IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca, et al.	ART UNIT:	Not Yet Assigned
SERIAL NUMBER:	Continuation of 14/854,629	CONF. NO.:	Not Yet Assigned
FILING DATE:	January 14, 2021	EXAMINER:	Not Yet Assigned
TITLE:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION		

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

FILED ELECTRONICALLY

PRELIMINARY AMENDMENT

Prior to examination of the above U.S. nonprovisional patent application, please amend the specification and claims and consider the following remarks.

Amendments to the specification begin on page 2.

Amendments to the claims begin on page 3.

Remarks begin on page 5.

Applicant believes that no fee is due with respect to this Preliminary Amendment. Nevertheless, if any fee is due, Applicants authorize such fee to be charged to Deposit Account No. 50-0369.

Amendments to the Specification

Please amend the "Related Application" section on page 1, lines 3-6 of the as-filed specification as follows and indicated by the marked changes:

Related Applications

The present application is a continuation application of U.S. patent application serial number 14/854,629, filed September 15, 2015, which is a divisional application of U.S. patent application serial number 13/081,660, filed April 7, 2011, which claims the benefit of and priority to U.S. provisional patent application serial number 61/426,817, filed December 23, 2010, the contents of each of which [[is]]are incorporated by reference herein in [[its]]their entirety.

An unmarked copy of the as-amended paragraph is provided below:

Related Applications

The present application is a continuation application of U.S. patent application serial number 14/854,629, filed September 15, 2015, which is a divisional application of U.S. patent application serial number 13/081,660, filed April 7, 2011, which claims the benefit of and priority to U.S. provisional patent application serial number 61/426,817, filed December 23, 2010, the contents of each of which are incorporated by reference herein in their entirety.

Amendments to the Claims:

Please amend the claims as follows.

1-46. (Canceled)

47. (New) A method for reducing template cross-over error introduced during sequencing workflow, the method comprising the steps of

incorporating at least two members of a plurality of identifier sequences into template nucleic acid obtained from at least two different samples, wherein said two members constitute a distinct pair associated with said template;

combining said nucleic acid templates into a single sample;

amplifying said nucleic acid templates thereby to form clusters, at least one of which comprises a chimeric sequence comprising a combination of identifier sequences that are different than any of said distinct pairs;

sequencing amplicons obtained in said amplifying step; and

discarding sequence reads obtained in said sequencing step that contain said combination of identifier sequences that are different than any of said distinct pairs, thereby to reduce cross-over error.

48. (New) The method of claim 47, wherein the identifier sequences are nucleic acid sequence tags.

49. (New) The method of claim 47, wherein the identifiers are first and second barcode sequences.

50. (New) The method of claim 47, wherein a first identifier sequence is incorporated into a 5' portion of the template, and a second identifier sequence is incorporated into a 3' portion of the template.

51. (New) The method of claim 50, wherein after incorporation of the identifier sequences, the template has the following configuration from 5' to 3': a first known sequence; a first

barcode sequence; a second known sequence; a target polynucleotide sequence; a third known sequence; a second barcode sequence; and a fourth known sequence.

52. (New) The method of claim 47, wherein a first identifier sequence is incorporated into a 5' end of the template, and a second identifier sequence is incorporated into a 3' end of the template.

53. (New) The method of claim 47, wherein prior to said sequencing step, the analyte is attached to a substrate.

54. (New) The method of claim 53, wherein the analyte is directly attached to the substrate.

Remarks

Amendments to the specification

Applicant submits a continuation of parent application patent application serial no. 14/854,629. With entry of this amendment, applicant has amended the specification to reflect priority information for this application.

No new matter is added.

Amendments to the claims

With entry of this amendment, claims 1-46 are cancelled and new claims 47-54 are added, with claim 47 being the only independent claim. Support for the amendments can be found throughout the application as-filed, including at page 2, lines 10-14, in which applicant recites the use of unique pairs of identifiers, and lines 17-25, in which applicant recites that error is determined in the presence of combinations of identifiers that were not in the starting population ("incorrect pairs"). Additional support is found at, for example, pages 8-9, and 12 and through the detailed description of the invention.

No new matter is added.

Summary

If there are any questions regarding these remarks, the Examiners are invited and encourage to contact applicant's representatives at the telephone number provided.

Dated: January 14, 2021

Respectfully submitted,
BROWN RUDNICK LLP

BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
Tel: 617-856-8483
Fax: 617-856-8201

/Thomas C. Meyers/
Thomas C. Meyers, Reg. No. 36,989
Attorney for Applicant
Email: tmeyers@brownrudnick.com

63792301

Illumina Exhibit 1007, Page 5 of 363

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers/Aditya Ramanathan
Attorney Docket Number:	MLB-001/03US 34468/41

Filed as Small Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	80	80
UTILITY SEARCH FEE	2111	1	350	350
UTILITY EXAMINATION FEE	2311	1	400	400
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2100	2100
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**3000**

Electronic Acknowledgement Receipt	
EFS ID:	41651446
Application Number:	17149504
International Application Number:	
Confirmation Number:	2551
Title of Invention:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Casey Suda
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-001/03US 34468/41
Receipt Date:	14-JAN-2021
Filing Date:	
Time Stamp:	18:28:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$3000
RAM confirmation Number	E20211DI29465099
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	34468_41US_-_Application_Data_Sheet_Fillable_PDF.pdf	1255878 a3b20a9bf24bd46a8876f93d59c717dfdbbe3ab1	no	9
Warnings:					
Information:					
2		MLB-001-03US_APPLICATION.pdf	1835058 fd275843586c9782c0634fdf3a657cba82a01514	yes	35

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	28
	Claims	29	34
	Abstract	35	35

Warnings:					
Information:					
3	Drawings-only black and white line drawings	MLB-001-03US_FIGURES.pdf	40661 67c94edc4ca64b4809c1275eb828c843ad48a51b	no	3
Warnings:					
Information:					
4	TrackOne Request	MLB-001-03US_PRIORITY_EXAM_REQUEST.pdf	120369 27d12c283c8cd7cd38dbb1a27e99d25201362477	no	1
Warnings:					
Information:					
5	Oath or Declaration filed	MLB-001-03US_DECS.pdf	316362 6bddef43bb0f81d671c4fca9d60989db6365b092	no	3

Warnings:					
Information:					
6		MLB-001-03US-Preliminary-Amendment.pdf	127965 d3e77b8c3f2bc3c0c6594cc9d4de621b2eedd071	yes	5
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Preliminary Amendment		1	1	
	Specification		2	2	
	Claims		3	4	
	Applicant Arguments/Remarks Made in an Amendment		5	5	
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	39993 831a0c6bf22e6ce7dfcff0040ca6dc60abe87bf9	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3736286		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MLB-001/03US 34468/41
	Application Number	
Title of Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Gregory		Porreca	

Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
Cambridge	MA	US

Mailing Address of Inventor:

Address 1	57 Reservoir Street
Address 2	
City	Cambridge
State/Province	MA
Postal Code	02138
Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mark		Umbarger	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
Brookline	MA	US

Mailing Address of Inventor:

Address 1	5 Winchester Street
Address 2	Unit 101
City	Brookline
State/Province	MA
Postal Code	02446
Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	George		Church	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

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	Application Number	
Title of Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION	

City	Brookline	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	218 Kent Street		
Address 2			
City	Brookline	**State/Province**	MA
Postal Code	02146	**Country**	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	21710		
Email Address	ip@brownrudnick.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION		
Attorney Docket Number	MLB-001/03US 34468/41	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	3	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	21710		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove

Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	14/854629	2015-09-15

Prior Application Status	Patented	Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/854629	Division of	13/081660	2011-04-07	9163281	2015-10-20

Prior Application Status	Expired	Remove

Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13/081660	Claims benefit of provisional	61/426817	2010-12-23

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MLB-001/03US 34468/41
	Application Number	
Title of Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MLB-001/03US 34468/41
	Application Number	
Title of Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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	Application Number	
Title of Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Molecular Loop Biosolutions		
Mailing Address Information For Applicant:			
Address 1	67 Reservoir Street		
Address 2			
City	Cambridge	**State/Province**	MA
Country	US	Postal Code	02138
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. — Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MLB-001/03US 34468/41
	Application Number	
Title of Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Thomas C. Meyers/			Date (YYYY-MM-DD)	2021-01-14
First Name	Thomas	Last Name	Meyers	Registration Number	36,989

Additional Signature may be generated within this form by selecting the Add button. Add

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	MLB-001/03US 34468/41
		Application Number	
Title of Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION		

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METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

Related Application

The present application claims the benefit of and priority to U.S. provisional patent application serial number 61/426,817, filed December 23, 2010, the content of which is incorporated by reference herein in its entirety.

Field of the Invention

The invention generally relates to methods for maintaining the integrity and identification of a nucleic acid template in a multiplex sequencing reaction.

Background

Sequencing-by-synthesis involves template-dependent addition of nucleotides to a template/primer duplex. Nucleotide addition is mediated by a polymerase enzyme and added nucleotides may be labeled in order to facilitate their detection. Single molecule sequencing has been used to obtain high-throughput sequence information on individual DNA or RNA. The ability to multiplex samples, i.e., pool different patient samples, is important for decreasing costs and increasing the through-put of sequencing-by-synthesis platforms.

One issue that presents itself in a multiplex sequencing reaction is maintaining accurate identification of a sample throughout the sequencing process. Unfortunately, the sample preparation phase frequently introduces errors into the subsequent sequencing reaction. For example, template molecules may physically overlap on a substrate; and in some cases result in a detectable erroneous signal. In any sequencing process that requires high accuracy, such errors can have a significant impact on results. Next generation sequencing typically involves the generation of an in vitro library; arraying of nucleic acid templates into physically distinct locations on a solid support (and optional clonal amplification of the templates into spatially localized clusters); and the sequencing-by-synthesis reaction itself. Errors can occur during generation of the library, arraying and amplification steps that result in molecular overlap of different patient samples. For example, heteroduplexes, i.e., improper pairing of template

strands from different samples, may form during the amplification of the multiplexed samples. Molecular overlap during any of the first three steps in the process may lead to assigning sequencing data to the wrong patient sample. Other errors can be introduced due to incomplete amplification, stray labeled primers, and other sources that result in erroneous signal detection. In a single molecule sequencing protocol, such errors can have a significant affect on the results. Accordingly, methods for reducing or eliminating errors in such procedures are needed.

Summary

The invention generally provides methods for validating the results of a molecular detection assay and for enabling the detection of errors introduced in sample preparation. The invention is applicable to nucleic acid sequencing, protein detection, and other methods that involve precise measurement of the presence and/or amount of an analyte. The invention utilizes two or more identifiers that are uniquely associated with an analyte of interest, such that the identifiers will only be present when the analyte of interest is detected. In this way, false positive and/or false negative results are avoided by requiring concomitant detection of two or more independent markers associated with the analyte to be detected.

The invention is especially useful in multiplex next-generation sequencing applications in which errors can have a significant impact on results, but is also applicable across a broad range of detection assays, including protein detection assays. The invention is based upon using two or more identifiers, such as nucleic acid barcodes that are uniquely associated with an analyte to be detected. For example, in sequencing applications, a pair of barcodes are placed such that they flank the sequence of interest. The identifiers are unique to the sample, so that valid sequence data are confirmed by the presence of the pair of flanking identifiers. In contrast, template containing only one identifier or an incorrect pair (i.e., a pair or more of identifiers not associated with the same template) will be excluded from analysis. Thus, methods of the invention make it possible to determine whether the integrity of a sample was maintained during a multiplex sequencing reaction, and prevent the assigning of sequence data to the wrong sample.

In other applications, two or more nucleic acid tags are associated with a protein or other analyte of interest. Identification of the sequence tags confirms the accuracy of the detection of the protein. In this embodiment of the invention, a protein is captured by a binding agent, such as an antibody, that is coupled to at least two oligonucleotides of known sequence. The

identification of the captured protein is confirmed via sequencing of the tags that are uniquely associated with the binding agent. The presence of both sequence tags validates the capture of the target protein.

In protein detection, identifiers can also include detectable labels, antibodies, other proteins, including glycoproteins, vitamins, steroids, viral particles, and the like that bind specifically to a protein of interest. Detection of the identifiers validates that the protein of interest has been found.

In nucleic acid sequencing, preferred identifiers are nucleic acid barcodes. The barcodes can be of any appropriate length (e.g., from about 2 to about 50 nucleotides) and any number of barcode sequences can be used. Preferably, the barcodes are present in pairs that flank the template to be sequenced, or portions thereof. While the pair of barcodes associated with any given template is unique, individual barcode sequences can be used with multiple templates as long as no pair is used across two different samples. While it is possible, and may be preferred in some circumstances, to use more than two barcoded sequences or other identifiers, the invention will be exemplified using pairs of identifier molecules. In a preferred configuration, each template from a particular sample is associated with the same unique pair of barcode sequences. The pairs ideally flank the region of the template that is to be sequenced. Thus, the pairs can be contiguous with a region of interest or can be separated from the region of interest by spacers (which include intervening sequence in the template or inserted spacer sequence) or by naturally-occurring sequence. Other identifiers, such as nucleic acid binding proteins, optical labels, nucleotide analogs, and others known in the art can be used as identifiers according to the invention.

In certain aspects, methods of the invention involve obtaining a template nucleic acid, incorporating a pair of sequence identifiers into the template, and sequencing the template. Methods of the invention may further include directly or indirectly attaching the template to a substrate. The template may be amplified prior to attachment to the substrate or may be amplified on the substrate after it has been attached to the substrate. In particular embodiments, the template is amplified after it has been attached to the substrate. In other embodiments, the template is amplified before being attached to the substrate and is also subsequently amplified after it has been attached to the substrate.

Identifiers can be incorporated anywhere on a template. For example, a first identifier can be incorporated into a 5' end of the template and a second identifier can incorporated into a 3' end of the template. The first and second identifiers are designed such that each set of identifiers is correlated to a particular sample (e.g., material obtained from a particular patient or group of patients), allowing samples to be distinguished and/or validated. The first and second identifiers may be the same or different, so long as the combination is unique with respect to the sample or sub-sample that one seeks to distinguish and/or validate.

After identifiers have been incorporated into the template, the template is sequenced. Sequencing may be by any method known in the art. Sequencing-by-synthesis is a common technique used in next generation procedures and works well with the instant invention. However, other sequencing methods can be used, including sequence-by-ligation, sequencing-by-hybridization; gel-based techniques and others. In general, sequencing involves hybridizing a primer to a template to form a template/primer duplex, contacting the duplex with a polymerase in the presence of a detectably-labeled nucleotides under conditions that permit the polymerase to add nucleotides to the primer in a template-dependent manner. Signal from the detectable label is then used to identify the incorporated base and the steps are sequentially repeated in order to determine the linear order of nucleotides in the template. Exemplary detectable labels include radiolabels, florescent labels, enzymatic labels, etc. In particular embodiments, the detectable label may be an optically detectable label, such as a fluorescent label. Exemplary fluorescent labels include cyanine, rhodamine, fluorescien, coumarin, BODIPY, alexa, or conjugated multi-dyes.

Numerous techniques are known for detecting sequence and for identifying barcodes and some are exemplified below. However, the exact means for detecting and compiling sequence data does not affect the function of the invention described herein.

