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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/471,785	03/28/2017	Doug AMORESE	25115-755.301	8042

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EXAMINER
BERTAGNA, ANGELA MARIE

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
08/18/2017	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):

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PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 15/471,785	Applicant(s) AMORESE ET AL.	
	Examiner Angela M. Bertagna	Art Unit 1637	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on 7/10/17.

☐ 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) 51-75 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) 51-75 is/are rejected.

8)☒ Claim(s) 51 and 60 is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

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

Application Papers

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

11)☒ The drawing(s) filed on 3/28/17 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.

Preliminary Amendment

2. Applicant's submission of a preliminary amendment on July 10, 2017 is acknowledged. Claims 51-75 are pending.

It is noted that declaration evidence concerning the method recited in the instant claims 51-75 was presented in the parent application. Since such evidence does not automatically become part of the instant application, Applicant is advised to submit a copy the declaration evidence and any supporting arguments if consideration of said evidence is desired.

Information Disclosure Statement

3. The information disclosure statement filed on July 10, 2017 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the copending US applications listed in citations 317-332 do not include the inventor(s). See 37 CFR 1.98. These references have not been considered.

As well, foreign patent documents 69, 74, 81, 82, 97, 102, 104, and 109 and non-patent literature documents 9, 34, 161, 175, 256, and 362 have not been considered because the copy required by 37 CFR 1.98(a)(2) has not been provided in the instant case or prior-filed Application Serial No. 13/750,768.

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).

Specification

4. The specification is objected to because the continuity information in the first paragraph should be updated to state that prior-filed Application Serial No. 13/750,768 has been issued as U.S. Patent No. 9,650,628.

Claim Objections

5. Claim 51 is objected to because it contains a typographical error in line 1 of step (a) where "partial duplex adaptor ," is recited.

Claim 60 is objected to because of the following informalities: Amending the concluding clause to state that each barcode is unique is suggested since doing so would be more succinct.

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 51-64 and 66-75 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.

Claim 51 is indefinite because the metes and bounds of "appended to" in step (a) are not clear. The specification states that ligation is encompassed by the term, but it is not clear what else is encompassed by the term "appended to". Neither the specification nor the claims gives any additional description as to what is encompassed by "appended to" other than ligation. It is unclear, for example, if "appended to" also encompasses partial duplex adaptors that are merely hybridized to the nucleic acid fragment. Claims 60, 64, and 66-68 are also indefinite for the same reason (i.e., the claims recite "appended to", the metes and bounds of which are unclear).

Claims 52-59, 61-63, and 69-75 are also indefinite since they depend from claim 51.

Claim Rejections - 35 USC § 103

7. 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, 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 negatived by the manner in which the invention was made.

8. 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 51, 52, 54-67, 69-71, and 75 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 2005/0142577 A1; IDS reference) in view of Tucker et al. (The American Journal of Human Genetics 2009; **85:** 142-154; IDS reference).

Regarding claims 51, 63-67, 69, and 75, 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 partial duplex adaptor to each 5' and each 3' end of the nucleic acid fragments, wherein the partial duplex adaptor comprises a first long strand containing a first adaptor sequence and second shorter strand; (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, 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 claims 52 and 54, Jones teaches that the nucleic acid sequence of interest comprises genomic DNA (paragraph 100) or RNA (paragraphs 43-44).

Regarding claim 55, Jones teaches that the first and second adaptor sequences are distinct from each other (Figure 3, paragraph 87, and paragraph 100).

Regarding claim 56, Jones teaches using a plurality of oligonucleotide to practice the capture and extension steps, and the plurality of oligonucleotides 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 same second adapter sequence (paragraphs 87, 99, and 100; see also Figure 3).

Regarding claim 57, Jones teaches that the second adaptor sequence may comprise a barcode sequence (paragraphs 58 and 61).

Regarding claim 60, as noted above, Jones teaches using a plurality of different oligonucleotides, each designed to capture a different nucleic acid sequence of interest and containing the same 5' adaptor (paras. 87, 99, and 100; see also Figure 3). Jones also teaches that the second adaptor may include a barcode sequence (paras. 58 & 61). Therefore, Jones teaches a plurality of different oligonucleotides, each designed to capture a different nucleic acid sequence of interest and containing the same 5' adaptor and a unique barcode.

Regarding claims 61 and 62, 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).

Jones does not teach massively parallel sequencing as required by independent claim 51. The reference 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 massively parallel sequencing is not disclosed.

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 states 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 51, 64-67, 70, 71, and 75, Tucker describes a massively parallel sequencing method developed by Illumina (Fig. 2). The method comprises bridge amplification and the use of four labeled reversible terminators (Fig. 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 (Fig. 2). Each of the two adaptors is also complementary to a sequencing primer (Fig. 2).

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 (i.e., as recited in claim 51) 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.

Further regarding claims 58 and 59, the teachings of Jones concerning barcodes do not include specific lengths for said barcodes (see paras. 58 and 61 of Jones), but the reference teaches that the preferred length for the adaptors in which the barcodes are contained preferably ranges from at least five to no more than 60 bases in length (para. 49). The length range of at

least eight nucleotides overlaps with the ranges disclosed in Jones, and the specific length of 12 nucleotides lies within the ranges of Jones. As well, no evidence of unexpected results with respect to the claimed barcode lengths has been presented. Therefore, a *prima facie* case of obviousness exists with respect to the barcode lengths recited in claims 58 and 59 (MPEP 2144.05 I).

