that the first adaptor sequence is in a ligation strand of a first adaptor, wherein the first adaptor comprises the ligation strand and a non-ligation strand, wherein the ligation strand ligates to a 5' end of the nucleic acid fragments (paragraph 59).

Regarding claim 40, Jones teaches a method for enriching a nucleic acid sequence of interest from a library (see Figure 3, paragraph 94, and Example 3 at paragraphs 129-132), wherein the library comprises nucleic acid inserts comprising the nucleic acid sequence of interest (Figure 3 and paragraphs 94 and 129), wherein the nucleic acid inserts have a first adaptor sequence attached on a first end and a second adaptor sequence attached on a second end (Figure 3 and paragraphs 94 and 129, where the fragments comprising the A2-A3 adaptor at each end are taught), the method comprising:

(a) denaturing the nucleic acid inserts, thereby generating a library of single-stranded nucleic acids with the first and second adaptor sequences flanking the nucleic acid sequence of interest (Figure 3 and paragraph 129);

(b) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the single-stranded nucleic acids, wherein the oligonucleotides comprise a 3' portion that is complementary to the nucleic acid sequence of interest and a 5' portion comprising a third adaptor sequence that is distinct from the first and second adaptor sequences (Figure 3, paragraph 94, and paragraph 129, where the A1-containing oligonucleotides are annealed);

(c) extending said annealed oligonucleotides using a polymerase to obtain extension products comprising sequence complementary to the first adaptor, sequence complementary to

the nucleic acid of interest, and the third adaptor (Figure 3, paragraph 94, and paragraph 129);  
and

(d) amplifying the extension products using a primer that anneals to the complement of the first adaptor sequence and a primer that anneals to the complement of the third adaptor sequence to enrich for the nucleic acid sequence of interest (Figure 3 and paragraphs 130-131).

Regarding claim 41, Jones teaches that the method further comprises sequencing the enriched nucleic acid sequence of interest (paragraph 132).

Regarding claim 42, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 129). The reference also teaches that the nucleic acid sequence of interest may comprise cDNA or RNA (paragraph 47).

Regarding claims 45 and 48, Jones teaches that the first and second adaptor sequence are the same among each of the inserts in the library (Figure 3 and paragraphs 94 and 129).

Regarding claim 46, Jones teaches that the third adaptor sequence is the same among the one or more oligonucleotides (Figure 3 and paragraphs 94 and 129).

Regarding claim 47, Jones teaches that the first and second adaptor sequence may be distinct from each other (Figure 3 and also paragraph 58).

Regarding claim 49, Jones teaches that the third adaptor sequence may comprise a barcode sequence (paragraphs 71-72).

9. Claims 1-3, 6, 9, 10, 14, 40-42, 45-49, 51-62 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Jones et al. (US 2005/0142577 A1).

Regarding claims 1, 2, 14, and 53, Jones teaches a method for enriching a nucleic acid sequence of interest in a sample comprising nucleic acids that comprises the following steps (see, for example, Figures 3-4 and paragraphs 86-90, 96, 99, and 100): (a) fragmenting nucleic acids in the sample to generate fragments comprising the sequence of interest, (b) ligating a first adaptor to a 5' end of the nucleic acid fragments, (c) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the fragments, wherein said oligonucleotides comprise a 3' portion that is complementary to the nucleic acid sequence of interest and a 5' portion comprising a second adaptor sequence, (d) extending said annealed oligonucleotides using a DNA polymerase to obtain extension products comprising sequence complementary to the ligated first adaptor, sequence complementary to the nucleic acid of interest, and the second adaptor, (e) amplifying the extension products using a primer that anneals to the complement of the first adaptor sequence and a primer that anneals to the complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest, and (f) sequencing the enriched nucleic acid of interest.

Regarding claim 3, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 100). The reference also teaches that the nucleic acid sequence of interest may comprise RNA (paragraphs 43-44).

Regarding claims 6 and 52, Jones teaches that the nucleic acid fragments are double-stranded and that method comprises denaturing the nucleic acid fragments before the step of annealing the oligonucleotides (step (c) above), thereby generating single-stranded nucleic acid fragments comprising the first adaptor sequence and the nucleic acid sequence of interest (Figure 3 and paragraphs 87 and 100).

Regarding claim 9, Jones teaches that the first and second adaptor sequence are distinct (Figure 3, paragraph 87, and paragraph 100).

Regarding claims 10 and 54, Jones teaches that the second adaptor sequence may comprise a barcode sequence (paragraphs 58 and 61) and also that the first adaptor may include a restriction site (paragraph 49).

Regarding claim 51, in the method of Jones, the oligonucleotides comprise a 3' portion that is complementary to a different nucleic acid sequence of interest in the nucleic acid fragments and a 5' portion comprising the second adapter sequence (paragraphs 87, 99, and 100; see also Figure 3).

Regarding claim 55, Jones teaches that the 3' portion of the oligonucleotides comprises a random sequence (see Figure 4, paragraph 100 and paragraphs 88-90).

Regarding claims 57-61, Jones teaches that the first adaptor sequence is in a long strand of a partial duplex adaptor comprising a long strand and a short strand, the long strand is ligated to a 5' end of the nucleic acid fragments, and the short strand is ligated to a 3' end of the nucleic acid fragments (see Figure 3 and paragraph 87).

Regarding claim 62, Jones teaches that the first adaptor sequence is in a ligation strand of a first adaptor, wherein the first adaptor comprises the ligation strand and a non-ligation strand, wherein the ligation strand ligates to a 5' end of the nucleic acid fragments (paragraph 50).

Regarding claim 40, Jones teaches a method for enriching a nucleic acid sequence of interest from a library (see Figure 3, paragraphs 86-90, 99, and 100), wherein the library comprises nucleic acid inserts comprising the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100), wherein the nucleic acid inserts have a first adaptor sequence attached

on a first end and a second adaptor sequence attached on a second end (Figure 3 and paragraphs 86 and 100), the method comprising:

(a) denaturing the nucleic acid inserts, thereby generating a library of single-stranded nucleic acids with the first and second adaptor sequences flanking the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100);

(b) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the single-stranded nucleic acids, wherein the oligonucleotides comprise a 3' portion that is complementary to the nucleic acid sequence of interest and a 5' portion comprising a third adaptor sequence that is distinct from the first and second adaptor sequences (Figure 3, paragraph 86, and paragraph 100, where the oligonucleotides containing an A1 or degenerate sequence are annealed);

(c) extending said annealed oligonucleotides using a polymerase to obtain extension products comprising sequence complementary to the first adaptor, sequence complementary to the nucleic acid of interest, and the third adaptor (Figure 3, paragraph 86, and paragraph 100); and

(d) amplifying the extension products using a primer that anneals to the complement of the first adaptor sequence and a primer that anneals to the complement of the third adaptor sequence to enrich for the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100).

Regarding claim 41, Jones teaches that the method further comprises sequencing the enriched nucleic acid sequence of interest (paragraph 100).

Regarding claim 42, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 100). The reference also teaches that the nucleic acid sequence of interest may comprise RNA (paragraphs 43-44).

Regarding claims 45 and 48, Jones teaches that the first and second adaptor sequence are the same among each of the inserts in the library (Figure 3 and paragraphs 86 and 100).

Regarding claim 46, Jones teaches that the third adaptor sequence is the same among the one or more oligonucleotides (Figure 3 and paragraphs 86 and 100).

Regarding claim 47, Jones teaches that the first and second adaptor sequence may be distinct from each other (Figure 3 and also paragraph 53).

Regarding claim 49, Jones teaches that the third adaptor sequence may comprise a barcode sequence (paragraph 58).

Regarding claim 56, Jones teaches that the 3' portion of the oligonucleotides comprises a random sequence (paragraph 100 and paragraphs 88-90).

### ***Claim Rejections - 35 USC § 103***

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

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

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made

absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

11. Claims 55 and 56 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 2003/0232348 A1; Jones 1 below) in view of Jones et al. (US 2005/0142577 A1; Jones 2 below).

As discussed above, Jones 1 teaches the method of claims 1-3, 6, 9, 10, 14, 40-42, 45-49, 51-54, and 57-62.

Jones 1 does not teach that the 3' portion of the one or more oligonucleotides comprises a random sequence as required by claims 55 and 56.

However, Jones 2 teaches that incorporating a degenerate sequence into the 3' portion of oligonucleotides used for the same purpose as the oligonucleotides of Jones 1 is advantageous because the degenerate sequence "may improve efficiency and reduce the cost of locus-specific genotyping applications" (paragraph 88). The reference further teaches that the degenerate sequence may include a random sequence (paragraphs 89-90).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to practice the method of Jones 1 using oligonucleotides having a 3' portion comprising a random sequence. The ordinary artisan would have been motivated to do so to obtain a more efficient and less expensive method as taught by Jones 2 and would have had a

reasonable expectation of success since the oligonucleotides of Jones 2 were used for the same purpose as the oligonucleotides of Jones 1. Thus, the methods of claims 55 and 56 are *prima facie* obvious.

### ***Conclusion***

12. No claims are currently allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

(1) Rabinowitz et al. (US 2011/0288780 A1) is cited for its disclosure on page 22, paragraphs 213-222 of a method comprising (i) forming a library of DNA fragments with universal adaptors on both ends, (ii) amplifying the library with universal primers, (iii) performing multiplexed target-specific amplification, (iv) barcoding the resulting amplification products, and (v) sequencing the barcoded amplification products.

(2) Rabinowitz et al. (US 2012/0270212 A1) is cited for its disclosure in Figure 6 and paragraphs 316 and 322 of a method comprising (i) forming a library of DNA fragments with adaptors on both ends, (ii) amplifying the library using an adaptor-specific primer and a target-specific primer, and (iii) further amplifying the resulting amplification products.

(3) Link et al. (US 2012/0309002 A1) is cited for its disclosure in Figures 3-5 of a method comprising (i) ligation of adaptors to both strands of a double-stranded nucleic acid, (ii) hybridization and extension of an oligonucleotide comprising a 3' target-specific portion and a 5' adaptor sequence, and amplification of the resulting extension products using a first primer that

targets an adaptor present in step (i) and a second primer that targets the adaptor added in step (ii).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela M. Bertagna whose telephone number is (571)272-8291. The examiner can normally be reached on Monday-Friday, 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. 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 <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Angela M. Bertagna/  
Primary Examiner, Art Unit 1637

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|                                                                                                                                    |                           |
|------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| In re Application:                                                                                                                 | Confirmation No.: 1162    |
| Inventor: Doug Amorese <i>et al.</i>                                                                                               | Examiner: Angela Bertagna |
| Application No.: 13/750,768                                                                                                        | Group Art Unit: 1637      |
| Filed: January 25, 2013                                                                                                            | Customer No. 12754        |
| Title: COMPOSITIONS AND METHODS<br>FOR TARGETED NUCLEIC ACID<br>SEQUENCE ENRICHMENT AND<br>HIGH EFFICIENCY LIBRARY<br>REGENERATION |                           |

FILED ELECTRONICALLY ON: October 15, 2015

**AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION**

M/S Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Commissioner:

This communication is in response to the Office Action dated July 15, 2015. The shortened statutory period for response expires on October 15, 2015. The Response is submitted prior to the expiration of the shortened statutory period for reply; therefore, the response is timely filed.

Prior to reconsidering this application on the merits, please amend the application as follows:

**Amendments to the claims** begin on page **2** of this paper.

**Remarks** begin on page **10** of this paper.

**Conclusion** begins on page **15** of this paper.

### **Amendments to the Claims**

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

#### **LISTING OF CLAIMS:**

1. **(Currently Amended)** A method for enriching for a nucleic acid sequence of interest in a sample comprising nucleic acids, the method comprising:
  - a. fragmenting nucleic acids in the sample comprising the nucleic acids, thereby generating nucleic acid fragments, wherein the nucleic acid fragments comprise the nucleic acid sequence of interest;
  - b. ligating a first adaptor sequence to a 5' end of the nucleic acid fragments, thereby generating nucleic acid fragments ~~comprising the~~ ligated to the first adaptor sequence;
  - c. annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the nucleic acid fragments ~~comprising the~~ ligated to the first adaptor sequence, wherein the one or more oligonucleotides in solution comprise a 3' portion with at least 10 bases that ~~[[is]]~~ are complementary to the nucleic acid sequence of interest and a 5' portion comprising a second adaptor sequence;
  - d. extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragments ~~comprising the~~ ligated to the first adaptor sequence with a polymerase in a reaction mixture, wherein the reaction mixture does not comprise a primer that anneals to sequence complementary to the first adaptor sequence, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the ligated first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end; and
  - e. amplifying the one or more oligonucleotide extension products using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals to ~~[[the]]~~ a complement of the second adaptor sequence to enrich for the nucleic acid

sequence of interest, wherein the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform.

2. **(Previously Presented)** The method of claim 1, further comprising an additional step of sequencing the enriched nucleic acid sequence of interest.

3. **(Previously Presented)** The method of claim 1, wherein the nucleic acid sequence of interest comprises genomic DNA, RNA, or cDNA.

4.-5. **(Canceled).**

6. **(Previously Presented)** The method of claim 52, further comprising denaturing the nucleic acid fragments prior to step c, thereby generating single-stranded nucleic acid fragments comprising the first adaptor sequence.

7.-8. **(Canceled).**

9. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

10. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence and/or the second adaptor sequence comprise barcode sequence.

11. -13. **(Canceled).**

14. **(Original)** The method of claim 1, wherein the polymerase is a DNA polymerase.

15.-39. **(Canceled).**

40. **(Currently Amended)** A method for enriching for a nucleic acid sequence of interest from a library, wherein the library comprises nucleic acid inserts comprising the nucleic acid sequence of interest, wherein the nucleic acid inserts have a first adaptor sequence attached on a first end and a second adaptor sequence attached on a second end, the method comprising:

- a. denaturing the nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end, thereby generating a library of single stranded nucleic acid inserts with the first adaptor sequence on a first end and the second adaptor sequence on a second end;
- b. annealing one or more oligonucleotides in solution to the sequence of interest in the single stranded nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end, wherein the one or more oligonucleotides in solution comprise a 3' portion with at least 10 bases that are complementary to the nucleic acid sequence of interest present in the nucleic acid inserts and a 5' portion comprising a third adaptor sequence, wherein the third adaptor sequence is distinct from the first adaptor sequence and the second adaptor sequence;
- c. extending the one or more oligonucleotides with a polymerase in a reaction mixture, wherein the reaction mixture does not comprise a primer that anneals to sequence complementary to the first adaptor sequence or the second adaptor sequence, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at the first end, sequence complementary to the nucleic acid sequence of interest, and the third adaptor sequence at the second end; and
- d. amplifying the one or more oligonucleotide extension products using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals to the complement of the third adaptor sequence to enrich for the nucleic acid sequence of interest, wherein the first adaptor sequence or its complement, the third adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform.

41. **(Currently Amended)** The method of claim 40, further comprising sequencing the enriched nucleic acid sequence of interest.

42. **(Previously Presented)** The method of claim 40, wherein the nucleic acid sequence of interest comprises genomic DNA, RNA or cDNA.

43.-45. **(Canceled).**

46. **(Previously Presented)** The method of claim 40, wherein the third adaptor sequence is the same among the one or more oligonucleotides.

47. **(Previously Presented)** The method of claim 40, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

48. **(Previously Presented)** The method of claim 40, wherein the first adaptor sequence and the second adaptor sequence are the same.

49. **(Previously Presented)** The method of claim 40, wherein the first adaptor sequence, the second adaptor sequence and/or the third adaptor sequence comprise barcode sequence.

50. **(Canceled).**

51. **(Previously Presented)** The method of claim 1, wherein the one or more oligonucleotides comprise a 3' portion that is complementary to a different nucleic acid sequence of interest in the nucleic acid fragments and a 5' portion comprising the second adaptor sequence.

52. **(Previously Presented)** The method of claim 1, wherein the nucleic acid fragments are double stranded.

53. **(Canceled).**

54. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence comprises a restriction and/or cleavage site for a nucleic acid modifying enzyme.

55. **(Currently amended)** The method of claim 1, wherein the 3' portion of the one or more oligonucleotides comprises a random sequence.

56. **(Previously Presented)** The method of claim 40, wherein the 3' portion of each of the one or more oligonucleotides comprises a random sequence.

57. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence is in a first strand of a partial duplex adaptor.

58. **(Previously Presented)** The method of claim 57, wherein the first strand is a long strand of the partial duplex adaptor.

59. **(Canceled).**

60. **(Previously Presented)** The method of claim 57, wherein the partial duplex adaptor comprises a second strand, wherein the second strand is a short strand.

61. **(Previously Presented)** The method of claim 60, wherein the short strand is ligated to a 3' end of the nucleic acid fragments.

62. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence is in a ligation strand of a first adaptor, wherein the first adaptor comprises the ligation strand and a non-ligation strand, wherein the ligation strand ligates to a 5' end of the nucleic acid fragments.

63. **(New)** The method of claim 2, wherein the sequencing comprises massively parallel sequencing.

64. **(New)** The method of claim 63, wherein the sequencing comprises bridge amplification.

65. **(New)** The method of claim 63, wherein the sequencing comprises use of four labeled reversible terminators.

66. **(New)** The method of claim 63, wherein the sequencing comprises nanopore sequencing.

67. **(New)** The method of claim 63, wherein the sequencing comprises semiconductor sequencing.

68. **(New)** The method of claim 1, wherein the sequence to initiate sequencing on the massively parallel sequencing platform is complementary to a sequencing primer.

69. **(New)** The method of claim 1, wherein the sequence to initiate sequencing on the massively parallel sequencing platform is a sequencing primer sequence.

70. **(New)** The method of claim 1, wherein the sequence to initiate sequencing on the massively parallel sequencing platform is a flow cell sequence.

71. **(New)** The method of claim 1, wherein the first adaptor sequence or its complement or the second adaptor sequence or its complement comprise the sequence to initiate sequencing on the massively parallel sequencing platform.

72. **(New)** The method of claim 1, wherein the first adaptor sequence or its complement and the second adaptor sequence or its complement comprise the sequence to initiate sequencing on the massively parallel sequencing platform.

73. **(New)** The method of claim 1, wherein the first primer or its complement or the second primer or its complement comprise the sequence to initiate sequencing on the massively parallel sequencing platform.

74. **(New)** The method of claim 1, wherein the first primer or its complement and the second primer or its complement comprise the sequence to initiate sequencing on the massively parallel sequencing platform.

75. **(New)** The method of claim 1, wherein the sequence to initiate sequencing on the massively parallel sequencing platform allows annealing of the enriched nucleic acid sequence of interest to a solid support.

76. **(New)** The method of claim 75, wherein the solid support is a bead.

77. **(New)** The method of claim 75, wherein the solid support is a flow cell.

78. **(New)** The method of claim 41, wherein the sequencing comprises massively parallel sequencing.

79. **(New)** The method of claim 78, wherein the sequencing comprises bridge amplification.

80. **(New)** The method of claim 78, wherein the sequencing comprises use of four labeled reversible terminators.

81. **(New)** The method of claim 78, wherein the sequencing comprises nanopore sequencing.

82. **(New)** The method of claim 78, wherein the sequencing comprises semiconductor sequencing.

83. **(New)** The method of claim 40, wherein the sequence to initiate sequencing on the massively parallel sequencing platform is complementary to a sequencing primer.

84. **(New)** The method of claim 40, wherein the sequence to initiate sequencing on the massively parallel sequencing platform is a sequencing primer sequence.

85. **(New)** The method of claim 40, wherein the sequence to initiate sequencing on the massively parallel sequencing platform is a flow cell sequence.

86. **(New)** The method of claim 40, wherein the first adaptor sequence or its complement or the third adaptor sequence or its complement comprise the sequence to initiate sequencing on the massively parallel sequencing platform.

87. **(New)** The method of claim 40, wherein the first adaptor sequence or its complement and the third adaptor sequence or its complement comprise the sequence to initiate sequencing on the massively parallel sequencing platform.

88. **(New)** The method of claim 40, wherein the first primer or its complement or the second primer or its complement comprise the sequence to initiate sequencing on the massively parallel sequencing platform.

89. **(New)** The method of claim 40, wherein the first primer or its complement and the second primer or its complement comprise the sequence to initiate sequencing on the massively parallel sequencing platform.

90. **(New)** The method of claim 40, wherein the sequence to initiate sequencing on the massively parallel sequencing platform allows annealing of the enriched nucleic acid sequence of interest to a solid support.

91. **(New)** The method of claim 90, wherein the solid support is a bead.

92. **(New)** The method of claim 90, wherein the solid support is a flow cell.

93. **(New)** The method of claim 40, wherein neither the first adaptor sequence nor the second adaptor sequence comprise a 3' block.

## REMARKS

### **I. STATUS OF THE CLAIMS**

Prior to entry of this amendment, claims 1-3, 6, 9, 10, 14, 40-42, 45-49, and 51-62 were pending. Claims 1, 40, 41, and 55 are currently amended; claims 63-95 are new; and claims 4-5, 7-8, 11-13, 15-39, 43-45, 50, 53, and 59 are canceled without prejudice. Following entry of this amendment, claims 1-3, 6, 9-10, 14, 40-42, 46-49, 51-52, 54-58, and 60-93 are pending.