If the analyte to be detected is not a nucleic acid, the identifiers can still be nucleic acid barcodes that are associated with the analyte binding moiety. Sequencing of the barcodes then validates detection of the analyte (i.e., the presence of two or more barcodes in association with the binder must be detected in order to validate the detection). In protein detection, the idenfiers can also be part of the primary structure of the protein to be detected. In this embodiment, the amino acid sequence of the protein is determined (e.g., by mass spectrometry or Edman

degradation). The embedded amino acid sequence identifiers would have to be present in the amino acid sequence in order to validate the identity of the protein.

Brief Description of the Drawings

Figure 1 is a set of drawings showing how molecular overlap can lead to apparent high quality, but incorrect sequence data.

Figure 2 is a set of drawings depicting how methods of the invention allow one to detect, during analysis, whether the integrity of a patient's sample was maintained during a multiplex sequencing reaction.

Figure 3 is a graph showing that methods of the invention dramatically reduce false positives in a multiplex sequencing reaction.

Detailed Description

Methods of the invention relate to validating and maintaining the integrity of a nucleic acid template in a multiplex sequencing reaction. Methods of the invention involve obtaining a template nucleic acid, incorporating a pair of sequence identifiers into the template, and sequencing the template.

Reference is now made to Figure 1, which shows a set of drawings depicting one example of how molecular overlap can lead to apparent high quality, but incorrect sequence data. Panel 1 shows the pooling of nucleic acid libraries from two patient samples, A and B. Each template has a gene fragment from that patient (e.g., GA), and a molecular barcode specific to that patient (e.g., A). As shown in panel 1, nucleic acids from patient A's sample include a barcode A and a gene fragment GA, and nucleic acids from patient B's sample include nucleic a barcode B and a gene fragment GB.

Panel 2 shows that after pooling, the samples are then hybridized to primers at discrete locations on a flow cell. In this figure, the nucleic acid from patient A and the nucleic acid from patient B land within a cluster radius on the solid support. When the amplification process begins, primers attached to the solid support extend on each template. In one case (patient A's nucleic acid template), the primer extends across a full length of the template. In the other case (patient B's nucleic acid template), the primer partially extends, incorporating the sequence of

barcode B and common priming sequence, but not the gene fragment sequence GB from patient B's nucleic acid template.

Panel 3 shows an example of improper molecular overlap. After extension, the duplexes are denatured and re-annealed for another amplification cycle. This example shows improper molecular overlap via formation of a heteroduplex between patient A's nucleic acid template and patient B's nucleic acid template. In this example, strand *i* hybridizes to strand *ii*, forming a bridge. Barcode regions of each strand are not complementary, but the strands still hybridize because of the amount of common priming sequence on both sides of the barcode. Consequently, a polymerase will extend strand *ii*, copying patient A's gene fragment onto a strand containing patient B's barcode. A chimeric molecule has been formed.

Panel 4 shows the results of this molecular overlap. Strand *ii* contains the barcode for patient B but the gene fragment for patient A. During the sequencing process, patient A's sequence data will be improperly and incorrectly associated with patient B. If the chimeric molecule is formed early in the amplification process, it can dominate the cluster of amplification products, leading to a homogenous clonal chimeric cluster. During sequencing, this would give a high-quality signal, but the data will be assigned to the wrong sample because it has become associated with the wrong barcode.

Reference is now made to Figure 2, which shows a set of drawings depicting how methods of the invention allow one to detect, during analysis, whether the integrity of a patient's sample was maintained during a multiplex sequencing reaction. Panel 1 shows the pooling of nucleic acid libraries from two patient samples, A and B. Each template has a gene fragment from that patient (e.g., GA), and a pair of sequence identifiers (first and second) specific to that patient (e.g., A1 and A2).

The first and second identifiers are designed such that each set of identifiers is correlated to a particular patient, allowing patient samples to be distinguished. The first and second identifiers may be the same. Alternatively, the first and second identifiers may be different. In certain embodiments, the pair of identifiers are first and second barcode sequences that are attached to the template. The barcode sequences may be attached to the template such that a first barcode sequence is attached to a 5' end of the template and a second barcode sequence is attached to a 3' end of the template. The first and second barcode sequences may be the same, or they may be different.

In this figure, the sequence identifiers are pairs of barcode sequences. This figure also shows that the pair of barcode sequences are attached to the nucleic acid template at the 5' and the 3' ends of the template, such that the barcode sequences flank the gene fragment of each template. As shown in panel 1, the pool includes patient A's sample which is nucleic acid templates having barcode sequences A1 and A2 that flank gene fragment GA, and also includes patient B's sample which is nucleic acid templates having barcode sequences B1 and B2 and gene fragment GB.

Panel 2 shows that after pooling, the samples are then hybridized to primers at discrete locations on a flow cell. In this figure, the nucleic acid from patient A and the nucleic acid from patient B land within a cluster radius on the solid support. When the amplification process begins, primers attached to the solid support extend on each template. In one case (patient A's nucleic acid template), the primer extends across a full length of the template. In the other case (patient B's nucleic acid template), the primer partially extends, incorporating the sequence of barcode B2 and common priming sequence, but not the gene fragment sequence GB from patient B's nucleic acid template or the sequence of barcode B1.

Panel 3 shows an example of improper molecular overlap. After extension, the duplexes are denatured and re-annealed for another amplification cycle. This example shows improper molecular overlap via formation of a heteroduplex between patient A's nucleic acid template and patient B's nucleic acid template. In this example, strand *i* hybridizes to strand *ii*, forming a bridge. Barcode regions A2 and B2 of each strand are not complementary, but the strands still hybridize because of the amount of common priming sequence on both sides of the barcode. Consequently, a polymerase will extend strand *ii*, copying patient A's gene fragment. However, in the case of two barcodes, only one of patient B's barcodes (B2) will be contained in the copied strand. The other barcode will be one of patient A's barcode sequences (A1). Unlike the example in Figure 1, the chimeric molecule formed in this example includes one barcode sequence from patient A (A1) and one barcode sequence from patient B (B2).

Panel 4 shows the results of this molecular overlap. While strand *ii* contains the gene fragment for patient A, it contains only one of patient B's barcodes (B2). The other barcode will be one of patient A's barcode sequences (A1). While each barcode sequence on its own is a valid barcode sequence, taken together, the two barcode sequences do not form a valid barcode sequence pair. During the sequencing process, this would yield a high-quality signal, but during

data analysis the molecules would be recognized as invalid because the data contains an invalid barcode sequence pair, i.e., it is known that barcode sequence A1 should not be seen together with barcode sequence B2 and hence a crossover has occurred. Thus during analysis, it is determined that the integrity of the patient's sample was not maintained and the data can then be excluded from final analysis.

Figure 3 is a graph showing that methods of the invention dramatically reduce false positives in a multiplex sequencing reaction. Two sample preparation procedures were performed prior to conducting a sequencing reaction as described herein. In the first sample preparation, only a single barcode sequence was attached to template molecules from different samples prior to pooling and then sequencing. In the second sample preparation, two barcode sequences were attached to template molecules from different samples prior to pooling and then sequencing.

Data in Figure 3 show that with use of only a single barcode sequence per template molecule, molecular overlap can lead to apparent high quality, but incorrect sequence data (diamond points). A single barcode sequence was attached to nucleic acids from sample A and a different single barcode sequence was attached to nucleic acids from sample B. The barcoded templates from each sample (A and B) were then pooled. After pooling, the samples were then hybridized to primers at discrete locations on a flow cell. Without being limited by any particular theory or mechanism of action, the data in Figure 3 suggest that the nucleic acid from sample A and the nucleic acid from sample B landed within a cluster radius on the solid support. When the amplification process began, primers attached to the solid support extended on each template. In some instances, the primer partially extended, incorporating the sequence of barcode B and common priming sequence, but not the gene fragment sequence of sample B.

After extension, the duplexes were denatured and re-annealed for another amplification cycle. In certain cases, a heteroduplex between sample A's nucleic acid template and sample B's nucleic acid template was formed. The barcode regions of each strand were not complementary, but the strands still hybridized because of the amount of common priming sequence on both sides of the barcode. Consequently, a polymerase extended the strand copying sample A's gene fragment onto a strand containing sample B's barcode. A chimeric molecule was formed. During the sequencing process, sample A's sequence data improperly and incorrectly associated with sample B. Since the chimeric molecule was formed early in the amplification process, it

dominated the cluster of amplification products, leading to a homogenous clonal chimeric cluster. During sequencing, this gave a high-quality signal, but the data was assigned to the wrong sample because it had become associated with the wrong barcode. See Figure 3, diamond points.

Figure 3 also provides data showing that methods of the invention dramatically reduce false positives in a multiplex sequencing reaction (square points). A pair of barcode sequences (A1 and A2 and B1 and B2) were attached to nucleic acids from two different samples, samples A and B. The pair of barcode sequences were attached to the nucleic acid templates at the 5' and the 3' ends of each template, such that the barcode sequences flanked the gene fragment of each template.

The barcoded templates from each sample (A and B) were then pooled. After pooling, the samples were then hybridized to primers at discrete locations on a flow cell. Without being limited by any particular theory or mechanism of action, the data in Figure 3 suggest that the nucleic acid from sample A and the nucleic acid from sample B landed within a cluster radius on the solid support. When the amplification process began, primers attached to the solid support extended on each template. In certain instances, the primer partially extended, incorporating the sequence of barcode B2 and common priming sequence, but not the gene fragment sequence from sample B's nucleic acid template or the sequence of barcode B1.

After extension, the duplexes were denatured and re-annealed for another amplification cycle. In this example, template from sample A and template from sample B hybridized, forming a bridge. Barcode regions A2 and B2 of each strand were not complementary, but the strands still hybridized because of the amount of common priming sequence on both sides of the barcode. Consequently, a polymerase extended the strand, copying sample A's gene fragment. However, in the case of two barcodes, only one of sample B's barcodes (B2) was contained in the copied strand. The other barcode was one of sample A's barcode sequences (A1). Unlike the single barcode amplification reaction, the chimeric molecule formed in this amplification reaction included one barcode sequence from sample A (A1) and one barcode sequence from sample B (B2).

While each barcode sequence on its own was a valid barcode sequence, taken together, the two barcode sequences did not form a valid barcode sequence pair. During the sequencing process, this yielded a high-quality signal, but during data analysis the molecules were

recognized as invalid because the data contained an invalid barcode sequence pair, i.e., it was known that barcode sequence A1 should not be seen together with barcode sequence B2 and hence a crossover has occurred. Thus during analysis, it was determined that the integrity of the patient's sample was not maintained and the data was excluded from final analysis (square points in Figure 3). Thus, data herein show that methods of the invention dramatically reduce crossover rate. High crossover rate makes it more likely that false positives and/or false negatives will occur.

The following sections discuss general considerations for barcode sequences, attaching barcode sequences to nucleic acid templates, and nucleic acid sequencing, for example, template considerations, polymerases useful in sequencing-by-synthesis, choice of surfaces, reaction conditions, signal detection and analysis.

Nucleic Acid Templates

Nucleic acid templates include deoxyribonucleic acid (DNA) and/or ribonucleic acid (RNA). Nucleic acid templates can be synthetic or derived from naturally occurring sources, or may include both synthetic and natural sequence; and may include PCR product. In one embodiment, nucleic acid template molecules are isolated from a biological sample containing a variety of other components, such as proteins, lipids and non-template nucleic acids. Nucleic acid template molecules can be obtained from any cellular material, obtained from an animal, plant, bacterium, fungus, or any other cellular organism. Biological samples for use in the present invention include viral particles or preparations. Nucleic acid template molecules can be obtained directly from an organism or from a biological sample obtained from an organism, e.g., from blood, urine, cerebrospinal fluid, seminal fluid, saliva, sputum, stool and tissue. Any tissue or body fluid specimen may be used as a source for nucleic acid for use in the invention. Nucleic acid template molecules can also be isolated from cultured cells, such as a primary cell culture or a cell line. The cells or tissues from which template nucleic acids are obtained can be infected with a virus or other intracellular pathogen. A sample can also be total RNA extracted from a biological specimen, a cDNA library, viral, or genomic DNA.

Nucleic acid obtained from biological samples typically is fragmented to produce suitable fragments for analysis. In one embodiment, nucleic acid from a biological sample is fragmented by sonication. Nucleic acid template molecules can be obtained as described in U.S. Patent

Application Publication Number US2002/0190663 A1, published Oct. 9, 2003. Generally, nucleic acid can be extracted from a biological sample by a variety of techniques such as those described by Maniatis, et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor, N.Y., pp. 280-281 (1982). Generally, individual nucleic acid template molecules can be from about 1 base to about 20 kb. Nucleic acid molecules may be single-stranded, double-stranded, or double-stranded with single-stranded regions (for example, stem- and loop-structures).

A biological sample as described herein may be homogenized or fractionated in the presence of a detergent or surfactant. The concentration of the detergent in the buffer may be about 0.05% to about 10.0%. The concentration of the detergent can be up to an amount where the detergent remains soluble in the solution. In a preferred embodiment, the concentration of the detergent is between 0.1% to about 2%. The detergent, particularly a mild one that is nondenaturing, can act to solubilize the sample. Detergents may be ionic or nonionic. Examples of nonionic detergents include triton, such as the Triton® X series (Triton® X-100 t-Oct-C_6H_4-$(OCH_2$-$CH_2)_xOH$, x=9-10, Triton® X-100R, Triton® X-114 x=7-8), octyl glucoside, polyoxyethylene(9)dodecyl ether, digitonin, IGEPAL® CA630 octylphenyl polyethylene glycol, n-octyl-beta-D-glucopyranoside (betaOG), n-dodecyl-beta, Tween® 20 polyethylene glycol sorbitan monolaurate, Tween® 80 polyethylene glycol sorbitan monooleate, polidocanol, n-dodecyl beta-D-maltoside (DDM), NP-40 nonylphenyl polyethylene glycol, C12E8 (octaethylene glycol n-dodecyl monoether), hexaethyleneglycol mono-n-tetradecyl ether (C14EO6), octyl-beta-thioglucopyranoside (octyl thioglucoside, OTG), Emulgen, and polyoxyethylene 10 lauryl ether (C12E10). Examples of ionic detergents (anionic or cationic) include deoxycholate, sodium dodecyl sulfate (SDS), N-lauroylsarcosine, and cetyltrimethylammoniumbromide (CTAB). A zwitterionic reagent may also be used in the purification schemes of the present invention, such as Chaps, zwitterion 3-14, and 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulf-onate. It is contemplated also that urea may be added with or without another detergent or surfactant.

Lysis or homogenization solutions may further contain other agents, such as reducing agents. Examples of such reducing agents include dithiothreitol (DTT), .beta.-mercaptoethanol, DTE, GSH, cysteine, cysteamine, tricarboxyethyl phosphine (TCEP), or salts of sulfurous acid.

Barcode Sequences

In certain embodiments, the sequence identifiers are barcode sequences that are attached to or incorporated into a nucleic acid template. The barcode sequences may be attached to the template such that a first barcode sequence is attached to a 5' end of the template and a second barcode sequence is attached to a 3' end of the template. The first and second barcode sequences may be the same, or they may be different. Barcode sequence may be incorporated into a contiguous region of a template that includes the target to be sequenced.

Exemplary methods for designing sets of barcode sequences and other methods for attaching barcode sequences are shown in U.S. paten numbers 6,138,077; 6,352,828; 5,636,400; 6,172,214; 6235,475; 7,393,665; 7,544,473; 5,846,719; 5,695,934; 5,604,097; 6,150,516; RE39,793; 7,537,897; 6172,218; and 5,863,722, the content of each of which is incorporated by reference herein in its entirety.

