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BROWN RUDNICK LLP ONE FINANCIAL CENTER BOSTON, MA 02111			BERTAGNA, ANGELA MARIE	
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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.

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DETAILED CORRESPONDENCE

Notice of Pre-AIA or AIA Status

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

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

Preliminary Amendment

2. The preliminary amendment filed on November 30, 2018 has been entered. Claims 51-70 are pending.

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

Information Disclosure Statement

3. The Information Disclosure Statement (IDS) containing 61 pages filed on December 4, 2018 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The transmittal letter

accompanying this IDS states that the copies may be found in the grandparent application (13/750,768), but copies of the citations that have been lined through were not found in the grandparent application.

Applicant is advised that the date of any re-submission of any item of information contained in this IDS 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 indicate that prior-filed Application Serial No. 15/471,785 has issued as U.S. Patent 10,036,012.

Claim Objections

5. Claim 51 is objected to because of the following informalities. Amending step (c) to replace “, thereby generating” in line 4 of the step with “by generating” is suggested. Also, replacing “an enriched nucleic acid” in the last line of step (c) with “the enriched nucleic acid is suggested” to maintain consistency within the step. As well, amending step (a) to replace “the nucleic acid fragment” in line 3 of the step with “the nucleic acid fragment to which the one or more oligonucleotides are annealed” or “the nucleic acid fragment comprising the nucleic acid sequence of interest” is suggested to improve clarity.

Claim 56 is objected to because “comprise” in line 1 should be replaced with “comprises.” As well, deleting “each of” in line 2 is suggested.

Claim 57 is objected to because the word “the” should be inserted before the word “second” in line 2.

Claim 58 is objected to because “comprise” in line 2 should be replaced with “comprise(s)” to account for the “and” option as well as the “or” option.

Claim 61 is objected to because the word “the” should be inserted before “use” in line 1.

Claim 64 is objected to because of the following informalities. Deleting “of each of the plurality of nucleic acid fragments” is suggested since it is redundant.

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 59 and 66 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 59 is indefinite because it appears to be missing at least one element or step. The claim depends from claim 51 and recites “further comprising denaturing double-stranded nucleic acid fragments prior to step a), thereby generating the nucleic acid fragment comprising the first adaptor sequence.” It is clear that this claim requires performance of a denaturation step before the annealing of step (a), but it is not clear how a denaturation step can generate an adaptor-

containing nucleic acid fragment. It seems that an additional step (e.g., adaptor ligation or polymerase-mediated adaptor addition) is needed to generate an adaptor-containing nucleic acid fragment. The claim would be clear and definite if the “thereby” clause was deleted.

Claim 66 is indefinite because the metes and bounds of “appended to” are unclear. The specification states that ligation is encompassed by the term, it is not clear as to what else is encompassed by “appended to.” Neither the specification nor the claims gives any additional description as to what is encompassed by this language. And, more specifically, it is unclear whether, for example, “appended to” also encompasses partial duplex adaptors that are merely hybridized to the nucleic acid fragments.

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 negated 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, 54-61, and 63-70 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, 56, 57, 60, and 64-67, 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 end of the nucleic acid fragments, thereby providing a plurality of fragments having a common first adaptor sequence ligated at a 5' end;
- (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 common second adaptor sequence that is not complementary to the nucleic acid sequence of interest;
- (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).

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

Regarding claim 59, 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. Therefore, the reference also does not meet the requirements of claims 61, 63, and 68-70, which further limit the sequencing step.

Tucker, though, 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, 61, and 68-70, 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). Further regarding claim 63, Tucker notes that nanopore sequencing is another form massively parallel sequencing (page 143).

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. Therefore, it would have been obvious to use any of the massively parallel sequencing methods disclosed in Tucker. The ordinary artisan would have had a reasonable expectation of success since many of the methods disclosed in Tucker have been commercialized and the reference provides guidance as to how the different sequencing methods are conducted. Lastly, when using the Illumina sequencing method, 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 68) 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. Thus, the methods of claims 51, 52, 54-61, and 63-70 are *prima facie* obvious.

10. Claim 53 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 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, 54-61, and 63-70.

Regarding claim 53, Jones does not teach that the nucleic acid fragment comprises cDNA. Tucker does not remedy this deficiency 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 claim 53, Gormley teaches that libraries for sequencing 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 practice the method suggested by Jones in view of Tucker using cDNA fragments of interest prepared from RNA by reverse transcription. Gormley provides motivation to do so as well as 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 Jones in view of Tucker and further in view of Gormley render obvious the method of claim 53.

11. Claim 62 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 + Supplemental Information).

As discussed above, the teachings of Jones in view of Tucker render obvious the methods of claims 51, 52, 54-61, and 63-70.