Thus, the methods of claims 51, 52, 54-67, 69-71, and 75 are *prima facie* obvious.

10. Claims 53, 68, 73, and 74 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 2005/0142577 A1; IDS reference) in view of Tucker et al. (The American Journal of Human Genetics 2009; **85:** 142-154; IDS reference) and further in view of Gormley et al. (US 7,741,463 B2; IDS reference).

As discussed above, the teachings of Jones in view of Tucker render obvious the methods of claims 51, 52, 54-67, 69-71, and 75.

Regarding claim 53, Jones does not teach that the nucleic acid fragment comprises cDNA. As a result, Jones also does not teach reverse transcription of RNA to generate the nucleic acid fragment of interest as required by claim 74. Tucker does not remedy these deficiencies in Jones.

Regarding claim 68 and 73, neither Jones nor Tucker teaches purifying the nucleic acid fragment appended to the partial duplex adaptor or end repair of nucleic acid fragments prior to appending said adaptor. Tucker does not remedy these deficiencies in Jones.

Gormley describes a method for preparing a library for sequencing that comprises fragmenting nucleic acids contained in a sample, purifying the fragments, end-repair of the

purified fragments, ligation of a partial duplex adaptor, and PCR (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; see also Figs. 2a-2b). 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). Further regarding claims 53 and 74, Gormley teaches that libraries may be prepared from cDNA fragments (col. 6, ll. 5-27).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to further include purification and end repair steps between the fragmentation and adaptor ligation steps when practicing the method suggested by Jones in view of Tucker. The teachings of Gormley cited above provide motivation to do so since they indicate that these steps are a useful part of a method for preparing a library of nucleic acids for massively parallel sequencing. Gormley also provides a reasonable expectation of success since the teachings cited above contain a detailed description of how to purify nucleic acid fragments and subject the purified fragments to end repair. Thus, the methods of claims 68 and 73 are *prima facie* obvious.

It also would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to practice the method suggested by Jones in view of Tucker using cDNA fragments of interest prepared from RNA by reverse transcription. Gormley provides motivation and a reasonable expectation of success since the teachings cited above indicate that cDNA libraries are a desirable template for massively parallel sequencing. Since it was routine and conventional to use reverse transcription to prepare cDNA, the teachings of Gormley cited above

also render obvious the method of claim 74. Thus, the methods of claims 53 and 74 are *prima facie* obvious.

11. Claim 72 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 2005/0142577 A1; IDS reference) in view of Tucker et al. (The American Journal of Human Genetics 2009; **85:** 142-154; IDS reference) and further in view of Rothberg et al. (Nature 2011; **475:** 348-352 + Supplementary Information; IDS reference).

As discussed above, the teachings of Jones in view of Tucker render obvious the methods of claims 51, 52, 54-67, 69-71, and 75.

Jones does not teach semiconductor sequences as recited in claim 72, and Tucker does not remedy this deficiency. Rothberg, however, describes massively parallel sequencing using a semiconductor device (Figure 1 and pages 348-350) and discloses that this sequencing method is highly robust, scalable, and advantageously does not require the use of optics or labeled nucleotides (abstract and page 348).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to select semiconductor sequencing as described by Rothberg as the massively parallel sequencing method when practicing the method of Jones in view of Tucker. Rothberg provides motivation to do so by stating that the disclosed semiconductor sequencing method is robust, highly scalable, and requires neither optical detection nor 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). Thus, the method of claim 72 is *prima facie* obvious.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

13. Claims 51-57, 60-72, 74, and 75 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 9,650,628 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because the patented claims teach or suggest all of the limitations contained in the instant claims. Each of the instant claims is discussed in relation to the claims of the '628 patent in more detail below.

The instant claim 51 is drawn to a method for sequencing an enriched nucleic acid of interest. The method comprises: (a) obtaining a nucleic acid fragment appended to a partial duplex adaptor containing a first adaptor sequence and having a long first strand and shorter second strand; (b) annealing one or more oligonucleotides to the nucleic acid sequence of interest, wherein said oligonucleotides have a 3' portion at least ten nucleotides in length that binds to the nucleic acid sequence of interest and a 5’ tail portion that comprises a second adaptor and is not complementary to the nucleic acid sequence of interest; (c) extending the oligonucleotides of step (b) to form extension products having a 5’ second adaptor sequence, a sequence complementary to the nucleic acid sequence of interest, and a sequence complementary

to the first sequence in the partial duplex adaptor; (d) amplifying the extension products of step (c) using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals to a complement of the second adaptor sequence to enrich for the sequence of interest and produce an amplification product with a 3' end that is complementary to a sequence on a surface; (e) hybridizing the amplification products to said sequence on a surface, and (f) sequencing the enriched nucleic acid of interest on a massively parallel sequencing platform.