Exemplary support for the new and amended claims can be found throughout the application as-filed and in the following exemplary claims, paragraphs, and/or figures:

Claim 1: Original claim 1, [0037], [0052], [0032], [0041], [0064], [0071], [0054], Fig. 1, Fig. 4

Claim 40: Original claim 40, [0052], [0032], [0041], [0064], [0071], [0060], [0054], Fig. 1, Fig. 4

Claims 63, 78: [0064]

Claims 64-65, 79-80: [0071]

Claims 66, 81: [0073]

Claims 67-69, 75-76, 82-84, 90-91: [0074]

Claims 70, 85: [0032], [0095], Fig. 4

Claims 71-72: [0032]

Claims 73-74, 88-89: [0041], [0095], Fig. 4

Claims 86-87: [0032], [0060]

Claims 77, 92: [0041]

Claim 93: [0037]

No new matter has been added.

### **II. INTERVIEW SUMMARY**

Applicant thanks Examiner Angela Bertagna for courtesies extended at a productive in-person interview with Applicant's representative Jeffrey Seidel on October 8, 2015. At the interview, Applicant's representative discussed the art cited and proposed claim amendments.

### **III. INFORMATION DISCLOSURE STATEMENTS**

Applicant acknowledges, with appreciation, the Office's indication that the references submitted in the Information Disclosure Statements filed October 1, 2014, November 21, 2014,

February 5, 2015, February 18, 2015, March 2, 2015, March 10, 2015, March 18, 2015, April 10, 2015, April 14, 2015, April 16, 2015, June 3, 2015, and June 26, 2015 have been considered.

#### **IV. DOUBLE PATENTING**

Claims 45 and 48 are alleged to be a substantial duplicate of each other. The Office Action states: “[a]pplicant is advised that should claim 45 be found allowable, claim 48 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof.” *Office Action*, page 3.

Applicant submits that claim 45 has been canceled, thus obviating the potential double patenting rejection of claim 48.

#### **V. CLAIM OBJECTIONS**

Claim 55 is objected to because the Office Action states that “comprise” should be replaced with “comprises”.

Applicant submits that claim 55 has been amended to recite “comprises”. Applicant respectfully requests that the objection be withdrawn.

#### **VI. CLAIM REJECTIONS UNDER 35 U.S.C. § 112(D)**

Claims 53 and 59 are rejected under pre-AIA 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4<sup>th</sup> paragraph, as allegedly being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or failing to include all the limitations of the claim upon which it depends. Applicant respectfully traverses the rejection. Specifically, the Office Action alleges that “steps (c)-(e) of claim 1 already require ligation of the first adaptor to a 5’ end of the nucleic acid fragments”. *Office Action*, page 4.

Without acquiescing, and solely to facilitate prosecution, claims 53 and 59 have been canceled, thus obviating the rejection with respect to these claims.

#### **VII. CLAIM REJECTIONS UNDER 35 U.S.C. § 102(B)**

Claims 1-3, 6, 9, 10, 14, 40-42, 45-49, 51-54, and 57-62 are rejected under pre-AIA 35 U.S.C. 102(b) as allegedly being anticipated by Jones et al. (US2003/0232348A1, “Jones 1”). *Office Action*, pp. 5-8. Applicant respectfully traverses the rejection.

Claims 1-3, 6, 9, 10, 14, 40-42, 45-49, and 51-62 are rejected under pre-AIA 35 U.S.C. 102(b) as allegedly being anticipated by Jones et al. (US2005/0142577A1, “Jones 2”). *Office Action*, pp. 8-12. Applicant respectfully traverses the rejection.

With respect to establishing a *prima facie* case of anticipation, MPEP 2131 states:

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). (emphasis added).

Claim 1 has been amended to recite, in part, “wherein the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform.”

Jones 1 does not anticipate amended claim 1 because Jones 1 does not disclose each and every element of amended claim 1. For example, Jones 1 does not disclose “wherein the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform”. Thus, since Jones 1 does not disclose each and every element of amended claim 1, Jones 1 does not anticipate amended claim 1.

Claims 2-3, 6, 9, 10, 14, 51-52, 54, 57-58, and 60-62 depend from claim 1. For at least the same reasons, claims 2-3, 6, 9, 10, 14, 51-52, 54, 57-58, and 60-62 are not anticipated by Jones 1.

Claims 53 and 59 have been canceled, thus obviating the rejection with respect to these claims.

Jones 2 does not anticipate amended claim 1 because Jones 2 does not disclose each and every element of amended claim 1. For example, Jones 2 does not disclose “wherein the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform”. Thus, since Jones 2 does not disclose each and every element of amended claim 1, Jones 2 does not anticipate amended claim 1.

Claims 2-3, 6, 9, 10, 14, 51-52, 54-55, 57-58, and 60-62 depend from claim 1. For at least the same reasons, claims 2-3, 6, 9, 10, 14, 51-52, 54-55, 57-58, and 60-62 are not anticipated by Jones 2.

Claims 53 and 59 have been canceled, thus obviating the rejection with respect to these claims.

Claim 40 has been amended to recite, in part, “wherein the first adaptor sequence or its complement, the third adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence for sequencing on a massively parallel sequencing platform.”

Jones 1 does not anticipate amended claim 40 because Jones 1 does not disclose each and every element of amended claim 40. For example, Jones 1 does not disclose “wherein the first adaptor sequence or its complement, the third adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform.” Thus, since Jones 1 does not disclose each and every element of amended claim 40, Jones 1 does not anticipate amended claim 40.

Claims 41-42 and 46-49 depend from claim 40. For at least the same reasons, claims 41-42 and 46-49 are not anticipated by Jones 1. Claim 45 has been canceled, thus obviating the rejection with respect to this claim.

Jones 2 does not anticipate amended claim 40 because Jones 2 does not disclose each and every element of amended claim 40. For example, Jones 2 does not disclose “wherein the first adaptor sequence or its complement, the third adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform.” Thus, since Jones 2 does not disclose each and every element of amended claim 40, Jones 2 does not anticipate amended claim 40.

Claims 41-42, 46-49, and 56 depend from claim 40. For at least the same reasons, claims 41-42, 46-49, and 56 are not anticipated by Jones 2. Claim 45 has been canceled, thus obviating the rejection with respect to this claim.

In view of the foregoing, Applicant respectfully requests that the rejection of claims 1-3, 6, 9, 10, 14, 40-42, 45-49, 51-54, and 57-62 under pre-AIA 35 U.S.C. 102(b) as allegedly being anticipated by Jones 1 and the rejection of claims 1-3, 6, 9, 10, 14, 40-42, 45-49, and 51-62 under pre-AIA 35 U.S.C. 102(b) as allegedly being anticipated by Jones 2 be withdrawn.

**VIII. CLAIM REJECTIONS UNDER 35 U.S.C. § 103(A):**

Claims 55 and 56 are rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Jones 1 in view of Jones 2. *Office Action*, pp. 12-14. Applicant respectfully traverses the rejection.

In order to establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. Further, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, in a manner which would have led a person of ordinary skill in the art to the invention as claimed. Finally, there must be a reasonable expectation of success.

As described herein, neither Jones 1 nor Jones 2 discloses all the elements of independent claims 1 and 40. Claim 55 depends from claim 1 and incorporates all the elements and limitations of claim 1. Claim 56 depends from claim 40 and incorporates all the elements and limitations of claim 40. Further, Jones 2, alone or in combination, does not cure the defects of Jones 1.

For at least the foregoing reasons, dependent claims 55 and 56 are not obvious in view of the cited references. Therefore, Applicant respectfully requests that the rejection of claims 55 and 56 under 35 U.S.C. 103(a) be withdrawn.

### CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any question, the Examiner is encouraged to telephone the undersigned.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 25115-755.201).

Respectfully submitted,

Date: October 15, 2015

By: /Jeffrey Seidel/  
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|--------------------------------------------------------------------------------------------------------------|-------------|----------------------|------------------------------------|------------------|
| APPLICATION NO.                                                                                              | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.                | CONFIRMATION NO. |
| 13/750,768                                                                                                   | 01/25/2013  | Doug Amorese         | 25115-755.201                      | 1162             |
| 12754 7590 10/30/2015<br>Wilson Sonsini Goodrich & Rosati/NUGEN<br>650 Page Mill Road<br>Palo Alto, CA 94304 |             |                      | EXAMINER<br>BERTAGNA, ANGELA MARIE |                  |
|                                                                                                              |             |                      | ART UNIT                           | PAPER NUMBER     |
|                                                                                                              |             |                      | 1637                               |                  |
|                                                                                                              |             |                      | NOTIFICATION DATE                  | DELIVERY MODE    |
|                                                                                                              |             |                      | 10/30/2015                         | ELECTRONIC       |

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

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

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

patentdocket@wsgr.com

|                              |                                       |                                       |                                                  |
|------------------------------|---------------------------------------|---------------------------------------|--------------------------------------------------|
| <b>Office Action Summary</b> | <b>Application No.</b><br>13/750,768  | <b>Applicant(s)</b><br>AMORESE ET AL. |                                                  |
|                              | <b>Examiner</b><br>Angela M. Bertagna | <b>Art Unit</b><br>1637               | <b>AIA (First Inventor to File) Status</b><br>No |

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

**Period for Reply**

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

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

**Status**

1) ☒ Responsive to communication(s) filed on 10/15/15.  
☐ 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) 1-3,6,9,10,14,40-42,46-49,51,52,54-58 and 60-93 is/are pending in the application.  
5a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

6) ☐ Claim(s) \_\_\_\_\_ is/are allowed.

7) ☒ Claim(s) 1-3,6,9,10,14,40-42,46-49,51,52,54-58 and 60-93 is/are rejected.

8) ☒ Claim(s) 1,40 and 93 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](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

**Application Papers**

10) ☐ The specification is objected to by the Examiner.

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

**Priority under 35 U.S.C. § 119**

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

**Certified copies:**

a) ☐ All    b) ☐ Some\*\*    c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)  
Paper No(s)/Mail Date \_\_\_\_\_.

3) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.

4) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Notice of Pre-AIA or AIA Status***

1. The present application is being examined under the pre-AIA first to invent provisions.

### ***Status of the Application***

2. Applicant's response filed on October 15, 2015 has been entered. Claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58, and 60-93 are pending and under examination.

### ***Response to Arguments***

3. Applicant's arguments filed on October 15, 2015 have been fully considered.

#### **Objection to claim 55**

Applicant argues that the objection should be withdrawn in view of the amendment to claim 55 (page 11). This argument was persuasive. The objection has been withdrawn.

#### **Duplicate Claims**

As noted by Applicant, see page 11, claim 45 has been canceled. The issue of whether claims 45 and 48 are duplicates is therefore moot.

#### **Rejection of claims 53 and 59 under pre-AIA 35 U.S.C. 112, fourth paragraph**

Applicant argues that the rejection should be withdrawn since claims 53 and 59 have been canceled (page 11). This argument was persuasive. The rejection has been withdrawn.

**Rejection of claims 1-3, 6, 9, 10, 14, 40-42, 45-49, 51-54, and 57-62 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Jones et al. (US 2003/0232348 A1, "Jones 1")**

Applicant argues that the rejection should be withdrawn in view of the amendments to independent claims 1 and 40, which require the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or the second primer or its complement to comprise sequence to initiate sequencing on a massively parallel sequencing platform (pages 12 and 13).

This argument was persuasive. The rejection has been withdrawn.

**Rejection of claims 1-3, 6, 9, 10, 14, 40-42, 45-49, and 51-62 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Jones et al. (US 2005/0142577 A1, "Jones 2")**

Applicant argues that the rejection should be withdrawn in view of the amendments to independent claims 1 and 40, which require the first adaptor sequence or its complement, the third adaptor sequence or its complement, the first primer or its complement, or the second primer or its complement to comprise sequence to initiate sequencing on a massively parallel sequencing platform (pages 12 and 13).

This argument was persuasive. The rejection has been withdrawn.

**Rejection of claims 55 and 56 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones 1 in view of Jones 2**

Applicant argues that the rejection should be withdrawn because neither reference teaches all of the elements of amended independent claims 1 and 40 (page 14).

This argument was persuasive. The rejection has been withdrawn.

#### ***Claim Objections***

4. Claims 1 and 40 are objected to because the word “the” should be inserted before

“second primer” in the third-to-last line of each claim.

Claim 93 is objected to because "comprise" should be replaced with "comprises".

***Claim Rejections - 35 USC § 112 (New Matter)***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58, and 60-93 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Independent claim 1 has been amended to state that “the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or the second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform”. Independent claim 40 has been amended to state that “the first adaptor sequence or its complement, the third adaptor sequence or its complement, the first primer or its complement, or the second primer or its complement comprise sequence to initiate

sequencing on a massively parallel sequencing platform”. Claims 68-77 and 83-92 further limit this clause in claims 1 and 40.

Applicant states that the amendments to claims 1 and 40 find support throughout the original disclosure and specifically points to Figure 1, Figure 4, and paragraphs 32, 37, 41, 52, 54, 60, 64, and 71 (page 10). Applicant states that claims 68-77 and 83-92 are supported throughout the original disclosure and specifically points to Figure 4 and paragraphs 32, 41, 60, 74, and 95 (page 10).

The original disclosure, including the portions cited by Applicant, has been reviewed, but support was not found for all of the options recited in independent claims 1 and 40. Paragraph 32 provides support a method in which the first adaptor or the second adaptor comprises sequence to initiate sequencing on a massively parallel sequencing platform. Paragraph 95 provides support for a method in which the first and second primers comprise the sequence to initiate sequencing on the massively parallel sequencing platform. Figure 4 and paragraphs 32 and 37 provide support for a method in which the third adaptor comprises sequence for initiating sequencing on a massively parallel sequencing platform. However, neither these passages nor the remainder of the original disclosure provides support for methods in which the complements of the first, second, or third adaptor or the complements of the first or second primer comprise the sequence to initiate sequencing on the massively parallel sequencing platform. As a result, claims 1 and 40, and those claims depending therefrom, contain new matter.

The following is suggested to overcome the rejection and also to facilitate prosecution in general: Replacing the concluding clause in claims 1 and 40 with a positively recited massively parallel sequencing step and canceling claims 68-77 and 83-92.

***Claim Rejections - 35 USC § 112***

6. 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.

Claims 1-3, 6-9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-67, 70-82, and 85-93 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 pre-AIA the applicant regards as the invention.

Claims 1 and 40 are indefinite because the requirements of “comprise sequence to initiate sequencing on a massively parallel sequencing platform”, which is recited in the concluding clause of each claim, are unclear. More specifically, it is entirely unclear as to what is meant by “to initiate sequencing”. The word “initiate” suggests that an active step occurs at the sequence, such as polymerase-mediated extension, ligation, or exonuclease digestion, but this does not make sense for all of the options in the claims because the adaptor sequences and their complements are covalently attached to the nucleic acid of interest and cannot be extended in a polymerase-mediated extension reaction. The language also suggests that particular structural features are required, but neither the claims nor the specification discusses what these features might be. Paragraphs 70-74 of the specification describe sequencing methods, but they do not use the language “comprises a sequence to initiate sequencing” and, therefore, do not clarify the language, particularly since paragraph 73 seems to indicate that no special structural features are required to initiate sequencing. In view of the above, the requirements of claims 1 and 40 are entirely unclear.

Claims 2, 3, 6, 9, 10, 14, 41, 42, 46-49, 51, 52, 54-58, 60-67, 70-82, and 85-93 are also indefinite since they depend from claim 1 or claim 40.

Claims 70 and 85 are also vague and indefinite because the requirements of the claims are unclear. The claims recite that “the sequence to initiate sequencing on the massively parallel sequencing platform is a flow cell sequence”. It is not clear whether this language requires a sequence that is immobilized in a flow cell or if it only requires a sequence capable of being used in a flow cell.

Claims 75-77 and 90-92 are further indefinite because it is unclear what is meant by the "allows annealing" language in each of claims 75 and 90. It is not clear whether the language requires annealing of the enriched nucleic acid of interest to a solid support via the sequence to initiate sequencing or if another, broader meaning is intended (e.g., that the sequence to initiate sequencing does not prevent annealing).

### ***Claim Rejections - 35 USC § 112***

7. The following is a quotation of 35 U.S.C. 112(d):

(d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), fourth paragraph:

Subject to the [fifth paragraph of 35 U.S.C. 112 (pre-AIA)], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

Claims 70 and 85 are rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of

the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.

Claims 70 and 85 depend from claims 1 and 40, respectively, and recite that “the sequence to initiate sequencing on the massively parallel sequencing platform is a flow cell sequence”. As discussed above, these claims are indefinite because it is not clear whether any structural difference relative to claims 1 and 40 is required. If no structural difference is required (i.e., if the language is intended to simply require the sequence to be capable of being used in a flow cell), the claims are not further limiting because the sequences in claims 1 and 40 are necessarily capable of being used in a flow cell. In other words, if no structural difference is required, claims 70 and 85 are not further limiting because they merely recite an inherent property of the sequences in claims 1 and 40.

Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

### ***Claim Rejections - 35 USC § 103***

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

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

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the

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

9. Claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-66, 68-81, and 83-93 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 2005/0142577 A1) in view of Tucker et al. (The American Journal of Human Genetics (2009) 85: 142-154).

Regarding claims 1, 2, and 14, Jones teaches a method for enriching a nucleic acid sequence of interest in a sample comprising nucleic acids that comprises the following steps (see, for example, Figures 3-4 and paragraphs 86-90, 96, 99, and 100): (a) fragmenting nucleic acids in the sample to generate fragments comprising the sequence of interest, (b) ligating a first adaptor to a 5' end of the nucleic acid fragments, (c) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the fragments, wherein said oligonucleotides comprise a 3' portion with at least ten bases that are complementary to the nucleic acid sequence of interest and a 5' portion comprising a second adaptor sequence, (d) extending said annealed oligonucleotides using a DNA polymerase in a reaction mixture that does not contain a primer that anneals to sequence complementary to the first adaptor sequence, thereby obtaining extension products comprising sequence complementary to the ligated first adaptor, sequence complementary to the nucleic acid of interest, and the second adaptor, (e) amplifying the extension products using a primer that anneals to the complement of the first adaptor sequence

and a primer that anneals to the complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest, and (f) sequencing the enriched nucleic acid of interest.

Regarding claim 3, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 100). The reference also teaches that the nucleic acid sequence of interest may comprise RNA (paragraphs 43-44).

Regarding claims 6 and 52, Jones teaches that the nucleic acid fragments are double-stranded and that method comprises denaturing the nucleic acid fragments before the step of annealing the oligonucleotides (step (c) above), thereby generating single-stranded nucleic acid fragments comprising the first adaptor sequence and the nucleic acid sequence of interest (Figure 3 and paragraphs 87 and 100).

Regarding claim 9, Jones teaches that the first and second adaptor sequences are distinct from each other (Figure 3, paragraph 87, and paragraph 100).

Regarding claims 10 and 54, Jones teaches that the second adaptor sequence may comprise a barcode sequence (paragraphs 58 and 61) and also that the first adaptor may include a restriction site (paragraph 49).

Regarding claim 51, in the method of Jones, the oligonucleotides comprise a 3' portion that is complementary to a different nucleic acid sequence of interest in the nucleic acid fragments and a 5' portion comprising the second adapter sequence (paragraphs 87, 99, and 100; see also Figure 3).

Regarding claim 55, Jones teaches that the 3' portion of the oligonucleotides comprises a random sequence (see Figure 4, paragraph 100 and paragraphs 88-90).

Regarding claims 57, 58, 60, and 61, Jones teaches that the first adaptor sequence is in a long strand of a partial duplex adaptor comprising a long strand and a short strand, the long strand is ligated to a 5' end of the nucleic acid fragments, and the short strand is ligated to a 3' end of the nucleic acid fragments (see Figure 3 and paragraph 87).

Regarding claim 62, Jones teaches that the first adaptor sequence is in a ligation strand of a first adaptor, wherein the first adaptor comprises the ligation strand and a non-ligation strand, wherein the ligation strand ligates to a 5' end of the nucleic acid fragments (paragraph 50).

Regarding claim 40, Jones teaches a method for enriching a nucleic acid sequence of interest from a library (see Figure 3, paragraphs 86-90, 99, and 100), wherein the library comprises nucleic acid inserts comprising the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100), wherein the nucleic acid inserts have a first adaptor sequence attached on a first end and a second adaptor sequence attached on a second end (Figure 3 and paragraphs 86 and 100), the method comprising:

(a) denaturing the nucleic acid inserts, thereby generating a library of single-stranded nucleic acids with the first and second adaptor sequences flanking the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100);

(b) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the single-stranded nucleic acids, wherein the oligonucleotides comprise a 3' portion with at least ten bases that are complementary to the nucleic acid sequence of interest and a 5' portion comprising a third adaptor sequence that is distinct from the first and second adaptor sequences (Figure 3, paragraph 86, and paragraph 100, where the oligonucleotides containing an A1 or degenerate sequence are annealed);

(c) extending said annealed oligonucleotides using a polymerase in a reaction mixture that does not include a primer that anneals to the complement of the first or second adaptor sequence to obtain extension products comprising sequence complementary to the first adaptor, sequence complementary to the nucleic acid of interest, and the third adaptor (Figure 3, paragraph 86, and paragraph 100); and

(d) amplifying the extension products using a primer that anneals to the complement of the first adaptor sequence and a primer that anneals to the complement of the third adaptor sequence to enrich for the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100).

Regarding claim 41, Jones teaches that the method further comprises sequencing the enriched nucleic acid sequence of interest (paragraph 100).