Jones does not teach semiconductor sequences as recited in claim 62, 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 62 is *prima facie* obvious.

Double Patenting

12. The non-statutory 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 time-wise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A non-statutory 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 non-statutory 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 e-Terminal Disclaimer may be filled out completely online using web-screens. An e-Terminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about e-Terminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

13. Claims 51-62 and 64-69 are rejected on the ground of non-statutory double patenting as being unpatentable over claims 1-37 of U.S. Patent No. 9,650,628 B2 (IDS reference).

Although the claims at issue are not identical, they are not patentably distinct from each other because the claims of the '628 patent teach or suggest all of the elements of the instant claims.

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 comprising a first adaptor sequence; (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 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 (e) sequencing the enriched nucleic acid of interest on a massively parallel sequencing platform.

Claims 1 and 23 of the '628 patent are also drawn to a method for sequencing an enriched nucleic acid of interest. The method recited in these claims includes all of the elements of the instant claim 51 as well as additional elements. For example, claim 1 of the '628 patent requires a post-ligation purification step that is not required by the instant claim 51, and claim 23 of the '628 patent requires a pre-sequencing purification step that is not required by the instant claim 51. Therefore, claims 1 and 23 of the '628 patent recite a species of the method more generically claimed in the instant claim 51. As discussed in MPEP 804 II.B.1, a species anticipates a more

generic claim, and the instant claim 51 is not patentably distinct from the claims of the '628 patent.

The limitations of the instant claims 52-54 are recited in claim 2 and 24 of the '628 patent.

The limitations of the instant claims 55-58 are recited in claims 1, 3, 4, and 7 of the '628 patent.

The limitations of the instant claim 59 are recited in claim 23 of the '628 patent.

The limitations of the instant claim 60 are recited in claims 5 and 37 of the '628 patent.

The limitations of the instant claims 61 and 62 are recited in claims 18, 19, 31, and 32 of the '628 patent.

The limitations of the instant claims 64-67 are recited in claim 1 of the '628 patent.

The limitations of the instant claims 68 and 69 are recited in claims 1 and 23 of the '628 patent.

Thus, the instant claims 51-62 and 64-69 are not patentably distinct from claims 1-37 of the '628 patent.

14. Claims 63 and 70 are rejected on the ground of non-statutory double patenting as being unpatentable over claims 1-37 of U.S. Patent No. 9,650,628 B2 (IDS reference) in view of Tucker et al. (The American Journal of Human Genetics 2009; **85**: 142-154; IDS reference).

As discussed above, the instant claims 51-62 and 64-69 are not patentably distinct from the claims of the '628 patent.

The claims of the '628 patent do not teach that nanopore sequencing is the massively parallel sequencing method as required by the instant claim 63.

The claims of the '628 patent also do not teach that the massively parallel sequencing method is conducted in a flow cell as required by the instant claim 70.

Tucker, though, 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). Tucker also teaches that nanopore sequencing is another form massively parallel sequencing (page 143).

The ordinary artisan practicing the sequencing method recited in the claims of the '628 patent would have recognized from the teachings of Tucker that a flow cell was suitable for use as the surface upon which the sequencing reaction was conducted and also that nanopore sequencing was a suitable massively parallel sequencing method. Since it is *prima facie* obvious to select a known material or method based on its suitability for the intended purpose in the absence of unexpected results (MPEP 2144.07) and no such evidence has been presented, the instant claims 63 and 70 are not patentably distinct from the claims of the '628 patent in view of Tucker.

15. Claims 51-62 and 64-69 are rejected on the ground of non-statutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 10,036,012 B2 (IDS reference).

Although the claims at issue are not identical, they are not patentably distinct from each other because the claims of the '012 patent teach or suggest all of the elements of the instant claims.

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 comprising a first adaptor sequence; (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 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 (e) sequencing the enriched nucleic acid of interest on a massively parallel sequencing platform.

Claim 1 of the '012 patent is also drawn to a method for sequencing an enriched nucleic acid of interest. The method recited in these claims includes all of the elements of the instant claim 51 as well as additional elements. For example, the partial duplex adapter required by claim 1 of the '012 patent is not required by the instant claim 51. Therefore, claim 1 of the '012 patent recites a species of the method more generically claimed in the instant claim 51. As discussed in MPEP 804 II.B.1, a species anticipates a more generic claim, and the instant claim 51 is not patentably distinct from the claims of the '012 patent.

The limitations of the instant claims 52-54 are recited in claim 2-4 of the '012 patent.

The limitations of the instant claims 55-58 are recited in claims 1 and 5-7 of the '012 patent.

The limitations of the instant claim 59 are recited in claims 11 and 12 of the '012 patent.

