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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/934,407	12/06/2022	11519035	N.012.US.32	2396

110711 7590 11/16/2022

Natera, Inc.
201 Industrial Road
Suite 410
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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.

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

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

Natera, Inc., San Carlos, CA;

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Art Unit	1637
Examiner Name	Stephanie Kane Mummert
Attorney Docket Number	N.012.US.32

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-10-12
Name/Print	Tianran Yan	Registration Number	67,162

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Electronic Patent Application Fee Transmittal

Application Number:	16934407
Filing Date:	21-Jul-2020
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Filer:	Nishita Alka Doshi/Jeremy Johnston
Attorney Docket Number:	N.012.US.32

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Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
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		Total in USD ($)		**260**

Electronic Acknowledgement Receipt	
EFS ID:	46812749
Application Number:	16934407
International Application Number:	
Confirmation Number:	2396
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Customer Number:	110711
Filer:	Nishita Alka Doshi/Jeremy Johnston
Filer Authorized By:	Nishita Alka Doshi
Attorney Docket Number:	N.012.US.32
Receipt Date:	13-OCT-2022
Filing Date:	21-JUL-2020
Time Stamp:	14:25:06
Application Type:	Utility under 35 USC 111(a)

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9	Foreign Reference	EP2315849B1.pdf	3305294 c18da2cabad0e2774069db15added9119dd3893a	no	81
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11	Non Patent Literature	Gusella_1979_PNAS_NPL.pdf	3310515 e8516eae5abceb1cb40af80d6014f9aba53fb044	no	5
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Warnings:					
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19	Non Patent Literature	LO_1998_p1734_NPL.pdf	599193 0859974c121cb582dfb0f4014b44d9e6cd5c80f7	no	5
Warnings:					
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20	Non Patent Literature	NAMLOS_VOL-17_2017_NPL.pdf	707268 995c1ab2976d01bfb9bfed1132e22772ab8c36d3	no	6
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22	Non Patent Literature	NILSSON-83-88-2006.pdf	839641 d2fa1eea6e9e9156a1539d688beddf07ba3f23d1	no	6
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23	Non Patent Literature	Ohya-1997-Jpn-Hum-Genet_NPL.pdf	1226570 7e620cf9ea005c01ffcd13900fd029f9ef74065d	no	12
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24	Non Patent Literature	Rechitsky_1998_NPL.pdf	869486 17e57ba48a1d8853071ea649ac479ce487c87e00	no	5
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25	Non Patent Literature	TIE_VOL-26-2015_NPL.pdf	1024463 1f5f90a288f9a583d308e744152962e84c7b2485	no	8
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27	Non Patent Literature	VOLCKMAR_123-139_2018-NPL.pdf	2531087 988c2acfe440b2bede3b2730898a772720b5e564	no	17
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28	Non Patent Literature	Wagner_2000_Blood_NPL.pdf	241562 f1df9d216f8882158061d5006083de300a467fcd	no	7
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29	Non Patent Literature	WANG-341-355-2012.pdf	2139863 b8aa76ecfb91d72e15c49178a79cfa262bbfd99d	no	15
Warnings:					
Information:					
30	Foreign Reference	WO2020104670A1.pdf	15678604 b8a3e80378ac944a8432af3f3f5a7b6e9421e349	no	221
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U.S. PATENTS

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FOREIGN PATENT DOCUMENTS

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		2315849	EP	B1	2017-11-08	DIEHL et al.		
		2020104670	WO	A1	2020- 05-28	HEIDER et al.		

NON-PATENT LITERATURE DOCUMENTS

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
		DIAZ, et al., "Liquid Biopsies: Genotyping Circulating Tumor DNA", JOURNAL OF CLINICAL ONCOLOGY, vol. 32, no. 6, 2014, 579-586	
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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

CERTIFICATION STATEMENT

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. 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 contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	16/934,407
Filing Date	Jul 21, 2020
First Named Inventor	Matthew RABINOWITZ
Art Unit	1637
Examiner Name	Stephanie Kane Mummert
Attorney Docket Number	N.012.US.32

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

The submission of this Information Disclosure Statement does not constitute an admission that a search was made, does not constitute an admission that any information cited is prior art, and does not constitute an admission that no other or better art exists.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-10-12
Name/Print	Tianran Yan	Registration Number	67,162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.
16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32	2396

110711 7590 08/02/2022

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

EXAMINER	
MUMMERT, STEPHANIE KANE	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
08/02/2022	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@natera.com

Corrected ***Notice of Allowability***	**Application No.** 16/934,407	**Applicant(s)** RABINOWITZ et al.	
	Examiner STEPHANIE K MUMMERT	**Art Unit** 1637	**AIA (FITF) Status** Yes

-- 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 1/31/22.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3. ☑ The allowed claim(s) is/are 1-15 . 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 6/27/22.
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 _____.

/STEPHANIE K MUMMERT/
Primary Examiner, Art Unit 1637

CORRECTED DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on January 31, 2022 has been entered.

Applicant's response filed on January 31, 2022 is acknowledged and has been entered. Claims 1-15 are pending.

Claims 1-15 are discussed in this Office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on June 27, 2022 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Allowable Subject Matter

Claims 1-15 are allowed.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: The amendment to the claim requires the claimed method excludes samples of cell free nucleic acid obtained from a pregnant female and that the plural 25-2000 loci are associated with cancer. The amendment is sufficient to overcome the rejection of record and over any other references in the prior art which are focused on multiplex amplification and sequencing of 25 to 2000 SNP targets in a sample. The prior art which is focused on combined amplification and sequencing of cell-free or circulating nucleic acid targets neither teach or suggest each of the claimed features of the method. It is noted that references such as Su et al. (J of Molec Diagn, 2011, 13(1):74-84), as cited in an attached IDS, may appear relevant but there are substantial differences between Su and the method as claimed. Su does not antedate the priority dates of the instant application, the SNaPshot format of multiplex is not applied to cell free nucleic acid and the multiplex format of Su does not include simultaneous amplification and analysis of plural SNP loci, as claimed. Instead, the panel of SNP loci of Su are analyzed in grouped panels of four or six mutations instead of all separate loci together. Therefore, the claims are novel and non-obvious over the prior art.

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

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE KANE MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F 9:00-5:30.

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.

/STEPHANIE K MUMMERT/
Primary Examiner, Art Unit 1637

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	Art Unit
	STEPHANIE K MUMMERT	1637

CPC - Searched*		
Symbol	Date	Examiner

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.