Regarding claim 42, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 100). The reference also teaches that the nucleic acid sequence of interest may comprise RNA (paragraphs 43-44).

Regarding claim 46, Jones teaches that the third adaptor sequence is the same among the one or more oligonucleotides (Figure 3 and paragraphs 86 and 100).

Regarding claim 47, Jones teaches that the first and second adaptor sequence may be distinct from each other (Figure 3 and also paragraph 53).

Regarding claim 48, Jones teaches that the first and second adaptor sequences are the same among each of the inserts in the library (Figure 3 and paragraphs 86 and 100).

Regarding claim 49, Jones teaches that the third adaptor sequence may comprise a barcode sequence (paragraph 58).

Regarding claim 56, Jones teaches that the 3' portion of the oligonucleotides comprises a random sequence (paragraph 100 and paragraphs 88-90).

Regarding claim 93, Jones teaches that the neither the first adaptor sequence nor the second adaptor sequence comprises a 3' block (see, for example, paragraph 87, which indicates that the 3' blocking group is optional).

In the method of Jones, the amplification products contain adaptor sequences at each end (see Figure 3, for example; see also paragraphs 87 and 100). It is not clear that these adaptor sequences, their complements, the amplification primers described in paragraph 100, or their complements comprise sequence to initiate sequencing on a massively parallel sequencing platform as required by independent claims 1 and 40. Also, Jones teaches that the nucleic acids amplified by the disclosed method may be analyzed by array hybridization or any other method known in the art to obtain sequence information about a region of interest (paragraph 79-80). The reference does not disclose massively parallel sequencing, however.

Tucker describes methods of obtaining sequence information about a region of interest in a nucleic acid, and specifically describes a number of massively parallel sequencing methods (abstract, pages 142-146, and Figures 2-5). The reference teaches that “Massively parallel sequencing will allow simultaneous screening for mutations in hundreds of loci in genetically heterogeneous disorders, whole-genome screening for novel mutations, and sequence-based detection of novel pathogens that cause human disease. In addition, massively parallel sequencing will permit clinical application of our expanding knowledge of pharmacogenetics, cancer genetics, epigenetics, and complex traits” (page 142, column 2). The reference further teaches that massively parallel sequencing “has reduced the cost and increased the throughput of

genomic sequencing by more than three orders of magnitude...and may also replace arrays and Sanger sequencing in clinical applications where they are currently being used” (abstract).

Further regarding claims 63 and 78, Tucker describes massively parallel methods developed by Illumina, Applied Biosystems, Roche, and Helicos (pages 142-144 and Figs. 2-5).

Regarding claims 64, 65, 79, and 80, the Illumina method comprises bridge amplification and the use of four labeled reversible terminators (Figure 2).

Regarding claims 68-72, 75, 77, 83-87, 90, and 92, the Illumina method comprises preparing a nucleic acid fragment of interest with an adaptor at each end (Figure 2). The adaptors hybridize to flow cell sequences (Figure 2). Each of the two adaptors is also complementary to a sequencing primer (Figure 2). In addition, the complement of each of the two adaptors contains a sequencing primer sequence as well as a flow cell sequence (Figure 2).

Further regarding claims 66 and 81, Tucker also describes nanopore sequencing (page 143, column 1).

Further regarding claims 76 and 91, the 454 method uses beads as the support for the sequencing method (Figure 4). As in the Illumina method, the adaptors contain a sequence that allows annealing to the solid support (Figure 4).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to analyze the amplification products generated by the method of Jones using one of the massively parallel sequencing methods described in Tucker. The ordinary artisan would have been motivated to do so since Tucker taught that such methods offered very high-throughput sequencing (abstract and page 142) and as well as the ability to accurately detect minor alleles (page 144, column 2). Additional motivation is provided in the abstract of Tucker,

which teaches that massively parallel sequencing methods may replace array methods. The ordinary artisan would have had a reasonable expectation of success in view of the guidance provided by Tucker concerning the use of massively parallel sequencing methods and also since Jones taught that the amplification products could be analyzed using any desired method. In using the Illumina sequencing method, for example, the ordinary artisan would have recognized that the adaptor sequences or their complements should include sequence to initiate sequencing on a parallel sequencing platform and would have been motivated to use such adaptors with a reasonable expectation of success since the methods of Illumina and 454 have been publicly disclosed and commercialized. Further regarding claims 73, 74, 88, and 89, since the disclosure of Tucker indicates that the adaptor sequences or their complements contain sequence to initiate sequencing on the massively parallel sequencing platform (Figure 2), the ordinary artisan also would have been motivated to perform the amplification step in the method of Jones using first and second primers that either contain the sequence to initiate sequencing on the massively parallel sequencing platform or contain a sequence complementary thereto. Thus, the methods of claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-66, 68-81, and 83-93 are *prima facie* obvious.

10. Claims 67 and 82 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 2005/0142577 A1) in view of Tucker et al. (The American Journal of Human Genetics (2009) 85: 142-154) and further in view of Rothberg et al. (US 2009/0127589 A1).

As discussed above, the teachings of Jones in view of Tucker render obvious the methods

of claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-66, 68-81, and 83-93.

Jones does not teach semiconductor sequencing as required by claims 67 and 82. Tucker does not remedy this deficiency.

However, Rothberg describes a massively parallel semiconductor sequencing method (abstract, paragraphs 28-29, 33, and 51-58; see also paragraphs 315-343).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to substitute semiconductor sequencing as taught by Rothberg for one of the massively parallel sequencing methods disclosed in Tucker. The ordinary artisan would have recognized from the teachings of Rothberg that the disclosed semiconductor sequencing method was a massively parallel sequencing method and, accordingly, would have considered it an art-recognized equivalent of the methods disclosed in Tucker. As discussed in MPEP 2144.06, it is *prima facie* obvious to substitute art-recognized equivalents in the absence of unexpected results. Attention is also directed to MPEP 2144.07, which states that it is *prima facie* obvious to select a known method based on its suitability for the intended purpose. In this case, the teachings of Rothberg indicate that the disclosed method is suitable for massively parallel sequencing. Accordingly, the ordinary artisan would have been motivated to select this method with a reasonable expectation of success. It is further noted that no evidence of unexpected results with respect to the sequencing method have been presented. Thus, the methods of claims 67 and 82 are *prima facie* obvious.

### ***Conclusion***

11. No claims are currently allowable.

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.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela M. Bertagna whose telephone number is (571)272-8291. The examiner can normally be reached on Monday-Friday, 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. 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 <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR

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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.

/Angela M. Bertagna/  
Primary Examiner, Art Unit 1637

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

Inventor: Doug Amorese *et al.*

Application No.: 13/750,768

Filed: January 25, 2013

Title: COMPOSITIONS AND METHODS  
FOR TARGETED NUCLEIC ACID  
SEQUENCE ENRICHMENT AND  
HIGH EFFICIENCY LIBRARY  
REGENERATION

Confirmation No.: 1162

Examiner: Angela Bertagna

Group Art Unit: 1637

Customer No. 12754

**FILED ELECTRONICALLY ON: February 1, 2016**

**AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION**

M/S Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Commissioner:

This communication is in response to the Final Office Action mailed October 30, 2015. The shortened statutory period for response expires on January 30, 2016. January 30, 2016, is a Saturday, and this response is filed the next business day, Monday February 1, 2016. Therefore, the response is timely filed in accordance with 35 U.S.C. § 21, 37 C.F.R. § 1.7, and MPEP 710.05.

Prior to reconsidering this application on the merits, please amend the application as follows:

**Amendments to the claims** begin on page **2** of this paper.

**Remarks** begin on page **9** of this paper.

**Conclusion** begins on page **14** of this paper.

### **Amendments to the Claims**

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

#### **LISTING OF CLAIMS:**

1. **(Currently Amended)** A method for enriching for a nucleic acid sequence of interest in a sample comprising nucleic acids, the method comprising:
  - a. fragmenting nucleic acids in the sample comprising the nucleic acids, thereby generating nucleic acid fragments, wherein the nucleic acid fragments comprise the nucleic acid sequence of interest;
  - b. ligating a first adaptor sequence to a 5' end of the nucleic acid fragments, thereby generating nucleic acid fragments ligated to the first adaptor sequence;
  - c. annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the nucleic acid fragments ligated to the first adaptor sequence, wherein the one or more oligonucleotides in solution comprise a 3' portion with at least 10 bases that are complementary to the nucleic acid sequence of interest and a 5' tail, wherein the 5' tail portion comprising comprises a second adaptor sequence non-hybridizable to other adaptor sequence appended to the nucleic acid fragments;
  - d. extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragments ligated to the first adaptor sequence with a polymerase in a reaction mixture, wherein the reaction mixture does not comprise a primer that anneals to sequence complementary to the first adaptor sequence during the extending, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the ligated first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;[[ and]]
  - e. amplifying the one or more oligonucleotide extension products using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals

to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface, wherein the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform;

f. annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and

g. sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

**2. (Canceled)**

**3. (Previously Presented)** The method of claim 1, wherein the nucleic acid sequence of interest comprises genomic DNA, RNA, or cDNA.

**4.-5. (Canceled).**

**6. (Currently Amended)** The method of claim 52, further comprising denaturing the nucleic acid fragments ligated to the first adaptor sequence prior to step c, thereby generating single-stranded nucleic acid fragments ~~comprising~~ ligated to the first adaptor sequence.

**7.-8. (Canceled).**

**9. (Previously Presented)** The method of claim 1, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

**10. (Previously Presented)** The method of claim 1, wherein the first adaptor sequence and/or the second adaptor sequence comprise barcode sequence.

**11. -13. (Canceled).**

14. **(Original)** The method of claim 1, wherein the polymerase is a DNA polymerase.

15.-39. **(Canceled)**.

40. **(Currently Amended)** A method for enriching for a nucleic acid sequence of interest from a library, wherein the library comprises nucleic acid inserts comprising the nucleic acid sequence of interest, wherein the nucleic acid inserts have a first adaptor sequence attached on a first end and a second adaptor sequence attached on a second end, the method comprising:

- a. denaturing the nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end, thereby generating a library of single stranded nucleic acid inserts with the first adaptor sequence on a first end and the second adaptor sequence on a second end;
- b. annealing one or more oligonucleotides in solution to the sequence of interest in the single stranded nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end, wherein the one or more oligonucleotides in solution comprise a 3' portion with at least 10 bases designed to be that are complementary to the nucleic acid sequence of interest present in the nucleic acid inserts and a 5' tail, wherein the 5' tail portion comprising comprises a third adaptor sequence, wherein the third adaptor sequence is distinct from and non-hybridizable to the first adaptor sequence and the second adaptor sequence;
- c. extending the one or more oligonucleotides with a polymerase in a reaction mixture, wherein the reaction mixture does not comprise a primer that anneals to sequence complementary to the first adaptor sequence or the second adaptor sequence during the extending, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the third adaptor sequence at a second end;[[ and]]
- d. amplifying the one or more oligonucleotide extension products using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals to a complement of the third adaptor sequence to enrich for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface, wherein the first adaptor sequence or its

~~complement, the third adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform;~~

- e. annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and
- f. sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

41. **(Canceled)**

42. **(Previously Presented)** The method of claim 40, wherein the nucleic acid sequence of interest comprises genomic DNA, RNA or cDNA.

43.-45. **(Canceled)**.

46. **(Previously Presented)** The method of claim 40, wherein the third adaptor sequence is the same among the one or more oligonucleotides.

47. **(Previously Presented)** The method of claim 40, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

48. **(Currently Amended)** The method of claim 40, wherein the first adaptor sequence and the complement of the second adaptor sequence are the same.

49. **(Previously Presented)** The method of claim 40, wherein the first adaptor sequence, the second adaptor sequence and/or the third adaptor sequence comprise barcode sequence.

50. **(Canceled)**.

51. **(Previously Presented)** The method of claim 1, wherein the one or more oligonucleotides comprise a 3' portion that is complementary to a different nucleic acid sequence of interest in the nucleic acid fragments and a 5' portion comprising the second adaptor sequence.

52. **(Previously Presented)** The method of claim 1, wherein the nucleic acid fragments are double stranded.

53. **(Canceled).**

54. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence comprises a restriction and/or cleavage site for a nucleic acid modifying enzyme.

55. **(Previously Presented)** The method of claim 1, wherein the 3' portion of the one or more oligonucleotides comprises a random sequence.

56. **(Previously Presented)** The method of claim 40, wherein the 3' portion of each of the one or more oligonucleotides comprises a random sequence.

57. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence is in a first strand of a partial duplex adaptor.

58. **(Previously Presented)** The method of claim 57, wherein the first strand is a long strand of the partial duplex adaptor.

59. **(Canceled).**

60. **(Previously Presented)** The method of claim 57, wherein the partial duplex adaptor comprises a second strand, wherein the second strand is a short strand.

61. **(Previously Presented)** The method of claim 60, wherein the short strand is ligated to a 3' end of the nucleic acid fragments.

62. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence is in a ligation strand of a first adaptor, wherein the first adaptor comprises the ligation strand and a non-ligation strand, wherein the ligation strand ligates to a 5' end of the nucleic acid fragments.

63. **(Canceled)**

64. **(Currently Amended)** The method of claim ~~[[63]]~~1, wherein the sequencing comprises bridge amplification.

65. **(Currently Amended)** The method of claim ~~[[63]]~~1, wherein the sequencing comprises use of four labeled reversible terminators.

66. **(Canceled)**

67. **(Currently Amended)** The method of claim ~~[[63]]~~1, wherein the sequencing comprises semiconductor sequencing.

68. – 78. **(Canceled)**

79. **(Currently Amended)** The method of claim ~~[[78]]~~40, wherein the sequencing comprises bridge amplification.

80. **(Currently Amended)** The method of claim ~~[[78]]~~40, wherein the sequencing comprises use of four labeled reversible terminators.

81. **(Canceled)**

82. **(Currently Amended)** The method of claim ~~[[78]]~~40, wherein the sequencing comprises semiconductor sequencing.

83. – 92. **(Canceled)**

93. **(Currently Amended)** The method of claim 40, wherein neither the first adaptor sequence nor the second adaptor sequence ~~comprise~~ comprises a 3' block.

## REMARKS

### **I. STATUS OF THE CLAIMS**

Prior to entry of this amendment, claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58 and 60-93 were pending. Claims 1, 6, 40, 48, 64, 65, 67, 79, 80, 82, and 93 are currently amended. Claims 2, 4-5, 7-8, 11-13, 15-39, 41, 43-45, 50, 53, 59, 63, 66, 68-78, 81, and 83-92 are canceled without prejudice. Following entry of this amendment, claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93 are pending.

Exemplary support for the new and amended claims can be found throughout the application as-filed and in the following exemplary claims, paragraphs, and/or figures:

Claim 1: [0030], [0038], [0039], [0041], [0050], [0054], [0057], [0064], [0071], [0074], [0087], [0095], [00103], FIGs. 1 and 4, Original Claim 2

Claim 40: [0030], [0038], [0039], [0041], [0045], [0050], [0054], [0057], [0064], [0071], [0087], [0095], [00103], FIGs. 1 and 4, Original Claim 41

No new matter is added.

### **II. INTERVIEW SUMMARY**

Applicant thanks Examiner Angela Bertagna for courtesies extended at a productive in-person interview with Applicant's representative Jeffrey Seidel on December 30, 2015. At the interview, Applicant's representative discussed the art cited and proposed claim amendments.

### **III. INFORMATION DISCLOSURE STATEMENTS**

Applicant acknowledges, with appreciation, the Office's indication that the references submitted in the Information Disclosure Statements filed July 22, 2015, and October 16, 2015, have been considered.

### **IV. CLAIM OBJECTIONS**

Claims 1 and 40 are objected to because the Office states that "the" should be inserted before "second primer" in the third-to-last line of each claim. Office Action at **Item 4**, pp. 3-4. Claims 1 and 40 are amended to delete "second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform." In view of the amendment, the objection is rendered moot.

Claim 93 is objected to because the Office states that "comprise" should be replaced with "comprises". Office Action at **Item 4**, p. 4. Claim 93 is amended to recite "comprises." Applicant respectfully requests that the objection be withdrawn.

**V. CLAIM REJECTIONS UNDER PRE-AIA 35 U.S.C. § 112 FIRST PARAGRAPH**

Claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58, and 60-93 are rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, as allegedly failing to comply with the written description requirement. *See* Office Action at **Item 5**, pp. 4-5. Specifically, the Office alleges that claims 1 and 40, and those claims depending therefrom, contain new matter because the original disclosure does not provide support for methods in which the complements of the first, second, or third adaptor or the complements of the first or second primer comprise the sequence to initiate sequencing on the massively parallel sequencing platform. Further, the Office states "[t]he following is suggested to overcome the rejection and also to facilitate prosecution in general: Replacing the concluding clause in claims 1 and 40 with a positively recited massively parallel sequencing step and canceling claims 68-77 and 83-92."

Without acquiescing, and solely to facilitate prosecution, claims 1 and 40 have been amended to delete: "wherein the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform." Claim 1 has been amended to recite, in part:

- "e. ...wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface;
- f. annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and
- g. sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform."

A similar amendment is made to claim 40. Claims 2, 41, 63, 66, 68-78, 81, and 83-92 are canceled, thus obviating the rejection with respect to these claims.

In view of the foregoing, Applicant respectfully requests that the rejection under pre-AIA 35 U.S.C. § 112 first paragraph be withdrawn.

**VI. CLAIM REJECTIONS UNDER PRE-AIA 35 U.S.C. § 112 SECOND PARAGRAPH**

Claims 1-3, 6-9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-67, 70-82, and 85-93 are rejected under 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 applicant regards as the invention. Specifically, the Office alleges that “[c]laims 1 and 40 are indefinite because the requirements of ‘comprise sequence to initiate sequencing on a massively parallel sequencing platform,’ which is recited in the concluding clause of each claim, are unclear.” Office Action at **Item 6**, pp. 6-7.

Without acquiescing, and solely to facilitate prosecution, claims 1 and 40 have been amended to delete: “wherein the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform”. Claims 2, 41, 63, 66, 70-78, 81, and 85-92 are canceled, thus obviating the rejection with respect to these claims.

The Office alleges that “claims 70 and 85 are also vague and indefinite because the requirements of the claims are unclear. The claims recite that ‘the sequence to initiate sequencing on the massively parallel sequencing platform is a flow cell sequence.’ It is not clear whether this language requires a sequence that is immobilized in a flow cell or if it only requires a sequence capable of being used in a flow cell.” Office Action at **Item 6**, page 7.

Without acquiescing, and solely to facilitate prosecution, claims 70 and 85 have been canceled, thus obviating the rejection with respect to these claims.

The Office alleges that “claims 75-77 and 90-92 are further indefinite because it is unclear what is meant by the ‘allows annealing’ language in each of claims 75 and 90.” Office Action at **Item 6**, page 7.

Without acquiescing, and solely to facilitate prosecution, claims 75-77 and 90-92 have been canceled, thus obviating the rejection with respect to these claims.

In view of the foregoing, Applicant respectfully requests that the rejection under pre-AIA 35 U.S.C. § 112 second paragraph be withdrawn.

**VII. CLAIM REJECTIONS UNDER PRE-AIA 35 U.S.C. § 112 FOURTH PARAGRAPH**

Claims 70 and 85 are rejected under pre-AIA 35 U.S.C. 112, fourth paragraph, as allegedly being of improper dependent form for failing to further limit the subject matter of the claim upon which

it depends, or for failing to include all the limitations of the claim upon which it depends. Specifically, the Office alleges that “if no structural difference is required, claims 70 and 85 are not further limiting because they merely recite an inherent property of the sequences in claims 1 and 40.” Office Action at **Item 7**, page 8.

Without acquiescing, and solely to facilitate prosecution, claims 70 and 85 have been canceled, thus obviating the rejection with respect to these claims.

#### **VIII. CLAIM REJECTIONS UNDER 35 U.S.C. § 103(A)**

Claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-66, 68-81, and 83-93 are rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Jones et al. (US 2005/0142577A1; “Jones”) in view of Tucker et al. (The American Journal of Human Genetics (2009) 85: 142-154; “Tucker”). Office Action at **Item 9**, pp. 9-16. Applicant respectfully traverses the rejection.

In order to establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. Further, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, in a manner which would have led a person of ordinary skill in the art to the invention as claimed. Finally, there must be a reasonable expectation of success.

Furthermore, MPEP 2143.01 VI indicates that “[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349, 352 (CCPA 1959).”

Without acquiescing, and solely to facilitate prosecution, claim 1 has been amended to recite, in part:

- “e. ...wherein products of the amplifying comprise a 3’ end with sequence complementary to a sequence on a surface;
- f. annealing a strand of the products of the amplifying to the sequence on the surface using the 3’ end with sequence complementary to the sequence on the surface; and
- g. sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.”

Similar amendments are made to independent claim 40.