The limitations of the instant claim 60 are recited in claim 13 of the '012 patent.

The limitations of the instant claims 61 and 62 are recited in claims 18 and 19 of the '012 patent.

The limitations of the instant claims 64-67 are recited in claims 1, 11, 14, 16, and 20 of the '012 patent.

The limitations of the instant claims 68 and 69 are recited in claim 1 of the '012 patent.

Thus, the instant claims 51-62 and 64-69 are not patentably distinct from claims 1-22 of the '012 patent.

16. Claims 63 and 70 are rejected on the ground of non-statutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 10,036,012 B2 (IDS reference) in view of Tucker et al. (The American Journal of Human Genetics 2009; **85**: 142-154; IDS reference).

As discussed above, the instant claims 51-62 and 64-69 are not patentably distinct from the claims of the '012 patent.

The claims of the '012 patent do not teach that nanopore sequencing is the massively parallel sequencing method as required by the instant claim 63.

The claims of the '012 patent also do not teach that the massively parallel sequencing method is conducted in a flow cell as required by the instant claim 70.

Tucker, though, 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). Tucker also teaches that nanopore sequencing is another form massively parallel sequencing (page 143).

The ordinary artisan practicing the sequencing method recited in the claims of the '012 patent would have recognized from the teachings of Tucker that a flow cell was suitable for use as the surface upon which the sequencing reaction was conducted and also that nanopore sequencing was a suitable massively parallel sequencing method. Since it is *prima facie* obvious to select a known material or method based on its suitability for the intended purpose in the absence of unexpected results (MPEP 2144.07) and no such evidence has been presented, the instant claims 63 and 70 are not patentably distinct from the claims of the '012 patent in view of Tucker.

Conclusion

17. No claims are currently allowable.

Rabinowitz et al. (US 2012/0270212 A1; IDS reference) is cited as reference of interest. This reference teaches amplification of a nucleic acid having a first adapter attached thereto with a tailed target-specific primer (see, e.g., Figures 1-8) but the disclosed method does not meet the requirements of steps (b) and (c) in the instant claim 51.

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 <https://ppair-my.uspto.gov/pair/PrivatePair>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: NUGEN TECHNOLOGIES, INC. ART UNIT: 1637
SERIAL NUMBER: 16/017,340 CONF. NO.: 2635
FILING DATE: June 25, 2018 EXAMINER: Angela Marie Bertagna
TITLE: **COMPOSITIONS AND METHODS FOR TARGETED NUCLEIC ACID SEQUENCE ENRICHMENT AND HIGH EFFICIENCY LIBRARY GENERATION**

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

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AMENDMENT AND RESPONSE

This Response is in reply to the non-final Office Action mailed April 30, 2020, from the United States Patent and Trademark Office. Applicant is filing a terminal disclaimer herewith and authorizes the require fee to be charged to Deposit Account No. 50-0369. Applicant believes that no other fee is due with this response. Nevertheless, Applicant authorizes any required fee to be charged to Deposit Account No. 50-0369.

Amendments to the specification begin on page 2.

Amendments to the claims begin on page 3.

Remarks begin on page 6.

AMENDMENTS TO THE SPECIFICATION

Please amend the as-filed specification at page 1, paragraph [0001], as follows:

This application is a continuation of U.S. application Ser. No. 15/471,785, filed Mar. 28, 2017, now U.S. Pat. No. 10,036,012, which claims the benefit of U.S. application Ser. No. 13/750,768, filed Jan. 25, 2013, now U.S. Pat. No. 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

Please amend the claims as follows:

Listing of claims

1. - 50. (Cancelled)

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

- a) annealing one or more oligonucleotides in solution in a reaction mixture to the nucleic acid sequence of interest in a nucleic acid fragment, wherein the reaction mixture comprises a plurality of nucleic acid fragments, wherein the nucleic acid fragment comprising the nucleic acid sequence of interest comprises a first adaptor sequence, 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;
- b) extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment comprising the first adaptor sequence with a polymerase, in the reaction mixture, 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;
- c) amplifying the one or more oligonucleotide extension products, in the reaction mixture, using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence, thereby enriching the nucleic acid sequence of interest, [[there]]by generating amplified products comprising [[an]]the enriched nucleic acid sequence of interest; and
- d) sequencing the amplified products comprising 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 sequence of interest comprises genomic DNA.