Claims 1 and 12-14 of the ‘628 patent are also drawn to a method for sequencing an enriched nucleic acid of interest that includes all of the elements of the instant claim 51. Claim 1 of the ‘628 patent includes the elements of steps (b)-(f) of the instant claim 1. Claim 1 of the '628 patent does not include the structural features of the adaptor set forth in the instant claim 51, but these elements are disclosed in claims 12-14 of the '628 patent. Therefore, the method set forth in the instant claim 51 clearly overlaps in scope with and is an obvious variant of the methods set forth in the '628 patent.

The limitations of the instant claims 52-54 are recited in claim 2 of the '628 patent.

The limitations of the instant claims 55-57 are recited in claims 3, 4, and 7 of the ‘628 patent.

The limitations of the instant claim 60 are suggested by claims 4 and 7 of the '628 patent. Claim 7 teaches the use of a plurality of different oligonucleotides, each designed to capture a different nucleic acid sequence of interest and containing the same 5' adaptor. Claim 4 teaches that the second adaptor may include a barcode sequence. These claims in combination suggest a plurality of different oligonucleotides, each designed to capture a different nucleic acid sequence of interest and containing the same 5' adaptor and a unique barcode.

The limitations of the instant claims 61 and 62 are recited in claims 8-9 of the '628 patent.

The limitations of the instant claim 63 are recited in claims 5 and 6 of the '628 patent.

The limitations of the instant claims 64-68 are recited in claims 1, 15, and 16 of the '628 patent.

The limitations of the instant claim 69 are recited in claim 12 of the ‘628 patent.

The limitations of the instant claims 70-72 are recited in claims 17-19 of the '628 patent.

The instant claim 74 requires using a nucleic acid fragment obtained by reverse transcription of RNA. This is clearly suggested by claim 2 of the ‘628 patent, which teaches using cDNA fragments.

The instant claim 75 requires the partial duplex adaptor to be appended to each end of the nucleic acid fragment of interest. This is clearly suggested by claims 1, 15, and 16 of the '628 patent, which state that the adaptor is ligated to an end of the fragment. This language in the claims of the '628 patent encompasses ligation to one or both ends. Therefore, the ordinary artisan would have been motivated to select either option with a reasonable expectation of success.

Thus, the instant claims 51-57, 60-72, 74, and 75 are not patentably distinct from claims 1-22 the ‘628 patent.

14. Claims 58 and 59 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 9,650,628 B2 in view of Jones et al. (US 2005/0142577 A1; IDS reference).

As discussed above, the instant claims 51-57, 60-72, 74, and 75 are not patentably distinct from claims 1-22 the ‘628 patent.

Regarding the instant claims 58 and 59, the claims of the ‘628 patent do not include any specific lengths for the barcodes.

The teachings of Jones are discussed in greater detail in the obviousness rejections set forth above. The reference describes a method that is quite similar to the method recited in the instant claims and the claims of the ‘628 patent and discloses that adaptors useful in said method preferably range from at least five to no more than 60 bases in length (para. 49). Jones additionally teaches that said adaptors may include barcodes (paras. 58 and 61).

It would have been *prima facie* obvious for the ordinary artisan practicing the method set forth in the claims of the '628 patent to select a barcode length of 12 nucleotides as recited in the instant claim 59 or a barcode length of at least eight nucleotides as recited in the instant claim 58. As discussed above, Jones teaches a similar method in which the preferred length for the adaptors is disclosed. The claimed length range of at least eight nucleotides overlaps with the ranges disclosed in Jones, and the specific length of 12 nucleotides lies within the ranges of Jones. As well, no evidence of unexpected results with respect to the claimed barcode lengths has been presented. Therefore, a *prima facie* case of obviousness exists with respect to the barcode lengths recited in the instant claims 58 and 59 (MPEP 2144.05 I), and these claims are not patentably distinct from the claims of the ‘628 patent in view of Jones.

15. Claim 73 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 9,650,628 B2 in view of Gormley et al. (US 7,741,463 B2; IDS reference)

As discussed above, the instant claims 51-57, 60-72, 74, and 75 are not patentably distinct from claims 1-22 the ‘628 patent.

End repair as recited in the instant claim 73 is not present in the claims of the '628 patent.

Gormley describes a method for preparing a library for sequencing that comprises fragmenting nucleic acids contained in a sample, purifying the fragments, end-repair of the purified fragments, ligation of a partial duplex adaptor, and PCR (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; see also Figs. 2a-2b). Gormley further teaches using sequencing the nucleic acids in the library using a massively parallel method comprising bridge amplification and the use of reversible terminators as recited in claims 17 and 18 of the ‘628 patent (column 20, line 18 – column 22, line 20).

It would have been *prima facie* obvious for the ordinary artisan practicing the method recited in the claims of the '628 patent to include an end repair step between the fragmentation and adaptor ligation steps. The teachings of Gormley cited above provide motivation to do so since they indicate that this step is a useful part of a method for preparing a library of nucleic acids for massively parallel sequencing. Gormley also provides a reasonable expectation of success since the teachings cited above contain a detailed description of how to purify nucleic acid fragments and subject the purified fragments to end repair. Thus, the instant claim 73 is not patentably distinct from the claims of the '628 patent in view of Gormley.