The claims are not obvious because making modifications to the amplified products of Jones in order to use the amplified products with a high-throughput sequencing technique of Tucker in the

manner recited in the claims would change the principle of operation of Jones. The instant claims recite “annealing a strand of the products of the amplifying to the sequence on the surface using the 3’ end” and “massively parallel sequencing.” As noted by the Office, Jones does not disclose massively parallel sequencing. Further, the Office has not shown that Jones discloses “annealing a strand of the products of the amplifying to the sequence on the surface using the 3’ end” and “massively parallel sequencing.” Indeed, the Office has not shown that Jones, following amplification using adaptor sequences, discloses any further function for a 3’ end of an amplified product. Rather, Jones uses the *target sequence* of an amplified product for further analysis. For example, Jones describes performing allele discrimination by hybridization to a high density DNA oligonucleotide array (Jones ¶[0077]), which would involve hybridization of the *target sequence* of the amplified product to a unique probe. Other analysis techniques described in Jones (*see e.g.*, Jones ¶[0080]) are not indicated to make use of a 3’ end that was not part of the original target sequence. Thus, use of an amplification product of Jones in a high-throughput sequencing technique of Tucker as recited in the claims would require another function to be incorporated into an end sequence of the amplified products of Jones. Use of such a modification would change the principle of operation of Jones. Thus, the claims are not obvious.

Furthermore, there is no motivation to select methods of Jones for use in massively parallel sequencing. Tucker discloses general detriments of performing enrichment before sequencing. Tucker states “[t]argeted sequencing requires substantial up-front preparation to select the DNA segments of interest.” Tucker, p. 147, c. 1, ll. 1-2. Tucker also notes that “any enrichment strategy is unlikely to be effective for all genomic applications.” Tucker, p. 147, c. 2, ll. 7-9. Tucker does not provide guidance to allow one of ordinary skill in the art to arrive at the claimed invention. Thus, the instant claims are not obvious.

In view of the foregoing arguments and amendments, Applicant respectfully requests that the rejections under 35 U.S.C. §103(a) be withdrawn.

### CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any question, the Examiner is encouraged to telephone the undersigned.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 25115-755.201).

Respectfully submitted,

Date: February 1, 2016

By: /Jeffrey Seidel/  
Jeffrey J. Seidel, Ph.D.  
Reg. No. 61,063

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## REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL (Submitted Only via EFS-Web)

|                      |              |             |            |                               |                        |          |      |
|----------------------|--------------|-------------|------------|-------------------------------|------------------------|----------|------|
| Application Number   | 13750768     | Filing Date | 2013-01-25 | Docket Number (if applicable) | 25115-755.201          | Art Unit | 1637 |
| First Named Inventor | Doug Amorese |             |            | Examiner Name                 | BERTAGNA, ANGELA MARIE |          |      |

**This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.** Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C. 371, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV.

### SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on \_\_\_\_\_

☐ Other \_\_\_\_\_

☒ Enclosed

☒ Amendment/Reply

☒ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☒ Other

Three month extension of time

### MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months \_\_\_\_\_. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other \_\_\_\_\_

### FEES

**The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No. 232415

### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

| Signature of Registered U.S. Patent Practitioner |                |                     |            |
|--------------------------------------------------|----------------|---------------------|------------|
| Signature                                        | /Rachna Ujwal/ | Date (YYYY-MM-DD)   | 2016-04-28 |
| Name                                             | Rachna Ujwal   | Registration Number | 73914      |

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|                                                                                                                                    |                           |
|------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| In re Application:                                                                                                                 | Confirmation No.: 1162    |
| Inventor: Doug Amorese <i>et al.</i>                                                                                               | Examiner: Angela Bertagna |
| Application No.: 13/750,768                                                                                                        | Group Art Unit: 1637      |
| Filed: January 25, 2013                                                                                                            | Customer No. 12754        |
| Title: COMPOSITIONS AND METHODS<br>FOR TARGETED NUCLEIC ACID<br>SEQUENCE ENRICHMENT AND<br>HIGH EFFICIENCY LIBRARY<br>REGENERATION |                           |

**FILED ELECTRONICALLY ON: April 28, 2016**

**RESPONSE TO FINAL OFFICE ACTION**

**AND**

**REQUEST FOR CONTINUED EXAMINATION**

M/S Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Commissioner:

This communication is in response to the Final Office Action mailed October 30, 2015. The shortened statutory period for response expired on January 30, 2016. Applicant submits a request for a three-month extension of time. Therefore, this response is timely filed with a request for a three-month extension of time.

A Request for Continued Examination is also submitted herewith.

Prior to reconsidering this application on the merits, please amend the application as follows:

**Amendments to the claims** begin on page **2** of this paper.

**Remarks** begin on page **9** of this paper.

**Conclusion** begins on page **15** of this paper.

### **Amendments to the Claims**

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

#### **LISTING OF CLAIMS:**

1. **(Currently Amended)** A method for enriching for a nucleic acid sequence of interest in a sample comprising nucleic acids, the method comprising:
  - a. fragmenting nucleic acids in the sample comprising the nucleic acids, thereby generating nucleic acid fragments, wherein the nucleic acid fragments comprise the nucleic acid sequence of interest;
  - b. ligating a first adaptor sequence to a 5' end of the nucleic acid fragments, thereby generating nucleic acid fragments ligated to the first adaptor sequence;
  - c. purifying the nucleic acid fragments ligated to the first adaptor sequence;
  - [[c.]]d. annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the purified nucleic acid fragments ligated to the first adaptor sequence, wherein the one or more oligonucleotides in solution comprise a 3' portion with at least 10 bases that are complementary to the nucleic acid sequence of interest and a 5' tail, wherein the 5' tail portion comprising comprises a second adaptor sequence non-hybridizable to other adaptor sequence appended to the nucleic acid fragments;
  - [[d.]]e. extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragments ligated to the first adaptor sequence with a polymerase in a reaction mixture, wherein the reaction mixture does not comprise a primer that anneals to sequence complementary to the first adaptor sequence, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the ligated first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;[[ and]]
  - [[e.]]f. amplifying the one or more oligonucleotide extension products using a first primer that anneals to the complement of the first adaptor sequence and a second primer that

anneals to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface, wherein the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform;

g. annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and

h. sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

2. (Canceled)

3. **(Previously Presented)** The method of claim 1, wherein the nucleic acid sequence of interest comprises genomic DNA, RNA, or cDNA.

4.-5. (Canceled).

6. **(Currently Amended)** The method of claim 52, further comprising denaturing the purified nucleic acid fragments ligated to the first adaptor sequence prior to step [[c]]d, thereby generating single-stranded nucleic acid fragments comprising ligated to the first adaptor sequence.

7.-8. (Canceled).

9. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

10. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence and/or the second adaptor sequence comprise barcode sequence.

11. -13. (Canceled).

14. **(Original)** The method of claim 1, wherein the polymerase is a DNA polymerase.

15.-39. **(Canceled)**.

40. **(Currently Amended)** A method for enriching for a nucleic acid sequence of interest from a library, wherein the library comprises nucleic acid inserts comprising the nucleic acid sequence of interest, wherein the nucleic acid inserts have a first adaptor sequence attached on a first end and a second adaptor sequence attached on a second end, the method comprising:

- a. denaturing the nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end, thereby generating a library of single stranded nucleic acid inserts with the first adaptor sequence on a first end and the second adaptor sequence on a second end;
- b. annealing one or more oligonucleotides in solution to the sequence of interest in the single stranded nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end, wherein the one or more oligonucleotides in solution comprise a 3' portion with at least 10 bases designed to be that are complementary to the nucleic acid sequence of interest present in the nucleic acid inserts and a 5' tail, wherein the 5' tail portion comprising comprises a third adaptor sequence, wherein the third adaptor sequence is distinct from and non-hybridizable to the first adaptor sequence and the second adaptor sequence;
- c. extending the one or more oligonucleotides with a polymerase in a reaction mixture, wherein the reaction mixture does not comprise a primer that anneals to sequence complementary to the first adaptor sequence or the second adaptor sequence, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the third adaptor sequence at a second end;[[ and]]
- d. amplifying the one or more oligonucleotide extension products using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals to a complement of the third adaptor sequence to enrich for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface, wherein the first adaptor sequence or its

~~complement, the third adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform;~~

e. purifying the products of the amplifying;

f. annealing a strand of the purified products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and

g. sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

41. **(Canceled)**

42. **(Previously Presented)** The method of claim 40, wherein the nucleic acid sequence of interest comprises genomic DNA, RNA or cDNA.

43.-45. **(Canceled).**

46. **(Previously Presented)** The method of claim 40, wherein the third adaptor sequence is the same among the one or more oligonucleotides.

47. **(Previously Presented)** The method of claim 40, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

48. **(Currently Amended)** The method of claim 40, wherein the first adaptor sequence and the complement of the second adaptor sequence are the same.

49. **(Previously Presented)** The method of claim 40, wherein the first adaptor sequence, the second adaptor sequence and/or the third adaptor sequence comprise barcode sequence.

50. **(Canceled).**

51. **(Previously Presented)** The method of claim 1, wherein the one or more oligonucleotides comprise a 3' portion that is complementary to a different nucleic acid sequence of interest in the nucleic acid fragments and a 5' portion comprising the second adaptor sequence.

52. **(Previously Presented)** The method of claim 1, wherein the nucleic acid fragments are double stranded.

53. **(Canceled)**.

54. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence comprises a restriction and/or cleavage site for a nucleic acid modifying enzyme.

55. **(Previously Presented)** The method of claim 1, wherein the 3' portion of the one or more oligonucleotides comprises a random sequence.

56. **(Previously Presented)** The method of claim 40, wherein the 3' portion of each of the one or more oligonucleotides comprises a random sequence.

57. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence is in a first strand of a partial duplex adaptor.

58. **(Previously Presented)** The method of claim 57, wherein the first strand is a long strand of the partial duplex adaptor.

59. **(Canceled)**.

60. **(Previously Presented)** The method of claim 57, wherein the partial duplex adaptor comprises a second strand, wherein the second strand is a short strand.

61. **(Previously Presented)** The method of claim 60, wherein the short strand is ligated to a 3' end of the nucleic acid fragments.

62. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence is in a ligation strand of a first adaptor, wherein the first adaptor comprises the ligation strand and a non-ligation strand, wherein the ligation strand ligates to a 5' end of the nucleic acid fragments.

63. **(Canceled)**

64. **(Currently Amended)** The method of claim [[63]]1, wherein the sequencing comprises bridge amplification.

65. **(Currently Amended)** The method of claim [[63]]1, wherein the sequencing comprises use of four labeled reversible terminators.

66. **(Canceled)**

67. **(Currently Amended)** The method of claim [[63]]1, wherein the sequencing comprises semiconductor sequencing.

68. – 78. **(Canceled)**

79. **(Currently Amended)** The method of claim [[78]]40, wherein the sequencing comprises bridge amplification.

80. **(Currently Amended)** The method of claim [[78]]40, wherein the sequencing comprises use of four labeled reversible terminators.

81. **(Canceled)**

82. **(Currently Amended)** The method of claim [[78]]40, wherein the sequencing comprises semiconductor sequencing.

83. – 92. **(Canceled)**

93. **(Currently Amended)** The method of claim 40, wherein neither the first adaptor sequence nor the second adaptor sequence ~~comprise~~ comprises a 3' block.

94. **(New)** The method of claim 1, further comprising purifying the nucleic acid fragments prior to step b.

95. **(New)** The method of claim 1, further comprising purifying the products of the amplifying prior to step g.

96. **(New)** The method of claim 1, wherein the 3' portion of the one or more oligonucleotides that hybridizes to the nucleic acid sequence of interest is synthesized precisely according to antisense sequence of the nucleic acid sequence of interest.

97. **(New)** The method of claim 40, further comprising ligating the first adaptor sequence to the first end and the second adaptor sequence to the second end of the nucleic acid inserts prior to step a, thereby generating the library of nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end.

98. **(New)** The method of claim 97, further comprising purifying the nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end after the ligating.

99. **(New)** The method of claim 40, wherein the 3' portion of the one or more oligonucleotides that hybridizes to the nucleic acid sequence of interest is synthesized precisely according to antisense sequence of the nucleic acid sequence of interest.

## REMARKS

### **I. STATUS OF THE CLAIMS**

Prior to entry of this amendment, claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58 and 60-93 were pending. Claims 1, 6, 40, 48, 64, 65, 67, 79, 80, 82, and 93 are currently amended. Claims 2, 4-5, 7-8, 11-13, 15-39, 41, 43-45, 50, 53, 59, 63, 66, 68-78, 81, and 83-92 are canceled without prejudice. Claims 94-99 are newly added. Following entry of this amendment, claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-99 are pending. Amendment markings in the claims are made relative to claims filed October 15, 2015.

Exemplary support for the new and amended claims can be found throughout the application as filed and in the following exemplary claims, paragraphs, and/or figures:

Claim 1: [0030], [0038], [0039], [0041], [0050], [0054], [0057], [0064], [0071], [0074], [0085], [0087], [0095], [00103], FIGs. 1 and 4, Original Claim 2

Claim 40: [0030], [0038], [0039], [0041], [0045], [0050], [0054], [0057], [0064], [0071], [0087], [0095], [00103], FIGs. 1 and 4, Original Claim 41

Claim 94: [0083]

Claim 95: [0087]

Claims 96 and 99: [0053]

Claim 97: [0033], [0035], FIGs. 1 and 4

Claim 98: [0085]

No new matter is added.

### **II. INTERVIEW SUMMARY**

Applicant thanks Examiner Angela Bertagna for courtesies extended at a productive telephonic interview with Applicant's representative Jeffrey Seidel on December 30, 2015. At the interview, Applicant's representative discussed the art cited and proposed claim amendments.

### **III. INFORMATION DISCLOSURE STATEMENTS**

Applicant acknowledges, with appreciation, the Office's indication that the references submitted in the Information Disclosure Statements filed July 22, 2015, October 16, 2015, November 9, 2015, and February 1, 2016 have been considered.

### **IV. CLAIM OBJECTIONS**

Claims 1 and 40 are objected to because the Office states that "the" should be inserted before "second primer" in the third-to-last line of each claim. Office Action at **Item 4**, pp. 3-4. Claims 1 and 40 are amended to delete "second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform." In view of the amendment, the objection is rendered moot.

Claim 93 is objected to because the Office states that "comprise" should be replaced with "comprises". Office Action at **Item 4**, p. 4. Claim 93 is amended to recite "comprises." Applicant respectfully requests that the objection be withdrawn.

**V. CLAIM REJECTIONS UNDER PRE-AIA 35 U.S.C. § 112 FIRST PARAGRAPH**

Claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58, and 60-93 are rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, as allegedly failing to comply with the written description requirement. *See* Office Action at **Item 5**, pp. 4-5. Specifically, the Office alleges that claims 1 and 40, and those claims depending therefrom, contain new matter because the original disclosure does not provide support for methods in which the complements of the first, second, or third adaptor or the complements of the first or second primer comprise the sequence to initiate sequencing on the massively parallel sequencing platform. Further, the Office states "[t]he following is suggested to overcome the rejection and also to facilitate prosecution in general: Replacing the concluding clause in claims 1 and 40 with a positively recited massively parallel sequencing step and canceling claims 68-77 and 83-92."

Without acquiescing, and solely to facilitate prosecution, claims 1 and 40 have been amended to delete: "wherein the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform." Claim 1 has been amended to recite, in part:

- "f. ...wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface;
- g. annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and
- h. sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform."

A similar amendment is made to claim 40. Claims 2, 41, 63, 66, 68-78, 81, and 83-92 are canceled, thus obviating the rejection with respect to these claims.

In view of the foregoing, Applicant respectfully requests that the rejection under pre-AIA 35 U.S.C. § 112 first paragraph be withdrawn.

**VI. CLAIM REJECTIONS UNDER PRE-AIA 35 U.S.C. § 112 SECOND PARAGRAPH**

Claims 1-3, 6-9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-67, 70-82, and 85-93 are rejected under 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 applicant regards as the invention. Specifically, the Office alleges that “[c]laims 1 and 40 are indefinite because the requirements of ‘comprise sequence to initiate sequencing on a massively parallel sequencing platform,’ which is recited in the concluding clause of each claim, are unclear.” Office Action at **Item 6**, pp. 6-7.

Without acquiescing, and solely to facilitate prosecution, claims 1 and 40 have been amended to delete: “wherein the first adaptor sequence or its complement, the second adaptor sequence or its complement, the first primer or its complement, or second primer or its complement comprise sequence to initiate sequencing on a massively parallel sequencing platform”. Claims 2, 41, 63, 66, 70-78, 81, and 85-92 are canceled, thus obviating the rejection with respect to these claims.

The Office alleges that “claims 70 and 85 are also vague and indefinite because the requirements of the claims are unclear. The claims recite that ‘the sequence to initiate sequencing on the massively parallel sequencing platform is a flow cell sequence.’ It is not clear whether this language requires a sequence that is immobilized in a flow cell or if it only requires a sequence capable of being used in a flow cell.” Office Action at **Item 6**, page 7.

Without acquiescing, and solely to facilitate prosecution, claims 70 and 85 have been canceled, thus obviating the rejection with respect to these claims.

The Office alleges that “claims 75-77 and 90-92 are further indefinite because it is unclear what is meant by the ‘allows annealing’ language in each of claims 75 and 90.” Office Action at **Item 6**, page 7.

Without acquiescing, and solely to facilitate prosecution, claims 75-77 and 90-92 have been canceled, thus obviating the rejection with respect to these claims.

In view of the foregoing, Applicant respectfully requests that the rejection under pre-AIA 35 U.S.C. § 112 second paragraph be withdrawn.

**VII. CLAIM REJECTIONS UNDER PRE-AIA 35 U.S.C. § 112 FOURTH PARAGRAPH**

Claims 70 and 85 are rejected under pre-AIA 35 U.S.C. 112, fourth paragraph, as allegedly being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Specifically, the Office alleges that “if no structural difference is required, claims 70 and 85 are not further limiting because they merely recite an inherent property of the sequences in claims 1 and 40.” Office Action at **Item 7**, page 8.

Without acquiescing, and solely to facilitate prosecution, claims 70 and 85 have been canceled, thus obviating the rejection with respect to these claims.

**VIII. CLAIM REJECTIONS UNDER 35 U.S.C. § 103(A)**

Claims 1-3, 6, 9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-66, 68-81, and 83-93 are rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Jones et al. (US 2005/0142577A1; “Jones”) in view of Tucker et al. (The American Journal of Human Genetics (2009) 85: 142-154; “Tucker”). Office Action at **Item 9**, pp. 9-16. Applicant respectfully traverses the rejection.

In order to establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. Further, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, in a manner which would have led a person of ordinary skill in the art to the invention as claimed. Finally, there must be a reasonable expectation of success.

Without acquiescing, and solely to facilitate prosecution, claim 1 has been amended to recite, in part:

- “c. purifying the nucleic acid fragments ligated to the first adaptor sequence”
- and
- “f. ...wherein products of the amplifying comprise a 3’ end with sequence complementary to a sequence on a surface;
- g. annealing a strand of the products of the amplifying to the sequence on the surface using the 3’ end with sequence complementary to the sequence on the surface; and
- h. sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.”

The Office has not established that Jones or Tucker, alone or in combination, teach or suggest each and every element of amended independent claim 1. For example, the Office has not established that Jones or Tucker, alone or in combination, disclose or suggest purifying the nucleic acid fragments ligated to the first adaptor sequence prior to the extension step. Further, the Office has not established that Jones or Tucker, alone or in combination, disclose or suggest an amplified product comprising a 3' end with sequence complementary to a sequence on a surface.

Without acquiescing, and solely to facilitate prosecution, claim 40 has been amended to recite, in part:

- “d. ...wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface;
- e. purifying the products of the amplifying;
- f. annealing a strand of the purified products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface;
- and
- g. sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.”

The Office has not established that Jones or Tucker, alone or in combination, teach or suggest each and every element of amended independent claim 40. For example, the Office has not established that Jones or Tucker, alone or in combination, disclose or suggest purifying the amplified products prior to sequencing. Moreover, the Office has not established that Jones or Tucker, alone or in combination, disclose or suggest an amplified product comprising a 3' end with sequence complementary to a sequence on a surface.

Furthermore, MPEP 2143.01 VI indicates that “[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349, 352 (CCPA 1959).”

The claims are not obvious because making modifications to the amplified products of Jones in order to use the amplified products with a high-throughput sequencing technique of Tucker in the manner recited in the claims would change the principle of operation of Jones. The instant claims recite “annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end” and “massively parallel sequencing.” As noted by the Office, Jones does not disclose massively parallel sequencing. Further, the Office has not shown that Jones discloses “annealing a strand of the

products of the amplifying to the sequence on the surface using the 3' end" and "massively parallel sequencing." Indeed, the Office has not shown that Jones, following amplification using adaptor sequences, discloses any further function for a 3' end of an amplified product. Rather, Jones uses the *target sequence* of an amplified product for further analysis. For example, Jones describes performing allele discrimination by hybridization to a high density DNA oligonucleotide array (Jones ¶¶0077), which would involve hybridization of the *target sequence* of the amplified product to a unique probe. Other analysis techniques described in Jones (*see e.g.*, Jones ¶¶0080) are not indicated to make use of a 3' end that was not part of the original target sequence. Thus, use of an amplification product of Jones in a high-throughput sequencing technique of Tucker as recited in the claims would require another function to be incorporated into an end sequence of the amplified products of Jones. Use of such a modification would change the principle of operation of Jones. Thus, the claims are not obvious.

Furthermore, there is no motivation to select methods of Jones for use in massively parallel sequencing. Tucker discloses general detriments of performing enrichment before sequencing. Tucker states "[t]argeted sequencing requires substantial up-front preparation to select the DNA segments of interest." Tucker, p. 147, c. 1, ll. 1-2. Tucker also notes that "any enrichment strategy is unlikely to be effective for all genomic applications." Tucker, p. 147, c. 2, ll. 7-9. Tucker does not provide guidance to allow one of ordinary skill in the art to arrive at the claimed invention. Thus, the instant claims are not obvious.