53. (Previously Presented) The method of claim 51, wherein the nucleic acid sequence of interest comprises cDNA.
54. (Previously Presented) The method of claim 51, wherein the nucleic acid sequence of interest 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. (Currently Amended) The method of claim 51, wherein the plurality of nucleic acid fragments comprises the first adaptor sequence, and wherein the first adaptor sequence is common to ~~each of~~ the plurality of nucleic acid fragments.
57. (Currently Amended) The method of claim 51, wherein the one or more oligonucleotides comprises more than one oligonucleotide, wherein the second adaptor sequence is common to the more than one oligonucleotide.
58. (Currently Amended) The method of claim 51, wherein the first adaptor sequence and/or the second adaptor sequence comprise(s) a barcode sequence.
59. (Currently Amended) The method of claim 51, further comprising denaturing double-stranded nucleic acid fragments prior to step a), ~~thereby generating the nucleic acid fragment comprising the first adaptor sequence.~~
60. (Previously Presented) The method of claim 51, wherein the polymerase is a DNA polymerase.
61. (Currently Amended) The method of claim 51, wherein the sequencing comprises the use of four labeled reversible terminators.
62. (Previously Presented) The method of claim 51, wherein the sequencing comprises semiconductor sequencing.
63. (Previously Presented) The method of claim 51, wherein the sequencing comprises nanopore sequencing.

64. (Currently Amended) The method of claim 51, wherein each of the plurality of nucleic acid fragments comprises the first adaptor sequence at a 5' end ~~of each of the plurality of nucleic acid fragments~~.

65. (Previously Presented) The method of claim 51, further comprising fragmenting nucleic acids prior to step a), thereby generating the plurality of nucleic acid fragments.

66. (Currently Amended) The method of claim 51, further comprising ~~appending~~ ligating the first adaptor sequence to a nucleic acid fragment in the plurality of nucleic acid fragments prior to step a), thereby generating the nucleic acid fragment comprising the first adaptor sequence.

67. (Cancelled)

68. (Previously Presented) The method of claim 51, wherein the amplified products comprise a 3' end with sequence complementary to a sequence on a surface.

69. (Previously Presented) The method of claim 68, further comprising 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 prior to step d).

70. (Previously Presented) The method of claim 68, wherein the surface is a surface of a flow cell.

REMARKS

Claims 51-70 were pending in the subject application. By this Amendment, Applicant has cancelled claim 67 and amended claims 51, 56-59, 64, and 66. The amendments to claims 51, 56-59, 64, and 66 were merely for the purposes of clarity and include no new matter. Upon entry of this Amendment, claims 51-66 and 68-70 will be pending with claim 51 as the sole independent claim.

Objection to the Specification

Page 3 of the non-final Office Action states that the specification is objected to because the continuity data information in the first paragraph should be updated to indicated that prior-filed Application Serial No. 15/471,785 issued as U.S. Patent No. 10,036,012.

Applicant has amendment to the specification to update the continuity data information in paragraph [0001] of the specification by stating that prior-filed Application Serial No. 15/471,785 issued as U.S. Patent No. 10,036,012. No new matter is introduced by this amendment to the specification.

Applicant believes that the objection to the specification is overcome.

Objections to the Claims

The Office Action states on pages 3-4 that claims 51, 56-58, 61, and 64 are objected to because of informalities.

Applicant has herein amended claims 51, 56-58, 61, and 64 in accordance with the suggestions provided on pages 3-4 of the Office Action.

Applicant believes that the objections to the claims are overcome.

Rejections under 35 U.S.C. §112

The Office Action states on pages 4-5 that claims 59 and 66 is rejected under 35 U.S.C. §112, second paragraph as indefinite.

Applicant has herein amended claim 59 as suggested on page 5 of the Office Action. Accordingly, Applicant submits that claim 59 is definite and complies with the requirements of 35 U.S.C. §112, second paragraph.

Applicant has herein amended claim 66 to replace the term "appending" with ligating. Applicant concurrently cancelled claim 67. Accordingly, Applicant submits that claim 66 is definite and complies with the requirements of 35 U.S.C. §112, second paragraph.

Applicant requests that the rejections under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

Rejections under 35 U.S.C. §103

The Office Action states on page 6 that claims 51, 52, 54-61 and 63-70 are rejected under 35 U.S.C. §103 over US 2005/0142577 to Jones in view of Tucker, 2009, Am. J. Hum. Gen., 85: 142-154. The Office Action states on page 9 that claim 53 is rejected under 35 U.S.C. §103 over Jones in view of Tucker, and in further view of U.S. 7,741,463 to Gormley. The Office Action states on page 10 that claim 62 is rejected under 35 U.S.C. §103 over Jones in view of Tucker, 2011, Nature, 475: 348-352 by Rothberg.

Applicant submits that the claims are non-obvious over the cited references.