Conclusion

16. 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.

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, 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

OPAP
FEB 16 2018
AKIMA-18
PATENT & TRADEMARK OFFICE

I hereby certify that this paper and all marked attachments are being deposited by Electronic Filing on February 16, 2018, via Express Mail addressed to:
Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

WILSON SONSINI GOODRICH & ROSATI

By:_____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Inventors: Doug Amorese et al.

Serial No.: 15/471,785

Filed: March 28, 2017

For: COMPOSITIONS AND METHODS FOR TARGETED NUCLEIC ACID SEQUENCE ENRICHMENT AND HIGH EFFICIENCY LIBRARY GENERATION

Confirmation No.: 8042

Art Unit: 1637

Examiner: Angela Marie Bertagna

Customer No. 12754

RESPONSE TO NON-FINAL OFFICE ACTION

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

Commissioner:

This communication is in response to the Office Action dated August 18, 2017 ("Office Action"). This response is submitted after the shortened statutory period for reply. Therefore, Applicant submits herewith a fee for a 3-month Extension of Time under §1.136 extending the time for response to February 18, 2018. Accordingly, this response is timely filed.

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

Amendments to the Specification begin on page **3**

Amendments to the Claims begin on page **4**

Remarks begin on page **8**

Conclusion is on page **15**

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AMENDMENTS TO THE SPECIFICATION

Please replace paragraph [0001] of the specification as-filed with the following replacement paragraph:

[0001] This application is a continuation of U.S. Application Serial No. 13/750,768, filed January 25, 2013, now U.S. Patent 9,650,628, which claims the benefit of U.S. Provisional Application No. 61/591,241, filed Jan. 26, 2012, all of which are incorporated herein by reference in their entirety.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in this application. 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.-50. (**Canceled**)

51. (**Currently Amended**) A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:

a) obtaining a nucleic acid fragment ligated~~appended~~ to a partial duplex adaptor[[ ]], wherein the nucleic acid fragment comprises a nucleic acid sequence of interest, wherein the partial duplex adaptor comprises a first adaptor sequence, and wherein the partial duplex adaptor comprises a first strand and a second strand, wherein the first strand is longer than the second strand;

b) annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the nucleic acid fragment ligated~~appended~~ to the partial duplex adaptor, wherein the one or more oligonucleotides comprise a 3' portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;

c) extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment ligated~~appended~~ to the partial duplex adaptor with a polymerase, 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 second adaptor sequence at a second end;

d) amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end 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;

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.

52. (**Previously Presented**) The method of claim 51, wherein the nucleic acid fragment comprises genomic DNA.

53. (**Previously Presented**) The method of claim 51, wherein the nucleic acid fragment comprises cDNA.

54. (**Previously Presented**) The method of claim 51, wherein the nucleic acid fragment comprises RNA.

55. (**Previously Presented**) The method of claim 51, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.

56. (**Previously Presented**) The method of claim 51, wherein the one or more oligonucleotides comprise more than one oligonucleotide, and wherein the second adaptor sequence is common to the more than one oligonucleotides.

57. (**Previously Presented**) The method of claim 51, wherein the first adaptor sequence, the second adaptor sequence, or both comprise barcode sequence.

58. (**Previously Presented**) The method of claim 57, wherein the barcode sequence is at least 8 nucleotides in length.

59. (**Previously Presented**) The method of claim 57, wherein the barcode sequence is 12 nucleotides in length.

60. (**Currently Amended**) The method of claim 51, wherein the obtaining comprises obtaining a plurality of nucleic acid fragments ligated~~appended~~ to a partial duplex adaptor, wherein each partial duplex adaptor of each nucleic acid fragment of the plurality of nucleic acid fragments comprises a barcode, and wherein each barcode is unique~~of each partial duplex adaptor of each nucleic fragment of the plurality of nucleic acid fragments appended to a partial duplex adaptor differs from each other~~.

61. (**Currently Amended**) The method of claim 51, wherein the nucleic acid fragment ligated~~appended~~ to the partial duplex adaptor is double-stranded prior to step b).

62. (**Currently Amended**) The method of claim 61, further comprising denaturing the nucleic acid fragment ligated~~appended~~ to the partial duplex adaptor prior to step b), thereby generating a single-stranded nucleic acid fragment comprising the nucleic acid sequence of interest ligated~~appended~~ to the first adaptor sequence.

63. (**Previously Presented**) The method of claim 51, wherein the polymerase is a DNA polymerase.

64. (**Currently Amended**) The method of claim 51, further comprising ligating~~appending~~ the partial duplex adaptor to the nucleic acid fragment, thereby generating the nucleic acid fragment ligated~~appended~~ to the partial duplex adaptor of step a).

65. (**Canceled**)

66. (**Currently Amended**) The method of claim 64, wherein the first strand of the partial duplex adaptor is ligated~~appended~~ to a 5' end of the nucleic acid fragment.

67. (**Currently Amended**) The method of claim 64, wherein the second strand of the partial duplex adaptor is ligated~~appended~~ to a 3' end of the nucleic acid fragment.

68. (**Currently Amended**) The method of claim 64, further comprising purifying the nucleic acid fragment ligated~~appended~~ to the partial duplex adaptor prior to step a).