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	16/934,407	RABINOWITZ et al.
	Examiner	Art Unit
	STEPHANIE K MUMMERT	1637

Search Notes		
Search Notes	**Date**	**Examiner**
inventor search - all names searched - PALM	08/31/2020	SKM
search Google/Scholar	09/03/2020	SKM
searched PE2E tool	09/03/2020	SKM
searched Google/Scholar	09/04/2020	SKM
searched using PE2E tool	01/01/2021	SKM
searched Google/Scholar	01/01/2021	SKM
considered 9/10/20 IDS and 12/2/20 IDS	01/01/2021	SKM
reviewed IDS	03/26/2021	SKM
search claims using PE2E search tool	03/26/2021	SKM
reviewed IDS	12/18/2021	SKM
searched claims using PE2E search tool	06/01/2022	SKM
reviewed IDS	06/01/2022	SKM
reviewed IDS	06/04/2022	SKM
reviewed IDS	07/27/2022	SKM

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
n/a	search claims using PE2E	03/26/2021	SKM
n/a	search claims using PE2E	12/18/2021	SKM
n/a	search claims using PE2E	06/04/2022	SKM

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	**Art Unit**
	STEPHANIE K MUMMERT	1637

CPC						
Symbol					**Type**	**Version**
C12Q	/	1	/	6883	F	2013-01-01
C12Q	/	1	/	6811	I	2013-01-01
C12Q	/	1	/	6848	I	2013-01-01
C12Q	/	1	/	6809	I	2013-01-01
C12Q	/	1	/	6851	I	2013-01-01
C12Q	/	1	/	6844	I	2013-01-01
C12Q	/	1	/	6869	I	2013-01-01
C12Q	/	1	/	6855	I	2013-01-01
C12Q	/	1	/	6874	I	2013-01-01
C12Q	/	2600	/	156	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
C12Q	/	1	/	6848	I	1	1	2013-01-01
C12Q	/	2527	/	107	I	1	2	2013-01-01
C12Q	/	2537	/	143	I	1	3	2013-01-01
C12Q	/	1	/	6809	I	2	1	2013-01-01
C12Q	/	2527	/	107	I	2	2	2013-01-01
C12Q	/	2537	/	143	I	2	3	2013-01-01
C12Q	/	1	/	6851	I	3	1	2013-01-01
C12Q	/	2531	/	113	I	3	2	2013-01-01
C12Q	/	2535	/	122	I	3	3	2013-01-01
C12Q	/	2537	/	143	I	3	4	2013-01-01
C12Q	/	2563	/	159	I	3	5	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	15	
/STEPHANIE K MUMMERT/ Primary Examiner, Art Unit 1637	27 July 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20220727

NeoGenomics
Exhibit 1003 Page 26

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	**Art Unit**
	STEPHANIE K MUMMERT	1637

INTERNATIONAL CLASSIFICATION					
CLAIMED					
C12Q	/	1	/	68	
NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
435	6.12

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					
435	91.2					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 15	
/STEPHANIE K MUMMERT/ Primary Examiner, Art Unit 1637 (Primary Examiner)	27 July 2022 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office — Part of Paper No.: 20220727

NeoGenomics
Exhibit 1003 Page 27

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	Art Unit
	STEPHANIE K MUMMERT	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 (Assistant Examiner)	(Date)	Total Claims Allowed: 15	
/STEPHANIE K MUMMERT/ Primary Examiner, Art Unit 1637 (Primary Examiner)	27 July 2022 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office Part of Paper No.: 20220727

NeoGenomics
Exhibit 1003 Page 28

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 07/27/2022

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

PTO/SB/08a (01-10)
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	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

U.S. PATENTS

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

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		20120028814	A1	2012-02-02	Toloue, Masoud et al.	
		20130157870	A1	2013-06-20	Pushkarev et al.	
		20130237431	A1	2013-09-12	LO et al.	
		20130288252	A1	2013-10-31	Sparks et al.	
		20130310260	A1	2013-11-21	KIM et al.	
		20140186827	A1	2014-07-03	Pieprzyk, Martin et al.	
		20140227691	A1	2014-08-14	MAY, A. et al.	
		20140242588	A1	2014-08-28	Van Den Boom et al.	
		20150167069	A1	2015-06-18	Schutz et al.	

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		20150218631	A1	2015-08-06	CHUU, Y.-J. et al.	
		20180320171	A1	2018-11-08	WITHEY, Gary	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
		COSTA, J.-M. et al., "Fetal RHD genotyping in maternal serum during the first trimester of pregnancy", British Journal of Haematology, Vol. 119, 2002, 255-260	
		DANIELS, G. et al., "Fetal blood group genotyping from DNA from maternal plasma: an important advance in the management and prevention of haemolytic disease of the fetus and newborn", Vox Sanguinis, Vol. 87, 2004, 223-232	

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		ILLUMINA, "HumanOmni1-Quad BeadChip", Illumina DNA Analysis, Pub. No. 370-21009-007, 2009, 1 page	
		ILLUMINA, "HumanOmni2.5-8 BeadChips: Next-Generation GWAS Content for Genotyping and CNV Analysis", Data Sheet: DNA Analysis, Pub. No. 370-2011-008, 2011, 1 page	
		KESHAVJEE, S. H. et al., "The role of dextran 40 and potassium in extended hypothermic lung preservation for transplantation", The Journal of Thoracic and Cardiovascular Surgery, Volume 103, Number 2, 1992,	
		RAEMDONCK, DIRK VAN et al., "Ex-vivo lung perfusion", Transplant International, Volume 28, Issue 6, Special Issue: Focus Issue: Machine Perfusion, 2014, 643-656	
		SELZNER, MARKUS et al., "Normothermic Ex Vivo Liver Perfusion Using Steen Solution as Perfusate for Human Liver Transplantation: First North American Results", Liver Transplantation, Volume 22, Issue 11, 2016,	
		TUNGWIWAT, et al., "Non-invasive fetal sex determination using a conventional nested PCR analysis of fetal DNA in maternal plasma", Clinica Chimica Acta, Vol. 334, No.1-2, 2003, 173-177	
		YE, et al., "Primer-BLAST: a tool to design target-specific primers for polymerase chain reaction", BMC Bioinformatics, 13:134, 2012, 11 pages	
EXAMINER SIGNATURE			

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OR

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☐ See attached certification statement.

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☐ None

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Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-06-24
Name/Print	Tianran Yan	Registration Number	67,162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 07/27/2022

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

U.S. PATENTS

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

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
		2011/118603	WO		2011-09-29	MAKINO, Y. et al.		

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

		BIRKENKAMP-DEMTRODER, et al., "Longitudinal assessment of multiplex patient-specific ctDNA biomarkers in bladder cancer for diagnosis, surveillance and recurrence", ANNALS OF ONCOLOGY, OXFORD UNIVERSITY PRESS NLD, Vol. 29, no. Supplement 8, 2018, viii26	
		EHLAYEL, A. et al., "Emerging monitoring technologies in kidney transplantation", Pediatric Nephrology, Vol. 36, 2021, 3077-3087	
		GLAAB, W. E. et al., "A novel assay for allelic discrimination that combines the fluorogenic 5' nuclease polymerase chain reaction (TaqMan) and mismatch amplification mutation assay", Mutation Research, Vol. 430, 1999, 12 pgs	
		SCHUTZ, E. et al., "Graft-derived cell-free DNA, a noninvasive early rejection and graft damage marker in liver transplantation: A prospective, observational, multicenter cohort study", PLOS Medicine, Vol. 14, No. 4, 25 APR 2017, 19 pgs	
		WANGKUMHANG, P. et al., "WASP: a Web-based Allele-Specific PCR assay designing tool for detecting SNPs and mutations", BMC Genomics, Vol. 8, No. 275, 14 AUG 2007, 9 pgs	
		WHITLAM, J. B. et al., "Diagnostic application of kidney allograft-derived absolute cell-free DNA levels during transplant dysfunction", Am J Transplant, Vol. 19, 2019, 1037-1049	

EXAMINER SIGNATURE

Examiner Signature	/STEPHANIE K MUMMERT/	Date Considered	07/27/2022

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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

The submission of this Information Disclosure Statement does not constitute an admission that a search was made, does not constitute an admission that any information cited is prior art, and does not constitute an admission that no other or better art exists.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-06-24
Name/Print	Tianran Yan	Registration Number	67,162