The barcode sequence generally includes certain features that make the sequence useful in sequencing reactions. For example the barcode sequences can be designed to have minimal or no homopolymer regions, i.e., 2 or more of the same base in a row such as AA or CCC, within the barcode sequence. The barcode sequences can also be designed so that they do not overlap the target region to be sequence or contain a sequence that is identical to the target.

The first and second barcode sequences are designed such that each pair of sequences is correlated to a particular sample, allowing samples to be distinguished and validated. Methods of designing sets of barcode sequences is shown for example in Brenner et al. (U.S. patent number 6,235,475), the contents of which are incorporated by reference herein in their entirety. In certain embodiments, the barcode sequences range from about 2 nucleotides to about 50; and preferably from about 4 to about 20 nucleotides. Since the barcode sequence is sequenced along with the template nucleic acid or may be sequenced in a separate read, the oligonucleotide length should be of minimal length so as to permit the longest read from the template nucleic acid attached. Generally, the barcode sequences are spaced from the template nucleic acid molecule by at least one base.

Methods of the invention involve attaching the barcode sequences to the template nucleic acids. Template nucleic acids are able to be fragmented or sheared to desired length, e.g. generally from 100 to 500 bases or longer, using a variety of mechanical, chemical and/or enzymatic methods. DNA may be randomly sheared via sonication, exposed to a DNase or one or more restriction enzymes, a transposase, or nicking enzyme. RNA may be fragmented by

brief exposure to an RNase, heat plus magnesium, or by shearing. The RNA may be converted to cDNA before or after fragmentation.

Barcode sequence is integrated with template using methods known in the art. Barcode sequence is integrated with template using, for example, a ligase, a polymerase, Topo cloning (e.g., Invitrogen's topoisomerase vector cloning system using a topoisomerase enzyme), or chemical ligation or conjugation. The ligase may be any enzyme capable of ligating an oligonucleotide (RNA or DNA) to the template nucleic acid molecule. Suitable ligases include T4 DNA ligase and T4 RNA ligase (such ligases are available commercially, from New England Biolabs). Methods for using ligases are well known in the art. The polymerase may be any enzyme capable of adding nucleotides to the 3' and the 5' terminus of template nucleic acid molecules. Barcode sequence can be incorporated via a PCR reaction as part of the PCR primer.

The ligation may be blunt ended or via use of over hanging ends. In certain embodiments, following fragmentation, the ends of the fragments may be repaired, trimmed (e.g. using an exonuclease), or filled (e.g., using a polymerase and dNTPs), to form blunt ends. Upon generating blunt ends, the ends may be treated with a polymerase and dATP to form a template independent addition to the 3'-end and the 5-end of the fragments, thus producing a single A overhanging. This single A is used to guide ligation of fragments with a single T overhanging from the 5'-end in a method referred to as T-A cloning.

Alternatively, because the possible combination of overhangs left by the restriction enzymes are known after a restriction digestion, the ends may be left as is, i.e., ragged ends. In certain embodiments double stranded oligonucleotides with complementary over hanging ends are used.

Surface Attachment

Methods of the invention may involve attaching or immobilizing barcoded nucleic acid templates to solid supports. Such methods are described for example in Sabot et al. (U.S. patent application number 2009/0226975), Adessi et al. (U.S. patent number 7,115,400), and Kawashima et al. (U.S. patent application number 2005/0100900), the content of each of which is incorporated by reference herein in its entirety.

The term immobilized as used herein is intended to encompass direct or indirect attachment to a solid support via covalent or non-covalent bond(s). In certain embodiments of

the invention, covalent attachment may be used, but generally all that is required is that template remain immobilized on the support. Typically oligonucleotides are immobilized such that a 3' end is available for enzymatic extension and at least a portion of the sequence is capable of hybridizing to a complementary sequence. Immobilization can occur via hybridization to a surface attached oligonucleotide. Alternatively, immobilization can occur by means other than base-pairing hybridization, such as the covalent attachment set forth above.

Substrates or supports for use in the invention include, but are not limited to, latex beads, dextran beads, polystyrene surfaces, polypropylene surfaces, polyacrylamide gel, gold surfaces, glass surfaces and silicon wafers. In certain embodiments, the solid support may include an inert substrate or matrix that has been functionalized, for example by the application of a layer or coating of an intermediate material including reactive groups that permit covalent attachment to molecules such as polynucleotides.

Amplification

In certain embodiments, methods of the invention involve amplifying barcoded nucleic acid templates prior to sequencing the templates. Such methods are described for example in Sabot et al. (U.S. patent application number 2009/0226975), Adessi et al. (U.S. patent number 7,115,400), and Kawashima et al. (U.S. patent application number 2005/0100900), the content of each of which is incorporated by reference herein in its entirety.

Primer oligonucleotides or amplification sequences are polynucleotide sequences that are capable of annealing specifically to a single stranded polynucleotide sequence to be amplified under conditions encountered in a primer annealing step of an amplification reaction. Generally, the terms nucleic acid, polynucleotide and oligonucleotide are used interchangeably herein. The different terms are not intended to denote any particular difference in size, sequence, or other property unless specifically indicated otherwise. For clarity of description the terms may be used to distinguish one species of molecule from another when describing a particular method or composition that includes several molecular species.

Primers may additionally include non-nucleotide chemical modifications, for example to facilitate covalent attachment of the primer to a solid support. Certain chemical modifications may themselves improve the function of the molecule as a primer or may provide some other useful functionality, such as providing a cleavage site that enables the primer (or an extended

polynucleotide strand derived therefrom) to be cleaved from a solid support. Useful chemical modifications can also provide reversible modifications that prevent hybridization or extension of the primer until the modification is removed or reversed. Similarly, other molecules attached to a surface in accordance with the invention can include cleavable linker moieties and or reversible modifications that alter a particular chemical activity of function of the molecule.

A plurality of oligonucleotides used in the methods set forth herein can include species that function as capture oligonucleotides. The capture oligonucleotides may include a template specific portion, namely a sequence of nucleotides capable of annealing to a primer binding sequence in a single stranded polynucleotide molecule of interest such as one that is to be amplified. The primer binding sequences will generally be of known sequence and will therefore be complementary to a region of known sequence of the single stranded polynucleotide molecule. The capture oligonucleotides may include a capture sequence and an amplification sequence. For example, a capture oligonucleotide may be of greater length than amplification primers that are attached to the same substrate, in which case the 5' end of the capture sequences may comprise a region with the same sequence as one of the amplification primers. A portion of a template, such as the 3' end of the template, may be complementary to the 3' of the capture sequences. The 5' end of the template may contain a region that comprises a sequence identical to one of the amplification primers such that upon copying the template, the copy can hybridize to the immobilized amplification primer. Thus, an oligonucleotide species that is useful in the methods set forth herein can have a capture sequence, an amplification sequence or both. Conversely, an oligonucleotide species can lack a capture sequence, an amplification sequence or both. In this way the hybridization specificity of an oligonucleotide species can be tailored for a particular application of the methods.

The length of primer binding sequences need not be the same as those of known sequences of polynucleotide template molecules and may be shorter, being particularly 16-50 nucleotides, more particularly 16-40 nucleotides and yet more particularly 20-30 nucleotides in length. The desired length of the primer oligonucleotides will depend upon a number of factors. However, the primers are typically long (complex) enough so that the likelihood of annealing to sequences other than the primer binding sequence is very low. Accordingly, known sequences that flank a template sequence can include a primer binding portion and other portions such as a capture sequence, barcode sequence or combination thereof.

In certain embodiments of the invention, amplification primers for solid phase amplification are immobilized by covalent attachment to the solid support at or near the 5' end of the primer, such that a portion of the primer is free to anneal to its cognate template and the 3' hydroxyl group is free to function in primer extension.

The chosen attachment chemistry will typically depend on the nature of the solid support and any functionalization or derivatization applied to it. In the case of nucleic acid embodiments, the primer itself may include a moiety which may be a non-nucleotide chemical modification to facilitate attachment. For example, the primer may include a sulfur containing nucleophile such as a phosphorothioate or thiophosphate at the 5' end. In the case of solid supported polyacrylamide hydrogels, this nucleophile may bind to a bromoacetamide group present in the hydrogel. In one embodiment, the means of attaching primers to the solid support is via St phosphorothioate attachment to a hydrogel comprised of polymerized acrylamide and N-(5-bromoacetamidylpentyl) acrylamide (BRAPA).

A uniform, homogeneously distributed lawn of immobilized oligonucleotides may be formed by coupling (grafting) a solution of oligonucleotide species onto the solid support. The solution can contain a homogenous population of oligonucleotides but will typically contain a mixture of different oligonucleotide species. The mixture can include, for example, at least two, three or more different species of oligonucleotide. Each surface that is exposed to the solution therefore reacts with the solution to create a uniform density of immobilized sequences over the whole of the exposed solid support. As such, a portion of the surface having a mixture of different immobilized sequences can be surrounded by an area of the surface having a mixture of the same immobilized sequences. A suitable density of amplification oligonucleotides is at least 1 fmol/mm^2 (6 x 10^{10} per cm^2), or more optimally at least 10 fmol/mm^2 (6 x 10^{11} per cm^2). The density of the capture oligonucleotides can be controlled to give an optimum cluster density of 10^6 - 10^9 clusters per cm^2 and optimum cluster brightness. The ratio of capture oligonucleotide species to the amplification oligonucleotide species can be any desired value including, but not limited to at least 1:100, 1:1000 or 1:100000 depending on the desired cluster density and brightness. Similar densities or ratios of other molecular species can be used in embodiments where molecules other than nucleic acids are attached to a surface.

In a particular embodiment, for each cluster of template molecules, a complementary copy of a single stranded polynucleotide template molecule is attached to the solid support by

hybridization. Methods of hybridization for formation of stable duplexes between complementary sequences by way of Watson-Crick base-pairing are known in the art. The immobilized capture oligonucleotides can include a region of sequence that is complementary to a region or template specific portion of the single stranded template polynucleotide molecule. An extension reaction may then be carried out in which the capture sequence is extended by sequential addition of nucleotides to generate a complementary copy of the single stranded polynucleotide sequence attached to the solid support via the capture oligonucleotide. The single stranded polynucleotide sequence not immobilized to the support may be separated from the complementary sequence under denaturing conditions and removed, for example by washing.

The terms separate and separating, when used in reference to strands of a nucleic acid, refer to the physical dissociation of the DNA bases that interact within for example, a Watson-Crick DNA-duplex of the single stranded polynucleotide sequence and its complement. The terms also refer to the physical separation of these strands. Thus, the term can refer to the process of creating a situation wherein annealing of another primer oligonucleotide or polynucleotide sequence to one of the strands of a duplex becomes possible. After the first extension reaction, the duplex is immobilized through a single 5' attachment, and hence strand separation can result in loss of one of the strands from the surface. In cases where both strands of the duplex are immobilized, separation of the strands means that the duplex is converted into two immobilized single strands.

In one aspect of the invention, one or more of the amplification primers can be modified to prevent hybridization of a region or template specific portion of the single stranded polynucleotide molecule. Alternatively or additionally, one or more of the amplification primers may be modified to prevent extension of the primer during one or more extension reactions, thus preventing copying of the hybridized templates. These modifications can be temporary or permanent.

Generally, the capture sequences will include a region of the same sequence as the plurality of amplification oligonucleotides. Once the 3' end of the extended immobilized template copy has hybridized to one of the amplification primers and been extended, the resulting duplex will be immobilized at both ends and all of the bases in the capture oligonucleotide sequence will have been copied. Thus the capture oligonucleotide may include both the amplification primer sequence, plus a further sequence that is complementary to the end

of the template. Typically the sequence complementary to the end of the template will not be present in any of the amplification primers. Alternatively, the amplification primers can contain the sequences complementary to the ends of the single stranded templates, but the amplification primers can be reversibly blocked to prevent hybridization and/or extension during one or more extension step, such as a first extension step in a particular amplification process.

According to one aspect of the invention, one or more of the amplification primers may include a modification that acts as a reversible block to either template hybridization or extension or both. By way of non-limiting example, such modifications can be presence of an additional sequence of nucleotides that is complementary to the amplification primer. This additional sequence can be present in a portion of the amplification primer and thus acts as an intramolecular hairpin duplex, or a 3' blocking group that prevents extension of the primer. Alternatively, the additional sequence can be found on a separate oligonucleotide that hybridizes to the amplification primer. A particular feature of such a modification is that it can be removed, altered or reversed such that the functionality of the modified primer oligonucleotide is restored and the primer is able to undergo hybridization and extension during later steps of the methods. Among other examples, the blocking group may be a small chemical species such as a 3' phosphate moiety that can be removed enzymatically, may be an a basic nucleotide such that the 3' end of the primer is not capable of hybridization (and thereby extension), or may be a sequence of nucleotides that can be selectively excised from the immobilized strands, for example, using restriction endonucleases that selectively cleave particular sequences or deglycosylases that selectively cleave oligonucleotides having exogenous bases such as uracil deoxyribonucleotides or 8-oxoguanine.

In one embodiment a plurality of three types of oligonucleotides (for example comprising capture sequences, forward and reverse primers) are immobilized to a solid support. Alternatively the three oligonucleotides may be forward amplification, blocked forward amplification and reverse amplification, where the unblocked forward primer acts as the capture sequence.

The single stranded polynucleotide molecules may have originated in single-stranded form, as DNA or RNA or may have originated in double-stranded DNA (dsDNA) form (e.g. genomic DNA fragments, PCR and amplification products and the like). Thus a single stranded polynucleotide may be the sense or antisense strand of a polynucleotide duplex. Methods of

preparation of single stranded polynucleotide molecules suitable for use in the method of the invention using standard techniques are well known in the art. The precise sequence of the primary polynucleotide molecules may be known or unknown during different steps of the methods set forth herein. It will be understood that a double stranded polynucleotide molecule can be hybridized to an immobilized capture oligonucleotide as exemplified herein for single stranded polynucleotide molecules, so long as a single stranded region of the double stranded polynucleotide is available and at least partially complementary to the capture oligonucleotide sequence.

An exemplary method for the isolation of one strand of a double stranded molecular construct is described herein. A sample of unknown sequence may be fragmented and have barcode sequences attached at both ends of the fragment. Adapters are then attached to the ends of each fragment. One strand of the adapters may contain a moiety for surface immobilization, for example a biotin that can be captured onto a streptavidin surface. The adapters may be mismatch adapters, for example as described in co-pending application US 2007/0128624, the contents of which are incorporated herein by reference in their entirety. Amplification of the mismatch or forked adapters using a pair of amplification primers, one of which carries a biotin modification means that one strand of each duplex carries a biotin modification. Immobilization of the strands onto a streptavidin surface means that the non-biotinylated strand can be eluted simply by denaturation/strand separation. The eluted constructs will be in single stranded form and upon exposure to hybridization conditions can be used to hybridize against the immobilized capture sequences which can be extended.

In a particular embodiment, the single stranded polynucleotide molecules are DNA molecules. More particularly, the single stranded polynucleotide molecules represent genomic DNA molecules, or amplicons thereof, which include both intron and exon sequence (coding sequence), as well as non-coding regulatory sequences such as promoter and enhancer sequences. Still yet more particularly, the single stranded polynucleotide molecules are human genomic DNA molecules, or amplicons thereof.