In view of the foregoing arguments and amendments, Applicant respectfully requests that the rejections under 35 U.S.C. §103(a) be withdrawn.

### CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any question, the Examiner is encouraged to telephone the undersigned.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 25115-755.201).

Respectfully submitted,

Date: April 28, 2016

By: /Jeffrey Seidel/  
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| 13/750,768                                                                                                   | 01/25/2013  | Doug Amorese         | 25115-755.201                      | 1162             |
| 12754 7590 06/02/2016<br>Wilson Sonsini Goodrich & Rosati/NUGEN<br>650 Page Mill Road<br>Palo Alto, CA 94304 |             |                      | EXAMINER<br>BERTAGNA, ANGELA MARIE |                  |
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|                                                                                                              |             |                      | 06/02/2016                         | ELECTRONIC       |

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

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

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

patentdocket@wsgr.com

|                              |                                       |                                       |                                                  |
|------------------------------|---------------------------------------|---------------------------------------|--------------------------------------------------|
| <b>Office Action Summary</b> | <b>Application No.</b><br>13/750,768  | <b>Applicant(s)</b><br>AMORESE ET AL. |                                                  |
|                              | <b>Examiner</b><br>Angela M. Bertagna | <b>Art Unit</b><br>1637               | <b>AIA (First Inventor to File) Status</b><br>No |

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

**Period for Reply**

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

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

**Status**

1) ☒ Responsive to communication(s) filed on 4/28/16.  
☐ 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) See Continuation Sheet is/are pending in the application.  
5a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

6) ☐ Claim(s) \_\_\_\_\_ is/are allowed.

7) ☒ Claim(s) 1,3,6,9,10,14,40,42,46-49,51,52,54-58,60-62,64,65,67,79,80,82 and 93-99 is/are rejected.

8) ☒ Claim(s) 1,40,96 and 99 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](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

**Application Papers**

10) ☐ The specification is objected to by the Examiner.

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

**Priority under 35 U.S.C. § 119**

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

**Certified copies:**

a) ☐ All    b) ☐ Some\*\*    c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)  
Paper No(s)/Mail Date \_\_\_\_\_.

3) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.

4) ☐ Other: \_\_\_\_\_.

Continuation of Disposition of Claims: Claims pending in the application are 1,3,6,9,10,14,40,42,46-49,51,52,54-58,60-62,64,65,67,79,80,82 and 93-99.

## **DETAILED ACTION**

### ***Notice of Pre-AIA or AIA Status***

1. The present application is being examined under the pre-AIA first to invent provisions.

### ***Continued Examination Under 37 CFR 1.114***

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 28, 2016 has been entered.

Claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-99 are pending and under examination.

### ***Response to Arguments***

3. Applicant's arguments filed on April 28, 2016 have been fully considered.

#### **Claim Objections**

Applicant argues that the objections to claims 1 and 40 are moot in view of the amendment (page 10).

This argument was persuasive. The objections have been withdrawn.

**Rejection of claims 1-3, 6-9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-67, 70-82, and 85-93 under pre-AIA 35 U.S.C. 112, first paragraph**

Applicant argues that the new matter rejection should be withdrawn in view of the amendments to claims 1 and 40 (pages 10-11).

This argument was persuasive. The rejection has been withdrawn.

**Rejection of claims 1-3, 6-9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-67, 70-82, and 85-93 under pre-AIA 35 U.S.C. 112, second paragraph**

Applicant argues that the issues raised in the rejection have been obviated by the amendment, which amends claims 1 and 40 and cancels claims 70 and 85 (page 11).

This argument was persuasive. The rejection has been withdrawn.

**Rejection of claims 70 and 85 under pre-AIA 35 U.S.C. 112, fourth paragraph**

Applicant argues that the issues raised in the rejection have been obviated by the amendment, which cancels claims 70 and 85 (page 12).

This argument was persuasive. The rejection has been withdrawn.

**Rejection of claims 1-3, 6-9, 10, 14, 40-42, 46-49, 51, 52, 54-58, 60-66, 70-81, and 85-93 under pre-AIA 35 U.S.C. 103(a) citing Jones and Tucker**

Applicant first argues that the references fail to teach or suggest the requirements of steps (c) and (f) of amended independent claim 1 (pages 12-13). Applicant also argues that the references fail to teach or suggest the requirements of steps (d) and (e) of amended independent claim 40 (page 13).

This argument was persuasive in part. The references fail to teach the purification steps added to claims 1 and 40. The rejection has been withdrawn for this reason. Applicant's argument regarding step (f) of claim 1 and step (d) of claim 40 was not persuasive because the references do, in fact, suggest producing an amplification product with a 3' end complementary

to a sequence on a surface. Jones teaches amplification using primers targeting the first and second adaptor of claim 1 or the first and third adaptor of claim 40 (see, for example, Figure 3 and paragraphs 87 and 100). The reference does not disclose that the 3' end of the amplification products is complementary to a sequence on a surface, but Tucker remedies this deficiency in Jones. Tucker provides motivation to substitute the array-based sequencing method of Jones with a massively parallel approach (abstract, page 142, and page 144) and also describes a massively parallel sequencing method that comprises attaching adaptors to each end of a nucleic acid to be sequenced, hybridizing the 3' end of the adaptor-ligated nucleic acid to a complementary sequence on a surface, and determining the sequence of the hybridized sequence in a massively parallel fashion (Figure 2). When using massively parallel sequencing as described by Tucker to sequence the adaptor-containing nucleic acids of Jones, the ordinary artisan would have recognized that the amplification reaction of Jones should produce amplicons with a 3' end capable of hybridizing to a surface-immobilized oligonucleotide and would have been motivated to design the adaptors accordingly.

Applicant also argues that the proposed modification would change the principle of operation of Jones because the claims require using the 3' end of the amplification product for analysis, whereas Jones analyzes an internal target sequence (pages 13-14).

This argument applies to the new rejection, which continues to cite Jones and Tucker. It is not persuasive for at least two reasons. First, Jones is not limited to methods that comprise analyzing the target sequence by hybridization to a unique probe. The reference does not disclose massively parallel sequencing, but it does teach that any known method may be used to analyze the target region (paragraph 80). As discussed in the rejection, the ordinary artisan would have

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recognized massively parallel sequencing as described by Tucker to be a method suitable for determining sequence information concerning a target region of interest and would have been motivated to select it for the analysis step in the method of Jones with a reasonable expectation of success. Using the adaptor portion of the enriched sequence of Jones to facilitate the sequencing step (e.g., by capture on a surface and/or as a binding site for a sequencing primer) would not change the principle of operation of Jones because massively parallel sequencing would not be used to obtain sequence information concerning the adaptor. Instead, the sequencing method would be used to obtain sequence information concerning the target sequence between the adaptor sequences. In other words, combining the references would not destroy the principle of operation of Jones' method. It would only result in the use of a different method to determine sequence information.

Applicant also argues that there is no motivation to select the methods of Jones for massively parallel sequencing and cites the teachings of Tucker in the first and last sentences of page 147 (page 14).

This argument was not persuasive for the following reasons. Regarding the teachings of Tucker at page 147, column 1, lines 1-2, it is true that Tucker states that "Targeted sequencing requires substantial up-front preparation to select the DNA sequences of interest", but the rest of the paragraph describes methods to selectively amplify hundreds of exons from a DNA sample (page 147, column 1, lines 2-7), and the following paragraph describes additional ways of preparing selected sequences for sequencing. Thus, Tucker does not teach away from using massively parallel sequencing with samples containing enriched nucleic acids, such as the samples of Jones. Tucker only states that the enrichment step may be time-consuming and goes

on to describe enrichment methods. This does not negatively impact the rejection since Jones teaches an enriched sample and the teachings of Tucker in no way indicate that sequencing such a sample would be problematic or undesirable. The last sentence of Tucker on page 147 also does not constitute a teaching away since it is merely a general statement indicating that different applications may require different enrichment strategies.

Lastly, Applicant argues that Tucker fails to provide sufficient guidance for the ordinary artisan to arrive at the claimed invention (page 13).

This argument was not persuasive to the extent that it applies to the previously made rejection since Tucker describes a number of massively parallel sequencing methods in detail and additionally points to the primary sources for each different method (pages 142-143, Figures 2-5, and pages 148-149).

**Rejection of claims 67 and 82 under pre-AIA 35 U.S.C. 103(a) citing Jones, Tucker, and Rothberg**

The response does not appear to address this rejection. It has been withdrawn because Rothberg fails to remedy the deficiencies of Jones and Tucker with respect to claims 1 and 40.

***Information Disclosure Statement***

4. The information disclosure statement filed on April 28, 2016 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Specifically, copies of the references listed in citations 51 and 57 have not been provided.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

### ***Claim Objections***

5. Claims 1 and 40 are objected to because the claims contain multiple periods. As discussed in MPEP 608.01(m), claims may not include periods in addition to the concluding period except for abbreviations. Enclosing the steps of the methods in parentheses is suggested. Also, replacing “other adaptor sequence appended to the nucleic acid fragments” in lines 5-6 of step (d) with “the first adaptor sequence” is suggested to improve consistency within the claim.

Claims 96 and 99 are objected to because the word “the” should be inserted before “antisense” in line 2 of each claim.

### ***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-99 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 1 and 40 have been amended to state that the second adaptor (claim 1) or the third adaptor (claim 40) is not hybridizable to the first adaptor (claim 1) or the first and second adaptor (claim 40). Applicant points to paragraphs 30, 38, 39, 41, 50, 54, 57, 64, 71, 74, 85, 87, 95, and 103, Figures 1 and 4, and original claim 2 for support (Remarks, page 9).

The original disclosure, including the portions cited by Applicant, has been reviewed, but support was not found for this amendment to claims 1 and 40. The original disclosure only provides support for a first or third adaptor that is different or distinct from the other adaptors (paragraph 30, for example). This language is not synonymous with “non-hybridizable” because it is much broader and only requires a difference of a single nucleotide or the presence of a label between two adaptors. There is no indication in the original disclosure that non-hybridizable adaptors were also contemplated. Claims 3, 6, 9, 10, 14, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-99 also contain new matter since they depend from claim 1 or claim 40.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

8. 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.

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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.

9. Claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-99 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 pre-AIA the applicant regards as the invention.

Claims 1 and 40 are indefinite because there is a lack of clear antecedent basis for “the enriched nucleic acid”, which is recited in the last step of each claim. Amending each claim to insert language such as “thereby providing an enriched nucleic acid” at the appropriate point is suggested.

Claims 3, 6, 9, 10, 14, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-99 are indefinite by way of their dependency on claim 1 or claim 40.

### ***Claim Rejections – 35 USC § 112***

10. The following is a quotation of 35 U.S.C. 112(d):

(d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), fourth paragraph:

Subject to the [fifth paragraph of 35 U.S.C. 112 (pre-AIA)], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

11. Claim 9 is rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.

Claim 9 depends from claim 1 and states that the first and second adaptor sequence are distinct from each other. This recitation is not further limiting because it broadens the scope relative to claim 1, which requires in step (d) that the second adaptor sequence is unable to hybridize to the first adaptor. To elaborate, two nucleic acids are distinct from one other if they differ by a single nucleotide or even the presence of a label or modification on one nucleic acid, but much more extensive differences in nucleotide sequence are necessary for two nucleic acids to be unable to hybridize to one another.

Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

### ***Claim Rejections - 35 USC § 103***

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

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

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made

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absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

13. Claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 79, 80, and 93-99 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 2005/0142577 A1) in view of Tucker et al. (The American Journal of Human Genetics (2009) 85: 142-154) and further in view of Gormley et al. (US 7,741,463 B2).

Regarding claims 1 and 14, Jones teaches a method for enriching a nucleic acid sequence of interest in a sample comprising nucleic acids that comprises the following steps (see, for example, Figures 3-4 and paragraphs 86-90, 96, 99, and 100): (a) fragmenting nucleic acids in the sample to generate fragments comprising the sequence of interest; (b) ligating a first adaptor to a 5' end of the nucleic acid fragments; (c) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the fragments, wherein said oligonucleotides comprise a 3' portion with at least ten bases that are complementary to the nucleic acid sequence of interest and a 5' portion comprising a second adaptor sequence; (d) extending said annealed oligonucleotides using a DNA polymerase in a reaction mixture that does not contain a primer that anneals to sequence complementary to the first adaptor sequence, thereby obtaining extension products comprising sequence complementary to the ligated first adaptor, sequence complementary to the nucleic acid of interest, and the second adaptor; (e) amplifying the

extension products using a primer that anneals to the complement of the first adaptor sequence and a primer that anneals to the complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest; and (f) sequencing the enriched nucleic acid of interest.

Regarding claim 3, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 100). The reference also teaches that the nucleic acid sequence of interest may comprise RNA (paragraphs 43-44).

Regarding claims 6 and 52, Jones teaches that the nucleic acid fragments are double-stranded and that method comprises denaturing the nucleic acid fragments before the step of annealing the oligonucleotides (step (c) above), thereby generating single-stranded nucleic acid fragments comprising the first adaptor sequence and the nucleic acid sequence of interest (Figure 3 and paragraphs 87 and 100).

Regarding claim 9, Jones teaches that the first and second adaptor sequences are distinct from each other (Figure 3, paragraph 87, and paragraph 100).

Regarding claims 10 and 54, Jones teaches that the second adaptor sequence may comprise a barcode sequence (paragraphs 58 and 61) and also that the first adaptor may include a restriction site (paragraph 49).

Regarding claim 51, in the method of Jones, the oligonucleotides comprise a 3' portion that is complementary to a different nucleic acid sequence of interest in the nucleic acid fragments and a 5' portion comprising the second adapter sequence (paragraphs 87, 99, and 100; see also Figure 3).

Regarding claim 55, Jones teaches that the 3' portion of the oligonucleotides comprises a random sequence (see Figure 4, paragraph 100 and paragraphs 88-90).

Regarding claims 57, 58, 60, and 61, Jones teaches that the first adaptor sequence is in a long strand of a partial duplex adaptor comprising a long strand and a short strand, the long strand is ligated to a 5' end of the nucleic acid fragments, and the short strand is ligated to a 3' end of the nucleic acid fragments (see Figure 3 and paragraph 87).

Regarding claim 62, Jones teaches that the first adaptor sequence is in a ligation strand of a first adaptor, wherein the first adaptor comprises the ligation strand and a non-ligation strand, wherein the ligation strand ligates to a 5' end of the nucleic acid fragments (paragraph 50).

Regarding claims 40 and 97, Jones teaches a method for enriching a nucleic acid sequence of interest from a library (see Figure 3, paragraphs 86-90, 99, and 100), wherein the library comprises nucleic acid inserts comprising the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100), wherein the nucleic acid inserts have a first adaptor sequence ligated to a first end and a second adaptor sequence ligated to a second end (Figure 3 and paragraphs 86 and 100), the method comprising:

(a) denaturing the nucleic acid inserts, thereby generating a library of single-stranded nucleic acids with the first and second adaptor sequences flanking the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100);

(b) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the single-stranded nucleic acids, wherein the oligonucleotides comprise a 3' portion with at least ten bases that are complementary to the nucleic acid sequence of interest and a 5' tail portion comprising a third adaptor sequence that is distinct from the first and second adaptor sequences (Figure 3, paragraph 86, and paragraph 100, where the oligonucleotides containing an A1 or degenerate sequence are annealed);

(c) extending said annealed oligonucleotides using a polymerase in a reaction mixture that does not include a primer that anneals to the complement of the first or second adaptor sequence to obtain extension products comprising sequence complementary to the first adaptor, sequence complementary to the nucleic acid of interest, and the third adaptor (Figure 3, paragraph 87, and paragraph 100);

(d) amplifying the extension products using a primer that anneals to the complement of the first adaptor sequence and a primer that anneals to the complement of the third adaptor sequence to enrich for the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100); and

(e) sequencing the enriched nucleic acid of interest (paragraph 100).

Regarding claim 42, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 100). The reference also teaches that the nucleic acid sequence of interest may comprise RNA (paragraphs 43-44).

Regarding claim 46, Jones teaches that the third adaptor sequence is the same among the one or more oligonucleotides (Figure 3 and paragraphs 87 and 100).

Regarding claim 47, Jones teaches that the first and second adaptor sequence may be distinct from each other (Figure 3 and also paragraph 53).

Regarding claim 48, Jones teaches that the first adaptor and the complement of the second adaptor are the same (Figure 3 and paragraphs 86 and 100).

Regarding claim 49, Jones teaches that the third adaptor sequence may comprise a barcode sequence (paragraph 58).

Regarding claim 56, Jones teaches that the 3' portion of the oligonucleotides comprises a random sequence (paragraph 100 and paragraphs 88-90).

Regarding claim 93, Jones teaches that the neither the first adaptor sequence nor the second adaptor sequence comprises a 3' block (see, for example, paragraph 87, which indicates that the 3' blocking group is optional).

Regarding claims 96 and 99, the 3' portion of the oligonucleotides of Jones is designed precisely according to the antisense sequence of the nucleic acid sequence of interest (paragraphs 87-89, 91, and 94).

Jones differs from the instant claims in the following ways. First, the reference does not teach massively parallel sequencing as required by amended claims 1 and 40. Jones teaches that nucleic acids amplified by the disclosed method may be analyzed by array hybridization or any other method known in the art to obtain sequence information about a region of interest (paragraph 79-80), but the reference does not disclose massively parallel sequencing. Second, Jones does not teach that the adaptor sequence contained on the capture probes, which correspond to the claimed one or more oligonucleotides in solution recited in step (d) of claim 1 and step (b) of claim 40, is incapable of hybridizing to the other adaptor sequences appended to the nucleic acid fragments as required by amended claims 1 and 40. The reference teaches that the different adaptors may be different from each other (Figure 3, paragraph 87, and paragraph 100), but this is broader than incapable of hybridizing as recited in the claims. Third, Jones does not teach purification as recited in step (c) of claim 1 and step (e) of claim 40.

Tucker describes methods of obtaining sequence information about a region of interest in a nucleic acid, and specifically describes a number of massively parallel sequencing methods

(abstract, pages 142-146, and Figures 2-5). The reference teaches that “Massively parallel sequencing will allow simultaneous screening for mutations in hundreds of loci in genetically heterogeneous disorders, whole-genome screening for novel mutations, and sequence-based detection of novel pathogens that cause human disease. In addition, massively parallel sequencing will permit clinical application of our expanding knowledge of pharmacogenetics, cancer genetics, epigenetics, and complex traits” (page 142, column 2). The reference further teaches that massively parallel sequencing “has reduced the cost and increased the throughput of genomic sequencing by more than three orders of magnitude...and may also replace arrays and Sanger sequencing in clinical applications where they are currently being used” (abstract).

Further regarding claims 1, 40, 64, 65, 79, and 80, Tucker describes a massively parallel sequencing method developed by Illumina (Figure 2). This method comprises bridge amplification and the use of four labeled reversible terminators (Figure 2). The Illumina method also comprises attaching an adaptor to each end of a nucleic acid fragment of interest and using the adaptors to hybridize the nucleic acid of interest to flow cell sequences (Figure 2). Each of the two adaptors is also complementary to a sequencing primer (Figure 2).

Tucker does not teach or suggest the purification steps present in claims 1, 40, 94, 95, and 98, but Gormley describes a method for preparing a library for sequencing that comprises purification after the fragmentation, adaptor ligation, and PCR steps (see the working example at columns 23-26 and especially column 23, lines 25-67, column 25, line 41 – column 26, line 20, and column 26, lines 25-62). Gormley further teaches using sequencing the nucleic acids in the library using a massively parallel method comprising the steps disclosed in Figure 2 of Tucker

(i.e., bridge amplification and the use of reversible terminators) (column 20, line 18 – column 22, line 20).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to analyze the amplification products generated by the method of Jones using one of the massively parallel sequencing methods described in Tucker. The ordinary artisan would have been motivated to do so since Tucker taught that such methods offered very high-throughput sequencing (abstract and page 142) and as well as the ability to accurately detect minor alleles (page 144, column 2). Additional motivation is provided in the abstract of Tucker, which teaches that massively parallel sequencing methods may replace array methods. The ordinary artisan would have had a reasonable expectation of success in view of the guidance provided by Tucker concerning the use of massively parallel sequencing methods and also since Jones taught that the amplification products could be analyzed using any desired method. In using the Illumina sequencing method, for example, the ordinary artisan would have recognized that the 3' end of the amplification products should be complementary to a surface-immobilized sequence and, accordingly, would have been motivated to design the adaptors such that they are complementary to sequences on a support to be used in the Illumina sequencing method. The ordinary artisan would have had a reasonable expectation of success since the Illumina method has been publicly disclosed and commercialized.

The ordinary artisan also would have been motivated to include purification steps after the fragmentation, adaptor ligation, and PCR amplification steps of Jones when subjecting the resulting library of amplification products to a massively parallel sequencing method. Motivation and a reasonable expectation of success are provided by Gormley, who describes including these

purification steps in a method for preparing a library for massively parallel sequencing using the Illumina method also described in Tucker.

Further regarding claims 1 and 40, it would have been obvious for the ordinary artisan to design the second and third adaptor such that they are incapable of hybridizing to the other adaptors. As noted above, Jones teaches that the adaptors may be different from each other. This in combination with the fact that the amplification is conducted using two different primers (Figure 3) would have provided strong motivation for the ordinary artisan to use adaptors incapable of hybridizing to each other, recognizing that adaptors capable of hybridizing to each other could compromise the accuracy and efficiency of the PCR step.