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PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	92	(multiplex SAME tagg$3 SAME barcode SAME universal)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:05 AM
L2	85	(multiplex SAME tagg$3 SAME barcode SAME universal SAME sequenc$3)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:07 AM
L3	0	(multiplex SAME tagg$3 SAME barcode SAME universal SAME sequenc$3 SAME "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:08 AM
L4	85	(multiplex SAME tagg$3 SAME barcode SAME universal SAME sequenc$3),clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:08 AM
L5	0	(multiplex SAME tagg$3 SAME barcode SAME (universal NEAR tail) SAME sequenc$3)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:09 AM
L6	0	(multiplex SAME tagg$3 SAME barcode SAME (universal NEAR tail)) AND sequenc$3	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:09 AM
L7	0	(multiplex SAME tagged SAME barcode) AND (universal NEAR tail) AND sequenc$3	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:11 AM
L8	0	(multiplex SAME tagged SAME barcode) AND (universal NEAR tail) AND sequencing	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:11 AM
L9	3	(multiplex SAME (universal NEAR tail)) AND tagged AND barcode AND sequencing	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:12 AM
L10	3711884	(universal adaptor) multiplex AND sequencing AND "cell free" AND tagging AND	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT;	OR	ON	ON	2020/09/02 10:54 PM

		barcode	IBM_TDB)				
L11	527	(universal SAME adaptor) AND multiplex AND sequencing AND "cell free" AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 10:56 PM
L12	91	(universal SAME adaptor) AND (multiplex SAME sequencing SAME "cell free") AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 10:57 PM
L13	0	(universal SAME adaptor) AND (multiplex NEAR sequencing NEAR "cell free") AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:02 PM
L14	91	(universal SAME adaptor) AND (multiplex SAME sequencing SAME "cell free") AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:02 PM
L15	91	(universal SAME adaptor) AND (multiplex SAME sequencing SAME "cell free") AND tagging	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:11 PM
L16	12948	"L19" NOT L14	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:11 PM
L17	26547	"L15" NOT L14	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:11 PM
L18	0	L15 NOT L14	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:12 PM
L19	472	(universal SAME adaptor) AND (multiplex SAME sequencing) AND "cell free" AND tagging	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:12 PM
L20	580	(universal SAME adaptor) AND (sequencing) AND "cell free" AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/03 09:11 PM
L21	22	((universal SAME adaptor) SAME	(US-PGPUB; USPAT; USOCR; FIT (CN, FR,	OR	ON	ON	2020/09/03 09:11 PM

		sequencing SAME "cell free") AND tagging AND barcode	WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L22	9	("universal tail" SAME "SNP" AND "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:56 PM
L23	0	("universal tail" SAME "SNP" SAME "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:56 PM
L24	107	("universal tail" AND "SNP" AND "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:56 PM
L25	107	("universal tail" AND "SNP" AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:57 PM
L26	67	(L25) AND @ay<2010	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:04 PM
L27	1	("universal tail" AND ("SNP" NEAR (plurality OR multiplex)) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:54 PM
L28	197	(((tail OR adaptor) NEAR universal) AND ("SNP" NEAR (plurality OR multiplex)) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:55 PM
L29	8	((((tail OR adaptor) NEAR universal) SAME ("SNP" NEAR (plurality OR multiplex))) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:56 PM
L30	8	((((tail OR adaptor) NEAR universal) SAME (("SNP" OR polymorphism) NEAR (plurality OR multiplex))) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:57 PM
L31	2	((tagged SAME (("SNP" OR polymorphism)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR,	OR	ON	ON	2021/01/01 06:52 PM

		NEAR (plurality OR multiplex))) AND "cell free" AND sequencing)	WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L32	170	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 06:53 PM
L33	16	(L32) AND @ay<2010	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 06:53 PM
L34	0	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 07:07 PM
L35	0	(((tail OR adaptor) NEAR universal) AND ("SNP" NEAR (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 07:07 PM
L36	0	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/03/26 07:04 PM
L37	251	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND ("cell free" OR plasma OR circulating) AND sequencing AND cancer)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/03 10:15 PM
L38	37	L37 AND @ay<"2010"	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/03 10:17 PM
L39	16	("11130995" OR "20100273159" OR "20110312503" OR "20150086477" OR "20150322507" OR "20150329891" OR "20180023128" OR "20220025455" OR "20220025456" OR "20220033908" OR "20220033909" OR	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/04 10:55 PM

		"20220042103" OR "20220056509" OR "20220056534" OR "20220073978" OR "20220073979").pn.					
L40	9	("20040115629" OR "20090280479" OR "20160186239" OR "20170152561" OR "20170218458" OR "20170283788" OR "20180288982" OR "20200109449" OR "20200316498").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/04 11:11 PM
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		"20180251553" OR "20180265917" OR "20190256924" OR "20200032323" OR "20210257048" OR "20210269879" OR "20210324463" OR "20210327538" OR "20210327542" OR "20210355536" OR "4683195" OR "4942124" OR "5648220" OR "5891734" OR "5962223" OR "6605451" OR "6858412" OR "7101663" OR "7153656" OR "7655399" OR "7981609" OR "8236503" OR "8318434" OR "8323897" OR "8372584" OR "8501409" OR "8679741" OR "8748103" OR "9005894" OR "9051602" OR "9206475" OR "9404150" OR "9493828" OR "9506119").pn.					
L42	11	("20120028814" OR "20130157870" OR "20130237431" OR "20130288252" OR "20130310260" OR "20140186827" OR "20140227691" OR "20140242588" OR "20150167069" OR "20150218631" OR "20180320171").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2022/07/27 06:54 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	0	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2021/12/18 10:18 PM

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16934407	06/27/2022

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I20226T726331829	1501	UTILITY APPL ISSUE FEE	$1,200.00	Deposit Account



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	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

U.S. PATENTS

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U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
		2011/118603	WO		2011-09-29	MAKINO, Y. et al.		

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

		BIRKENKAMP-DEMTRODER, et al., "Longitudinal assessment of multiplex patient-specific ctDNA biomarkers in bladder cancer for diagnosis, surveillance and recurrence", ANNALS OF ONCOLOGY, OXFORD UNIVERSITY PRESS NLD, Vol. 29, no. Supplement 8, 2018, viii26	
		EHLAYEL, A. et al., "Emerging monitoring technologies in kidney transplantation", Pediatric Nephrology, Vol. 36, 2021, 3077-3087	
		GLAAB, W. E. et al., "A novel assay for allelic discrimination that combines the fluorogenic 5' nuclease polymerase chain reaction (TaqMan) and mismatch amplification mutation assay", Mutation Research, Vol. 430, 1999, 12 pgs	
		SCHUTZ, E. et al., "Graft-derived cell-free DNA, a noninvasive early rejection and graft damage marker in liver transplantation: A prospective, observational, multicenter cohort study", PLOS Medicine, Vol. 14, No. 4, 25 APR 2017, 19 pgs	
		WANGKUMHANG, P. et al., "WASP: a Web-based Allele-Specific PCR assay designing tool for detecting SNPs and mutations", BMC Genomics, Vol. 8, No. 275, 14 AUG 2007, 9 pgs	
		WHITLAM, J. B. et al., "Diagnostic application of kidney allograft-derived absolute cell-free DNA levels during transplant dysfunction", Am J Transplant, Vol. 19, 2019, 1037-1049	

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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Approved for use through 07/31/2012. OMB 0651-0031
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

CERTIFICATION STATEMENT

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☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

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☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-06-24
Name/Print	Tianran Yan	Registration Number	67,162