In a particular embodiment, a single stranded target polynucleotide molecule has at least two regions of known sequence. Yet more particularly, the 5' and 3' termini of the single stranded polynucleotide molecule will have the regions of known sequence such that the single stranded polynucleotide molecule will be of the structure:

5'[known sequence I]-[barcode sequence]-[known sequence II]-[target polynucleotide sequence]-[known sequence III]-[barcode sequence]-[known sequence IV]-3'

Typically "known sequence I", "known sequence II", "known sequence III", and "known sequence IV" will consist of more than 20, or more than 40, or more than 50, or more than 100, or more than 300 consecutive nucleotides. The precise length of the four sequences may or may not be identical. The primer binding sequences generally will be of known sequence and will therefore particularly be complementary to a sequence within ""known sequence I", "known sequence II", "known sequence III", and "known sequence IV" of the single stranded polynucleotide molecule. The length of the primer binding sequences need not be the same as those of known sequence I-IV, and may be shorter, being particularly 16-50 nucleotides, more particularly 16-40 nucleotides and yet more particularly 20-30 nucleotides in length. Known sequences I-IV can be the same or different for each other.

Methods of hybridization for formation of stable duplexes between complementary sequences by way of Watson-Crick base pairing are known in the art. A region or part of the single stranded polynucleotide template molecules can be complementary to at least a part of the immobilized capture sequence oligonucleotides. Since the amplification oligonucleotides are either modified to prevent hybridization and/or extension, or are non-complementary to the known ends of the template strands, only the capture sequences will be capable of hybridization and extension. An extension reaction may then be carried out wherein the capture sequence primer is extended by sequential addition of nucleotides to generate a complementary copy of the single stranded template polynucleotide attached to the solid support via the capture sequence oligonucleotide. The single stranded template polynucleotide sequence not immobilized to the support may be separated from the complementary sequence under denaturing conditions and removed, for example by washing. The distance between the individual capture sequence oligonucleotides on the surface therefore controls the density of the single stranded template polynucleotides and hence the density of clusters formed later on the surface is also controlled.

In certain embodiments in which the modified forward primer oligonucleotides are blocked and are unable to be extended, generally all of the amplification primer oligonucleotides

will hybridize to the single stranded template polynucleotides. When the extension reaction is carried out only the unmodified forward capture primer oligonucleotides are extended by sequential addition of nucleotides to generate a complementary copy of the single stranded template polynucleotide attached to the solid support via the unmodified forward primer oligonucleotide. The single stranded template polynucleotide sequences not hybridized to the support may be separated from the un-extended blocked forward primer oligonucleotides under denaturing conditions and removed, for example by washing with a chemical denaturant such as formamide. The distance between the individual unmodified forward primer oligonucleotides on the surface therefore controls the density of the single stranded template polynucleotides and hence the density of clusters formed later on the surface is also controlled.

Following the attachment of the complementary single stranded template polynucleotides, the modified/blocked primers can be treated to reverse, remove or alter the modification such that they become functionally equivalent to the unmodified forward primer oligonucleotides. For example, the double stranded structure may be removed either by denaturation, for example by heating or treatment with an alkaline solution when it is formed by a separate hybridized polynucleotide. Alternatively, where the hybridized polynucleotide is covalently linked, enzymatic digestion could be used to sequence-selectively cleave the strand, followed by denaturation. Such methods for removing the double stranded structure are known in the art and would be apparent to the skilled person (Sambrook and Russell, Molecular Cloning, A Laboratory Manual, third edition, Cold Spring Harbor Laboratory Press (2001)).

In one embodiment of the invention, the single stranded template polynucleotide molecule can be attached to the solid support by ligation to double stranded primers immobilized to the solid support using ligation methods known in the art (Sambrook and Russell, supra). Such methods utilize ligase enzymes such as DNA ligase to effect or catalyze the joining of the ends of the two polynucleotide strands, in this case, the single stranded template polynucleotide molecule and the primer oligonucleotide ligate such that covalent linkages are formed. In this context "joining" means covalent linkage of two polynucleotide strands that were not previously covalently linked. Thus, an aim of the invention can also be achieved by modifying the 3' end of a subset of primer oligonucleotides such that they are unable to ligate to the single stranded template polynucleotides. By way of non-limiting example, the addition of 2'3'dideoxy AMP (dideoxyAMP) by the enzyme terminal deoxynucleotidyl transferase (TdT) effectively prevents

T4 DNA ligase from ligating treated molecules together.

An alternative method would be to have the capture sequences as duplex strands and the amplification sequences as single strands. Upon ligation of the single strands to the capture duplexes (which would be the only immobilized species carrying a free 5' phosphate) the 3' end of the immobilized strand can be extended as described above. Upon denaturation of the hybridized template sequence, amplification of the immobilized strand can proceed as described. Other such methods for attaching single strands will be apparent to others skilled in the art.

In a next step according to particular embodiments of the present invention, suitable conditions are applied to the immobilized single stranded polynucleotide molecule and the plurality of amplification primer oligonucleotides such that the single stranded polynucleotide molecule hybridizes to an amplification primer oligonucleotide to form a complex in the form of a bridge structure. Suitable conditions such as neutralizing and/or hybridizing buffers are well known in the art (See Sambrook et al., supra; Ausubel et al., Current Protocols in Molecular Biology, John Wiley and Sons, Baltimore, Md. (1998)). The neutralising and/or hybridising buffer may then be removed.

Next by applying suitable conditions for extension an extension reaction is performed. The primer oligonucleotide of the complex is extended by sequential addition of nucleotides to generate an extension product complimentary to the single stranded polynucleotide molecule. The resulting duplex is immobilized at both 5' ends such that each strand is immobilized.

Suitable conditions such as extension buffers/solutions comprising an enzyme with polymerase activity are well known in the art (See Sambrook et al., supra; Ausubel et al. supra). In a particular embodiment dNTP's may be included in the extension buffer. In a further embodiment dNTP's could be added prior to the extension buffer. This bridge amplification technique can be carried out as described, for example, in Adessi et al. (U.S. patent number 7,115,400), and Kawashima et al. (U.S. patent application number 2005/0100900), the contents of which are incorporated herein by reference.

Examples of enzymes with polymerase activity which can be used in the present invention are DNA polymerase (Klenow fragment, T4 DNA polymerase), heat-stable DNA polymerases from a variety of thermostable bacteria (such as Taq, VENT, Pfu, or Tfl DNA polymerases) as well as their genetically modified derivatives (TaqGold, VENTexo, or Pfu exo). A combination of RNA polymerase and reverse transcriptase can also be used to generate the

extension products. Particularly the enzyme has strand displacement activity, more particularly the enzyme will be active at a pH of about 7 to about 9, particularly pH 7.9 to pH 8+, yet more particularly the enzymes are Est or Klenow.

The nucleoside triphosphate molecules used are typically deoxyribonucleotide triphosphates, for example dATP, dTTP, dCTP, dGTP, or are ribonucleoside triphosphates for example ATP, UTP, CTP, GTP, The nucleoside triphosphate molecules may be naturally or non-naturally occurring.

After the hybridization and extension steps, the support and attached nucleic acids can be subjected to denaturation conditions. A flow cell can be used such that, the extension buffer is generally removed by the influx of the denaturing buffer. Suitable denaturing buffers are well known in the art (See Sambrook et al., supra; Ausubel et al. supra). By way of example it is known that alterations in pH and low ionic strength solutions can denature nucleic acids at substantially isothermal temperatures. Formamide and urea form new hydrogen bonds with the bases of nucleic acids disrupting hydrogen bonds that lead to Watson-Crick base pairing. In a particular embodiment the concentration of formamide is 50% or more. These result in single stranded nucleic acid molecules. If desired, the strands may be separated by treatment with a solution of very low salt (for example less than 0.01 M cationic conditions) and high pH (>12) or by using a chaotropic salt (e.g. guanidinium hydrochloride). In a particular embodiment a strong base is used. A strong base is a basic chemical compound that is able to deprotonate very weak acids in an acid base reaction. The strength of a base is indicated by its pK.sub.b value, compounds with a pK_b value of less than about 1 are called strong bases and are well known to one skilled in the art. In a particular embodiment the strong base is Sodium Hydroxide (NaOH) solution used at a concentration of from 0.05 M to 0.25 M, particularly 0.1 M.

Following the hybridization, extension and denaturation steps exemplified above, two immobilized nucleic acids will be present, the first being the first template single stranded polynucleotide molecule (that was initially immobilized) and the second being a nucleic acid complementary thereto, extending from one of the immobilized primer oligonucleotides. Both the original immobilized single stranded polynucleotide molecule and the immobilized extended primer oligonucleotide formed are then able to initiate further rounds of amplification by subjecting the support to further cycles of hybridization, extension and denaturation.

It may be advantageous to perform optional washing steps in between each step of the

amplification method. For example an extension buffer without polymerase enzyme with or without dNTP's could be applied to the solid support before being removed and replaced with the full extension buffer.

Such further rounds of amplification can be used to produce a nucleic acid colony or cluster comprising multiple immobilized copies of the single stranded polynucleotide sequence and its complementary sequence.

The initial immobilization of the single stranded polynucleotide molecule means that the single stranded polynucleotide molecule can hybridize with primer oligonucleotides located at a distance within the total length of the single stranded polynucleotide molecule. Other surface bound primers that are out of reach will not hybridize to the polynucleotide. Thus the boundary of the nucleic acid colony or cluster formed is limited to a relatively local area surrounding the location in which the initial single stranded polynucleotide molecule was immobilized.

Once more copies of the single stranded polynucleotide molecule and its complement have been synthesized by carrying out further rounds of amplification, i.e. further rounds of hybridization, extension and denaturation, then the boundary of the nucleic acid colony or cluster being generated will be able to be extended further, although the boundary of the colony formed is still limited to a relatively local area around the location in which the initial single stranded polynucleotide molecule was immobilized. For example the size of each amplified cluster may be 0.5-5 microns.

It can thus be seen that the method of the present invention allows the generation of a plurality of nucleic acid colonies from multiple single immobilized single stranded polynucleotide molecules and that the density of these colonies can be controlled by altering the proportions of modified capture/amplification oligonucleotides used to graft the surface of the solid support.

In one embodiment, the hybridization, extension and denaturation steps are all carried out at the same, substantially isothermal temperature. For example the temperature is from 37°C to about 75°C, particularly from 50°C to 70°C, yet more particularly from 60°C to 65°C. In a particular embodiment the substantially isothermal temperature may be the optimal temperature for the desired polymerase.

In a particular aspect, the method according to the first aspect of the invention is used to prepare clustered arrays of nucleic acid colonies, analogous to those described in U.S. Pat. No.

7,115,400, US 2005/0100900 A1, WO 00/18957 and WO 98/44151 (the contents of which are herein incorporated by reference), by solid-phase amplification.

In yet another aspect more than one capture sequences and more than two amplification sequences, for example, at least three or four or more, different amplification primer sequences may be grafted to the solid support. In this manner more than one library, with common sequences which differ between the libraries, could be utilized to prepare clusters, such as, for example libraries prepared from two different patients. Whilst the cluster may overlap in space, they would be able to be sequenced one after the other due to the differences between the ends of the templates. For example, two different samples can be captured using two different capture sequences. These can be amplified from the same two amplification primers. The samples can be differentiated due to the two different capture sequences, which can be used as the sites for hybridization of two different sequencing primers. The use of different capture sequences thereby gives rise to a method of sample indexing using different sequencing primers.

Clustered arrays formed by the methods of the invention are suitable for use in applications usually carried out on ordered arrays such as micro-arrays. Such applications by way of non-limiting example include hybridization analysis, gene expression analysis, protein binding analysis, sequencing, genotyping, nucleic acid methylation analysis and the like. The clustered array may be sequenced before being used for downstream applications such as, for example, hybridization with fluorescent RNA or binding studies using fluorescent labelled proteins.

Sequencing Methods

The invention also encompasses methods of sequencing amplified nucleic acids generated by solid-phase amplification. Thus, the invention provides a method of nucleic acid sequencing comprising amplifying a pool of nucleic acid templates using solid-phase amplification as described above and carrying out a nucleic acid sequencing reaction to determine the sequence of the whole or a part of at least one amplified nucleic acid strand produced in the solid-phase amplification reaction.

Sequencing can be carried out using any suitable sequencing technique. A particularly useful method is one wherein nucleotides are added successively to a free 3’ hydroxyl group, resulting in synthesis of a polynucleotide chain in the 5' to 3' direction. The nature of the

nucleotide added may be determined after each nucleotide addition or at the end of the sequencing process. Sequencing techniques using sequencing by ligation, wherein not every contiguous base is sequenced, and techniques such as massively parallel signature sequencing (MPSS) where bases are removed from, rather than added to the strands on the surface are also within the scope of the invention.

The initiation point for the sequencing reaction may be provided by annealing of a sequencing primer to a product of the solid-phase amplification reaction. In this connection, one or both of the adaptors added during formation of the template library may include a nucleotide sequence which permits annealing of a sequencing primer to amplified products derived by whole genome or solid-phase amplification of the template library.

The products of solid-phase amplification reactions wherein both forward and reverse amplification primers are covalently immobilized on the solid surface are so-called bridged structures formed by annealing of pairs of immobilized polynucleotide strands and immobilized complementary strands, both strands being attached to the solid support at the 5' end. Arrays comprised of such bridged structures provide inefficient templates for typical nucleic acid sequencing techniques, since hybridization of a conventional sequencing primer to one of the immobilized strands is not favored compared to annealing of this strand to its immobilized complementary strand under standard conditions for hybridization.

In order to provide more suitable templates for nucleic acid sequencing, it may be advantageous to remove or displace substantially all or at least a portion of one of the immobilized strands in the bridged structure in order to generate a template which is at least partially single-stranded. The portion of the template which is single-stranded will thus be available for hybridization to a sequencing primer. The process of removing all or a portion of one immobilized strand in a `bridged` double-stranded nucleic acid structure may be referred to herein as linearization, and is described in further detail in WO07010251, the contents of which are incorporated herein by reference in their entirety.

Bridged template structures may be linearized by cleavage of one or both strands with a restriction endonuclease or by cleavage of one strand with a nicking endonuclease. Other methods of cleavage can be used as an alternative to restriction enzymes or nicking enzymes, including inter alia chemical cleavage (e.g. cleavage of a diol linkage with periodate), cleavage of abasic sites by cleavage with endonuclease (for example `USER`, as supplied by NEB, part

number M5505S), or by exposure to heat or alkali, cleavage of ribonucleotides incorporated into amplification products otherwise comprised of deoxyribonucleotides, photochemical cleavage or cleavage of a peptide linker.

Following the cleavage step, regardless of the method used for cleavage, the product of the cleavage reaction may be subjected to denaturing conditions in order to remove the portion(s) of the cleaved strand(s) that are not attached to the solid support. Suitable denaturing conditions, for example sodium hydroxide solution, formamide solution or heat, will be apparent to the skilled reader with reference to standard molecular biology protocols (Sambrook et al., supra; Ausubel et al. supra). Denaturation results in the production of a sequencing template which is partially or substantially single-stranded. A sequencing reaction may then be initiated by hybridization of a sequencing primer to the single-stranded portion of the template.

Thus, the invention encompasses methods wherein the nucleic acid sequencing reaction comprises hybridizing a sequencing primer to a single-stranded region of a linearized amplification product, sequentially incorporating one or more nucleotides into a polynucleotide strand complementary to the region of amplified template strand to be sequenced, identifying the base present in one or more of the incorporated nucleotide(s) and thereby determining the sequence of a region of the template strand.