69. (**Previously Presented**) The method of claim 51, wherein the first adaptor sequence is in the first strand of the partial duplex adaptor.

70. (**Previously Presented**) The method of claim 51, further comprising performing bridge amplification of the annealed strand after step e).

71. (**Previously Presented**) The method of claim 51, wherein the sequencing comprises use of four labeled reversible terminators.

72. (**Previously Presented**) The method of claim 51, wherein the sequencing comprises semiconductor sequencing.

73. (**Previously Presented**) The method of claim 51, further comprising performing end repair on the nucleic acid fragment prior to step a).

74. (**Previously Presented**) The method of claim 51, wherein the nucleic acid fragment of step a) is obtained by performing reverse transcription on an RNA fragment.

75. (**Currently Amended**) The method of claim 51, wherein each end of the nucleic acid fragment is ligated~~appended~~ to a partial duplex adaptor.

REMARKS

I. STATUS OF THE CLAIMS

Following entry of this amendment, claims 51-64 and 66-75 are pending. Claim 65 is canceled. Claims 51, 60-62, 64, 66-68, and 75 are currently amended.

Support for amended claims can be found throughout the application as-filed and the following exemplary paragraphs of the application as-filed:

Claim 51: [0027]- [0029]

Claim 60: [0060]

No new matter is added.

II. INFORMATION DISCLOSURE STATEMENTS

The Information Disclosure Statement (IDS) filed on July 10, 2017, allegedly fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP 609. *See* Office Action at Item 3, p. 2. The Office alleges that inventor information for copending US applications listed in citations 317-332 in the IDS filed on July 10, 2017, was not included on the IDS. *Id.* Additionally, copies of foreign patent documents 69, 74, 81, 82, 97, 102, 104 and 109 and non-patent literature documents 9, 34, 161, 175, 256 and 362 listed in the IDS filed on July 10, 2017, have allegedly not been provided in the instant case or prior-filed Application Serial No. 13/750,768. *Id.*

Copending US applications listed in citations 317-332 are being re-submitted with inventor information in a supplemental IDS.

Applicant respectfully notes that copies of foreign patent documents 69, 74, 81, 82, 97, and 102 were filed with a supplemental IDS on October 16, 2015, in parent Application Serial No. 13/750,768. Copies of non-patent literature documents 34 and 175 were filed with a supplemental IDS on June 23, 2014, in parent Application Serial No. 13/750,768. A copy of non-patent literature document 256 was filed with a supplemental IDS on April 28, 2016, in parent Application Serial No. 13/750,768. A copy of non-patent literature document 362 was filed with a supplemental IDS on July 10, 2017, in the instant application. Copies of foreign patent documents 104 and 109, and non-patent literature documents 9 and 161 are being submitted in a supplemental IDS for the Office's consideration.

III. OBJECTIONS TO THE SPECIFICATION

The specification is objected to because the continuity information in the first paragraph has allegedly not been updated to state that prior-filed Application Serial No. 13/1750,768 has been issued as U.S. Patent No. 9,650,628. *See* Office Action at Item 4, p. 3.

An amendment to the specification is submitted herewith to update the Cross-Reference information in paragraph [0001] to state that prior-filed Application Serial No. 13/750,768 has issued as U.S. Patent No. 9,650,628. No new matter is added by this amendment. In view of the foregoing amendment, Applicant respectfully requests that the objection to the specification be withdrawn.

IV. OBJECTIONS TO THE CLAIMS

Claim 51 is objected to because the claim allegedly contains a typographical error in line 1 of step (a), *i.e.* the space before the comma in "partial duplex adaptor ,". *See* Office Action at Item 5, p. 3. Claim 51 is amended to delete the space before the comma in "partial duplex adaptor," in line 1 of step a).

Claim 60 is objected to because the Office suggests amending the concluding clause in claim 60 to state that each barcode is unique to make the claim more succinct. *Id.* Applicant thanks the Examiner for the suggestion. Claim 60 is amended to recite, in part, "wherein each barcode is unique."

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

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

Claims 51-64 and 66-75 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 the applicant regards as the invention. *See* Office Action at Item 6, pp. 3-4. Specifically, the Office Action alleges that the claims are indefinite because the

metes and bounds of "appended to" in step (a) of claim 51 are not clear. *Id.* Applicant respectfully traverses.

Without acquiescing, and solely to facilitate prosecution, step a) of claim 51 is amended to incorporate limitations from claim 65 and recite, in part, "ligated to...." Applicant respectfully submits that amended claim 51, and its dependent claims 52-64 and 66-75, are not indefinite or unclear. In view of the foregoing amendments, Applicant respectfully requests that the rejection under 35 U.S.C. § 112 (pre-AIA), second paragraph be withdrawn.

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

Claims 51, 52, 54-67, 69-71, and 75 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). *See* Office Action at Item 9, pp. 5-9. Applicant respectfully traverses.

Claims 53, 68, 73, and 74 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). *See* Office Action at Item 10, pp. 9-11. Applicant respectfully traverses.

Claim 72 is 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). *See* Office Action at Item 11, p. 11. Applicant respectfully traverses.