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EFS ID:	46050329
Application Number:	16934407
International Application Number:	
Confirmation Number:	2396
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Customer Number:	110711
Filer:	Nishita Alka Doshi/Angela McGowan
Filer Authorized By:	Nishita Alka Doshi
Attorney Docket Number:	N.012.US.32
Receipt Date:	27-JUN-2022
Filing Date:	21-JUL-2020
Time Stamp:	12:58:35
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	Information Disclosure Statement (IDS) Form (SB08)	03_N012US32_SB08__foreign_SIGNED.pdf	81414 d94747d63bd0f9e5b4b62f3ec8635f0c879f3d62	no	4

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New Applications Under 35 U.S.C. 111

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

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U.S. PATENTS

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

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		20120028814	A1	2012-02-02	Toloue, Masoud et al.	
		20130157870	A1	2013-06-20	Pushkarev et al.	
		20130237431	A1	2013-09-12	LO et al.	
		20130288252	A1	2013-10-31	Sparks et al.	
		20130310260	A1	2013-11-21	KIM et al.	
		20140186827	A1	2014-07-03	Pieprzyk, Martin et al.	
		20140227691	A1	2014-08-14	MAY, A. et al.	
		20140242588	A1	2014-08-28	Van Den Boom et al.	
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	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

		20150218631	A1	2015-08-06	CHUU, Y.-J. et al.	
		20180320171	A1	2018-11-08	WITHEY, Gary	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS

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		COSTA, J.-M. et al., "Fetal RHD genotyping in maternal serum during the first trimester of pregnancy", British Journal of Haematology, Vol. 119, 2002, 255-260	
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		RAEMDONCK, DIRK VAN et al., "Ex-vivo lung perfusion", Transplant International, Volume 28, Issue 6, Special Issue: Focus Issue: Machine Perfusion, 2014, 643-656	
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EXAMINER SIGNATURE			

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Examiner Signature		Date Considered	

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☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

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	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-06-24
Name/Print	Tianran Yan	Registration Number	67,162

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Electronic Patent Application Fee Transmittal

Application Number:	16934407
Filing Date:	21-Jul-2020
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Filer:	Nishita Alka Doshi/Angela McGowan
Attorney Docket Number:	N.012.US.32

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
		Total in USD ($)		**260**

Electronic Acknowledgement Receipt	
EFS ID:	46049848
Application Number:	16934407
International Application Number:	
Confirmation Number:	2396
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Customer Number:	110711
Filer:	Nishita Alka Doshi/Angela McGowan
Filer Authorized By:	Nishita Alka Doshi
Attorney Docket Number:	N.012.US.32
Receipt Date:	27-JUN-2022
Filing Date:	21-JUL-2020
Time Stamp:	12:32:20
Application Type:	Utility under 35 USC 111(a)

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17	Foreign Reference	WO2011118603.pdf	3157855 da2c62ec7200ded3ec034f9f5ef3eaa458ee7d87	no	57
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Information:					
18	Non Patent Literature	YE_2012-134_NPL.pdf	1777108 a57c46f37e8e9fb7f2e484721d291160cb1d8c6e	no	11
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San Carlos, CA 94070

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.
16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32	2396

TITLE OF INVENTION: METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	09/12/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
MUMMERT, STEPHANIE KANE	1637	435-006120

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/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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

1 _____
2 _____
3 _____

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

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document 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: Natera, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): San Carlos, California

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. 50-6075

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.

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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 /Tianran Yan/ Date 6-24-2022

Typed or printed name Tianran Yan Registration No. 67162

NeoGenomics
Exhibit 1003 Page 68

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
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 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)

110711 7590 06/10/2022

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070



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16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32	2396

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nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	09/12/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
MUMMERT, STEPHANIE KANE	1637	435-006120

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(A) NAME OF ASSIGNEE: Natera, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): San Carlos, California

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 _____

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Authorized Signature /Tianran Yan/ Date 6-24-2022

Typed or printed name Tianran Yan Registration No. 67162

PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

NeoGenomics
Exhibit 1003 Page 69

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

110711 7590 06/10/2022

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

EXAMINER
MUMMERT, STEPHANIE KANE

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/10/2022

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32	2396

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nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	09/12/2022

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. 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.

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Exhibit 1003 Page 70

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Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

NeoGenomics
Exhibit 1003 Page 71

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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110711 7590 06/10/2022

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/10/2022

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)

NeoGenomics
Exhibit 1003 Page 72

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

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

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

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

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

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

Notice of Allowability	Application No. 16/934,407	Applicant(s) RABINOWITZ et al.	
	Examiner STEPHANIE K MUMMERT	Art Unit 1637	AIA (FITF) Status Yes

-- 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 1/31/22.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3. ☑ The allowed claim(s) is/are 1-15 . 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 1/5/22, 1/31/22, 3/14/22 and 4/27/22.
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 _____.

/STEPHANIE K MUMMERT/
Primary Examiner, Art Unit 1637

CORRECTED DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on January 31, 2022 has been entered.

Applicant's response filed on January 31, 2022 is acknowledged and has been entered. Claims 1-15 are pending.

Claims 1-15 are discussed in this Office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on January 5, 2022, January 31, 2022, March 14, 2022 and April 27, 2022 were filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Allowable Subject Matter

Claims 1-15 are allowed.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: The amendment to the claim requires the claimed method excludes samples of cell free nucleic acid obtained from a pregnant female and that the plural 25-2000 loci are associated with cancer. The amendment is sufficient to overcome the rejection of record and over any other references in the prior art which are focused on multiplex amplification and sequencing of 25 to 2000 SNP targets in a sample. The prior art which is focused on combined amplification and sequencing of cell-free or circulating nucleic acid targets neither teach or suggest each of the claimed features of the method. It is noted that references such as Su et al. (J of Molec Diagn, 2011, 13(1):74-84), as cited in an attached IDS, may appear relevant but there are substantial differences between Su and the method as claimed. Su does not antedate the priority dates of the instant application, the SNaPshot format of multiplex is not applied to cell free nucleic acid and the multiplex format of Su does not include simultaneous amplification and analysis of plural SNP loci, as claimed. Instead, the panel of SNP loci of Su are analyzed in grouped panels of four or six mutations instead of all separate loci together. Therefore, the claims are novel and non-obvious over the prior art.

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

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE KANE MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F 9:00-5:30.

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.

/STEPHANIE K MUMMERT/
Primary Examiner, Art Unit 1637

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	Art Unit
	STEPHANIE K MUMMERT	1637

CPC - Searched*		
Symbol	Date	Examiner

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	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	Art Unit
	STEPHANIE K MUMMERT	1637

Search Notes		
Search Notes	**Date**	**Examiner**
inventor search - all names searched - PALM	08/31/2020	SKM
search Google/Scholar	09/03/2020	SKM
searched PE2E tool	09/03/2020	SKM
searched Google/Scholar	09/04/2020	SKM
searched using PE2E tool	01/01/2021	SKM
searched Google/Scholar	01/01/2021	SKM
considered 9/10/20 IDS and 12/2/20 IDS	01/01/2021	SKM
reviewed IDS	03/26/2021	SKM
search claims using PE2E search tool	03/26/2021	SKM
reviewed IDS	12/18/2021	SKM
searched claims using PE2E search tool	06/01/2022	SKM
reviewed IDS	06/01/2022	SKM
reviewed IDS	06/04/2022	SKM

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
n/a	search claims using PE2E	03/26/2021	SKM
n/a	search claims using PE2E	12/18/2021	SKM
n/a	search claims using PE2E	06/04/2022	SKM

NeoGenomics
Exhibit 1003 Page 79

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	Art Unit
	STEPHANIE K MUMMERT	1637