Thus, the methods of claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 79, 80, and 93-99 are *prima facie* obvious.

14. Claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 67, 82, 93, and 95-99 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 2005/0142577 A1) in view of Tucker et al. (The American Journal of Human Genetics (2009) 85: 142-154) and further in view of Rothberg et al. (Nature (2011) 475: 348-352 + Supplementary Information).

Regarding claims 1 and 14, Jones teaches a method for enriching a nucleic acid sequence of interest in a sample comprising nucleic acids that comprises the following steps (see, for example, Figures 3-4 and paragraphs 86-90, 96, 99, and 100): (a) fragmenting nucleic acids in the sample to generate fragments comprising the sequence of interest; (b) ligating a first adaptor to a 5' end of the nucleic acid fragments; (c) annealing one or more oligonucleotides in solution

to the nucleic acid sequence of interest in the fragments, wherein said oligonucleotides comprise a 3' portion with at least ten bases that are complementary to the nucleic acid sequence of interest and a 5' portion comprising a second adaptor sequence; (d) extending said annealed oligonucleotides using a DNA polymerase in a reaction mixture that does not contain a primer that anneals to sequence complementary to the first adaptor sequence, thereby obtaining extension products comprising sequence complementary to the ligated first adaptor, sequence complementary to the nucleic acid of interest, and the second adaptor; (e) amplifying the extension products using a primer that anneals to the complement of the first adaptor sequence and a primer that anneals to the complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest; and (f) sequencing the enriched nucleic acid of interest.

Regarding claim 3, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 100). The reference also teaches that the nucleic acid sequence of interest may comprise RNA (paragraphs 43-44).

Regarding claims 6 and 52, Jones teaches that the nucleic acid fragments are double-stranded and that method comprises denaturing the nucleic acid fragments before the step of annealing the oligonucleotides (step (c) above), thereby generating single-stranded nucleic acid fragments comprising the first adaptor sequence and the nucleic acid sequence of interest (Figure 3 and paragraphs 87 and 100).

Regarding claim 9, Jones teaches that the first and second adaptor sequences are distinct from each other (Figure 3, paragraph 87, and paragraph 100).

Regarding claims 10 and 54, Jones teaches that the second adaptor sequence may comprise a barcode sequence (paragraphs 58 and 61) and also that the first adaptor may include a restriction site (paragraph 49).

Regarding claim 51, in the method of Jones, the oligonucleotides comprise a 3' portion that is complementary to a different nucleic acid sequence of interest in the nucleic acid fragments and a 5' portion comprising the second adapter sequence (paragraphs 87, 99, and 100; see also Figure 3).

Regarding claim 55, Jones teaches that the 3' portion of the oligonucleotides comprises a random sequence (see Figure 4, paragraph 100 and paragraphs 88-90).

Regarding claims 57, 58, 60, and 61, Jones teaches that the first adaptor sequence is in a long strand of a partial duplex adaptor comprising a long strand and a short strand, the long strand is ligated to a 5' end of the nucleic acid fragments, and the short strand is ligated to a 3' end of the nucleic acid fragments (see Figure 3 and paragraph 87).

Regarding claim 62, Jones teaches that the first adaptor sequence is in a ligation strand of a first adaptor, wherein the first adaptor comprises the ligation strand and a non-ligation strand, wherein the ligation strand ligates to a 5' end of the nucleic acid fragments (paragraph 50).

Regarding claims 40 and 97, Jones teaches a method for enriching a nucleic acid sequence of interest from a library (see Figure 3, paragraphs 86-90, 99, and 100), wherein the library comprises nucleic acid inserts comprising the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100), wherein the nucleic acid inserts have a first adaptor sequence ligated to a first end and a second adaptor sequence ligated to a second end (Figure 3 and paragraphs 86 and 100), the method comprising:

(a) denaturing the nucleic acid inserts, thereby generating a library of single-stranded nucleic acids with the first and second adaptor sequences flanking the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100);

(b) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the single-stranded nucleic acids, wherein the oligonucleotides comprise a 3' portion with at least ten bases that are complementary to the nucleic acid sequence of interest and a 5' tail portion comprising a third adaptor sequence that is distinct from the first and second adaptor sequences (Figure 3, paragraph 86, and paragraph 100, where the oligonucleotides containing an A1 or degenerate sequence are annealed);

(c) extending said annealed oligonucleotides using a polymerase in a reaction mixture that does not include a primer that anneals to the complement of the first or second adaptor sequence to obtain extension products comprising sequence complementary to the first adaptor, sequence complementary to the nucleic acid of interest, and the third adaptor (Figure 3, paragraph 87, and paragraph 100);

(d) amplifying the extension products using a primer that anneals to the complement of the first adaptor sequence and a primer that anneals to the complement of the third adaptor sequence to enrich for the nucleic acid sequence of interest (Figure 3 and paragraphs 86 and 100); and

(e) sequencing the enriched nucleic acid of interest (paragraph 100).

Regarding claim 42, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 100). The reference also teaches that the nucleic acid sequence of interest may comprise RNA (paragraphs 43-44).

Regarding claim 46, Jones teaches that the third adaptor sequence is the same among the one or more oligonucleotides (Figure 3 and paragraphs 87 and 100).

Regarding claim 47, Jones teaches that the first and second adaptor sequence may be distinct from each other (Figure 3 and also paragraph 53).

Regarding claim 48, Jones teaches that the first adaptor and the complement of the second adaptor are the same (Figure 3 and paragraphs 86 and 100).

Regarding claim 49, Jones teaches that the third adaptor sequence may comprise a barcode sequence (paragraph 58).

Regarding claim 56, Jones teaches that the 3' portion of the oligonucleotides comprises a random sequence (paragraph 100 and paragraphs 88-90).

Regarding claim 93, Jones teaches that the neither the first adaptor sequence nor the second adaptor sequence comprises a 3' block (see, for example, paragraph 87, which indicates that the 3' blocking group is optional).

Regarding claims 96 and 99, the 3' portion of the oligonucleotides of Jones is designed precisely according to the antisense sequence of the nucleic acid sequence of interest (paragraphs 87-89, 91, and 94).

Jones differs from the instant claims in the following ways. First, the reference does not teach massively parallel sequencing as required by amended claims 1 and 40. Jones teaches that nucleic acids amplified by the disclosed method may be analyzed by array hybridization or any other method known in the art to obtain sequence information about a region of interest (paragraph 79-80), but the reference does not disclose massively parallel sequencing. Second, Jones does not teach that the adaptor sequence contained on the capture probes, which

correspond to the claimed one or more oligonucleotides in solution recited in step (d) of claim 1 and step (b) of claim 40, is incapable of hybridizing to the other adaptor sequences appended to the nucleic acid fragments as required by amended claims 1 and 40. The reference teaches that the different adaptors may be different from each other (Figure 3, paragraph 87, and paragraph 100), but this is broader than incapable of hybridizing as recited in the claims. Third, Jones does not teach purification as recited in step (c) of claim 1 and step (e) of claim 40.

Tucker describes methods of obtaining sequence information about a region of interest in a nucleic acid, and specifically describes a number of massively parallel sequencing methods (abstract, pages 142-146, and Figures 2-5). The reference teaches that “Massively parallel sequencing will allow simultaneous screening for mutations in hundreds of loci in genetically heterogeneous disorders, whole-genome screening for novel mutations, and sequence-based detection of novel pathogens that cause human disease. In addition, massively parallel sequencing will permit clinical application of our expanding knowledge of pharmacogenetics, cancer genetics, epigenetics, and complex traits” (page 142, column 2). The reference further teaches that massively parallel sequencing “has reduced the cost and increased the throughput of genomic sequencing by more than three orders of magnitude...and may also replace arrays and Sanger sequencing in clinical applications where they are currently being used” (abstract).

Tucker does not teach or suggest the purification steps present in claims 1, 40, 95, and 98 or semiconductor sequencing as required by claims 67 and 82, but Rothberg describes massively parallel sequencing using a semiconductor device (Figure 1 and pages 348-350) and discloses that this sequencing method is highly robust and scalable and advantageously does not require the use of optics or labeled nucleotides (abstract and page 348). Rothberg further teaches that the

disclosed massively parallel sequencing method includes a purification step after adaptor ligation and also after amplification (Supplemental Methods, paragraphs 4 and 5).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to analyze the amplification products generated by the method of Jones using a massively parallel sequencing method. The ordinary artisan would have been motivated to do so since Tucker taught that such methods offered very high-throughput sequencing (abstract and page 142) and as well as the ability to accurately detect minor alleles (page 144, column 2). Additional motivation is provided in the abstract of Tucker, which teaches that massively parallel sequencing methods may replace array methods. The ordinary artisan would have had a reasonable expectation of success in view of the guidance provided by Tucker concerning the use of massively parallel sequencing methods and also since Jones taught that the amplification products could be analyzed using any desired method. The ordinary artisan would have been further motivated to select semiconductor sequencing as described by Rothberg as the massively parallel sequencing method since Rothberg described the disclosed method as robust, highly scalable and further taught that the method required neither optical detection or modified nucleotides (abstract and page 348). The ordinary artisan would have had a reasonable expectation of success in view of Rothberg's guidance concerning practice of the method (pages 349-350 and the Supplemental Methods).

The ordinary artisan also would have been motivated to include purification steps after the adaptor ligation and PCR amplification steps of Jones when subjecting the resulting library of amplification products to massively parallel semiconductor sequencing. Motivation and a reasonable expectation of success are provided by Rothberg, who describes including these

purification steps in a method for preparing a library for sequencing using this method (Supplemental Methods, paragraphs 4-5). As well, when using massively parallel semiconductor sequencing as described by Rothberg to sequence the adaptor-containing nucleic acids of Jones, the ordinary artisan would have recognized that the amplification reaction of Jones should produce amplicons with a 3' end capable of hybridizing to a surface-immobilized oligonucleotide and would have been motivated to design the adaptors accordingly since the method of Rothberg includes hybridization of the nucleic acid to a solid support for sequencing (Figure 1).

Finally, further regarding claims 1 and 40, it would have been obvious for the ordinary artisan to design the second and third adaptor such that they are incapable of hybridizing to the other adaptors. As noted above, Jones teaches that the adaptors may be different from each other. This in combination with the fact that the amplification is conducted using two different primers (Figure 3) would have provided strong motivation for the ordinary artisan to use adaptors incapable of hybridizing to each other, recognizing that adaptors capable of hybridizing to each other could compromise the accuracy and efficiency of the PCR step.

Thus, the methods of claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 67, 82, 93, and 95-99 are *prima facie* obvious.

### ***Conclusion***

15. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela M. Bertagna whose telephone number is (571)272-8291. The examiner can normally be reached on Monday-Friday, 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. 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 <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Angela M. Bertagna/  
Primary Examiner, Art Unit 1637

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application:

Inventor: Doug Amorese et al.

Application No.: 13/750,768

Filed: 01-25-2013

Title: COMPOSITIONS AND METHODS  
FOR TARGETED NUCLEIC ACID  
SEQUENCE ENRICHMENT AND  
HIGH EFFICIENCY LIBRARY  
REGENERATION

Confirmation No.: **1162**

Examiner: ANGELA MARIE BERTAGNA

Art Unit: 1637

Customer No. 12754

**Filed electronically on: December 22, 2016**

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

**SUPPLEMENTAL RESPONSE TO NON-FINAL OFFICE ACTION**

Dear Commissioner:

Applicant respectfully requests entry of the proposed amendments prior to allowance of the pending claims.

**Amendments to the Claims** begin on page **2** of this paper.

**Remarks** begin on page **10** of this paper.

**Conclusion** begins on page **17** of this paper.

## **AMENDMENTS TO THE CLAIMS**

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

### **LISTING OF CLAIMS:**

1. **(Currently Amended)** A method for enriching for a nucleic acid sequence of interest in a sample comprising nucleic acids, the method comprising:
  - (a)[[.]] fragmenting nucleic acids in the sample comprising the nucleic acids, thereby generating nucleic acid fragments, wherein the nucleic acid fragments comprise the nucleic acid sequence of interest;
  - (b)[[.]] ligating a first adaptor sequence to a 5' end of the nucleic acid fragments, thereby generating nucleic acid fragments ligated to the first adaptor sequence;
  - (c)[[.]] purifying the nucleic acid fragments ligated to the first adaptor sequence;
  - (d)[[.]] annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the purified nucleic acid fragments ligated to the first adaptor sequence, wherein the one or more oligonucleotides in solution comprise a 3' portion with at least 10 bases that are complementary to the nucleic acid sequence of interest and a 5' tail, wherein the 5' tail comprises a second adaptor sequence non-complementary to the sequence of interest~~non-hybridizable to other adaptor sequence appended to the nucleic acid fragments~~;
  - (e)[[.]] extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragments ligated to the first adaptor sequence with a polymerase in a reaction mixture, wherein the reaction mixture does not comprise a primer that anneals to sequence complementary to the first adaptor sequence, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the ligated first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;

(f)[[.]] amplifying the one or more oligonucleotide extension products using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface, thereby providing an enriched nucleic acid sequence of interest;

(g)[[.]] annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and

(h)[[.]] sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

2. **(Canceled)**

3. **(Previously Presented)** The method of claim 1, wherein the nucleic acid sequence of interest comprises genomic DNA, RNA, or cDNA.

4.-5. **(Canceled)**.

6. **(Currently Amended)** The method of claim 52, further comprising denaturing the purified nucleic acid fragments ligated to the first adaptor sequence prior to step (d), thereby generating single-stranded nucleic acid fragments ligated to the first adaptor sequence.

7.-8. **(Canceled)**.

9. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

10. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence and/or the second adaptor sequence comprise barcode sequence.

11. -13. **(Canceled)**.

14. **(Original)** The method of claim 1, wherein the polymerase is a DNA polymerase.

15.-39. **(Canceled)**.

40. **(Currently Amended)** A method for enriching for a nucleic acid sequence of interest from a library, wherein the library comprises nucleic acid inserts comprising the nucleic acid sequence of interest, wherein the nucleic acid inserts have a first adaptor sequence attached on a first end and a second adaptor sequence attached on a second end, the method comprising:

(a)[[.]] denaturing the nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end, thereby generating a library of single-stranded nucleic acid inserts with the first adaptor sequence on a first end and the second adaptor sequence on a second end;

(b)[[.]] annealing one or more oligonucleotides in solution to the sequence of interest in the single-stranded nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end, wherein the one or more oligonucleotides in solution comprise a 3' portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest present in the nucleic acid inserts and a 5' tail, wherein the 5' tail comprises a third adaptor sequence, wherein the third adaptor sequence is distinct from ~~and non-hybridizable to~~ the first adaptor sequence and the second adaptor sequence, and the 5' tail is non-complementary to the sequence of interest;

(c)[[.]] extending the one or more oligonucleotides with a polymerase in a reaction mixture, wherein the reaction mixture does not comprise a primer that anneals to sequence complementary to the first adaptor sequence or the second adaptor sequence, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the third adaptor sequence at a second end;

(d)[[.]] amplifying the one or more oligonucleotide extension products using a first primer that anneals to the complement of the first adaptor sequence and a second primer

that anneals to a complement of the third adaptor sequence to enrich for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface, thereby providing an enriched nucleic acid sequence of interest;

- (e)[[.]] purifying the products of the amplifying;
- (f)[[.]] annealing a strand of the purified products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and
- (g)[[.]] sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

41. **(Canceled)**

42. **(Previously Presented)** The method of claim 40, wherein the nucleic acid sequence of interest comprises genomic DNA, RNA or cDNA.

43.-45. **(Canceled)**.

46. **(Previously Presented)** The method of claim 40, wherein the third adaptor sequence is the same among the one or more oligonucleotides.

47. **(Previously Presented)** The method of claim 40, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

48. **(Previously Presented)** The method of claim 40, wherein the first adaptor sequence and the complement of the second adaptor sequence are the same.

49. **(Previously Presented)** The method of claim 40, wherein the first adaptor sequence, the second adaptor sequence and/or the third adaptor sequence comprise barcode sequence.

50. **(Canceled)**.

51. **(Currently Amended)** The method of claim 1, wherein the one or more oligonucleotides comprise more than one oligonucleotide, and wherein each of the more than one oligonucleotide comprises a 3' portion that is complementary to a different nucleic acid sequence of interest in the nucleic acid fragments and a 5' portion comprising the second adaptor sequence.

52. **(Currently Amended)** The method of claim 1, wherein the nucleic acid fragments are double-stranded.

53. **(Canceled).**

54. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence comprises a restriction and/or cleavage site for a nucleic acid modifying enzyme.

55. **(Previously Presented)** The method of claim 1, wherein the 3' portion of the one or more oligonucleotides comprises a random sequence.

56. **(Previously Presented)** The method of claim 40, wherein the 3' portion of each of the one or more oligonucleotides comprises a random sequence.

57. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence is in a first strand of a partial duplex adaptor.

58. **(Previously Presented)** The method of claim 57, wherein the first strand is a long strand of the partial duplex adaptor.

59. **(Canceled).**

60. **(Previously Presented)** The method of claim 57, wherein the partial duplex adaptor comprises a second strand, wherein the second strand is a short strand.

61. **(Previously Presented)** The method of claim 60, wherein the short strand is ligated to a 3' end of the nucleic acid fragments.

62. **(Previously Presented)** The method of claim 1, wherein the first adaptor sequence is in a ligation strand of a first adaptor, wherein the first adaptor comprises the ligation strand and a non-ligation strand, wherein the ligation strand ligates to a 5' end of the nucleic acid fragments.

63. **(Canceled)**

64. **(Previously Presented)** The method of claim 1, wherein the sequencing comprises bridge amplification.

65. **(Previously Presented)** The method of claim 1, wherein the sequencing comprises use of four labeled reversible terminators.

66. **(Canceled)**

67. **(Previously Presented)** The method of claim 1, wherein the sequencing comprises semiconductor sequencing.

68. – 78. **(Canceled)**

79. **(Previously Presented)** The method of claim 40, wherein the sequencing comprises bridge amplification.

80. **(Previously Presented)** The method of claim 40, wherein the sequencing comprises use of four labeled reversible terminators.

81. **(Canceled)**

82. **(Previously Presented)** The method of claim 40, wherein the sequencing comprises semiconductor sequencing.

83. – 92. **(Canceled)**

93. **(Previously Presented)** The method of claim 40, wherein neither the first adaptor sequence nor the second adaptor sequence comprises a 3' block.

94. **(Currently Amended)** The method of claim 1, further comprising purifying the nucleic acid fragments prior to step (b).

95. **(Currently Amended)** The method of claim 1, further comprising purifying the products of the amplifying prior to step (g).

96. **(Previously Presented)** The method of claim 1, wherein the 3' portion of the one or more oligonucleotides that hybridizes to the nucleic acid sequence of interest is synthesized precisely according to antisense sequence of the nucleic acid sequence of interest.

97. **(Currently Amended)** The method of claim 40, further comprising ligating the first adaptor sequence to the first end and the second adaptor sequence to the second end of the nucleic acid inserts prior to step (a), thereby generating the library of nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end.

98. **(Previously Presented)** The method of claim 97, further comprising purifying the nucleic acid inserts with the first adaptor sequence on the first end and the second adaptor sequence on the second end after the ligating.

99. **(Previously Presented)** The method of claim 40, wherein the 3' portion of the one or more oligonucleotides that hybridizes to the nucleic acid sequence of interest is synthesized precisely according to antisense sequence of the nucleic acid sequence of interest.

100. **(New)** The method of claim 14, wherein the DNA polymerase is a DNA polymerase without 3'-exonuclease activity.

101. **(New)** The method of claim 40, wherein the polymerase is a DNA polymerase without 3'-exonuclease activity.

## **REMARKS**

Applicant thanks Examiner Bertagna for the telephone conference on December 15, 2016, and December 22, 2016, with Applicant's representative Jeffrey Seidel. Applicant appreciates the examiner's suggestions for placing the case in condition for allowance.

This supplemental response includes additional claim amendments and amended arguments relative to those in the Response to Non Final Office Action filed December 2, 2016. Claim amendments are presented relative to the claims filed on April 28, 2016. An amended Declaration Under 37 C.F.R. § 1.132 of Andrew Brooks (*see* "Brooks Declaration") is also submitted herewith.

### **I. STATUS OF THE CLAIMS**

Following entry of this amendment, claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-101 are pending. Claims 1, 6, 40, 51, 52, 94, 95, and 97 are currently amended. Claims 100 and 101 are new. Claims 2, 4, 5, 7, 8, 11-13, 15-39, 41, 43-45, 50, 53, 59, 63, 66, 68-78, 81, and 83-92 are canceled. Support for new and amended claims can be found throughout the application as-filed and the following exemplary paragraphs of the application as-filed:

Claim 1: ¶[0030]

Claim 40: ¶[0030]

Claim 100: ¶[0063]

Claim 101: ¶[0063]

No new matter is added.

### **II. INFORMATION DISCLOSURE STATEMENTS**

The Office indicates that legible copies of references 51 and 57 submitted in the Information Disclosure Statement filed April 28, 2016, have not been provided. *See* Office Action at Item 4, p. 6. Copies of the references were filed with a supplemental Information Disclosure Statement on December 2, 2016.