Claim 65 is canceled, thus rendering the rejection with respect to this claim moot.

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 Declaration Under 37 C.F.R. § 1.132 of Andrew Brooks (*see* "Brooks Declaration"). The 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 9, p. 8. 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.

VII. DOUBLE PATENTING

Claims 51-57, 58-72, 74, and 75 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-22 of U.S. Patent No. 9,650,628 B2. *See* Office Action at Item 13, pp. 13-15. Applicant respectfully traverses the Office's assertion of nonstatutory double patenting.

Claims 58 and 59 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-22 of U.S. Patent No. 9,650,628 B2 in view of Jones et al. (US 2005/0142577 A1). *See* Office Action at Item 14, pp. 15-16. Applicant respectfully traverses the Office's assertion of nonstatutory double patenting.

Claim 73 is rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-22 of U.S. Patent No. 9,650,628 B2 in view of Gormley et al. (US 7,741,463 B2). *See* Office Action at Item 15, p. 17. Applicant respectfully traverses the Office's assertion of nonstatutory double patenting.

Without acquiescing, and solely to facilitate prosecution, Applicant submits a Terminal Disclaimer to US Patent No. 9,650,628 in compliance with 37 CFR 1.321(c) or 1.321(d). In view of the foregoing, Applicant respectfully requests that the nonstatutory double patenting rejection be withdrawn.

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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. 25115-755.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: February 16, 2018

By: _____
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OPAP AKMA-18
FEB 16 2018
PATENT & TRADEMARK OFFICE

PATENT
Attorney Docket No. 25115-755.301

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:		Confirmation No.:	8042
Inventor:	Doug Amorese *et al.*	Examiner:	Angela Bertagna
Application No.:	15/471,785	Group Art Unit:	1637
Filed:	March 28, 2017	Customer No.	12754
Title:	COMPOSITIONS AND METHODS FOR TARGETED NUCLEIC ACID SEQUENCE ENRICHMENT AND HIGH EFFICIENCY LIBRARY REGENERATION		

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.

9547256

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 August 18, 2017. I understand that the United States Patent and Trademark Office ("Patent Office") has rejected the pending claims of U.S. Patent Application No. 15/471,785 ("'785 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 '785 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 '785 patent application.

15 Feb 2018

Dated: February , 2018

By:
Andrew I. Brooks

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Appendix A

CURRICULUM VITAE

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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
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Molecular Medicine & Gene Therapy — M.S. 1998

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Appendix A

Andrew I. Brooks, Ph.D.

ACADEMIC APPOINTMENTS

2009 – Present	Chief Operating Officer RUCDR Infinite Biologics Rutgers University - Rutgers Medical School Associate Professor of Genetics Associate Director for Technology Development Rutgers, The State University of New Jersey
2012 – Present	Co-Founding Director BioProcessing Solutions Alliance BioStorage Technologies Indianapolis, Indiana
2006- Present	Director and Founder, Harlan GenScreen™ Laboratory Harlan Laboratories Indianapolis, Indiana
2005 – 2009	Associate Professor of Genetics Associate Director for Technology Development Rutgers University Cell & DNA Repository Rutgers, The State University of New Jersey
2005 – Present	Director, Bionomics Research & Technology Center Associate Professor of Environmental Medicine Environmental & Occupational Health Sciences Institute University of Medicine & Dentistry of New Jersey
2004 – Present	President and Founder, Brooks Biomedical Consulting, BBC LLC Consulting services for Personalized Medicine, Animal Model Development, Gene-based Therapeutics, Molecular Diagnostics
May 2004 – Present	Adjunct Associate Professor Rochester Institute of Technology School of Computer Science and Bioinformatics
May 2003 – Present	Food and Drug Administration (FDA), Special appointment for the Pharmacology Toxicology Subcommittee of the Advisory Committee for Pharmaceutical Science
September 2001-2005	Director, AMDeC Microarray Resource Center, Host Institution: University of Rochester Medical Center
January 2001-2005	Assistant Professor Director, Functional Genomics Center Department of Environmental Medicine

Appendix A

Andrew I. Brooks, Ph.D.

	Aab Institute for Biomedical Science University of Rochester Medical School
January 2001-2005	Director, University of Rochester Medical Center Core Facilities Microarray Core Services Nucleic Acid Core Services Proteomics Core Services Bioinformatics Training Services
January 2001- June 2002	Director, Microarray Analysis Core Facility, NIA Nathan Shock Center for Excellence
September 1999-December 2000	Research Assistant Professor Director, University Microarray Core Facility Center for Aging & Development Division of Molecular Medicine & Gene Therapy Aab Institute for Biomedical Science 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 3rd 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 5th 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, URMC Office of Corporate Alliance (OCA)
2005 Co-Director, Planning Committee, Expanded Regional Translational Research Center
2015 American Association for Clinical Chemistry (AACC)'s Outstanding Speaker Award

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)

Appendix A

Andrew I. Brooks, Ph.D.

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 12th 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

Appendix A

Andrew I. Brooks, Ph.D.

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 59th 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 3rd 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 2011in 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 7th Annual Biorepositories & Sample Management Conference in Boston, MA

Appendix A

Andrew I. Brooks, Ph.D.