CPC							
Symbol						Type	Version
C12Q	/	1	/	6883		F	2013-01-01
C12Q	/	1	/	6811		I	2013-01-01
C12Q	/	1	/	6848		I	2013-01-01
C12Q	/	1	/	6809		I	2013-01-01
C12Q	/	1	/	6851		I	2013-01-01
C12Q	/	1	/	6844		I	2013-01-01
C12Q	/	1	/	6869		I	2013-01-01
C12Q	/	1	/	6855		I	2013-01-01
C12Q	/	1	/	6874		I	2013-01-01
C12Q	/	2600	/	156		A	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
C12Q	/	1	/	6848	I	1	1	2013-01-01
C12Q	/	2527	/	107	I	1	2	2013-01-01
C12Q	/	2537	/	143	I	1	3	2013-01-01
C12Q	/	1	/	6809	I	2	1	2013-01-01
C12Q	/	2527	/	107	I	2	2	2013-01-01
C12Q	/	2537	/	143	I	2	3	2013-01-01
C12Q	/	1	/	6851	I	3	1	2013-01-01
C12Q	/	2531	/	113	I	3	2	2013-01-01
C12Q	/	2535	/	122	I	3	3	2013-01-01
C12Q	/	2537	/	143	I	3	4	2013-01-01
C12Q	/	2563	/	159	I	3	5	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	15	
/STEPHANIE K MUMMERT/ Primary Examiner, Art Unit 1637	04 June 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20220604

NeoGenomics
Exhibit 1003 Page 80

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	**Art Unit**
	STEPHANIE K MUMMERT	1637

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C12Q	/	1	/	68

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
435	6.12

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					
435	91.2					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 15	
/STEPHANIE K MUMMERT/ Primary Examiner, Art Unit 1637 (Primary Examiner)	04 June 2022 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office — Part of Paper No.: 20220604

NeoGenomics
Exhibit 1003 Page 81

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	Art Unit
	STEPHANIE K MUMMERT	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 (Assistant Examiner)	(Date)	Total Claims Allowed: 15	
/STEPHANIE K MUMMERT/ Primary Examiner, Art Unit 1637 (Primary Examiner)	04 June 2022 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office — Part of Paper No.: 20220604

NeoGenomics
Exhibit 1003 Page 82

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

PTO/SB/08a (01-10)
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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 contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

U.S. PATENTS						
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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	Attorney Docket Number	N.012.US.32

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

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	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

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	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

		WEI, TING et al., "Novel Approaches to Mitigate Primer Interaction and Eliminate Inhibitors in Multiplex PCR, Demonstrated Using an Assay for Detection of three Strawberry Viruses", Journal of Virological Methods, vol. 151, 2008, pp 132-139	
		WILKINSON, SARAH T. et al., "Decreased MHC Class II Expression in Diffuse Large B-Cell Lymphoma does not Correlate with CPG Methylation of Ciita Promoters III and IV", Leuk Lymphoma, vol. 50, 2009, pp 1875-1878	
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		WONG, K. H. et al., "Multiplex Illumina Sequencing Using DNA Barcoding", Current Protocols in Molecular Biology, Vol. 101, JAN 2013, 7.11.1-7.11.11	
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EXAMINER SIGNATURE			
Examiner Signature	/STEPHANIE K MUMMERT/	Date Considered	06/04/2022

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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	Attorney Docket Number	N.012.US.32

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

The submission of this Information Disclosure Statement does not constitute an admission that a search was made, does not constitute an admission that any information cited is prior art, and does not constitute an admission that no other or better art exists.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-01-05
Name/Print	Tianran Yan	Registration Number	67,162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

Web Search History

date, time	web site	search string
6/3/2022 11:10:30 PM	Google	detection of tumor-derived point mutations in cancer patients (Anker, P. et al. Gastroenterology 112, 1114-1120 (1997))
6/3/2022 11:20:15 PM	Google	detection of tumor-derived point mutations in cancer patients
6/3/2022 11:23:54 PM	Google Scholar	detection of tumor-derived point mutations in cancer patients
6/3/2022 11:30:25 PM	Google Scholar	detection of tumor-derived point mutations in cancer patients [before:2010]
6/3/2022 11:31:45 PM	Google Scholar	[before:2010] ((tagged ("SNP" OR polymorphism) (plurality OR plural or multiplex)) AND ("cell free" OR plasma OR circulating) AND sequencing AND cancer)
6/3/2022 11:33:02 PM	Google Scholar	((cancer or tumor) tagged ("SNP" OR polymorphism) (plurality OR plural or multiplex)) AND ("cell free" OR plasma OR circulating) AND sequencing) [before:2010]
6/3/2022 11:33:42 PM	Google Scholar	[before:2010] ((cancer or tumor) tagged ("SNP" OR polymorphism) (plurality OR plural or multiplex)) AND ("cell free" OR plasma OR circulating) AND sequencing)

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	92	(multiplex SAME tagg$3 SAME barcode SAME universal)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:05 AM
L2	85	(multiplex SAME tagg$3 SAME barcode SAME universal SAME sequenc$3)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:07 AM
L3	0	(multiplex SAME tagg$3 SAME barcode SAME universal SAME sequenc$3 SAME "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:08 AM
L4	85	(multiplex SAME tagg$3 SAME barcode SAME universal SAME sequenc$3),clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:08 AM
L5	0	(multiplex SAME tagg$3 SAME barcode SAME (universal NEAR tail) SAME sequenc$3)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:09 AM
L6	0	(multiplex SAME tagg$3 SAME barcode SAME (universal NEAR tail)) AND sequenc$3	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:09 AM
L7	0	(multiplex SAME tagged SAME barcode) AND (universal NEAR tail) AND sequenc$3	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:11 AM
L8	0	(multiplex SAME tagged SAME barcode) AND (universal NEAR tail) AND sequencing	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:11 AM
L9	3	(multiplex SAME (universal NEAR tail)) AND tagged AND barcode AND sequencing	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:12 AM
L10	3711884	(universal adaptor) multiplex AND sequencing AND "cell free" AND tagging AND	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT;	OR	ON	ON	2020/09/02 10:54 PM

		barcode	IBM_TDB)				
L11	527	(universal SAME adaptor) AND multiplex AND sequencing AND "cell free" AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 10:56 PM
L12	91	(universal SAME adaptor) AND (multiplex SAME sequencing SAME "cell free") AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 10:57 PM
L13	0	(universal SAME adaptor) AND (multiplex NEAR sequencing NEAR "cell free") AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:02 PM
L14	91	(universal SAME adaptor) AND (multiplex SAME sequencing SAME "cell free") AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:02 PM
L15	91	(universal SAME adaptor) AND (multiplex SAME sequencing SAME "cell free") AND tagging	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:11 PM
L16	12948	"L19" NOT L14	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:11 PM
L17	26547	"L15" NOT L14	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:11 PM
L18	0	L15 NOT L14	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:12 PM
L19	472	(universal SAME adaptor) AND (multiplex SAME sequencing) AND "cell free" AND tagging	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:12 PM
L20	580	(universal SAME adaptor) AND (sequencing) AND "cell free" AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/03 09:11 PM
L21	22	((universal SAME adaptor) SAME	(US-PGPUB; USPAT; USOCR; FIT (CN, FR,	OR	ON	ON	2020/09/03 09:11 PM

		sequencing SAME "cell free") AND tagging AND barcode	WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L22	9	("universal tail" SAME "SNP" AND "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:56 PM
L23	0	("universal tail" SAME "SNP" SAME "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:56 PM
L24	107	("universal tail" AND "SNP" AND "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:56 PM
L25	107	("universal tail" AND "SNP" AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:57 PM
L26	67	(L25) AND @ay<2010	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:04 PM
L27	1	("universal tail" AND ("SNP" NEAR (plurality OR multiplex)) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:54 PM
L28	197	(((tail OR adaptor) NEAR universal) AND ("SNP" NEAR (plurality OR multiplex)) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:55 PM
L29	8	((((tail OR adaptor) NEAR universal) SAME ("SNP" NEAR (plurality OR multiplex))) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:56 PM
L30	8	((((tail OR adaptor) NEAR universal) SAME (("SNP" OR polymorphism) NEAR (plurality OR multiplex))) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:57 PM
L31	2	((tagged SAME (("SNP" OR polymorphism)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR,	OR	ON	ON	2021/01/01 06:52 PM