### **III. INTERVIEW SUMMARY**

Applicant thanks Examiner Bertagna for the productive telephonic interview with Applicant's representatives Esther Kepplinger, Jeffrey Seidel, and Rachna Ujwal on November 16, 2016. The rejections in the Non-Final Office Action mailed June 2, 2016, and declaration evidence were discussed.

### **IV. CLAIM OBJECTIONS**

Claim 1 and 40 are objected to because the claims allegedly contain multiple periods. *See* Office Action at Item 5, p. 7. The claims are amended to enclose labels of the steps of the methods in parentheses.

The Office suggests replacing "other adaptor sequence appended to the nucleic acid fragments" in lines 5-6 of step (d) of claim 1. *See id.* Claim 1 is amended to delete recitation of "non-hybridizable to other adaptor sequence appended to the nucleic acid fragments."

Claims 96 and 99 are objected to because the word "the" allegedly should be inserted before "antisense" in line 2 of each claim. *See id.* Applicant respectfully notes that there is not antecedent basis for the term "antisense" in independent claim 1 or 40, from which claims 96 and 99 depend, respectively.

In view of the foregoing arguments and amendments, Applicant respectfully requests that the claim objections be withdrawn.

### **V. CLAIM REJECTIONS UNDER PRE-AIA 35 U.S.C. § 112 FIRST PARAGRAPH**

Claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-99 are rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, as allegedly failing to comply with the written description requirement. *See* Office Action at Item 7, p. 8. Specifically, the Office alleges that "[c]laims 1 and 40 have been amended to state that the second adaptor (claim 1) or the third adaptor (claim 40) is not hybridizable to the first adaptor (claim 1) or the first and second adaptor (claim 40)" and that "[t]he original disclosure, including the portions cited by Applicant, has been reviewed, but support was not found for this amendment." *Id.* Applicant respectfully traverses.

Without acquiescing, and solely to facilitate prosecution, claim 1 is amended to delete recitation of “non-hybridizable to other adaptor sequence appended to the nucleic acid fragments.” Claim 40 is amended to delete recitation of “and non-hybridizable to.” In view of the foregoing amendments, Applicant respectfully requests that the rejection under 35 U.S.C. 112 (pre-AIA), first paragraph be withdrawn.

**VI. CLAIM REJECTIONS UNDER PRE-AIA 35 U.S.C. § 112 SECOND PARAGRAPH**

Claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-99 are rejected under 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 applicant regards as the invention. *See* Office Action at Item 9, p. 9. Specifically, the Office alleges that claims 1 and 40 are indefinite because there is a lack of clear antecedent basis for “the enriched nucleic acid” which is recited in the last step of each claim. *Id.* Applicant respectfully traverses.

Without acquiescing, and solely to facilitate prosecution, step (f) of claim 1 is amended to recite, in part, “thereby providing an enriched nucleic acid sequence of interest,” and step (d) of claim 40 is amended to recite, in part, “thereby providing an enriched nucleic acid sequence of interest.” In view of the foregoing amendments, Applicant respectfully requests that the rejection under 35 U.S.C. 112 (pre-AIA), second paragraph be withdrawn.

**VII. CLAIM REJECTIONS UNDER PRE-AIA 35 U.S.C. § 112 FORTH PARAGRAPH**

Claim 9 is rejected under pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for allegedly failing to further limit the subject matter of the claim upon which it depends, or for allegedly failing to include all the limitations of the claim upon which it depends. *See* Office Action at Item 11, p. 10. Specifically, the Office alleges that claim 9 is not further limiting because it broadens the scope relative to claim 1. *See id.* Applicant respectfully traverses.

Without acquiescing, and solely to facilitate prosecution, claim 1 is amended to delete recitation of “non-hybridizable to other adaptor sequence appended to the nucleic acid fragments.” In view of the foregoing amendment, Applicant respectfully requests that the rejection under pre-AIA 35 U.S.C. 112, 4th paragraph be withdrawn.

### **VIII. CLAIM REJECTIONS UNDER PRE-AIA 35 U.S.C. § 103(A)**

Claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 79, 80, and 93-99 are rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Jones et al. (US 2005/0142577 A1) in view of Tucker et al. (The American Journal of Human Genetics (2009) 85: 142-154) and further in view of Gormley et al. (US 7,741,463 B2). *See* Office Action at Item **13**, pp. 11-18. Applicant respectfully traverses.

Claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 67, 82, 93, and 95-99 are rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Jones et al. (US 2005/0142577 A1) in view of Tucker et al. (The American Journal of Human Genetics (2009) 85: 142-154) and further in view of Rothberg et al. (Nature (2011) 475: 348-352 + Supplementary Information). *See* Office Action at Item **14**, pp. 18-25. Applicant respectfully traverses.

The Supreme Court set the standard for obviousness in *Graham v. John Deere*, 383 U.S. 1 (1966), identifying the factual inquiries for determining obviousness. Secondary considerations such as commercial success, long felt but unsolved needs, failure of others, etc., can be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Reconsideration and allowance of the claims is respectfully requested in light of the following remarks and accompanying amended Declaration Under 37 C.F.R. § 1.132 of Andrew Brooks (*see* “Brooks Declaration”). The amended declaration is timely filed in accordance with MPEP 716.01(a). “Evidence traversing rejections, when timely presented, must be considered by the examiner whenever present.” MPEP 716.01(b).

#### **Skepticism of an expert**

Skepticism of an expert is a secondary consideration of nonobviousness. MPEP 716.05. “Expressions of disbelief by experts constitute strong evidence of nonobviousness.” *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 698, 218 USPQ 865, 869 (Fed. Cir. 1983) (citing *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 483-484 (1966)). “The skepticism of an expert, expressed before these inventors proved him wrong, is

entitled to fair evidentiary weight, . . . as are the five to six years of research that preceded the claimed invention.” *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988); *Burlington Industries Inc. v. Quigg*, 822 F.2d 1581, 3 USPQ2d 1436 (Fed. Cir. 1987) (testimony that the invention met with initial incredulity and skepticism of experts was sufficient to rebut the prima facie case of obviousness based on the prior art).” MPEP 716.05.

An expert in the field of nucleic acid analysis expressed skepticism that the claimed methods of generating enriched nucleic acid sequences would provide sufficient specificity to justify analysis on a massively parallel sequencing. *See* Brooks Declaration. Applicant approached Andrew Brooks (“Declarant”) in 2012 to encourage Declarant to use the claimed methods for analyzing nucleic acids. Brooks Declaration at ¶13. Declarant is a Chief Operating Officer at a facility that provides solutions for clients seeking to analyze nucleic acids. Brooks Declaration at ¶2. Declarant was skeptical that the claimed technology would yield enriched sequences that would provide sequencing results with high on-target specificity. Brooks Declaration at ¶14. Declarant thought that target-specific primers would bind to off-target sites at a relatively high rate, leading to non-specific enriched sequences that would flood the sequencing system and confound sequence analysis. Brooks Declaration at ¶14. Declarant thought that in order to generate enriched sequences with high specificity, one would want to use, for example, a primer pair with a forward target-specific primer and reverse target-specific primer in a polymerase chain reaction for each sequence of interest. Brooks Declaration at ¶14.

Negative consequences would be associated with sequencing nucleic acids enriched using a method that provides a low level of specificity. For example, significant costs would be associated with performing massively parallel sequencing on enriched nucleic acid sequences generated using a technology that provides low specificity. Brooks Declaration at ¶15. Thus, Declarant was skeptical of using the claimed methods.

### **Unexpected Results**

A *prima facie* case of obviousness may be rebutted by evidence establishing that applicant’s invention produces unexpected results. *See* MPEP 716.02. “Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed

invention with the closest prior art which is commensurate in scope with the claims.” See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980); MPEP 716.02(b).

In view of Declarant’s skepticism, the Declarant believed that sequencing enriched sequences generated using the claimed methods would result in observing about fifty percent of sequences of interest in the sequencing results. Brooks Declaration at ¶16. However, Declarant performed an experiment using the claimed methods and observed greater than ninety percent of on-target sequences of interest. Brooks Declaration at ¶16. These results were highly unexpected by the Declarant.

The observed level of specificity would not inherently be expected based on the disclosure of Jones et al. Jones discloses a method for analyzing nucleic acids comprising amplifying target sequences that makes use of locus specific primers and array based analysis of genotype. See e.g., Jones et al., Fig. 3. Microarray analysis relies on hybridization of the target sequence of the amplified product to a unique complementary probe on the microarray. Using the methods of Jones, non-target-specific enriched sequences would likely not bind to a probe on the microarray because the microarray would likely not have a probe corresponding to the non-target-specific enriched sequence. Such non-target-specific enriched sequences would be analyzed by massively parallel sequencing. Thus, on-target hybridization specificity of the locus-specific primers is less of a concern for the microarray genotype analysis of Jones et al. than for a massively parallel sequencing platform because off-target enriched sequences would not be analyzed using a microarray.

**The secondary evidence outweighs evidence supporting the *prima facie* case**

“The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence.” *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992) (MPEP 716.01(d)). The claimed subject matter is nonobvious for at least the reason that the secondary considerations of skepticism of an expert and unexpected results as described by Declarant outweigh the evidence supporting the *prima facie* case of obviousness. The Office alleges that the ordinary artisan would have been motivated to combine Jones et al. with Tucker because Tucker taught that massively parallel sequencing methods “offered very high-throughput

sequencing...and as well as the ability to accurately detect minor alleles.” *See* Office Action at Item **13**, p. 17. The Office also alleges that the “ordinary artisan would have had a reasonable expectation of success in view of the guidance provided by Tucker concerning the use of massively parallel sequencing methods and also since Jones taught that the amplification products could be analyzed using any desired method.” *Id.* However, Declarant’s insights about the specificity of the claimed methods and the generation of unexpected results render the claimed methods nonobvious.

Because the claimed subject matter is not obvious in view of the cited references, Applicant respectfully requests that the rejections under 35 U.S.C. § 103(a) be withdrawn.

**CONCLUSION**

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any question, the Examiner is encouraged to telephone the undersigned.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 25115-755.201).

Respectfully submitted,  
WILSON SONSINI GOODRICH & ROSATI  
Professional Corporation

Date: December 22, 2016

By: /Jeffrey Seidel/  
Jeffrey J. Seidel, Ph.D., J.D.  
Registration No. 61,063

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

Inventor: Doug Amorese *et al.*

Application No.: 13/750,768

Filed: January 25, 2013

Title: COMPOSITIONS AND METHODS  
FOR TARGETED NUCLEIC ACID  
SEQUENCE ENRICHMENT AND  
HIGH EFFICIENCY LIBRARY  
REGENERATION

Confirmation No.: 1162

Examiner: Angela Bertagna

Group Art Unit: 1637

Customer No. 12754

**DECLARATION OF ANDREW BROOKS**  
**UNDER 37 C.F.R. §1.132**

M/S Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION OF ANDREW BROOKS**

Commissioner:

I, Andrew I. Brooks, declare as follows:

**I. QUALIFICATIONS**

1. My name is Andrew I. Brooks.
2. I am the Chief Operating Officer at RUCDR Infinite Biologics at Rutgers. RUCDR Infinite Biologics provides a wide array of genotyping, gene expression, and microarray services, and provides consultation for experimental design, platform and microarray selection, as well as bioinformatics support. RUCDR Infinite Biologics offers massively parallel next-generation sequencing on the latest platforms from Ion Torrent and Illumina. Comprehensive service bundles offered by RUCDR Infinite Biologics include nucleic acid extraction, integrated sample quality control, and fully automated construction of sequencing libraries.
3. I am also President and Founder of Brooks Biomedical Consulting, BBC LLC, which provides consulting services for personalized medicine, animal model development, gene-based therapeutics, molecular diagnostics, and enterprise level biobanking.

4. I am an Associate Professor of Genetics at Rutgers, The State University of New Jersey and am Director of the Bionomics Research & Technology Center at the Environmental & Occupational Health Sciences Institute at Rutgers University.
5. Previously, I served as the Director of the Functional Genomics Center at the Department of Environmental Medicine at the Aab Institute for Biomedical Science at the University of Rochester Medical School and Director of the Academic Medicine Development Company (AMDeC) Microarray Resource Center (MRC) at the University of Rochester Medical Center.
6. I also previously served as Director of the University of Rochester Medical Center Core Facilities, which provided microarray core services and nucleic acid core services, and was a Director of the Microarray Analysis Core Facility at the National Institute of Aging Nathan Shock Center for Excellence.
7. I hold a B.S. in Animal Science from Cornell University, and a M.S. and Ph.D. in Molecular Medicine and Gene Therapy from University of Rochester School of Medicine.
8. I am a member of the Board of Directors for several companies including NuGEN Technologies and previously was a member of the Scientific and Commercial Advisory Board at NuGEN Technologies.
9. I am a member of the American Society for Human Genetics, American Society for Gene Therapy, The Association of Biomolecular Resource Facilities, and Society for Neuroscience among others. I serve or have served on several committees including NIEHS CEED Center Internal Advisory Board, EOHSI Directors Cabinet, University of Rochester Scientific Advisory Board (SAC), and Microarray Research Group at the Association of Biomolecular Resource Facilities. I am a peer reviewer for several journals, most notably Nature Genetics, Nature Medicine, and Nucleic Acid Research.
10. I have published numerous peer-reviewed manuscripts and presented at various international conferences. My research interest has focused on the development and implementation of cutting edge molecular based technologies for nucleic acid and protein analyses.
11. A copy of my *curriculum vitae* is attached as Appendix A.

## II. SCOPE OF REVIEW

12. I have read the pending claims of the above-referenced application, and am familiar with the Office Action mailed on June 2, 2016. I understand that the United States Patent and Trademark Office (“Patent Office”) has rejected the pending claims of U.S. Patent Application No. 13/750,768 (“’768 application”) under pre-AIA U.S.C. § 103(a) over U.S. Publication No. 2005/0142577 (“Jones”) in view of Tucker et al. (The American Journal of Human Genetics (2009) 85: 142-154; “Tucker”), and further in view of U.S. Patent No. 7,741,463 (“Gormley”) or Rothberg et al. (Nature (2011) 475: 348-352; “Rothberg”).

## III. SKEPTICISM AND UNEXPECTED RESULTS

13. NuGEN approached me in 2012 and encouraged me to use methods claimed in the ’768 application to generate enriched sequences for sequencing on a massively parallel sequencing platform.

14. Based on my experience in the field, I was skeptical that the claimed methods would provide efficient sequencing data. Because the claimed methods involve annealing and extending a target-specific primer to enrich a sequence of interest (rather than, for example, annealing a forward target-specific and reverse target-specific primer pair at a sequence of interest and performing a polymerase chain reaction with the forward target-specific and reverse target-specific primer), I thought the technology would provide poor target specificity that is not consistent with enrichment worthy of high quality sequencing data. I thought that the target-specific primers would bind to off-target sites at a relatively high rate, leading to non-specific enriched nucleic acid sequences that would flood the sequencing system and confound sequence analysis. I thought that in order to generate enriched sequences that would provide highly specific sequencing results, one would want to amplify a sequence of interest with, for example, a primer pair including a forward target-specific primer and reverse target-specific primer in a polymerase chain reaction using the forward target-specific primer and reverse target-specific primer for each sequence of interest.

15. The lack of specificity that I expected would have been a significant detriment. For example, inability to achieve high specificity would result in significant waste associated with performing massively parallel sequencing runs. Additionally, I felt that significant off-target activity would affect the ability to reliably create a uniform distribution of on target sequences leading not only to an

incomplete (or less complex) library but one that had such an uneven distribution of targets that our ability to make quantitative analyses would be severely impaired.

16. In view of my skepticism, I observed unexpected results when enriched nucleic acid sequences generated using the claimed methods were sequenced by massively parallel sequencing. Based on my skepticism, using the claimed methods I expected to observe about fifty percent of sequences of interest in the sequencing results. We actually observed greater than ninety percent of on-target sequences of interest in the sequencing results. Based on my knowledge and experience in this field, I did not expect and would not have predicted this level of specificity. The results were surprising to me. I would not have thought to utilize massively parallel sequencing in this manner and did so because I was asked by NuGEN to perform the method.

17. Jones describes an enrichment method employing a target-specific primer for generation of amplification products for analysis with microarrays. In contrast to the claimed methods, microarray analysis relies on hybridization of the target sequence of the amplified product to a unique complementary probe on the microarray. If a target-specific primer anneals to the target sequence, the resulting on-target amplified product will hybridize to the unique complementary probe on the microarray. On the other hand, if the target-specific primer anneals to off-target sequences, there would be no equivalent complementary probe on the microarray to hybridize to the resulting off-target amplified product. Thus, unlike on a massively parallel sequencing platform, the off-target product that may be produced would not confound analysis since the noise from off-target sequences would be minimal or absent.

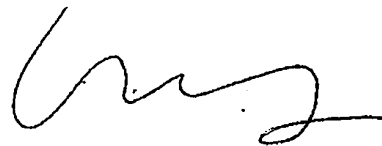
#### **IV. CONCLUDING STATEMENTS**

18. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

19. While I am being compensated for my time in connection with this declaration, that compensation does not depend in any way on the outcome of the prosecution of the '768 patent application.

Dated: December <sup>21</sup>, 2016

By:



Andrew I. Brooks

**CURRICULUM VITAE****NAME:** Andrew I. Brooks**ADDRESS:** Office: Environmental & Occupational Health Sciences Institute  
Bionomics Research & Technology Center  
170 Frelinghuysen Road - Room 236H  
Piscataway, NJ 08854Home: 3 Hanover Square, PH23A  
New York, New York 10004**TELEPHONE:** Office: (848) 445-0225**FACSIMILE:** (732) 445-0152**EMAIL:** brooks@dls.rutgers.edu**CITIZENSHIP:** USA**EDUCATION**Cornell University, Ithaca, NY  
Animal Science

B.S. 1991

Albert Einstein College of Medicine, Bronx, NY  
Neuroscience

Ph.D. candidate 1994-1995

University of Rochester School of Medicine, Rochester, NY 14642  
Department of Microbiology and Immunology  
Molecular Medicine & Gene Therapy

M.S. 1998

University of Rochester School of Medicine, Rochester, NY 14642  
Department of Microbiology and Immunology  
Molecular Medicine & Gene Therapy

Ph.D. 1999

## ACADEMIC APPOINTMENTS

|                     |                                                                                                                                                                                                                                           |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2009 – Present      | Chief Operating Officer<br>RUCDR Infinite Biologics<br>Rutgers University - Rutgers Medical School<br><br>Associate Professor of Genetics<br>Associate Director for Technology Development<br>Rutgers, The State University of New Jersey |
| 2012 – Present      | Co-Founding Director<br>BioProcessing Solutions Alliance<br>BioStorage Technologies<br>Indianapolis, Indiana                                                                                                                              |
| 2006- Present       | Director and Founder, Harlan GenScreen™ Laboratory<br>Harlan Laboratories<br>Indianapolis, Indiana                                                                                                                                        |
| 2005 – 2009         | Associate Professor of Genetics<br>Associate Director for Technology Development<br>Rutgers University Cell & DNA Repository<br>Rutgers, The State University of New Jersey                                                               |
| 2005 – Present      | Director, Bionomics Research & Technology Center<br>Associate Professor of Environmental Medicine<br>Environmental & Occupational Health Sciences Institute<br>University of Medicine & Dentistry of New Jersey                           |
| 2004 – Present      | President and Founder, Brooks Biomedical Consulting, BBC LLC<br>Consulting services for Personalized Medicine, Animal Model<br>Development, Gene-based Therapeutics, Molecular Diagnostics                                                |
| May 2004 – Present  | Adjunct Associate Professor<br>Rochester Institute of Technology<br>School of Computer Science and Bioinformatics                                                                                                                         |
| May 2003 – Present  | Food and Drug Administration (FDA), Special appointment for the<br>Pharmacology Toxicology Subcommittee of the Advisory Committee for<br>Pharmaceutical Science                                                                           |
| September 2001-2005 | Director, AMDeC Microarray Resource Center, Host Institution:<br>University of Rochester Medical Center                                                                                                                                   |
| January 2001-2005   | Assistant Professor<br>Director, Functional Genomics Center<br>Department of Environmental Medicine<br>Aab Institute for Biomedical Science<br>University of Rochester Medical School                                                     |

|                              |                                                                                                                                                                                                                                                    |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| January 2001-2005            | Director, University of Rochester Medical Center Core Facilities<br>Microarray Core Services<br>Nucleic Acid Core Services<br>Proteomics Core Services<br>Bioinformatics Training Services                                                         |
| January 2001- June 2002      | Director, Microarray Analysis Core Facility, NIA Nathan Shock<br>Center for Excellence                                                                                                                                                             |
| September 1999-December 2000 | Research Assistant Professor<br>Director, University Microarray Core Facility<br>Center for Aging & Development<br>Division of Molecular Medicine & Gene Therapy<br>Aab Institute for Biomedical Science<br>University of Rochester Medical School |