A determination of obviousness requires basic factual inquiries into the scope and content of the prior art as well as the difference between the claimed invention and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1 (1996). For a claim to be obvious over a combination of references, there must be some articulated reason with a rational underpinning for why one would have made the proposed combination. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). The Office must consider objective evidence of non-obviousness, including evidence of unexpected results, skepticism of experts, and other 'secondary considerations'. *MPEP §716.01*. Such evidence may be presented in an affidavit or declaration, which is considered timely submitted when presented prior to a final Office Action. *MPEP §716.01; 37 C.F.R. §1.132(A)(1)*.

The claims recite sequencing methods in which a sequence of interest is enriched using a single target-specific oligonucleotide. The sequence of interest has a first adapter attached to one end. The target-specific oligonucleotide has a portion complementary to the sequence of interest and a non-complementary portion at the 5' end. This non-complementary portion contains a second adapter sequence. The oligonucleotide anneals to the target of interest and is extended to produce an extension product that has the sequence of interest flanked by the first and second adapters.

Each adapter contains a priming site. Thus, the enriched sequence of interest can be amplified using a common primer pair. The ability to use a common primer pair circumvents the need to use multiplex PCR with multiple primer pairs. *As-filed application*, [0019].

Unexpectedly, the claimed methods result in low amounts of off-target sequence enrichment, a requirement for effective, massively parallel sequencing.

The claims are not obvious over the cited references because the combination of references do not teach enrichment with a single target-specific oligonucleotide and subsequent amplification using a common set of primers. Further, the references cannot be combined to arrive at Applicant's invention with a reasonable expectation of success.

Jones fails to disclose enrichment by extending a single target-specific oligonucleotide as claimed. In fact, Jones provides no disclosure of enrichment through an extension reaction. Jones likewise does not disclose the recited target-specific oligonucleotide with a non-complementary 5' adapter. Furthermore, Jones does not disclose sequencing, nor suggest that its teachings can extend to massively parallel sequencing.

Jones reports methods for preparing nucleic acids for microarray analysis. *Jones*, [0002]. Amplified products are hybridized to a microarray for analysis. *Id.* The methods use "capture probes" to incorporate amplification priming sites into target sequences. *Id.*, [0079] and [0087]. These capture probes contain a "common sequence" that is complementary to a portion of a target sequence. *Id.*, [0005]. Extension products with this complementary common sequence "are amplified by PCR using primers to the common sequences". *Id.*, [0079].

Unlike the claimed methods, Jones' disclosure does not use extension of a target-specific oligonucleotide for enrichment. Rather, Jones requires additional steps for sequence enrichment prior to amplification. *Id.*, [0011], [0087], [0102]-[0104], and FIG. 3. Enrichment in Jones requires either positively selecting extended capture probes or depleting non-extended products. *Id.*

Jones also fails to disclose the recited target-specific oligonucleotide, which has a non-complementary second adapter that serves as a priming site. Rather, Jones' capture probes employ a "common sequence", complementary to the target sequence. The common sequences serve as priming sites for "common sequence primers". *Id.*, [0102].

Further, because Jones does not rely on a non-complementary adapter to provide a priming site, Jones cannot avoid using multiple primer pairs when amplifying different target

sequences. Jones' priming sites (the "common sequence") are complementary to the target sequence. Thus, for each different target amplified, a different "common sequence" and "common sequence primer" is required.

Furthermore, Applicant respectfully notes that because Jones does not disclose sequencing, the disclosure is not relevant to the claimed methods.

A person of skill in the art would not find Jones' disclosure applicable to sequencing because sequencing demands less off-target enrichment than microarray hybridization. Consequently, one would not have a reasonable expectation of success in applying Jones' enrichment methods to massively parallel sequencing.

Microarray hybridization is far more tolerant of off-target sequence enrichment than is massively-parallel sequencing. This is due to the fundamental nature of microarray hybridization assays, in which many amplified products are hybridized to spots on an array and their aggregate signals detected. Because microarrays rely on hybridization to probes, off-target amplicons may simply not find a complementary probe to bind to on the array. This precludes the off-target products from impacting the analysis. Similarly, because the aggregate signal of many products are detected, signals from any off-target products on the array fall into the background compared to the intense aggregate signals produced by the on-target products hybridized to the array.

In contrast, in massively parallel sequencing, off-target amplicons are sequenced just like on-target amplicons. As a result, off-target amplicons can flood the sequencing system, confounding sequence analysis. Sequencing lacks the intrinsic abilities of microarray hybridization to overcome off-target enrichment, and nothing in Jones suggests otherwise.

Accordingly, because Jones does not disclose sequencing, but rather microarray-based techniques, Jones' enrichment techniques could not be applied to sequencing with a reasonable expectation of success.