One sequencing method which can be used in accordance with the invention relies on the use of modified nucleotides having removable 3' blocks, for example as described in WO04018497, US 2007/0166705A1 and U.S. Pat. No. 7,057,026, the contents of which are incorporated herein by reference in their entirety. Once the modified nucleotide has been incorporated into the growing polynucleotide chain complementary to the region of the template being sequenced there is no free 3'-OH group available to direct further sequence extension and therefore the polymerase can not add further nucleotides. Once the nature of the base incorporated into the growing chain has been determined, the 3' block may be removed to allow addition of the next successive nucleotide. By ordering the products derived using these modified nucleotides, it is possible to deduce the DNA sequence of the DNA template. Such reactions can be done in a single experiment if each of the modified nucleotides has a different label attached thereto, known to correspond to the particular base, to facilitate discrimination between the bases added during each incorporation step. Alternatively, a separate reaction may be carried out containing each of the modified nucleotides separately.

The modified nucleotides may carry a label to facilitate their detection. A fluorescent label, for example, may be used for detection of modified nucleotides. Each nucleotide type may thus carry a different fluorescent label, for example, as described in WO07135368, the contents of which are incorporated herein by reference in their entirety. The detectable label need not, however, be a fluorescent label. Any label can be used which allows the detection of an incorporated nucleotide.

One method for detecting fluorescently labeled nucleotides comprises using laser light of a wavelength specific for the labelled nucleotides, or the use of other suitable sources of illumination. The fluorescence from the label on the nucleotide may be detected by a CCD camera or other suitable detection means. Suitable instrumentation for recording images of clustered arrays is described in WO07123744, the contents of which are incorporated herein by reference in their entirety.

The invention is not intended to be limited to use of the sequencing method outlined above, as essentially any sequencing methodology which relies on successive incorporation of nucleotides into a polynucleotide chain can be used. Suitable alternative techniques include, for example, the Genome Sequencers from Roche/454 Life Sciences (Margulies et al. (2005) Nature, 437:376-380; U.S. Pat. Nos. 6,274,320; 6,258,568; 6,210,891), and the SOLiD system from Applied Biosystems (solid.appliedbiosystems.com), and the sequencer from Ion Torrent (www.iontorrent.com).

Incorporation by Reference

References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, have been made throughout this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes.

Equivalents

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein.

What is claimed is:

1. A method for validating the integrity of a nucleic acid template in a multiplex sequencing reaction, the method comprising:

obtaining a template nucleic acid;

incorporating at least two sequence identifiers into the template; and

sequencing the template.

2. The method according to claim 1, wherein a first identifier is incorporated into a 5' portion of the template and a second identifier is incorporated into a 3' portion of the template.

3. The method according to claim 2, wherein after incorporation of the identifiers, the template has the following configuration from 5' to 3': a first known sequence; a first barcode sequence; a second known sequence; a target polynucleotide sequence; a third known sequence; a second barcode sequence; and a fourth known sequence.

4. The method according to claim 1, wherein a first identifier is incorporated into a 5' end of the template and a second identifier is incorporated into a 3' end of the template.

5. The method according to claim 2, wherein the first and second identifiers are the same.

6. The method according to claim 2, wherein the first and second identifiers are different.

7. The method according to claim 1, wherein prior to sequencing, the template is attached to a substrate.

8. The method according to claim 2, wherein the template is directly attached to the substrate.

9. The method according to claim 2, wherein the template is indirectly attached to the substrate.

10. The method according to claim 7, further comprising, amplifying the template.

11. The method according to claim 1, wherein sequencing is sequencing by synthesis.

12. The method according to claim 11, wherein the sequencing by synthesis is single molecule sequencing by synthesis.

13. The method according to claim 1, wherein sequencing comprises:

hybridizing a primer to the template to form a template/primer duplex;

contacting the duplex with a polymerase enzyme in the presence of at least one detectably labeled nucleotide under conditions that permit the polymerase to add nucleotides to the primer in a template-dependent manner;

detecting a signal from the incorporated labeled nucleotide; and

sequentially repeating the contacting and detecting steps at least once, wherein sequential detection of incorporated labeled nucleotide determines the sequence of the nucleic acid.

14. The method according to claim 13, wherein the detectably labeled nucleotide is an optically labeled nucleotide.

15. The method according to claim 14, wherein the optically labeled nucleotide is a fluorescently labeled nucleotides.

16. The method according to claim 1, wherein the pair of identifiers are first and second barcode sequences that are attached to the template.

17. The method according to claim 16, wherein a first barcode sequence is attached to a 5' end of the template and a second barcode sequence is attached to a 3' end of the template.

18. The method according to claim 17, wherein the first and second barcode sequences are the same.

19. The method according to claim 17, wherein the first and second barcode sequences are different.

20. A method for analyzing a nucleic acid, the method comprising:

obtaining a nucleic acid template;

attaching a pair of barcode sequences to the template; and

sequencing the template.

21. The method according to claim 20, wherein a first identifier is incorporated into a 5' portion of the template and a second identifier is incorporated into a 3' portion of the template.

22. The method according to claim 21, wherein after attaching of the pair of barcode sequences, the template has the following configuration from 5' to 3': a first known sequence; a first barcode sequence; a second known sequence; a target polynucleotide sequence; a third known sequence; a second barcode sequence; and a fourth known sequence.

23. The method according to claim 20, wherein a first identifier is incorporated into a 5' end of the template and a second identifier is incorporated into a 3' end of the template.

24. The method according to claim 20, wherein prior to sequencing, the template is attached to a substrate.

25. The method according to claim 24, wherein the template is directly attached to the substrate.

26. The method according to claim 24, wherein the template is indirectly attached to the substrate.

27. The method according to claim 24, further comprising, amplifying the template.

28. The method according to claim 20, wherein sequencing is sequencing by synthesis.

29. The method according to claim 28, wherein the sequencing by synthesis is single molecule sequencing by synthesis.

30. The method according to claim 20, wherein sequencing comprises:

hybridizing a primer to the template to form a template/primer duplex;

contacting the duplex with a polymerase enzyme in the presence of at least one detectably labeled nucleotide under conditions that permit the polymerase to add nucleotides to the primer in a template-dependent manner;

detecting a signal from the incorporated labeled nucleotide; and

sequentially repeating the contacting and detecting steps at least once, wherein sequential detection of incorporated labeled nucleotide determines the sequence of the nucleic acid.

31. The method according to claim 29, wherein the detectably labeled nucleotide is an optically labeled nucleotide.

32. The method according to claim 31, wherein the optically labeled nucleotide is a fluorescently labeled nucleotides.

33. The method according to claim 23, wherein the first and second barcode sequences are the same.

34. The method according to claim 23, wherein the first and second barcode sequences are different.

35. A method for analyzing a nucleic acid, the method comprising:

obtaining a nucleic acid template;

attaching a first barcode sequence to a 5' portion of the template and a second barcode sequence to a 3' portion of the template;

amplifying the template; and

sequencing the template.

36. The method according to claim 35, wherein after attaching of the first and second barcode sequences, the template has the following configuration from 5' to 3': a first known sequence; a first barcode sequence; a second known sequence; a target polynucleotide sequence; a third known sequence; a second barcode sequence; and a fourth known sequence.

37. The method according to claim 35, wherein a first identifier is incorporated into a 5' end of the template and a second identifier is incorporated into a 3' end of the template.

38. The method according to claim 35, wherein prior to amplifying, the template is immobilized to a solid support.

39. The method according to claim 35, wherein the first and second barcode sequences are the same.

40. The method according to claim 35, wherein the first and second barcode sequences are different.

41. The method according to claim 35, wherein sequencing comprises:

hybridizing a primer to the template to form a template/primer duplex;

contacting the duplex with a polymerase enzyme in the presence of at least one detectably labeled nucleotide under conditions that permit the polymerase to add nucleotides to the primer in a template-dependent manner;

detecting a signal from the incorporated labeled nucleotide; and

sequentially repeating the contacting and detecting steps at least once, wherein sequential detection of incorporated labeled nucleotide determines the sequence of the nucleic acid.

42. A method for validating detection of an analyte, the method comprising detecting the presence of two or more identifiers that are uniquely associated with said analyte.

43. The method of claim 42, wherein said identifiers are nucleic acid sequence tags.

44. The method of claim 43, wherein said sequence tags are associated with a moiety that binds said analyte.

45. The method of claim 42, wherein said analyte is a protein.

46. The method of claim 45, wherein said identifiers are peptides.

Abstract

The invention generally relates to methods for maintaining the integrity and identification of a nucleic acid template in a multiplex sequencing reaction. In certain embodiments, methods of the invention involve obtaining a template nucleic acid, incorporating a pair of sequence identifiers into the template, and sequencing the template.

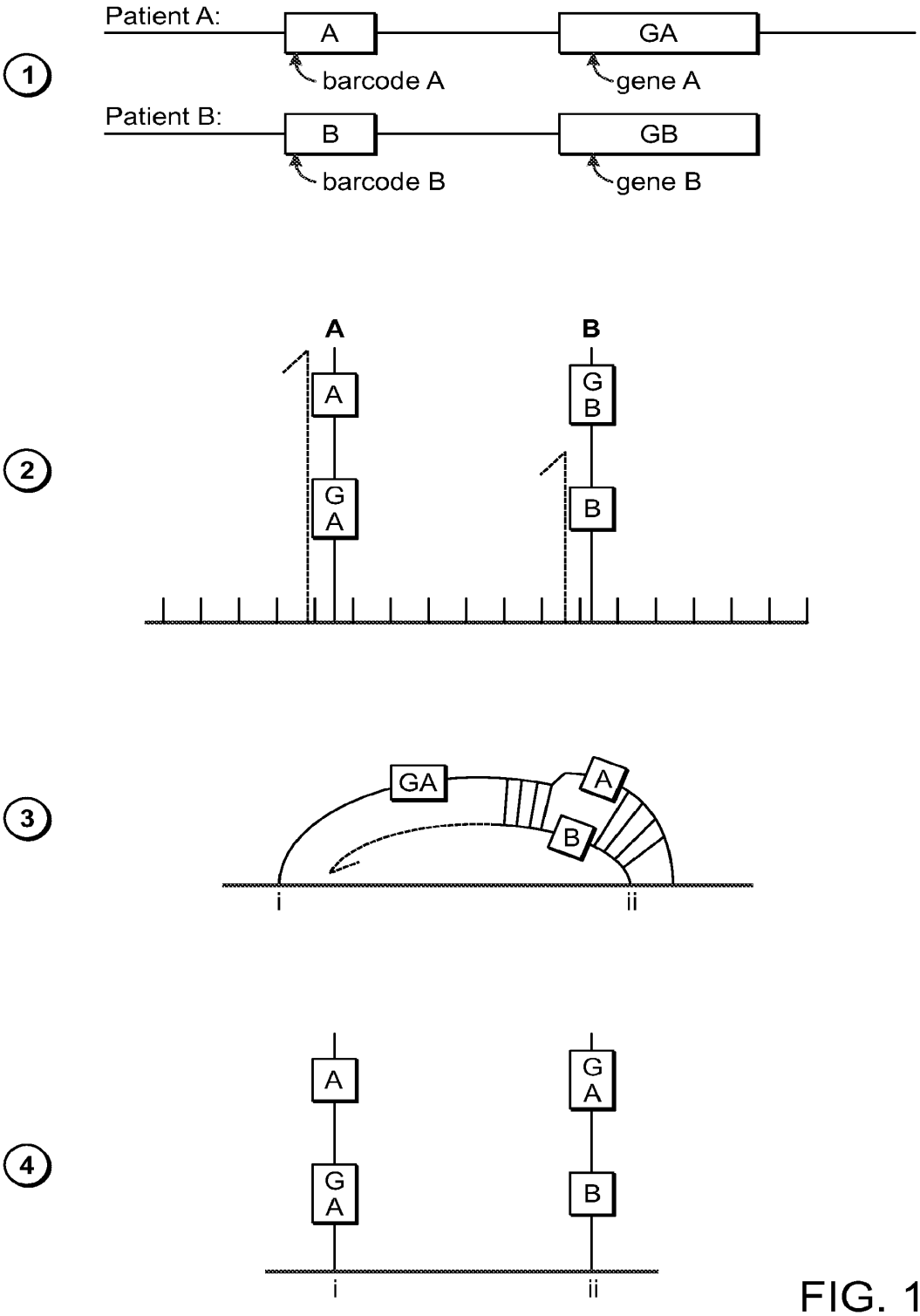

1
Patient A:
A
GA
barcode A
gene A
Patient B:
B
GB
barcode B
gene B
2
A
B
A
GA
GB
B
3
GA
A
B
i
ii
4
A
GA
G
A
B
i
ii

FIG. 1

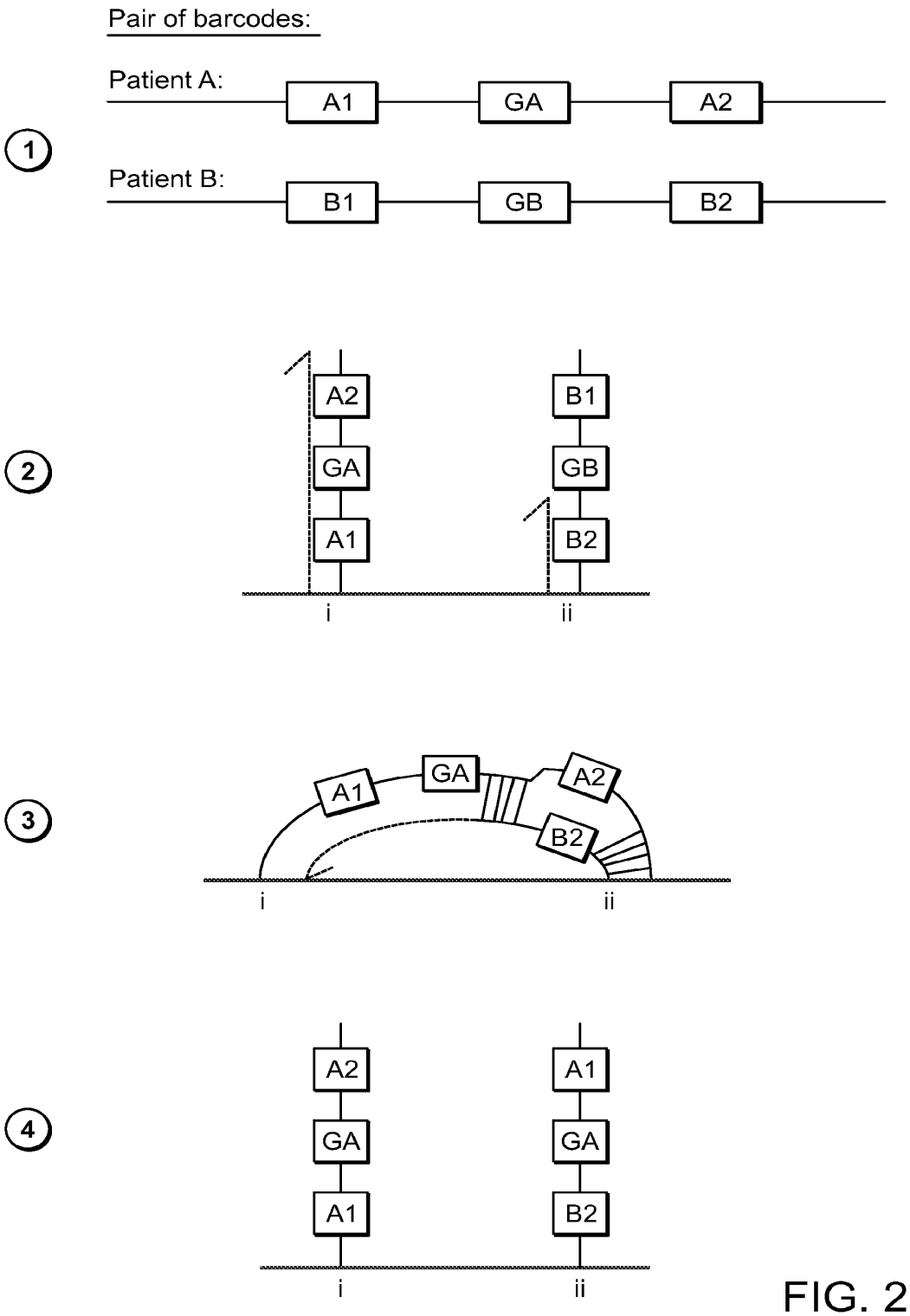

Pair of barcodes:
Patient A:
A1
GA
A2
1
Patient B:
B1
GB
B2
A2
GA
A1
B1
GB
B2
2
i
ii
A1
GA
A2
B2
3
i
ii
A2
GA
A1
A1
GA
B2
4
i
ii