		NEAR (plurality OR multiplex))) AND "cell free" AND sequencing)	WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L32	170	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 06:53 PM
L33	16	(L32) AND @ay<2010	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 06:53 PM
L34	0	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 07:07 PM
L35	0	(((tail OR adaptor) NEAR universal) AND ("SNP" NEAR (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 07:07 PM
L36	0	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/03/26 07:04 PM
L37	251	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND ("cell free" OR plasma OR circulating) AND sequencing AND cancer)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/03 10:15 PM
L38	37	L37 AND @ay<"2010"	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/03 10:17 PM
L39	16	("11130995" OR "20100273159" OR "20110312503" OR "20150086477" OR "20150322507" OR "20150329891" OR "20180023128" OR "20220025455" OR "20220025456" OR "20220033908" OR "20220033909" OR	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/04 10:55 PM

		"20220042103" OR "20220056509" OR "20220056534" OR "20220073978" OR "20220073979").pn.					
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L41	77	("10041127" OR "10061890" OR "10174369" OR "11111543" OR "11111544" OR "11111545" OR "20020119478" OR "20020182622" OR "20030044388" OR "20030087276" OR "20030138780" OR "20030232353" OR "20040096874" OR "20040146866" OR "20050043894" OR "20050282185" OR "20060094010" OR "20060216153" OR "20060292599" OR "20070037166" OR "20070134658" OR "20080280292" OR "20080286783" OR "20080299562" OR "20090053719" OR "20090263800" OR "20100041048" OR "20100086914" OR "20100105049" OR "20100129792" OR "20100285478" OR "20110294699" OR "20120264618" OR "20130022973" OR "20130085681" OR "20140066317" OR "20150299812" OR "20160046986" OR "20160239602" OR "20170011166" OR "20170314014" OR "20170362649" OR "20180187241" OR	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/04 11:20 PM

		"20180251553" OR "20180265917" OR "20190256924" OR "20200032323" OR "20210257048" OR "20210269879" OR "20210324463" OR "20210327538" OR "20210327542" OR "20210355536" OR "4683195" OR "4942124" OR "5648220" OR "5891734" OR "5962223" OR "6605451" OR "6858412" OR "7101663" OR "7153656" OR "7655399" OR "7981609" OR "8236503" OR "8318434" OR "8323897" OR "8372584" OR "8501409" OR "8679741" OR "8748103" OR "9005894" OR "9051602" OR "9206475" OR "9404150" OR "9493828" OR "9506119").pn.					

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	0	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2021/12/18 10:18 PM

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 06/04/2022

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

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U.S. PATENTS

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
		11130995	B2	2021-09-28	QUAKE, S. et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		20100273159	A1	2010-10-28	Melo, Francisco	
		20110312503	A1	2011-12-22	CHUU, Y.-J. et al.	
		20150086477	A1	2015-03-26	MITCHELL, A. T., et al.	
		20150322507	A1	2015-11-12	ZIMMERMANN, B. et al.	
		20180023128	A1	2018-01-25	YANAI, I. et al.	
		20150329891	A1	2022-01-21	TAN, Y. C., et al.	
		20220025455	A1	2022-01-27	ZIMMERMANN, B. et al.	
		20220025456	A1	2022-01-27	RABINOWITZ, M. et al.	

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

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		20220033908	A1	2022-02-03	RABINOWITZ, M. et al.	
		20220033909	A1	2022-02-03	BABIARZ, J. et al.	
		20220042103	A1	2022-02-10	RABINOWITZ, M. et al.	
		20220056509	A1	2022-02-24	ZIMMERMANN, Bernhard	
		20220056534	A1	2022-02-24	RIVERS, Elizabeth	
		20220073978	A1	2022-03-10	RABINOWITZ, M. et al.	
		20220073979	A1	2022-03-10	RABINOWITZ, M. et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
		2014/150300	WO	A2	2014-09-25	HUANG, S. X., et al.		
		104736722	CN	A	2015-06-24	HEAD, S. R., et al.		
		105229175	CN	A	2016-01-06	HUANG, S. X., et al.		

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

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	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

		2016009224	WO	A1	2016-01-21	Rosenfeld, Nitzan et al.		
		2018/237081	WO	A1	2018-12-27	MITCHELL, A. T., et al.		
		2022/015676	WO	A1	2022-01-20	MITCHELL, A. T., et al.		
		3443119	EP	B1	2022-02-23	ZIMMERMANN, B. et al.		

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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EXAMINER SIGNATURE

Examiner Signature	/STEPHANIE K MUMMERT/	Date Considered	06/04/2022

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

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reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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The submission of this Information Disclosure Statement does not constitute an admission that a search was made, does not constitute an admission that any information cited is prior art, and does not constitute an admission that no other or better art exists.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-03-14
Name/Print	Tianran Yan	Registration Number	67,162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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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	1	2015134552	WO	A1	2015-03-03	SWIFT BIOSCIENCES, INC.		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16934407
	Filing Date	2020-07-21
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

	1	LANMAN, et al., "Analytical and Clinical Validation of a Digital Sequencing Panel for Quantitative, Highly Accurate Evaluation of Cell-Free Circulating Tumor DNA", PLOS ONE, 2015, 1-27	
	2	LEE, et al., "ERBB2 kinase domain mutation in the lung squamous cell carcinoma", Cancer Letters, 2006, 89-94	
	3	PARK, et al., "First-Line Erlotinib Therapy Until and Beyond Response Evaluation Criteria in Solid Tumors Progression in Asian Patients With Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer", JAMA Oncol., 2015, 305-312	
	4	TSENG, JENG-SEN , et al., "Dynamic Plasma EGFR Mutation Status as a Predictor of EGFR-TKI Efficacy in Patients with fGFR-Mutant Lung Adenocarcinoma", Thorac Oncol., 2015, 603-610	

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Examiner Signature	/STEPHANIE K MUMMERT/	Date Considered	06/04/2022

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-04-27
Name/Print	Tianran Yan	Registration Number	67162

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Doc description: Information Disclosure Statement (IDS) Filed

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	Examiner Name	Stephanie Kane Mummert
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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
	1	8822153	B2	2014-09-02	HAYES, et al.	

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	1	2022-009866	A1	2022-03-31	RABINOWITZ, et al.	