This conclusion is supported in the attached expert declaration of Dr. Brooks, filed in the parent of the subject application, U.S. 15/471,785. *Brooks Declaration*, ¶¶ 14-17.

Gromley does not cure Jones' omissions.

Gormley provides methods for generating nucleic acid libraries by *ligating two adapters* to a target sequence. *Gromley*, Col. 6, lines 48-59. The adapters contain a priming site, and "a key feature of the method of the invention [is] that the initial primer extension reaction is carried out using a 'universal primer' which binds specifically to a cognate sequence within an adapter

portion of the adapter-target construct, and is not carried out using a target-specific primer". *Gormley, col. 12, lines 22-27*. Thus, Gormley actually teaches away from the claimed methods, which use a target-specific oligonucleotide for the initial extension and incorporating a second adapter.

Tucker is merely an overview of sequencing techniques. *Tucker, page 142*. Tucker provides an overview of enrichment techniques used in sequencing. *Id., Figure 6*. However, not a single one of these methods enriches a target sequence using a single target-specific oligonucleotide.

Rothberg reports semiconductor sequencing. *Rothberg, abstract*. Rothberg only teaches a method of enrichment in which "unique forward and reverse adapters were ligated" to target sequences. *Rothberg Supplement, p. 22*.

Thus, the combination of references fails to teach all claimed elements as required to reject the claims as obvious.

Further, Applicant notes that an expert in the relevant art expressed disbelief that the claimed sequencing methods would provide adequate specificity for use with massively parallel sequencing. As the MPEP states, "[e]xpressions of disbelief by experts constitute strong evidence of nonobviousness". *MPEP §716.05* (quoting *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713, F.2d 693, 698 (Fed. Cir. 1983)).

In the attached declaration, Dr. Brooks explains that in 2012 he was approached to use the claimed methods. *Brooks Declaration, ¶14*. At that time, Dr. Brooks believed the methods would provide poor target specificity, which would lead to poor quality sequencing data. *Id.* Dr. Brooks thought 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. *Id.* Dr. Brooks felt that this off-target activity would affect the ability to create a uniform distribution of on-target sequences, which would lead, not only to an incomplete or less complex library, but one that had such an uneven distribution of targets that it would severely impair quantitative analyses. *Id., ¶15*.

Importantly, none of the cited references provide a disclosure that contradicts Dr. Brook's initial skepticism that the claimed methods would work.

Applicant further notes that the claimed methods provided unexpected results, and "[e]vidence of unobvious or unexpected advantages or properties, can rebut *prima facie* obviousness". *MPEP* §716.02(a).

In the attached declaration, Dr. Brooks provides evidence that the claimed methods provided unexpected and advantageous results.

Owing to his initial skepticism, Dr. Brooks expected to observe about fifty percent of sequence reads having the sequence of interest when using the claimed methods. *Brooks Declaration*, ¶16. However, unexpectedly, when using the methods, Dr. Brooks observed that over ninety percent of the sequence reads contained on-target sequences. *Id.* Dr. Brooks explained that this finding was unexpected, and that he would never have thought to use the claimed methods unless specifically asked to do so. *Id.*

Further, nothing in the cited references would render this as an expected result.

As discussed above, Dr. Brooks stated that Jones' microarray-based disclosure was inapplicable to massively-parallel sequencing. *Id.*, ¶17. Thus, nothing in Jones would render the success of the claimed methods as an expected result. Furthermore, Jones required separate enrichment steps.

Not only are the claimed results unexpected over Gormley, as explained, Gormley actually teaches away from the claimed methods.

Tucker or Rothberg never even mention enrichment using a target-specific oligonucleotide as claimed, and therefore do not render the results expected.

Based on the foregoing remarks and the attached declaratory evidence, Applicant submits that the claims are non-obvious. Accordingly, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

Double Patenting

The Office Action states on page 12 that claims 51-62 and 64-69 are rejected on the ground of non-statutory double patenting over claims 1-37 of U.S. Patent No. 9,650,628. The Office Action states on page 14 that claims 63 and 70 are rejected on the ground of non-statutory double patenting over claims 1-37 of U.S. Patent No. 9,650,628 in view of Tucker (*The American Journal of Human Genetics* 2009; 85: 142-154). The Office Action states on page 15 that claims 51-62 and 64-69 are rejected on the ground of non-statutory double patenting over

claims 1-22 of U.S. Patent No. 10,036,012. The Office Action states on page 17 that claims 63 and 70 are rejected on the ground of non-statutory double patenting over claims 1-22 of U.S. Patent No. 10,036,012 in view of Tucker.

Applicant is filing herewith a terminal disclaimer in compliance with 37 C.F.R. §1.321 over U.S. Patent Nos. 9,650,628 and 10,036,012. Accordingly, Applicant submits that the rejections on the ground of non-statutory double patenting are overcome.