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
2016 Genetic Toxicology Association Meeting in Newark, DE
2016 European Society Human Genetics in Barcelona, Spain
2016 2016 University-Industry Interaction Conference in Amsterdam, The Netherlands
2016 Liquid Biopsy Summit in San Francisco, CA
2016 Leaders in Biobanking Congress in Baltimore, MD
2016 Annual Biorepositories & Sample Management Conference in Boston, MA
2016 World Life Science Conference in Beijing, China
2017 National Biobank Conference in Shanghai, China
2017 Molecular Med Tri-Con, San Francisco, CA
2017 The Impact of Biobanking in Qatar - Precision Medicine Initiative in Doha, Qatar
2017 International Society for Biological and Environmental Repositories in Toronto, Canada
2017 European, Middle Eastern & African Society for Biopreservation in Copenhagen, Denmark
2017 American Society of Human Genetics Annual Meeting in Orlando, FL
2017 Leaders in Biobanking Congress in Nashville, TN
2017 6th Annual Biobank China and International Symposium of Precision Medicine in Changsha, China

PUBLICATIONS

1. **Brooks AI**, Standifer KM, Chang J, Ciszewska, G and Pasternak GW. – Characterization and isolation of opioid binding sites expressed in giant toad and goldfish brain. Receptor, 4 (1): 55-62 (1994)

2. Standifer KM, Cheng J, **Brooks AI**, Honrado CP, Su W, Visconti LM, 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. Khanolkar, AD, Dali, Y, Makruyannis, A, **Brooks, AI,** Pasternak, GW, Froimowitz, M. – The Morphine-like and Nonmorphine-like Conformers of Prodine Opioids. Medicinal Chemistry Research, 6:11-21 (1996)

6. 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)

7. **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)

8. 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)

9. **Brooks AI**, Muhkerjee B, Panahian N, Cory-Slechta DA, 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)

10. **Brooks AI**, Halterman MW, Chadwick CA, Davidson BL, Haak-Frendscho M, Radel CA, Wong R, Federoff HJ. – Reproducible and efficient murine CNS gene delivery using a microprocessor controlled injector. Journal of Neuroscience Methods, 80: 137-147 (1998)

11. **Brooks AI**, Federoff HJ. – Tfx-20 reagent for efficient gene delivery into mouse CNS. Neural Notes, 4 (1): 20-23 (1998)

12. Charton, M., Ciszewska, G. R., Ginos, J., Standifer, K. M., **Brooks, AI**, Brown, G. P., Ryan-Moro, JP, Pasternak, GW. – Quantitative Structure Activity Relationships for Substituted Naloxone Benzoylhydrazones. 4′-substituted Naloxone Benzoylhydrazones. Quant. Struct.-Act. Relat., 17: 109–121. doi:10.1002/(SICI)1521-3838(199804)17:02<109:AID-QSAR109>3.0.CO;2-1 (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 ß-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. PMID: 10523756

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17. Tong N1, Perry SW, Zhang Q, James HJ, Guo H, **Brooks AI**, Bal H, Kinnear SA, Fine S, Epstein LG, Dairaghi D, Schall TJ, Gendelman HE, Dewhurst S, Sharer LR, Gelbard HA. – Neuronal fractalkine expression in HIV-1 encephalitis: roles for macrophage recruitment and neuroprotection in the central nervous system. J Immunol. 2000 Feb 1;164(3):1333-9. PMID: 10640747

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27. Chattopadhyay S, **Brooks AI**, Curren TM, Powers JM, Pearce DA, Ito M, Cooper JD, Pearce DA. – An inhibitory auto antibody to glutamic acid decarboxylase in the neurodegenerative disorder Batten disease. Human Molecular Genetics (2002), 1:11(12), 1421-31.

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35. **Brooks AI**, Viale, A. – Assessing, Understanding and Minimizing Variability of DNA Microarrays. American Pharmaceutical Review, (2003), Vol. 6, Issue 4, 102-105.

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BERTAGNA, ANGELA MARIE

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/10/2018

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/471,785	03/28/2017	Doug AMORESE	25115-755.301	8042

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR TARGETED NUCLEIC ACID SEQUENCE ENRICHMENT AND HIGH EFFICIENCY LIBRARY GENERATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0	$0	$1000	07/10/2018

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/471,785	03/28/2017	Doug AMORESE	25115-755.301	8042

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APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0	$0	$1000	07/10/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
BERTAGNA, ANGELA MARIE	1637	435-006120

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❑ "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.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1_____
2_____
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 (B) RESIDENCE: (CITY and STATE OR COUNTRY)

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
❑ Publication Fee (No small entity discount permitted)
❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
❑ A check is enclosed.
❑ Payment by credit card. Form PTO-2038 is attached.
❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
❑ Applicant certifying micro entity status. See 37 CFR 1.29 — 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.
❑ Applicant asserting small entity status. See 37 CFR 1.27 — 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.
❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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.

Authorized Signature _____ Date _____
Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/471,785	03/28/2017	Doug AMORESE	25115-755.301	8042

12754 7590 04/10/2018
Wilson Sonsini Goodrich & Rosati/NUGEN
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER
BERTAGNA, ANGELA MARIE

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/10/2018

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.