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EFS ID:	45576944
Application Number:	16934407
International Application Number:	
Confirmation Number:	2396
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Customer Number:	110711
Filer:	Anton John Bokal/Angela McGowan
Filer Authorized By:	Anton John Bokal
Attorney Docket Number:	N.012.US.32
Receipt Date:	27-APR-2022
Filing Date:	21-JUL-2020
Time Stamp:	15:26:28
Application Type:	Utility under 35 USC 111(a)

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3	Non Patent Literature	LANMAN_2015_1-27_NPL.pdf	2190302 d065d46ca46b837b47bd4f821abd5fd2aced5c95	no	27
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U.S. PATENTS

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		11130995	B2	2021-09-28	QUAKE, S. et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		20100273159	A1	2010-10-28	Melo, Francisco	
		20110312503	A1	2011-12-22	CHUU, Y.-J. et al.	
		20150086477	A1	2015-03-26	MITCHELL, A. T., et al.	
		20150322507	A1	2015-11-12	ZIMMERMANN, B. et al.	
		20180023128	A1	2018-01-25	YANAI, I. et al.	
		20150329891	A1	2022-01-21	TAN, Y. C., et al.	
		20220025455	A1	2022-01-27	ZIMMERMANN, B. et al.	
		20220025456	A1	2022-01-27	RABINOWITZ, M. et al.	

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		20220033908	A1	2022-02-03	RABINOWITZ, M. et al.	
		20220033909	A1	2022-02-03	BABIARZ, J. et al.	
		20220042103	A1	2022-02-10	RABINOWITZ, M. et al.	
		20220056509	A1	2022-02-24	ZIMMERMANN, Bernhard	
		20220056534	A1	2022-02-24	RIVERS, Elizabeth	
		20220073978	A1	2022-03-10	RABINOWITZ, M. et al.	
		20220073979	A1	2022-03-10	RABINOWITZ, M. et al.	

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		2014/150300	WO	A2	2014-09-25	HUANG, S. X., et al.		
		104736722	CN	A	2015-06-24	HEAD, S. R., et al.		
		105229175	CN	A	2016-01-06	HUANG, S. X., et al.		

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		2016009224	WO	A1	2016-01-21	Rosenfeld, Nitzan et al.		
		2018/237081	WO	A1	2018-12-27	MITCHELL, A. T., et al.		
		2022/015676	WO	A1	2022-01-20	MITCHELL, A. T., et al.		
		3443119	EP	B1	2022-02-23	ZIMMERMANN, B. et al.		

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		BAU, STEPHAN et al., "Targeted next-generation sequencing by specific capture of multiple genomic loci using low-volume microfluidic DNA arrays", Anal Bioanal Chem, Vol. 393, 2009, 171-175	
		GONCALVES-PRIMO, A. et al., "Investigation of Apoptosis-Related Gene Expression Levels in Preimplantation Biopsies as Predictors of Delayed Kidney Graft Function", Transplantation, Vol. 97, No. 12, 27 JUN 2014,	
		NAKAMURA, N. et al., "Ex Vivo Liver Perfusion with Arterial Blood from A Pig with Ischemic Liver Failure", Artificial Organs, Vol. 23, No. 2, 1999, 153-160	
		NUI, A. et al., "The Functional Integrity of a Normothermic Perfusion System Using Artificial Blood in Pig Liver", Journal of Surgical Research, Vo. 131, 2006, 189-198	
		OLERUP, O. et al., "HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: an alternative to serological DR typing in clinical practice including donor-recipient	

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		matching in cadaveric transplantation", Tissue Antigens, Vol. 39, No. 5, MAY 1992, 225-235	
		PARUZYNSKI, A. et al., "Genome-wide high-throughput integrome analyses by nrLAM-PCR and next-generation sequencing", Nature Protocols, Vol. 5, No. 8, 8 JUL 2010, 1379-1395	

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[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

The submission of this Information Disclosure Statement does not constitute an admission that a search was made, does not constitute an admission that any information cited is prior art, and does not constitute an admission that no other or better art exists.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-03-14
Name/Print	Tianran Yan	Registration Number	67,162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

Electronic Acknowledgement Receipt

EFS ID:	45223740
Application Number:	16934407
International Application Number:	
Confirmation Number:	2396
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Customer Number:	110711
Filer:	Anton John Bokal/Jeremy Johnston
Filer Authorized By:	Anton John Bokal
Attorney Docket Number:	N.012.US.32
Receipt Date:	14-MAR-2022
Filing Date:	21-JUL-2020
Time Stamp:	18:11:45
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	Information Disclosure Statement (IDS) Form (SB08)	N012US32_SB08_SIGNED.pdf	620422 1bccd962d86155cc0d7d4dde67fad8a55bf9345b	no	5

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Information:					
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2	Non Patent Literature	BAU_2009_171-175_NPL.pdf	595252 6754c581c610dd9d17a74967ea063ae7df2081c1	no	5
Warnings:					
Information:					
3	Foreign Reference	CN104736722A_WO2013177220A1.pdf	2404339 75143f7250c287c892fef25009e606eed1edf468	no	184
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4	Foreign Reference	CN105229175A_WO2014150300A2.pdf	10796943 a40a961f0726f8bec747ca15b2373d62d5c570f8	no	384
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5	Foreign Reference	EP3443119B1.pdf	16006939 323e40ff3988619d6541f9a4ddaddf77e6a78259	no	194
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6	Non Patent Literature	Gonecalves_Primo_2014_1260_NPL.pdf	297125 f7f7820b0b50e5b829d27ceab7c2455d39b68fc1	no	6
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9	Non Patent Literature	Olerup_Zetterquist_1992_225_NPL.pdf	2205122 1c5c4e48285e29b2dc21938de588e0aa2ab2f174	no	11
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10	Non Patent Literature	PARUZYNSKI_2010_p1379_NPL.pdf	1718918 c4cb7a6012141928067e0e172fa19abe6edf47bf	no	17
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11	Foreign Reference	WO2014150300A2.pdf	917060 402f3a922475def508bbba72059e5300181b416c	no	113
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12	Foreign Reference	WO2016009224A1.pdf	4873217 19143089b81d4a7b1f97c61ea849cabc841792c1	no	71
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Warnings:					
Information:					
		Total Files Size (in bytes):	55654252		

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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.

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/934,407	**01/31/2022 03:02:57 PM ET**	**N.012.US.32**

Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2396	FILED BY	Natera MaxVal
PATENT CENTER #	60505247	FILING DATE	07/21/2020
CUSTOMER #	110711	FIRST NAMED INVENTOR	Matthew RABINOWITZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Anton Bokal

Documents

TOTAL DOCUMENTS: 38

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
RUSCHENDORF_2005_p2125_NPL.pdf	3	Non Patent Literature	262 KB
SANGER_1982_p773_NPL.pdf	45	Non Patent Literature	3384 KB
SHARPLES_2003_p679_NPL.pdf	4	Non Patent Literature	121 KB
SMITH_2008_p337_NPL.pdf	8	Non Patent Literature	138 KB
SMITH_2008_p1642_NPL.pdf	5	Non Patent Literature	270 KB

SOLEXA_2006_p2_NPL.pdf	2	Non Patent Literature	674 KB
SPES_1999_p515_NPL.pdf	7	Non Patent Literature	174 KB
STILLER_2009_p1848_NPL.pdf	6	Non Patent Literature	860 KB
STOLERMAN_2008_p1977_NPL.pdf	7	Non Patent Literature	125 KB
TAKALA_2006_p10_NPL.pdf	10	Non Patent Literature	561 KB
TONG_2005_p196_NPL.pdf	10	Non Patent Literature	214 KB
TOSHIKAZU_2003_p398_NPL.pdf	15	Non Patent Literature	291 KB
TROEGER_1999_p1165_NPL.pdf	4	Non Patent Literature	95 KB
TSANG_2007_p207_NPL.pdf	11	Non Patent Literature	206 KB
TUZCU_2005_p1542_NPL.pdf	5	Non Patent Literature	117 KB
UMETANI_2006_p1062_NPL.pdf	9	Non Patent Literature	851 KB
VERLAAN_2009_p127_NPL.pdf	10	Non Patent Literature	488 KB
VERLAAN_2009_p393_NPL.pdf	17	Non Patent Literature	966 KB
VOELKERDING_2009_p164_NPL.pdf	8	Non Patent Literature	316 KB
VOELKERDING_2009_p658_NPL.pdf	18	Non Patent Literature	2507 KB