Conclusion

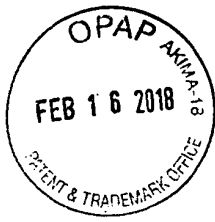
Applicant submits that the pending claims are in a condition for allowance, and Applicant requests a Notice of Allowance.

Dated: July 28, 2020

Respectfully submitted,
BROWN RUDNICK LLP

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PATENT
Attorney Docket No. 25115-755.301

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

Inventor: Doug Amorese *et al.*

Application No.: 15/471,785

Filed: March 28, 2017

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

Confirmation No.: 8042

Examiner: Angela Bertagna

Group Art Unit: 1637

Customer No. 12754

DECLARATION OF ANDREW BROOKS
UNDER 37 C.F.R. §1.132

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

DECLARATION OF ANDREW BROOKS

Commissioner:

I, Andrew I. Brooks, declare as follows:

I. QUALIFICATIONS

1. My name is Andrew I. Brooks.
2. I am the Chief Operating Officer at RUCDR Infinite Biologics at Rutgers. RUCDR Infinite Biologics provides a wide array of genotyping, gene expression, and microarray services, and provides consultation for experimental design, platform and microarray selection, as well as bioinformatics support. RUCDR Infinite Biologics offers massively parallel next-generation sequencing on the latest platforms from Ion Torrent and Illumina. Comprehensive service bundles offered by RUCDR Infinite Biologics include nucleic acid extraction, integrated sample quality control, and fully automated construction of sequencing libraries.
3. I am also President and Founder of Brooks Biomedical Consulting, BBC LLC, which provides consulting services for personalized medicine, animal model development, gene-based therapeutics, molecular diagnostics, and enterprise level biobanking.

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.

Dated: February , 2018

By:

Andrew I. Brooks

15 Feb 2018

Appendix A

Andrew I. Brooks, Ph.D.

CURRICULUM VITAE

NAME: Andrew I. Brooks

ADDRESS: Office: Environmental & Occupational Health Sciences Institute
Bionomics Research & Technology Center
170 Frelinghuysen Road - Room 236H
Piscataway, NJ 08854

Home: 3 Hanover Square, PH23A
New York, New York 10004

TELEPHONE: Office: (848) 445-0225

FACSIMILE: (732) 445-0152

EMAIL: brooks@dls.rutgers.edu

CITIZENSHIP: USA

EDUCATION

Cornell University, Ithaca, NY
Animal Science

B.S. 1991

Albert Einstein College of Medicine, Bronx, NY
Neuroscience

Ph.D. candidate 1994-1995

University of Rochester School of Medicine, Rochester, NY 14642
Department of Microbiology and Immunology
Molecular Medicine & Gene Therapy

M.S. 1998

University of Rochester School of Medicine, Rochester, NY 14642
Department of Microbiology and Immunology
Molecular Medicine & Gene Therapy

Ph.D. 1999

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.

January 2001-2005	Aab Institute for Biomedical Science University of Rochester Medical School 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 3 rd Annual American Society for Gene Therapy Annual Meeting
2000	University of Rochester Fenn Award for Distinguished Ph.D. Thesis
2002	Scientific Director, Convergence Biotechnology Conference
2002	Chair, Microarray Research Group (MARG), Association of Biomedical Resource Facilities
2002	Co-Chair Neurology Session 5 th 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, URMCC 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

Appendix A

Andrew I. Brooks, Ph.D.

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

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- 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 2011 in Palm Springs, CA
- 2011 Global Sample Management Asia Event in San Francisco, CA
- 2011 American Society of Human Genetics Annual Meeting in Montreal, Canada
- 2011 Cryo2011 Event at Oregon State University in Corvallis, OR
- 2012 Society of Laboratory Automation and Screening in San Diego, CA
- 2012 Advances in Genome Biology & Technology on Marco Island, FL
- 2012 5th Annual Biospecimen Research Network Symposium in Bethesda, MD
- 2012 International Society for Biological and Environmental Repositories in Vancouver, Canada
- 2012 Association of Biomolecular Resource Facilities Conference in Orlando, FL
- 2012 European Lab Automation in Hamburg, Germany
- 2012 Genomics Research Europe in Frankfurt, Germany
- 2012 Institute for International Research Biorepositories Clinical Business Expo in Boston, MA
- 2012 Leaders in BioBanking Congress in Chapel Hill, NC
- 2012 Digital PCR - Applications and Advances in San Diego, CA
- 2012 American Society of Human Genetics in San Francisco, CA
- 2013 Society of Laboratory Automation and Screening in Orlando, FL
- 2013 Human Genome Meeting in Singapore
- 2013 BioCor, University of Minnesota
- 2013 Biobanking UK Conference in London, UK
- 2013 European, Middle Eastern & African Society for Biopreservation & BioBanking in Verona, Italy
- 2013 Hands On Biobanks, Amsterdam, Netherlands
- 2014 Ninth Annual Biomarkers Congress in Manchester, UK
- 2014 European, Middle Eastern & African Society for Biopreservation & BioBanking LIMS Workshop in Milan, Italy
- 2014 Association of Biomolecular Resource Facilities Conference in Albuquerque, NM
- 2014 American Association for Cancer Research in San Diego, CA
- 2014 International Society for Biological and Environmental Repositories in Orlando, FL
- 2014 7th Annual Biorepositories & Sample Management Conference in Boston, MA