PTOL-85 (Rev. 02/11)

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.

Notice of Allowability	Application No. 15/471,785	Applicant(s) AMORESE et al.	
	Examiner Angela Bertagna	Art Unit 1637	AIA Status 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 2/16/18 and the interview of 3/30/18.
   ☐ 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 See Continuation Sheet . 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** or send an inquiry to **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 areply 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. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ANGELA M. BERTAGNA/
Primary Examiner, Art Unit 1637

Continuation of 3. The allowed claim(s) is/are: 51-63,66-68 and 70-75

DETAILED CORRESPONDENCE

Notice of Pre-AIA or AIA Status

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

Status of the Application

Applicant's response filed on February 16, 2018 is acknowledged and has been entered.

Information Disclosure Statement

Reference 17 on the IDS filed on February 17, 2018 has not been considered because the copy filed is not legible. This is required by 37 CFR 1.98(a)(2)(ii).

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).

Terminal Disclaimer

The terminal disclaimer filed on February 16, 2018 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent No. 9,650,628 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Response to Amendment

The declaration of Dr. Andrew Brooks, which was filed on February 16, 2018, under 37 CFR 1.132 is sufficient to overcome the rejections of claims 51-75 made previously under pre-AIA 35 U.S.C. 103(a) citing Jones and Tucker.

Response to Arguments

Applicant's arguments filed on February 16, 2018 have been fully considered.

Information Disclosure Statement

Applicant states that copies of foreign patent documents 69, 74, 81, 82, 97, and 102 listed in the IDS filed on 7/10/17 were, in fact, filed in Application Serial No. 13/750,768, to which the instant application claims priority (Remarks, page 8). Applicant also states that copies of non-patent literature documents 34, 175, and 256 on the 7/10/17 IDS were, in fact, filed in the '768 application (Remarks, page 8).

Applicant's remarks regarding the IDS of 7/10/17 were persuasive. It is noted that foreign patent document 81 was not filed in the '768 application on 10/16/15, but a copy was filed on 4/28/16 in that application. An updated annotated copy of the IDS filed on 7/10/17 is attached.

Objection to the Specification

Applicant argues that the objection to the specification should be withdrawn in view of the amendments to the specification (Remarks, page 9).

This argument was persuasive. The objection has been withdrawn.

Claim Objections

Applicant argues that the objections to claims 51 and 60 should be withdrawn in view of the amendments to those claims (Remarks, page 9).

This argument was persuasive. The objections have been withdrawn.

Rejection of claims 51-64 and 66-75 under pre-AIA 35 U.S.C. 112, second paragraph

Applicant argues that the rejection should be withdrawn in view of the claim amendments, which replace "appended to" with "ligated to" (Remarks, page 10).

This argument was persuasive. The rejection has been withdrawn.

Rejections of claims 51-75 under pre-AIA 35 U.S.C. 103(a) citing Jones and Tucker as the primary combination of references

Applicant argues that the rejections should be withdrawn in view of the declaration of Dr. Andrew Brooks, which was submitted on February 16, 2018 under 37 CFR 1.32 (Remarks, pages 10-13).

This argument was persuasive. As discussed above, the Brooks declaration was sufficient to overcome the rejections. They have been withdrawn accordingly.

Double Patenting

Applicant argues that the rejections of claims 51-75 should be withdrawn in view of the submission of a proper terminal disclaimer (Remarks, page 14).

This argument was persuasive. The rejection has been withdrawn.

EXAMINER'S AMENDMENT

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 Rachna Ujwal (Reg. No. 73,914) on March 30, 2018.

The application has been amended as follows:

In the claims:

CANCEL CLAIMS 64 AND 69.

In claim 66, line 1, please delete "of claim 64" and insert --of claim 51-- therefor.

In claim 67, line 1, please delete "of claim 64" and insert --of claim 51-- therefor.

68. (currently amended) The method of claim **51** **[[64]]**, further comprising **fragmenting a nucleic acid, thereby generating a nucleic acid fragment; and purifying the nucleic acid fragment prior to obtaining the nucleic acid fragment ligated to the partial duplex adaptor in step a)** ~~purifying the nucleic acid fragment ligated to the partial duplex adaptor prior to step a)~~.

73. (currently amended) The method of claim 51, further comprising **fragmenting a nucleic acid, thereby generating a nucleic acid fragment; and performing end repair on the nucleic acid fragment prior to obtaining the nucleic acid fragment ligated to the partial duplex adaptor in step a)** ~~performing end repair on the nucleic acid fragment prior to step a)~~.

74. (currently amended) The method of claim 51, **wherein the nucleic acid fragment of the nucleic acid fragment ligated to the partial duplex adaptor in step a) is**

obtained by performing reverse transcription on an RNA fragment prior to obtaining the nucleic acid fragment ligated to the partial duplex adaptor in step a) ~~wherein the nucleic acid fragment of step a) is obtained by performing reverse transcription on an RNA fragment~~.

Conclusion

Claims 51-63, 66-68, and 70-75 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571)272-8291. The examiner can normally be reached on 8-5, M-F.

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, 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