FIG. 2

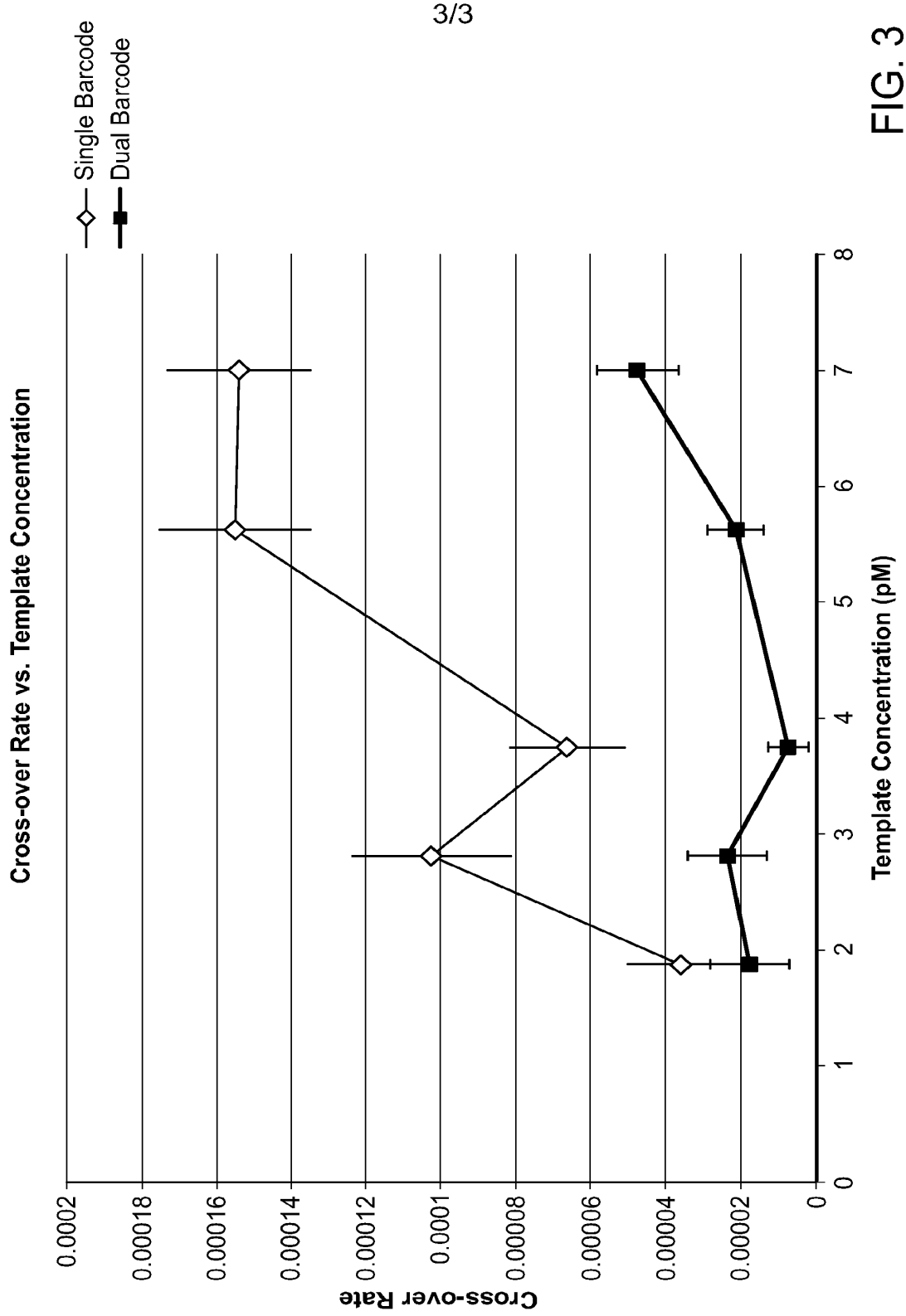

Cross-over Rate vs. Template Concentration
Single Barcode
Dual Barcode
Cross-over Rate
0.0002
0.00018
0.00016
0.00014
0.00012
0.0001
0.00008
0.00006
0.00004
0.00002
0
0
1
2
3
4
5
6
7
8
Template Concentration (pM)

FIG. 3

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Gregory Porreca	Nonprovisional Application Number (if known):	Not Yet Assigned
Title of Invention:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:

I. [x] **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. [ ] **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature	/Thomas C. Meyers/	Date	January 14, 2021
Name (Print/Typed)	Thomas C. Meyers	Practitioner Registration Number	36,989

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

[ ] *Total of 1 forms are submitted.

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Illumina Exhibit 1007, Page 58 of 363

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 14/854,629

filed on September 15, 2015.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

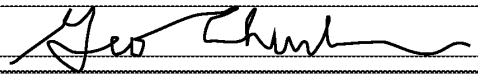
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LEGAL NAME OF INVENTOR

Inventor: George Church Date (Optional): _____

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

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☐ The attached application, or

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filed on September 15, 2015.

The above-identified application was made or authorized to be made by me.

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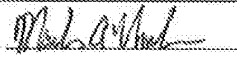
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LEGAL NAME OF INVENTOR

Inventor: Mark Umbarger Date (Optional):

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

■ United States application or PCT international application number 14/854,629 filed on September 15, 2015.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Gregory Porreca Date (Optional): 2-2-16

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17149504
	Filing Date	2021-01-14
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	MLB-001/03US 34468/41

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	Art Unit	1634
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	MLB-001/03US 34468/41

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	Attorney Docket Number	MLB-001/03US 34468/41

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	Attorney Docket Number	MLB-001/03US 34468/41

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Name/Print	Thomas C. Meyers	Registration Number	36,989

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	Application Number	17149504
	Filing Date	2021-01-14
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	MLB-001/03US 34468/41

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Name/Print	Thomas C. Meyers	Registration Number	36,989

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International Application Number:	
Confirmation Number:	2551
Title of Invention:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Kelley Warren
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Attorney Docket Number:	MLB-001/03US 34468/41
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40	Non Patent Literature	Cremer.pdf	750689 e2e281b9585013ddad754d535ade9652348c473e	no	8
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54	Transmittal Letter	34468_41_Information_Disclosure_Statement.pdf	78571 357f06396b57e0958ae340690eda26ce611ad793	no	8
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55	Information Disclosure Statement (IDS) Form (SB08)	34468_41_Information_Disclosure_Statement_Fillable_PDF_1_of_6.pdf	1046563 fda3603186fca67b1a6fbc70eaf8b7d14fd5a342	no	40
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56	Information Disclosure Statement (IDS) Form (SB08)	34468_41_Information_Disclosure_Statement_Fillable_PDF_2_of_6.pdf	1039640 f4fadae9b9fc17bd7236c91670a66c8c350cde83	no	14
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57	Information Disclosure Statement (IDS) Form (SB08)	34468_41_Information_Disclosure_Statement_Fillable_PDF_3_of_6.pdf	1037846 5488c3fa3d3e26b628e08c4466f20db1ffa98f15	no	8
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58	Information Disclosure Statement (IDS) Form (SB08)	34468_41_Information_Disclosure_Statement_Fillable_PDF_4_of_6.pdf	1038018 946ffebe676e108c84f2ae9d6716d45b81cb4da9	no	8
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60	Information Disclosure Statement (IDS) Form (SB08)	34468_41_Information_Disclosure_Statement_Fillable_PDF_6_of_6.pdf	1038099 d76dd669dcfe45845363a7e20c43b1ae5fd3c9bb	no	8
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Docket No.: MLB-001/03US
34468/41
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Molecular Loop Biosolutions

Application No.: 17/149,504 | Confirmation No.: 2551

Filed: January 14, 2021 | Art Unit: 1634

For: METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION | Examiner: Not Yet Assigned

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

INFORMATION DISCLOSURE STATEMENT (IDS)

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

Copies of the references listed below are attached:

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In accordance with 37 C.F.R. § 1.98(d)(1) the remaining references are not supplied because they were previously cited by or submitted to the Office in prior application numbers 14/854,629 filed September 15, 2015 and 13/081,660 filed April 7, 2011 and relied on in the above-identified application for an earlier effective filing date under 35 U.S.C. § 120.

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this response.

Dated: January 22, 2021

Respectfully submitted,

Electronic signature: /Thomas C. Meyers/
Thomas C. Meyers
Registration No.: 36,989
BROWN RUDNICK LLP
Brown Rudnick LLP
One Financial Center
Boston, Massachusetts 02111
(617) 856-8200
Attorney for Applicant

63950695 v1-WorkSiteUS-034468/0041

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EFS ID:	41707945
Application Number:	17149504
International Application Number:	
Confirmation Number:	2551
Title of Invention:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Kelley Warren
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<u>National Stage of an International Application under 35 U.S.C. 371</u>
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<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt	
EFS ID:	41708058
Application Number:	17149504
International Application Number:	
Confirmation Number:	2551
Title of Invention:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Kelley Warren
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-001/03US 34468/41
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Time Stamp:	17:16:45
Application Type:	Utility under 35 USC 111(a)

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File Listing:

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27	Non Patent Literature	Umbarger-2013-ASHGmtg.pdf	151332 f8be1dabb3cbfe55849819409 4953b265d6be9b3	no	2
Warnings:					
Information:					
28	Non Patent Literature	Umbarger-2014-GenMed.pdf	622377 cb2ae2ae6b12a4e2a7dc679236feb5dbf3b854e1	no	9
Warnings:					
Information:					
29	Non Patent Literature	Veeneman-2012-BMCBioinformatics.pdf	1122602 c8c11834f06bd911cbf3533fed4830329e5a06eb	no	8
Warnings:					
Information:					

30	Non Patent Literature	34468_30US_-_Wahl-1979-PNAS.pdf	1446306 1948e732454e8e31fe6988253942fd14029 31777	no	5
Warnings:					
Information:					
31	Non Patent Literature	Wallace-1987-MethEnz.pdf	1762524 2e17f2140c8ec9afed4417753cc4057474c4 7028	no	11
Warnings:					
Information:					
32	Non Patent Literature	Wang-2005-NAR.pdf	5620018 faece68fde444ced0d9bb7bf2ae8d53b1d1 112c6	no	14
Warnings:					
Information:					
33	Non Patent Literature	Waszak.pdf	7817346 ea652b0deff7a0975ecaafcdd01922c76060 c6b9	no	20
Warnings:					
Information:					
34	Non Patent Literature	34468_8US_-_Wirth-1999-AJHG.pdf	512549 1856a39dfac0106df1d67c774a0ce7fc0bb8 c274	no	17
Warnings:					
Information:					
35	Non Patent Literature	WittungBiochemistry1997.pdf	640605 cacd6fb222e1df5c9893f66d11f702220058 7b5e	no	7
Warnings:					
Information:					
36	Non Patent Literature	Xu-2012-PLoSOne.pdf	578950 bbfef5eeb7ddb3f4bdc9505748550dffc2c1f 074	no	6
Warnings:					
Information:					

37	Non Patent Literature	Ye-2009-Bioinformatics.pdf	3639685 4c5be5e1011489d9b9eb143e0194a3bca4698643	no	7
Warnings:					
Information:					
38	Non Patent Literature	Yershov.pdf	2169403 4c508766a534413e46703ae0d481df9bf50d2d0b	no	6
Warnings:					
Information:					
39	Non Patent Literature	Yoon-2014-NuclAcRes.pdf	1362007 2e86e26d7098222569c815e720dabba63698ebb2	no	9
Warnings:					
Information:					
40	Non Patent Literature	Zhou-2014-Bioinformatics.pdf	814470 dd4a58e3b2c5f96b58e4408d8b3f4718e2bb621a	no	13
Warnings:					
Information:					
41	Non Patent Literature	34468_8US_-_Zhulidov-2004-NAR.pdf	252359 e077ebd4b761872ae65e25b6de3698fc89981314	no	8
Warnings:					
Information:					
42	Non Patent Literature	34468_8US_-_Zimran-1990-JCI.pdf	841016 2ae65475aa765a03c1fe08820e74029be8fdff10	no	4
Warnings:					
Information:					
43	Non Patent Literature	Zuckerman-1987-NuclAcidsRes.pdf	1331481 fd594a38248dee553573220158 34cc0615237036	no	17
Warnings:					
Information:					
		Total Files Size (in bytes):	69730984		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/149,504

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	80		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	350		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	400		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	8 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 240 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	830		TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/149,504	01/14/2021	1634	830	MLB-001/03US 34468/41	8	1

CONFIRMATION NO. 2551

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

FILING RECEIPT

OC000000122938092

Date Mailed: 01/28/2021

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Gregory Porreca, Cambridge, MA;
Mark Umbarger, Brookline, MA;
George Church, Brookline, MA;

Applicant(s)

Molecular Loop Biosolutions, Cambridge, MA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 14/854,629 09/15/2015
which is a DIV of 13/081,660 04/07/2011 PAT 9163281
which claims benefit of 61/426,817 12/23/2010

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 01/26/2021
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/149,504**
Projected Publication Date: 05/06/2021
Non-Publication Request: No
Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Illumina Exhibit 1007, Page 189 of 363

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41	2551

21710 7590 02/11/2021

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
02/11/2021	ELECTRONIC

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

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

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

ip@brownrudnick.com
usactions@brownrudnick.com

PTOL-90A (Rev. 04/07)

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 17/149,504	**Applicant(s)** Porreca et al.	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (FITF) Status** No

1. THE REQUEST FILED 14 January 2021 IS **GRANTED** .

   The above-identified application has met the requirements for prioritized examination
   - A. ☑ for an original nonprovisional application (Track I).
   - B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:
   - A. filing a **petition for extension of time** to extend the time period for filing a reply;
   - B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;
   - C. filing a **request for continued examination** ;
   - D. filing a notice of appeal;
   - E. filing a request for suspension of action;
   - F. mailing of a notice of allowance;
   - G. mailing of a final Office action;
   - H. completion of examination as defined in 37 CFR 41.102; or
   - I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41	2551

21710 7590 02/26/2021

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
02/26/2021	ELECTRONIC

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

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

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

ip@brownrudnick.com
usactions@brownrudnick.com

PTOL-90A (Rev. 04/07)

Office Action Summary	**Application No.** 17/149,504	**Applicant(s)** Porreca et al.	
	Examiner TERESA E STRZELECKA	**Art Unit** 1637	**AIA (FITF) Status** No

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

Period for Reply

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

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

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 47-54 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 47-54 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

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

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

Application Papers

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

11)☑ The drawing(s) filed on 1/14/21 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 1/22/21.