### **AWARDS AND HONORS**

|      |                                                                                                        |
|------|--------------------------------------------------------------------------------------------------------|
| 1990 | Scholarship from Dialogue House Inc. for work in cancer research                                       |
| 1997 | Excellence in Graduate Research Award Division of Molecular Medicine & Gene Therapy                    |
| 1998 | American Society for Gene Therapy Young Investigator Award                                             |
| 2000 | Co-chair Neuromuscular Session 3 <sup>rd</sup> Annual American Society for Gene Therapy Annual Meeting |
| 2000 | University of Rochester Fenn Award for Distinguished Ph.D. Thesis                                      |
| 2002 | Scientific Director, Convergence Biotechnology Conference                                              |
| 2002 | Chair, Microarray Research Group (MARG), Association of Biomedical Resource Facilities                 |
| 2002 | Co-Chair Neurology Session 5 <sup>th</sup> Annual American Society for Gene Therapy Annual Meeting     |
| 2003 | Executive Board Member, UNYCoR                                                                         |
| 2003 | Scientific and Commercial Advisory Board, NuGen Technologies                                           |
| 2003 | Chair, Microarray Research Group (MARG), Association of Biomedical Resource Facilities                 |
| 2003 | Scientific Advisory Board, Biocept Inc.                                                                |
| 2005 | Chief Scientific Officer, URM Co Office of Corporate Alliance (OCA)                                    |
| 2005 | Co-Director, Planning Committee, Expanded Regional Translational Research Center                       |

### **CORPORATE PROGRAMS**

|      |                                                                               |
|------|-------------------------------------------------------------------------------|
| 2000 | Affymetrix Inc.; Academic Center of Excellence                                |
| 2001 | Socratech LLC; Microarray/Gene Expression Services                            |
| 2001 | Corning Inc.; Life Sciences Division, Technology Development Program          |
| 2001 | STS Biopolymers; High Technology of Rochester Technology Development Contract |
| 2003 | Early Access Program, NuGen Technologies                                      |
| 2014 | NuGEN Center of Excellence Director                                           |
| 2014 | Raindance Center of Excellence Director                                       |

### **BOARD SEATS**

|                                                   |
|---------------------------------------------------|
| BioDX Technologies, San Diego CA                  |
| NuGen Technologies, San Francisco CA              |
| GenScreen, Indianapolis IN                        |
| Angiocrine, San Diego CA                          |
| BioProcessing Solutions Alliance, Indianapolis IN |
| iSpecimen, Boston MA                              |

## **PROFESSIONAL MEMBERSHIP**

Society for Neuroscience (SFN)  
American Society for Gene Therapy(ASGT)  
The Association of Biomolecular Resource Facilities (ABRG)  
Academic Medicine Development Company (AMDeC)  
Upstate New York Coalition of Biomedical Research (UNYCoR)  
American Association for Laboratory Animal Science (AALAS)  
American Society for Human Genetics (ASHG)  
International Society for Biological and Environmental Repositories (ISBER)  
Society for Laboratory Automation and Screening (SLAS)

## **TEACHING EXPERIENCE**

Medical Microbiology (Teaching Assistant)  
Cellular Neuroscience (Lecturer)  
Oral Biology Seminar Series (Lecturer)  
Fundamentals of Computational Biology (Lecturer)  
Genes Development and Disease (GEN 508) (Lecturer)  
Introductory Toxicology (TOX 508) (Lecturer)  
Introduction to Basic Concepts of Molecular Biology & Bioinformatics (Lecturer)  
Molecular Epidemiology Series (Lecturer)  
Toxicogenomics/Proteomics (TOX 521) (Lecturer)  
Functional Genomics of Neuronal and Neurodegeneration: A Case Study (Lecturer)

## **COMMITTEE SERVICE**

2000 / 2002 Abstract peer review committee (American Society for Gene Therapy; by invitation)  
2000 – 2005 University of Rochester Biohazard Committee  
2001 – 2005 University of Rochester Biomedical Research Capital Facility Planning Committee  
2001 – 2013 AMDeC Functional Genomics Advisory Committee  
2001 – 2006 Microarray Research Group; Association of Biomolecular Resource Facilities  
2003 – 2005 Rochester Center for Computational Systems Biology (RCCSB)  
2004 – 2005 University of Rochester Office of Corporate Alliances Planning Committee  
2004 – 2005 University of Rochester Wyeth Building Planning Committee  
2005 – 2005 University of Rochester Intellectual Property Advisory Committee  
2005 – 2008 University of Rochester Scientific Advisory Board (SAC)  
2005 – 2008 External Scientific Advisory Bd-Regional Translational Research Center (NYU-HHC-RTRC)  
2005 – Present Rutgers, The State University of New Jersey Joint Graduate Program in Toxicology Committee  
2005 – Present EOHSI Directors Cabinet  
2005 – Present NIEHS CEED Center Internal Advisory Board

## **PEER REVIEWER**

### Journals

Neurobiology of Aging (Editor in chief: Paul D. Coleman, PhD)  
Leukemia Research (Editor in chief: John M. Bennett, MD)  
Nucleic Acid Research  
European Journal of Neuroscience  
Microbiology UK  
Nature Genetics  
Nature Medicine

The Journal of Gene Medicine

Meetings

American Society for Gene Therapy

NERLSCD-Regional Core Directors Meeting

Grants

Alzheimer's Association

NIEHS

Mehta Foundation

Marsden Foundation

Northwest Cancer Research Fund

Environmental Protection Agency

American Federation of Aging Research (AFAR)

NINDS Microarray Consortium

AAAS Applications Review

NIAAA Applications Review

**INVITED PRESENTATIONS: 2005 – Present**

- 2005 ABRF Annual Meeting in Atlanta, Georgia
- 2005 SOT-ToxExpo in New Orleans, Louisiana
- 2005 CHI Quantitative PCR Conference in La Jolla, California
- 2005 SUNY Upstate Translational Research Conference (Panel Speaker)
- 2005 Hills Pet Nutrition (Speaker)
- 2005 IBC 12<sup>th</sup> Annual Chips to Hits International Conference
- 2006 Society of Toxicology Annual Meeting in San Diego, California (Panel Speaker)
- 2006 CHI, QPCR Conference in San Diego, California (Panel Speaker)
- 2006 CHI QPCR Short Course in Boston, Massachusetts
- 2006 International Seminar for Toxicogenomics (Pavia, Italy)
- 2007 NuGEN Scientific Advisory Board Meeting
- 2007 ABRF 2007 Annual Meeting in Tampa, Florida (Conference Co-Chair)
- 2007 International Society for Biological and Environmental Repositories in Singapore (Panel Speaker)
- 2007 CHI Point of Care Diagnostics in Washington, DC (Panel Speaker)
- 2007 NIH Workshop in Rockville, MD (Speaker)
- 2007 World Congress on Psychiatric Genetics XV Conference
- 2008 ABRF 2008 Annual Meeting in Salt Lake City, UT (Panel Speaker)
- 2008 CHI QPCR Conference in San Diego, CA (Speaker)
- 2008 International Society for Prenatal Diagnosis (Speaker)
- 2008 Institute for International Research Biorepositories Conference in Philadelphia, PA (Speaker)
- 2008 CHI Data Driven Discovery Conference in Providence, RI
- 2009 Next Gen Sequencing, San Diego, CA
- 2009 International Society for Biological and Environmental Repositories in Portland, OR
- 2009 Institute for International Research Biorepositories Conference, Philadelphia, PA
- 2009 American Society of Human Genetics 59<sup>th</sup> Annual Meeting in Honolulu, HI
- 2009 Biobanking at Cornell University, Ithaca, NY
- 2009 Science of Biobanking in Philadelphia, PA
- 2010 Lab Automation 2010 in Palm Springs, CA
- 2010 STARLIMS Forum in Orlando, FL
- 2010 3<sup>rd</sup> Annual Biospecimen Research Network Symposium in Bethesda, MD

2010 International Society for Biological and Environmental Repositories in Rotterdam, Netherlands  
2010 CHI Beyond Sequencing in San Francisco, CA  
2010 Institute for International Research Biorepositories Conference in Boston, MA  
2010 World Congress on Psychiatric Genetics in Athens, Greece  
2010 American Association for Laboratory Animal Science National Meeting in Atlanta, GA  
2010 Northeast Regional Life Sciences Core Directors Biorepositories & Biobanking Conference in Worcester, MA  
2010 Trends in Science and Technology Relevant to the Biological Weapons Convention in Beijing, China  
2010 American Society of Human Genetics Annual Meeting in Washington, DC  
2010 World Congress of Gene-2010 in Foshan, China  
2010 CHI Biobanking Meeting in Providence, RI  
2011 Lab Automation 2011 in Palm Springs, CA  
2011 Global Sample Management Asia Event in San Francisco, CA  
2011 American Society of Human Genetics Annual Meeting in Montreal, Canada  
2011 Cryo2011 Event at Oregon State University in Corvallis, OR  
2012 Society of Laboratory Automation and Screening in San Diego, CA  
2012 Advances in Genome Biology & Technology on Marco Island, FL  
2012 5th Annual Biospecimen Research Network Symposium in Bethesda, MD  
2012 International Society for Biological and Environmental Repositories in Vancouver, Canada  
2012 Association of Biomolecular Resource Facilities Conference in Orlando, FL  
2012 European Lab Automation in Hamburg, Germany  
2012 Genomics Research Europe in Frankfurt, Germany  
2012 Institute for International Research Biorepositories Clinical Business Expo in Boston, MA  
2012 Leaders in BioBanking Congress in Chapel Hill, NC  
2012 Digital PCR - Applications and Advances in San Diego, CA  
2012 American Society of Human Genetics in San Francisco, CA  
2013 Society of Laboratory Automation and Screening in Orlando, FL  
2013 Human Genome Meeting in Singapore  
2013 BioCor, University of Minnesota  
2013 Biobanking UK Conference in London, UK  
2013 European, Middle Eastern & African Society for Biopreservation & BioBanking in Verona, Italy  
2013 Hands On Biobanks, Amsterdam, Netherlands  
2014 Ninth Annual Biomarkers Congress in Manchester, UK  
2014 European, Middle Eastern & African Society for Biopreservation & BioBanking LIMS Workshop in Milan, Italy  
2014 Association of Biomolecular Resource Facilities Conference in Albuquerque, NM  
2014 American Association for Cancer Research in San Diego, CA  
2014 International Society for Biological and Environmental Repositories in Orlando, FL  
2014 7<sup>th</sup> Annual Biorepositories & Sample Management Conference in Boston, MA  
2014 Leaders in BioBanking Congress in Seattle, WA  
2014 North American Saliva Symposium, Boston, MA  
2014 NBDA Convergence Conference, Scottsdale, AZ  
2015 Qatar Biobank Launch Conference, Al Gharafa, Ar-Rayyan, Qatar  
2015 CHI PCR for Molecular Medicine conference, San Francisco, CA  
2016 Society of Laboratory Automation and Screening in San Diego, CA  
2016 Molecular Med Tri-Con in San Francisco, CA  
2016 National Biobank Conference in Shanghai, China  
2016 International Society for Biological and Environmental Repositories in Berlin, Germany

## PUBLICATIONS

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2. Standifer, KM, Cheng, J, **Brooks, AI**, Honrado, CP, Su, W, Visconti, L.M., , Beidler, JL, and Pasternak, GW. Biochemical and pharmacological characterization of mu, delta, and novel kappa3 binding sites expressed in BE(2)-C neuroblastoma cells. Journal of Pharmacology and Experimental Therapeutics, 270 (3): 1246-1255, 1994
3. Pan YX; Cheng J; Xu J; Rossi G; Jacobson E; Ryan-Moro J; **Brooks AI**; Dean GE; Standifer KM; Pasternak GW. Cloning and functional characterization through antisense mapping of a kappa 3-related opioid receptor. Molecular Pharmacology 47 (6): 1180-8, 1995
4. **Brooks AI**, Standifer KM, Rossi GC, Mathis JP, and Pasternak GW. Characterizing kappa3 opioid receptors with a selective monoclonal antibody. Synapse, 22 (3): 247-253, 1996
5. Charton M, Ciszewska G, Ginos J, Standifer K, **Brooks AI**, and Pasternak GW. Quantitative structure activity relationships for 4'-substituted naloxone benzoylhydrazones. Medicinal Chemistry Research (In Press)
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7. Ciszewska, GR, Ginos, JA, Charton M, Standifer, KM, **Brooks AI**, Brown, GP, Ryan-Moro JP, Berzetei-Gurske I, Toll L, and Pasternak, GW Synthesis and Characterization of Substituted Benzoylhydrazones of Naloxone. Synapse, 24: 193-201, 1996
8. **Brooks AI**, Halterman MW, and Federoff HJ. Use of the Herpes Amplicon System as Vehicle for Somatic Gene Transfer. Advanced Delivery Drug Reviews 27 (1): 29-39, 1997
9. Federoff HJ, **Brooks AI**, Muhkerjee B, Corden T. Somatic Gene Transfer Approaches to Manipulate Neural Networks. Journal of Neuroscience Methods 71 (1): 133-142, 1997
10. **Brooks AI**, Muhkerjee B, Panahian N, Cory-Slechta DA, and Federoff HJ. Nerve Growth Factor Somatic Mosaicism Produced by Herpes Virus-directed Expression of cre Recombinase in Mice Harboring a Recombinational Substrate. Nature Biotechnology , 15 (1): 57-63, 1997
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12. **Brooks AI**, Federoff HJ. Tfx-20 reagent for efficient gene delivery into mouse CNS. Neural Notes, 4 (1): 20-23, 1998
13. Heath BM, Xia J, Dong E, An RH, **Brooks AI**, Liang C-S, Federoff HJ and Kass RS. Overexpression of nerve growth factor in the heart alters ion channel activity and  $\beta$ -adrenergic signaling in an adult transgenic mouse. Journal of Physiology, 512: 779-791, 1998

14. **Brooks AI**, Halterman MW and Federoff HJ. Focal hippocampal gain of NGF function elicits specific septal cholinergic reorganization. Neuroreport (Cover), 10: 337-344, 1999
15. Hom J, Goldberg I, Mathis J, Pan YX, **Brooks AI**, Ryan-Moro J, Scheinberg DA, Pasternak GW. [(125)I]orphanin FQ/nociceptin binding in Raji cells. Synapse. 1999 Dec;34(3):187-91.
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17. **Brooks AI**, Murg SM, Cory-Slechta DA, Federoff HJ. Repeated acquisition and performance chamber for mice: A paradigm for assessment of spatial learning and memory. Neurobiology of Learning and Memory, 74, 241-258 (2000)
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26. **Brooks AI**, Stein CS, Hughes SM, Heth J, McCray PM, Sauter SL, Johnston JC, Cory-Slechta DA, Federoff HJ and Davidson BL. Functional correction of established CNS deficits in an animal model of lysosomal storage disease using feline immunodeficiency virus-based vectors. PNAS (2002) 99:6216-6221.
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28. Detrait E, **Brooks AI**, Cox C, Ogihara M, Federoff HJ, Richfield EK. High-throughput behavioral and gene expression analysis of cognitive decline in a model of normative aging. (In preparation)

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## NOTICE OF ALLOWANCE AND FEE(S) DUE

12754 7590 01/05/2017  
Wilson Sonsini Goodrich & Rosati/NUGEN  
650 Page Mill Road  
Palo Alto, CA 94304

EXAMINER

BERTAGNA, ANGELA MARIE

ART UNIT

PAPER NUMBER

1637

DATE MAILED: 01/05/2017

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
|-----------------|-------------|----------------------|---------------------|------------------|

13/750,768

01/25/2013

Doug Amorese

25115-755.201

1162

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR TARGETED NUCLEIC ACID SEQUENCE ENRICHMENT AND HIGH EFFICIENCY LIBRARY REGENERATION

| APPLN. TYPE    | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE   |
|----------------|---------------|---------------|---------------------|----------------------|------------------|------------|
| nonprovisional | UNDISCOUNTED  | \$960         | \$0                 | \$0                  | \$960            | 04/05/2017 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

### HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**

## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** **Mail Stop ISSUE FEE**  
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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12754 7590 01/05/2017  
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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

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| (Depositor's name) |
| (Signature)        |
| (Date)             |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 13/750,768      | 01/25/2013  | Doug Amorese         | 25115-755.201       | 1162             |

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR TARGETED NUCLEIC ACID SEQUENCE ENRICHMENT AND HIGH EFFICIENCY LIBRARY REGENERATION

| APPLN. TYPE    | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE   |
|----------------|---------------|---------------|---------------------|----------------------|------------------|------------|
| nonprovisional | UNDISCOUNTED  | \$960         | \$0                 | \$0                  | \$960            | 04/05/2017 |

| EXAMINER               | ART UNIT | CLASS-SUBCLASS |
|------------------------|----------|----------------|
| BERTAGNA, ANGELA MARIE | 1637     | 435-006000     |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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- 3 \_\_\_\_\_

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

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Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
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5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

**NOTE:** Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

**NOTE:** If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

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**NOTE:** This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

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Date \_\_\_\_\_

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|--------------------------------------------------------------------------------------------------------------|-------------|----------------------|---------------------|------------------|
| APPLICATION NO.                                                                                              | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
| 13/750,768                                                                                                   | 01/25/2013  | Doug Amorese         | 25115-755.201       | 1162             |
| 12754 7590 01/05/2017<br>Wilson Sonsini Goodrich & Rosati/NUGEN<br>650 Page Mill Road<br>Palo Alto, CA 94304 |             |                      |                     |                  |
| EXAMINER<br>BERTAGNA, ANGELA MARIE                                                                           |             |                      |                     |                  |
| ART UNIT                                                                                                     |             | PAPER NUMBER         |                     |                  |
| 1637                                                                                                         |             |                      |                     |                  |
| DATE MAILED: 01/05/2017                                                                                      |             |                      |                     |                  |

## Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

### Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

|                               |                                       |                                       |                                                  |
|-------------------------------|---------------------------------------|---------------------------------------|--------------------------------------------------|
| <b>Notice of Allowability</b> | <b>Application No.</b><br>13/750,768  | <b>Applicant(s)</b><br>AMORESE ET AL. |                                                  |
|                               | <b>Examiner</b><br>Angela M. Bertagna | <b>Art Unit</b><br>1637               | <b>AIA (First Inventor to File) Status</b><br>No |

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the response filed on 12/22/16 and the interview of 12/22/16.  
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_\_.
2. ☐ 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.
3. ☒ The allowed claim(s) is/are 1,3,6,9,10,14,40,42,46-49,51,52,54-58,60-62,64,65,67,79,80,82 and 93-101. As a result of the allowed claim(s), 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](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).
4. ☐ 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)).

\* Certified copies not received: \_\_\_\_\_.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.  
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_\_.  
**Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

- |                                                                                                                    |                                                                           |
|--------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892)                                                   | 5. <input checked="" type="checkbox"/> Examiner's Amendment/Comment       |
| 2. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO/SB/08),<br>Paper No./Mail Date _____ | 6. <input type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit<br>of Biological Material         | 7. <input type="checkbox"/> Other _____.                                  |
| 4. <input checked="" type="checkbox"/> Interview Summary (PTO-413),<br>Paper No./Mail Date _____.                  |                                                                           |

/Angela M. Bertagna/  
Primary Examiner, Art Unit 1637

## **DETAILED ACTION**

### ***Notice of Pre-AIA or AIA Status***

1. The present application is being examined under the pre-AIA first to invent provisions.

### ***Status of the Application***

2. Applicant's response filed on December 2, 2016 is acknowledged. The supplemental response filed on December 22, 2016 is also acknowledged.

### ***Response to Amendment***

3. The declaration under 37 CFR 1.132 filed on December 22, 2016 is sufficient to overcome the rejection of claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 79, 80, and 93-99 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones in view of Tucker and further in view of Gormley. The declaration is also sufficient to overcome the rejections of claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 67, 82, 93, and 95-99 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones in view of Tucker and further in view of Rothberg.

### ***Response to Arguments***

4. Applicant's arguments filed on December 2 and December 22, 2016 have been fully considered.

### **Claim Objections**

Applicant argues that the objections to claims 1, 40, 96, and 99 should be withdrawn in view of the amendments to claims 1, 40, 96, and 99 (page 11).

This argument was persuasive. The objections have been withdrawn.

**Rejection of claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-99 under pre-AIA 35 U.S.C. 112, first paragraph (new matter)**

Applicant argues that the rejection should be withdrawn in view of the amendments to claims 1 and 40 (page 12).

This argument was persuasive. The rejection been withdrawn.

**Rejection of claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-99 under pre-AIA 35 U.S.C. 112, second paragraph**

Applicant argues that the rejection should be withdrawn in view of the amendments to claims 1 and 40 (page 12).

This argument was persuasive. The rejection been withdrawn.

**Rejection of claim 9 under pre-AIA 35 U.S.C. 112, fourth paragraph**

Applicant argues that the rejection should be withdrawn in view of the amendments to claim 1 (page 12).

This argument was persuasive. The rejection been withdrawn.

**Rejections under pre-AIA 35 U.S.C. 103(a)**

Applicant argues that the rejections should be withdrawn in view of the declaration evidence (pages 13-16).

This argument was persuasive. The rejections have been withdrawn.

### **EXAMINER'S AMENDMENT**

5. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Jeffrey Seidel (Reg. No. 61,063) on December 22, 2016.

The application has been amended as follows:

**In the claims:**

In claim 51, line 2, please delete the words "each of the more than one oligonucleotide" and insert --each of the more than one oligonucleotides-- therefor.

### ***Conclusion***

6. Claims 1, 3, 6, 9, 10, 14, 40, 42, 46-49, 51, 52, 54-58, 60-62, 64, 65, 67, 79, 80, 82, and 93-101 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela M. Bertagna whose telephone number is (571)272-8291. The examiner can normally be reached on Monday-Friday, 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Angela M. Bertagna/  
Primary Examiner, Art Unit 1637