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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

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NOTICE OF ALLOWANCE AND FEE(S) DUE

21710 7590 08/19/2020
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER

BERTAGNA, ANGELA MARIE

ART UNIT

PAPER NUMBER

1637

DATE MAILED: 08/19/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/017,340	06/25/2018	Doug AMORESE	NUGN-037/04US 34079/440	2635

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	\$0.00	\$0.00	\$1000	11/19/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/017,340	06/25/2018	Doug AMORESE	NUGN-037/04US 34079/440	2635

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	\$0.00	\$0.00	\$1000	11/19/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
BERTAGNA, ANGELA MARIE	1637	435-006100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

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Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

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5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

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NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/017,340	06/25/2018	Doug AMORESE	NUGN-037/04US 34079/440	2635
21710	7590	08/19/2020	EXAMINER BERTAGNA, ANGELA MARIE	
BROWN RUDNICK LLP ONE FINANCIAL CENTER BOSTON, MA 02111			ART UNIT 1637	PAPER NUMBER

DATE MAILED: 08/19/2020

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 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. 16/017,340	Applicant(s) AMORESE et al.	
	Examiner Angela Bertagna	Art Unit 1637	AIA (FITF) 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 Applicant's responses filed on 7/28/20 and 7/29/20.
☐ 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 51-66 and 68-70. 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 a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ 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 _____.
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/ANGELA M. BERTAGNA/
Primary Examiner, Art Unit 1637

DETAILED CORRESPONDENCE

Notice of Pre-AIA or AIA Status

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

Status of the Application

2. Applicant's response filed on July 28, 2020 has been entered. Claims 51-66 and 68-70 are pending.

As discussed in greater detail below, Applicant's response has overcome all of the outstanding issues.

Terminal Disclaimer

3. The terminal disclaimer filed on July 29, 2020 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US 10,036,012 B2 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The terminal disclaimer filed on July 29, 2020 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US 9,650,628 B2 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Response to Amendment

4. The declaration of Dr. Andrew Brooks, filed on July 28, 2020, under 37 CFR 1.132 is sufficient to overcome all of the rejections made previously under 35 U.S.C. 103(a) citing Jones and Tucker as the primary combination of references.

Response to Arguments

5. Applicant's arguments filed on July 28, 2020 have been fully considered.

Objection to the Specification

Applicant argues that the objection should be withdrawn in view of the amendment to the specification (Remarks, page 6).

This argument was persuasive. The objection has been withdrawn.

Claim Objections

Applicant argues that the objections to claims 51, 56-58, 61, and 64 should be withdrawn in view of the claim amendments (Remarks, page 6).

This argument was persuasive. All of the previously made objections have been withdrawn.

Rejection of claims 59 and 66 under pre-AIA 35 U.S.C. 112, second paragraph

Applicant argues that the rejection should be withdrawn in view of the claim amendments (Remarks, pages 6-7).

This argument was persuasive. The rejection has been withdrawn.

Rejections of claims 51-70 under pre-AIA 35 U.S.C. 103(a) citing Jones and Tucker as the primary combination of references

Applicant's argument, see pages 10-11 of the Remarks, that the rejections should be withdrawn in view of the declaration evidence, was persuasive. All of the obviousness rejections made previously have been withdrawn.

Applicant's additional arguments on pages 7-10 of the Remarks have been considered, but they are moot since the rejections have been withdrawn in view of the declaration evidence.

Double Patenting

Applicant argues that the nonstatutory double patenting rejections citing US 10,036,012 and US 9,650,628 should be withdrawn in view of the terminal disclaimer submission (Remarks, pages 11-12).

As noted above, the terminal disclaimer was proper. The rejections have been withdrawn accordingly.

Allowable Subject Matter

6. Claims 51-66 and 68-70 are allowed.

Conclusion

7. 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 <https://ppair-my.uspto.gov/pair/PrivatePair>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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