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

2. Claims 47-54 are pending and under consideration.

Information Disclosure Statement

3. The information disclosure statements (7 IDSes) submitted on January 22, 2021 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner, with the exception of one of the IDSes, which was not filed on a proper form and therefore was not considered.

Claim Rejections - 35 USC § 112

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

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

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

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 53 and 54 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Claim 53 recites the limitation "the analyte" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 47, from which claim 53 and 54 depend, does not contain a limitation “an analyte”.

Claim Rejections - 35 USC § 102

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

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

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

8. Claims 47-54 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Parameswaran et al. (Nucl. Acids Res., vol. 35, e130, pp. 1-9, 2007; cited in the IDS).

Regarding claim 47, Parameswaran et al. teach a method for reducing template cross-over error introduced during sequencing workflow, the method comprising the steps of

incorporating at least two members of a plurality of identifier sequences into template nucleic acid obtained from at least two different samples, wherein said two members constitute a distinct pair associated with said template (Fig. 1; page 2, paragraphs 2-6; page 3; page 4, first paragraph);

combining said nucleic acid templates into a single sample (page 2, second paragraph; page 4, third paragraph);

amplifying said nucleic acid templates thereby to form clusters, at least one of which comprises a chimeric sequence comprising a combination of identifier sequences that are different than any of said distinct pairs (page 4, third paragraph, where emulsion bead amplification is taught; the amplicons on the beads will form clusters; Table e, which shows mismatched 5' and 3'-barcodes);

sequencing amplicons obtained in said amplifying step (page 4, third paragraph); and

discarding sequence reads obtained in said sequencing step that contain said combination of identifier sequences that are different than any of said distinct pairs, thereby to reduce crossover error (Table 3; page 7, paragraphs 2-4; page 8, first paragraph).

Regarding claims 48 and 49, Parameswaran et al. teach identifier sequences being barcodes (Fig. 1).

Regarding claim 50 and 52, Parameswaran et al. teach one barcode at the 5' end of the template and a second barcode at the 3' end (Fig. 1).

Regarding claim 51, Parameswaran et al. teach the amplified template having the claimed structure (Fig. 1 C).

Regarding claims 53 and 54, if "the analyte" is interpreted as barcoded, amplified template, Parameswaran et al. teach bead emulsion amplification of the libraries, therefore they inherently teach the amplicons attached directly to the beads.

9. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F 9-7.

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.

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/TERESA E STRZELECKA/
Primary Examiner, Art Unit 1637
February 23, 2021

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/149,504	Porreca et al.
	Examiner	Art Unit
	TERESA E STRZELECKA	1637

CPC - Searched*		
Symbol	Date	Examiner
C12Q1/6869 | C12Q2525/191 plus text search	02/22/2021	/TS/

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

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Search Notes	Date	Examiner
Inventor name search	02/22/2021	/TS/
Google	02/22/2021	/TS/
WEST	02/22/2021	/TS/
IDS (1/22/21)	02/22/2021	/TS/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	C12Q1/6869 | C12Q2525/191 plus text search	02/22/2021	/TS/

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/149,504	Porreca et al.
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✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/23/2021								
	47	✓								
	48	✓								
	49	✓								
	50	✓								
	51	✓								
	52	✓								
	53	✓								
	54	✓								

Bibliographic Data

Application No: 17/149,504

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /TERESA E STRZELECKA/ Examiner's Signature | Initials

Title: METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
01/14/2021	506	1637	MLB-001/03US 34468/41
RULE			

APPLICANTS

Molecular Loop Biosolutions, Cambridge, MA, UNITED STATES

INVENTORS

Gregory Porreca, Cambridge, MA, UNITED STATES

Mark Umbarger, Brookline, MA, UNITED STATES

George Church, Brookline, MA, UNITED STATES

CONTINUING DATA

This application is a CON of 14854629 09/15/2015

14854629 is a DIV of 13081660 04/07/2011 PAT 9163281

13081660 has PRO of 61426817 12/23/2010

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Docket No.: MLB-001/03US
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Molecular Loop Biosolutions

Application No.: 17/149,504 Confirmation No.: 2551

Filed: January 14, 2021 Art Unit: 1634

For: METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

Examiner: Not Yet Assigned

Commissioner for Patents
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In accordance with 37 C.F.R. § 1.98(d)(1) the remaining references are not supplied because they were previously cited by or submitted to the Office in prior application numbers 14/854,629 filed September 15, 2015 and 13/081,660 filed April 7, 2011 and relied on in the above-identified application for an earlier effective filing date under 35 U.S.C. § 120.

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this response.

Dated: January 22, 2021

Respectfully submitted,

Electronic signature: /Thomas C. Meyers/
Thomas C. Meyers
Registration No.: 36,989
BROWN RUDNICK LLP
Brown Rudnick LLP
One Financial Center
Boston, Massachusetts 02111
(617) 856-8200
Attorney for Applicant

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(Not for submission under 37 CFR 1.99)

Application Number	17149504
Filing Date	2021-01-14
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	Not Yet Assigned Teresa Strzelecka
Attorney Docket Number	MLB-001/03US 34468/41

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	Application Number	17149504
	Filing Date	2021-01-14
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	Not Yet Assigned Teresa Strzelecka
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Interference Searches

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Illumina Exhibit 1007, Page 298 of 363

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC		
SERIAL NUMBER:	17/149,504	ART UNIT:	1637
FILING DATE:	January 14, 2021	CONF. NO.:	2551
EXAMINER:	Teresa E. Strzelecka		
TITLE:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION		

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

FILED ELECTRONICALLY

AMENDMENT AND RESPONSE

This paper is in response to the non-final Office Action mailed February 26, 2021, from the United States Patent and Trademark Office.

Amendments to the claims begins on page 2.

Remarks begin on page 4.

Applicant believes this amendment and response is timely filed and that no fees are due. Nevertheless, Applicant authorizes any required fees due to be charged to Deposit Account No. 50-0369.

Amendments to the Claims:

Please amend the claims as follows.

1-46. (Canceled)

47. (Currently amended) A method for reducing template cross-over error introduced during sequencing workflow, the method comprising the steps of

incorporating at least two members of a plurality of identifier sequences into template nucleic acids obtained from at least two different samples, wherein said two members constitute a distinct pair associated with said template;

combining said nucleic acid templates into a single sample;

amplifying said nucleic acid templates on a surface of a flow cell thereby to form clusters, at least one of which comprises a chimeric sequence comprising a combination of identifier sequences that are different than any of said distinct pairs;

sequencing amplicons obtained in said amplifying step; and

discarding sequence reads obtained in said sequencing step that contain said combination of identifier sequences that are different than any of said distinct pairs, thereby to reduce cross-over error.

48. (Previously presented) The method of claim 47, wherein the identifier sequences are nucleic acid sequence tags.

49. (Previously presented) The method of claim 47, wherein the identifiers are first and second barcode sequences.

50. (Previously presented) The method of claim 47, wherein a first identifier sequence is incorporated into a 5' portion of the template, and a second identifier sequence is incorporated into a 3' portion of the template.

51. (Previously presented) The method of claim 50, wherein after incorporation of the identifier sequences, the template has the following configuration from 5' to 3': a first known sequence; a first barcode sequence; a second known sequence; a target polynucleotide sequence; a third known sequence; a second barcode sequence; and a fourth known sequence.

52. (Previously presented) The method of claim 47, wherein a first identifier sequence is incorporated into a 5' end of the template, and a second identifier sequence is incorporated into a 3' end of the template.

53. (Currently amended) The method of claim 47, wherein prior to said sequencing step, the ~~analyte~~ template is attached to a substrate.

54. (Currently amended) The method of claim 53, wherein the ~~analyte~~ template is directly attached to the substrate.

Remarks

With entry of this amendment, claims 47-54 are pending, with claim 47 being the only independent claim. Claim 47 has been amended to recite forming clusters at discrete locations on a flow cell. Claims 53 and 54 have been amended for the purpose of clarity and to address the rejection under 35 U.S.C. §112(b) discussed below. Support for the amendments to claim 47 is found throughout the as-filed application including, for example, at page 5, lines 8-10; pages 8-9; pages 20-28, and in Figure 2 and Figure 3.

Examiner Interview Summary

A telephonic interview took place on April 13, 2021 between Examiner Strzelecka and Applicant's representative Thomas C. Meyers, Aditya Dean Ramanathan, and inventor Gregory Porreca.

The prior art rejection in the non-final Office Action dated February 26, 2021 was discussed. During the interview, Applicant pointed to the prior art reference Parameswaran as being limited to pyrosequencing, and therefore failing to disclose amplifying nucleic acids to form clusters, as recited in claim 47. Examiner Strzelecka understood the distinction pointed out by Applicant but requested that applicant distinguish in the claim from the bead-based amplification methods reported in Parameswaran.

Applicant thanks the Examiner for the helpful discussion and have amended the claims in view of her comments. If the Examiner believes further amendments are needed, the Examiner is invited to contact Applicant's representative.

Rejections under 35 U.S.C. §112

Claims 53 and 54 were rejected under 35 U.S.C. §112(b) as lacking sufficient antecedent basis for the limitation "analyte."

In response, applicant has amended each of claims 53 and 54 to no longer recite the term "analyte." In view of the amendment to the claims, applicant submits that the rejection under 35 U.S.C. §112(b) has been overcome.

Rejections under 35 U.S.C. §102

Claims 47-54 are rejected under Pre-AIA 35 USC §102(b) as anticipated by Parameswaran, et al., Nucl. Acids Res., vol 35, e130, pp1-9, 2007 ("Parameswaran").

A claim is anticipated only if each and every element as set forth in the claim is found in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Anticipation can only be asserted where the discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim". *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). The prior art reference must "clearly and unequivocally" disclose the claimed invention "without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference". *Net MoneyIN, Inc.*, 545 F.3d at 1371.

Applicant submits that the claims as amended include a limitation not present in Parameswaran, namely that templates are amplified "to form clusters in a surface of a flow cell". The Parameswaran paper is directed to overcoming a problem unique to pyrosequencing in which bead-bound DNA must be physically separated on a sequencing medium, thus limiting the number of output sequences. *See*, Parameswaran at pages 1 and 2. Parameswaran reports a barcoding approach in which homopolymer length must be strictly limited due limitations inherent in pyrosequencing. *See*, Parameswaran at page 4. However, Parameswaran does not mention forming clusters in a flow cell. That is not at all surprising given that Parameswaran is all about pyrosequencing. In pyrosequencing, one prepares a series of bead-bound templates and ultimately monitors the liberation of diphosphates as and indication of base incorporation during sequencing.

In contrast to the pyrosequencing disclosure in Parameswaran, Applicant discloses and claims hybridization of primers at "discrete locations on a flow cell", *See*, *e.g.,* Figure Panel 2 and page 5, lines 8-10 of the as-filed application, within "a cluster radius on the solid support". *Id.* In addition, Figure 3 and the associated text at page 8-9 of the as-filed application shows sequencing using hybridized primers at discrete locations on a flow cell that form within clusters on a solid support. In addition, Applicant provides details on amplification and sequencing using clusters of polynucleotides in sequencing-by-synthesis methods at, for example, pages 20-25 of the as-filed application. Finally, sequencing methods are discussed beginning at page 25 of the

as-filed application and, in particular at the bottom of page 26 in which Applicant discuses the use of "bridged" template structures that are unique to sequencing-by-hybridization, and the use of modified nucleotides at pages 26-28 of the as-filed specification. These features of sequencing-by-synthesis are reflected in the amended claim language and are unique to sequencing-by-synthesis and would not only be of no value in the pyrosquencing methods reported by Parameswaran but would render the pyrosequencing reaction inoperable because one could not detect base incorporation in a pyrosequencing reaction in clusters at discrete locations in a flow cell.

Accordingly, in view of the amendments to the claims and the above remarks, applicant submits that the rejection under 35 U.S.C. §102 has been overcome.

Conclusion

Applicant submits that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited to contact Applicant's representative.

Dated: April 13, 2021

Respectfully submitted,
BROWN RUDNICK LLP

BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
Tel: 617-856-8483

/Thomas C. Meyers/
Thomas C. Meyers, Reg. No. 36,989
Attorney for Applicant
Email: tmeyers@brownrudnick.com

63947614

Electronic Acknowledgement Receipt	
EFS ID:	42442706
Application Number:	17149504
International Application Number:	
Confirmation Number:	2551
Title of Invention:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Casey Suda
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-001/03US 34468/41
Receipt Date:	13-APR-2021
Filing Date:	14-JAN-2021
Time Stamp:	17:42:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		MLB-001-03US-Response-04-13-2021.pdf	116724 7766aed9ee8197871389c56c0df8661e9500d8e9	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	6
Warnings:			
Information:			
	Total Files Size (in bytes):	116724	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/149,504	Filing Date 01/14/2021	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	04/13/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/CAROLYN E THOMAS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41	2551

21710 7590 04/21/2021
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
04/21/2021	ELECTRONIC

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

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

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

ip@brownrudnick.com
usactions@brownrudnick.com

PTOL-90A (Rev. 04/07)

Applicant-Initiated Interview Summary	**Application No.** 17/149,504	**Applicant(s)** Porreca et al.		
	Examiner TERESA E STRZELECKA	**Art Unit** 1637	**AIA (First Inventor to File) Status** No	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
TERESA E STRZELECKA	Primary Examiner	Telephonic
Thomas Meyers	Attorney of Record	
Aditya Dean Ramanathan	Attorney	
Gregory Porreca	Inventor	

Date of Interview: 13 April 2021

Issues Discussed:

35 U.S.C. 102

Mr. Meyers argued that the claims are not anticipated by Parameswaran et al. since the claims require amplification using clusters, which are used in Illumina sequencing machines. However, Applicant did not define the term "cluster", therefore bead emulsion amplification of Parameswaran et al. forms clusters on beads. The claims should be amended to read on Illumina-type clusters to distinguish from Parameswaran et al.

/TERESA E STRZELECKA/ Primary Examiner, Art Unit 1637	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

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NOTICE OF ALLOWANCE AND FEE(S) DUE

21710 7590 04/27/2021

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/27/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41	2551

TITLE OF INVENTION: METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	07/27/2021

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

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

HOW TO REPLY TO THIS NOTICE:

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

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
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By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21710 7590 04/27/2021
BROWN RUDNICK LLP
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BOSTON, MA 02111

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41	2551

TITLE OF INVENTION: METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	07/27/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
STRZELECKA, TERESA E	1637	506-004000

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

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

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

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

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

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

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Illumina Exhibit 1007, Page 313 of 363

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41	2551

21710 7590 04/27/2021

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/27/2021

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

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

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

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

PTOL-85 (Rev. 02/11)

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

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

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 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.

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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.** 17/149,504	**Applicant(s)** Porreca et al.	
	Examiner TERESA E STRZELECKA	**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 amendment filed 13 April 2021.
   ☐ 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 47-54 . 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 _____.

/TERESA E STRZELECKA/
Primary Examiner, Art Unit 1637

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

2. This office action is in response to an amendment filed April 13, 2021. Claims 47-54 were previously pending. Applicant amended claims 47, 53 and 54. Claims 47-54 are under consideration.

3. Applicant's claim amendments overcame the previously presented claim rejections. Since no new references were found teaching or suggesting the claims as amended, they are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F 9-7.

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.

/TERESA E STRZELECKA/
Primary Examiner, Art Unit 1637
April 19, 2021

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/149,504	Porreca et al.
	Examiner	**Art Unit**
	TERESA E STRZELECKA	1637

CPC						
Symbol					**Type**	**Version**
G01N	/	33	/	543	F	2013-01-01
C12Q	/	1	/	6869	I	2013-01-01
G01N	/	2458	/	10	A	2013-01-01
C12Q	/	2525	/	155	A	2013-01-01
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C12Q	/	2525	/	191	A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	8	
/TERESA E STRZELECKA/ Primary Examiner, Art Unit 1637	19 April 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	47	None

U.S. Patent and Trademark Office — Part of Paper No.: 20210419

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/149,504	Porreca et al.
	Examiner	Art Unit
	TERESA E STRZELECKA	1637

INTERNATIONAL CLASSIFICATION					
CLAIMED					
C12Q1/6869	/	1	/	6869	

NON-CLAIMED					
G01N33/543	/	33	/	543	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE (Assistant Examiner)	(Date)	Total Claims Allowed: 8	
/TERESA E STRZELECKA/ Primary Examiner, Art Unit 1637 (Primary Examiner)	19 April 2021 (Date)	O.G. Print Claim(s) 47	O.G. Print Figure None

U.S. Patent and Trademark Office

Part of Paper No.: 20210419

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/149,504	Porreca et al.
	Examiner	Art Unit
	TERESA E STRZELECKA	1637

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE		Total Claims Allowed:	
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(Primary Examiner)	(Date)	47	None

U.S. Patent and Trademark Office Part of Paper No.: 20210419

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/149,504	Porreca et al.
	Examiner	Art Unit
	TERESA E STRZELECKA	1637

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/23/2021	04/19/2021							
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/149,504	Porreca et al.
	Examiner	Art Unit
	TERESA E STRZELECKA	1637

CPC - Searched*		
Symbol	Date	Examiner
C12Q1/6869 | C12Q2525/191 plus text search	02/22/2021	/TS/
C12Q1/6869 | C12Q2525/191 plus text search	04/19/2021	/TS/

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor name search	02/22/2021	/TS/
Google	02/22/2021	/TS/
WEST	02/22/2021	/TS/
IDS (1/22/21)	02/22/2021	/TS/
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/149,504	Porreca et al.
	Examiner	Art Unit
	TERESA E STRZELECKA	1637

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	C12Q1/6869 | C12Q2525/191 plus text search	02/22/2021	/TS/
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Web Search History

date, time	web site	search string
4/19/2021 5:49:18 PM	Google	"bridge amplification" barcode crossover
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WEST Search History for Application 17149504

Creation Date: 2021041918:19

Interference Searches

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Prior Art Searches

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(index$6 or tag$7 or barcod$7) near3 (hopping or swith$6 or cross-talk or missassign$8)						
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"7510829" | "7523117" | "7537889" | "7537897" | "7544473" | "7582431" | "7598035" | "7629151" | "7642056" | "7666593" | "7700323" | "7774962" | "7776616" | "7790388" | "7809509" | "7835871" | "7862999" | "7865534" | "7883849" | "7957913" | "7960120" | "7985716" | "7993880" | "8024128" | "8114027" | "8165821" | "8209130" | "8283116" | "8462161" | "8463895" | "8474228" | "8496166" | "8529744" | "8738300" | "8778609" | "8812422" | "8847799" | "8976049" | "9074244" | "9115387" | "9228233" | "9292527" | "9535920" | "9567639" | "9677124" | "RE39793" | "RE41780").PN.) and (dual or double) near3 (index$6 or tag$7 or barcod$7)						
17/149504.app.	PGPB	0	ADJ	YES	ASSIGNEE	02-22-2021
14/854629.app.	PGPB	1	ADJ	YES	ASSIGNEE	02-22-2021
(dual or double) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or switch$6 or cross-talk or missassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)	PGPB	24	ADJ	YES	ASSIGNEE	02-22-2021
(two or multiple or plurality) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or switch$6 or cross-talk or missassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)	PGPB	65	ADJ	YES	ASSIGNEE	02-22-2021
(two or multiple or plurality) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or switch$6 or cross-talk or missassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)	USPT	30	ADJ	YES	ASSIGNEE	02-22-2021
(two or multiple or plurality) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or switch$6 or cross-talk or missassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)	DWPI	3	ADJ	YES	ASSIGNEE	02-22-2021
(dual or double) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or switch$6 or cross-talk or missassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)	USPT	5	ADJ	YES	ASSIGNEE	02-22-2021
	DWPI	2	ADJ	YES	ASSIGNEE	02-22-2021

(dual or double) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or switch$6 or cross-talk or missassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)						
17/149504.app.	PGPB	0	ADJ	YES	ASSIGNEE	04-19-2021
14/854629.app.	PGPB	1	ADJ	YES	ASSIGNEE	04-19-2021
(two or multiple or plurality) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or cross-talk or crosstalk or switch$7 or cross-over or crossover or misassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)	PGPB	71	ADJ	YES	ASSIGNEE	04-19-2021
(two or multiple or plurality) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or cross-talk or crosstalk or switch$7 or cross-over or crossover or misassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)	PGPB	71	ADJ	YES	ASSIGNEE	04-19-2021
((two or multiple or plurality) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or cross-talk or crosstalk or switch$7 or cross-over or crossover or misassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)) and bridge near3 (amplif$8 or PCR)	PGPB	47	ADJ	YES	ASSIGNEE	04-19-2021
(two or multiple or plurality) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or cross-talk or crosstalk or switch$7 or cross-over or crossover or misassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)	USPT	39	ADJ	YES	ASSIGNEE	04-19-2021
((two or multiple or plurality) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or cross-talk or crosstalk or switch$7 or cross-over or crossover or misassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)) and bridge near3 (amplif$8 or PCR)	USPT	n/a	ADJ	YES	ASSIGNEE	04-19-2021
((two or multiple or plurality) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or cross-talk or crosstalk or switch$7 or cross-over or crossover or misassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)) and	USPT	30	ADJ	YES	ASSIGNEE	04-19-2021

bridge near3 (amplif$8 or PCR)						
(two or multiple or plurality) near3 (index$6 or tag$7 or barcod$7) and (index$6 or tag$7 or barcod$7) near3 (hopping or cross-talk or crosstalk or switch$7 or cross-over or crossover or misassign$8) and ((C12Q1/6869 | C12Q2525/191).CPC.)	DWPI	3	ADJ	YES	ASSIGNEE	04-19-2021

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41

CONFIRMATION NO. 2551

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PUBLICATION NOTICE



Title:METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

Publication No.US-2021-0132048-A1
Publication Date:05/06/2021

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PART B–FEE(S) TRANSMITTAL

Complete and send this form, together with the applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By fax, send to: (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

BROWN RUDNICK LLP
One Financial Center
Boston, Massachusetts 02111

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41	2551

TITLE OF INVENTION: METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

APPLN: TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600.00	$0.00	$0.00	$600.00	07/27/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
T. E. Strzelecka	1637	506-004000

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

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

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. Brown Rudnick LLP
2. Thomas C. Meyers
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Molecular Loop Biosciences, Inc.

(B) RESIDENCE: (CITY and STATE or COUNTRY): Cambridge, MA

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

4a. Fees Submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 50-0369

5. Change of Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29. NOTE: Absent a valid Certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27. NOTE: If the application was previously under micro entity status, checking this box will be taken as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Thomas C. Meyers/ Date May 14, 2021

Typed or printed name Thomas C. Meyers Registration No. 36,989

Electronic Patent Application Fee Transmittal	
Application Number:	17149504
Filing Date:	14-Jan-2021
Title of Invention:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers/Jeanne Waters
Attorney Docket Number:	MLB-001/03US 34468/41
Filed as Small Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	600	600

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**600**

Electronic Acknowledgement Receipt	
EFS ID:	42724709
Application Number:	17149504
International Application Number:	
Confirmation Number:	2551
Title of Invention:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Jeanne Waters
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-001/03US 34468/41
Receipt Date:	14-MAY-2021
Filing Date:	14-JAN-2021
Time Stamp:	16:18:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$600
RAM confirmation Number	E20215DG18191192
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	MLB-001-03US_Issue-Fee-Transmittal.pdf	191818 d9f834062dc105ffefc9bcc7004b784516eab91c	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30829 03dab89fea1cb44311b14c5d18fdd3fb0497d39a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	222647		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17149504
	Filing Date	2021-01-14
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	Not Yet Assigned Teresa Strzelecka
	Attorney Docket Number	MLB-001/03US 34468/41

	64	6613516		2003-09-02	Christians et al.	
	65	6714874		2004-03-30	Myers et al.	
	66	6716580		2004-04-06	Gold et al.	
	67	6719449		2004-04-13	Laugham, Jr. et al.	
	68	6818395	B1	2004-11-16	Quake et al.	
	69	6828100		2004-12-07	Ronaghi	
	70	6833246		2004-12-21	Balasubramanian	
	71	6858412		2005-02-22	Willis et al.	
	72	6911345		2005-06-28	Quake et al.	
	73	6913879		2005-07-05	Schena ~~TeleChem International Inc.~~	
	74	6927024		2005-08-09	Dodge et al.	

Change(s) applied to document.
/D.M./
4/30/2021

EFS Web 2.1.18

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.E.S/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/149,504	06/22/2021	11041852	MLB-001/03US 34468/41	2551

21710 7590 06/02/2021

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

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 Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Gregory Porreca, Cambridge, MA;
Molecular Loop Biosolutions, Cambridge, MA;
Mark Umbarger, Brookline, MA;
George Church, Brookline, MA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

IR103 (Rev. 10/09)

PTO/AIA/80 (07-17)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no person is required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[x] Practitioners associated with Customer Number: 21710

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[ ] The address associated with Customer Number:

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address:

Molecular Loop Biosciences, Inc.

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature	Date **June 22, 2021**
Name **Gregory Porreca**	Telephone
Title **President and CEO**	

64069697

PTO/AIA/96 (08-12)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Molecular Loop Biosciences, Inc.

Application No./Patent No.: 11,014,852 Filed/Issue Date: June 22, 2021

Titled: METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

Molecular Loop Biosciences, Inc. , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☐ The assignee of the entire right, title, and interest.

2. ☒ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____ %. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☒ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Molecular Loop Biosciences, Inc.

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____ , Frame _____ , or for which a copy thereof is attached.

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: Good Start Genetics, Inc.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 054932 , Frame 0540 , or for which a copy thereof is attached.

2. From: Good Start Genetics, Inc. To: Molecular Loop Biosolutions, LLC
   The document was recorded in the United States Patent and Trademark Office at
   Reel 054932 , Frame 0569 , or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: Molecular Loop Biosolutions, LLC To: Molecular Loop Biosciences, Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 56135 , Frame 830 , or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Thomas C. Meyers/	June 24, 2021
Signature	Date
Thomas C. Meyers	36,989
Printed or Typed Name	Title or Registration Number

Electronic Acknowledgement Receipt	
EFS ID:	43067237
Application Number:	17149504
International Application Number:	
Confirmation Number:	2551
Title of Invention:	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Jeanne Waters
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-001/03US 34468/41
Receipt Date:	24-JUN-2021
Filing Date:	14-JAN-2021
Time Stamp:	12:52:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	Molecular-Loop-Inc_POA-USPTO.pdf	83779 414324d2a0928bfa04da2bf1a72149a62be d0538	no	1
Warnings:					

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	MLB-001-03US_373-Statement.pdf	157734 3d34640f61039f68ad03a47f624fbd2d81e0faad	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	241513	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41

CONFIRMATION NO. 2551

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

POA ACCEPTANCE LETTER

OC000000126627007

Date Mailed: 07/01/2021

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/24/2021.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/ggasgedom/

PTO/AIA/81A (02-15)
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PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	11,041,852
Issue Date	June 22, 2021
First Named Inventor	Gregory PORRECA
Title	METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION
Attorney Docket No.	MLBS-001/C01US 344251-2003

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the Customer Number identified in the box at right as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 58249

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number	Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-identified Customer Number.

OR

☐ The address associated with the Customer Number identified in the box at right:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant

OR

☒ Patent owner.

Statement under 37 CFR 3.73(c) (Form PTO/AIA/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Patent Owner

Signature	/ Gregory Porreca /	Date	03-Jan-2023
Name	Gregory Porreca	Telephone	978-254-7799
Title and Company	Molecular Loop Biosciences, Inc. President and CEO		

NOTE: Signatures of all the applicants or patent owners of the entire interest or their representative(s) are required. If more than one signature is required, submit multiple forms, check the box below, and identify the total number of forms submitted in the blank below.

☐ A total of 1 forms are submitted.

UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/149,504	**02/06/2023 03:57:57 PM ET**	**MLB-001/03US 34468/41**

Title of Invention

METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	11041852
CONFIRMATION #	2551	FILED BY	Johanna Vecchia
PATENT CENTER #	61548587	FILING DATE	01/14/2021
CUSTOMER #	21710	FIRST NAMED INVENTOR	Gregory Porreca
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Edith Cheng

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
POA_RevPOA_MLBS_001C01US.pdf	1	Power of Attorney	89 KB
Statement_373c_MLBS_001C01US.pdf	2	Assignee showing of ownership per 37 CFR 3.73	83 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
POA_RevPOA_MLBS_001C01US.pdf	1598D89D70092445E44ACC40C0442AF098473978F73363B0E1CE794CCB3B0031AA87D4357E918C1EF698AB2C021FB336C1

	B2D3DF91356DACDFCC8390A41827A1
Statement_373c_MLBS_001C01US.pdf	92AFFC028606F6AEA91158394FB5EB71E9C1C70EA81C88C795C81667A8C507AC53AA4284C49A1ED574EE618240788D904381EDC876489BFF73FBBBB0044BDE8B

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

MLBS-001/C01US

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Molecular Loop Biosciences, Inc.

Application No./Patent No.: 11,041,852 Filed/Issue Date: June 22, 2021

Titled: METHODS FOR MAINTAINING THE INTEGRITY AND IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

Molecular Loop Biosciences, Inc. (Name of Assignee) , a corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [x] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. [x] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Gregory PORRECA, Mark UMBARGER, George CHURCH To: GOOD START GENETICS, INC.
   The document was recorded in the United States Patent and Trademark Office at Reel 054932, Frame 0540, or for which a copy thereof is attached.

2. From: GOOD START GENETICS, INC. To: MOLECULAR LOOP BIOSOLUTIONS, LLC
   The document was recorded in the United States Patent and Trademark Office at Reel 054932, Frame 0569, or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: MOLECULAR LOOP BIOSOLUTIONS, LLC To: MOLECULAR LOOP BIOSCIENCES, INC.
The document was recorded in the United States Patent and Trademark Office at
Reel 056135 , Frame 0830 , or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Edith Hang Yu Cheng/	February 6, 2023
Signature	Date
Edith Hang Yu Cheng	Limited Recognition No. L1258
Printed or Typed Name	Title or Registration Number

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41

CONFIRMATION NO. 2551

58249
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

POA ACCEPTANCE LETTER

OC000000137363414

Date Mailed: 02/09/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/06/2023.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sltorres/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/149,504	01/14/2021	Gregory Porreca	MLB-001/03US 34468/41

CONFIRMATION NO. 2551

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

POWER OF ATTORNEY NOTICE

OC000000137363401

Date Mailed: 02/09/2023

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/06/2023.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sltorres/