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WELLNHOFER_2010_P1094_NPL.pdf	11	Non Patent Literature	357 KB
WIEDMANN_2008_p7_NPL.pdf	7	Non Patent Literature	258 KB
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WRIGHT_2009_p64_NPL.pdf	64	Non Patent Literature	1484 KB
XIA_2009_p24_NPL.pdf	5	Non Patent Literature	97 KB
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XIE_2009_p9_NPL.pdf	9	Non Patent Literature	1195 KB
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YANG_2009_p801_NPL.pdf	7	Non Patent Literature	241 KB
YIJEN_2009_p741_NPL.pdf	11	Non Patent Literature	1650 KB
ZHANG_2001_p381_NPL.pdf	2	Non Patent Literature	76 KB
ZHANG_2003_p194_NPL.pdf	5	Non Patent Literature	1092 KB
ZHANG_2009_p618_NPL.pdf	14	Non Patent Literature	715 KB
Zhao_1997_p881_NPL.pdf	9	Non Patent Literature	248 KB
ZHONG_2001_p257_NPL.pdf	8	Non Patent Literature	183 KB
ZHOU_2006_p3910_NPL.pdf	11	Non Patent Literature	348 KB

ZIMMER_2010_p377_NPL.pdf	11	Non Patent Literature	1028 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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New Applications Under 35 U.S.C. 111

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

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New International Application Filed with the USPTO as a Receiving Office

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Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
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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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	16934407	Filing Date	2020-07-21	Docket Number (if applicable)	N.012.US.32	Art Unit	1637
First Named Inventor	Matthew RABINOWITZ			Examiner Name	Stephanie Mummert		

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

SUBMISSION REQUIRED UNDER 37 CFR 1.114

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

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

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

☐ Other _____

☑ Enclosed

☐ Amendment/Reply

☑ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

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

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FEES

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

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

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Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-01-11
Name	Tianran Yan	Registration Number	67162

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

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	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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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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EXAMINER SIGNATURE

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Application Number:	16934407
Filing Date:	21-Jul-2020
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Filer:	Anton John Bokal/Angela McGowan
Attorney Docket Number:	N.012.US.32

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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EFS ID:	44878446
Application Number:	16934407
International Application Number:	
Confirmation Number:	2396
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Customer Number:	110711
Filer:	Anton John Bokal/Angela McGowan
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Attorney Docket Number:	N.012.US.32
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MUMMERT, STEPHANIE KANE

ART UNIT	PAPER NUMBER
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16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32	2396

TITLE OF INVENTION: METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	04/06/2022

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. 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)

NeoGenomics
Exhibit 1003 Page 196

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
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 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)

110711 7590 01/06/2022

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

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.
16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32	2396

TITLE OF INVENTION: METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1200.00	$0	04/06/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
MUMMERT, STEPHANIE KANE	1637	435-006120

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/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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

1 _____
2 _____
3 _____

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

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document 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. _____

NeoGenomics
Exhibit 1003 Page 197

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.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32	2396

110711 7590 01/06/2022

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 01/06/2022

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.

NeoGenomics
Exhibit 1003 Page 198

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

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

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

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

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

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

Notice of Allowability	Application No. 16/934,407	Applicant(s) RABINOWITZ et al.	
	Examiner STEPHANIE K MUMMERT	Art Unit 1637	AIA (FITF) Status Yes

-- 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 8/23/21.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3. ☑ The allowed claim(s) is/are 1-15 . 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 8/23/21.
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 _____.

/STEPHANIE K MUMMERT/
Primary Examiner, Art Unit 1637

CORRECTED DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on August 23, 2021 has been entered.

Applicant's response filed on August 23, 2021 is acknowledged and has been entered. Claims 1-15 are pending.

Claims 1-15 are discussed in this Office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on August 23, 2021 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Allowable Subject Matter

Claims 1-15 are allowed.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: The amendment to the claim requires the claimed method excludes samples of cell free nucleic acid obtained from a pregnant female and that the plural 25-2000 loci are associated with cancer. The amendment is sufficient to overcome the rejection of record and over any other references in the prior art which are focused on multiplex amplification and sequencing of 25 to 2000 SNP targets in a sample. The prior art which is focused on combined amplification and sequencing of cell-free or circulating nucleic acid targets neither teach or suggest each of the claimed features of the method. It is noted that references such as Su et al. (J of Molec Diagn, 2011, 13(1):74-84), as cited in an attached IDS, may appear relevant but there are substantial differences between Su and the method as claimed. Su does not antedate the priority dates of the instant application, the SNaPshot format of multiplex is not applied to cell free nucleic acid and the multiplex format of Su does not include simultaneous amplification and analysis of plural SNP loci, as claimed. Instead, the panel of SNP loci of Su are analyzed in grouped panels of four or six mutations instead of all separate loci together. Therefore, the claims are novel and non-obvious over the prior art.

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

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE KANE MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F 9:00-5:30.

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.

/STEPHANIE K MUMMERT/
Primary Examiner, Art Unit 1637

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	Art Unit
	STEPHANIE K MUMMERT	1637

CPC - Searched*		
Symbol	Date	Examiner

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 search - all names searched - PALM	08/31/2020	SKM
search Google/Scholar	09/03/2020	SKM
searched PE2E tool	09/03/2020	SKM
searched Google/Scholar	09/04/2020	SKM
searched using PE2E tool	01/01/2021	SKM
searched Google/Scholar	01/01/2021	SKM
considered 9/10/20 IDS and 12/2/20 IDS	01/01/2021	SKM
reviewed IDS	03/26/2021	SKM
search claims using PE2E search tool	03/26/2021	SKM
reviewed IDS	12/18/2021	SKM

NeoGenomics
Exhibit 1003 Page 204

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	Art Unit
	STEPHANIE K MUMMERT	1637

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
n/a	search claims using PE2E	03/26/2021	SKM
n/a	search claims using PE2E	12/18/2021	SKM

NeoGenomics
Exhibit 1003 Page 205

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	**Art Unit**
	STEPHANIE K MUMMERT	1637

CPC						
Symbol					**Type**	**Version**
C12Q	/	1	/	6883	F	2013-01-01
C12Q	/	1	/	6811	I	2013-01-01
C12Q	/	1	/	6848	I	2013-01-01
C12Q	/	1	/	6809	I	2013-01-01
C12Q	/	1	/	6851	I	2013-01-01
C12Q	/	1	/	6844	I	2013-01-01
C12Q	/	1	/	6869	I	2013-01-01
C12Q	/	1	/	6855	I	2013-01-01
C12Q	/	1	/	6874	I	2013-01-01
C12Q	/	2600	/	156	A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
C12Q	/	1	/	6848	I	1	1	2013-01-01
C12Q	/	2527	/	107	I	1	2	2013-01-01
C12Q	/	2537	/	143	I	1	3	2013-01-01
C12Q	/	1	/	6809	I	2	1	2013-01-01
C12Q	/	2527	/	107	I	2	2	2013-01-01
C12Q	/	2537	/	143	I	2	3	2013-01-01
C12Q	/	1	/	6851	I	3	1	2013-01-01
C12Q	/	2531	/	113	I	3	2	2013-01-01
C12Q	/	2535	/	122	I	3	3	2013-01-01
C12Q	/	2537	/	143	I	3	4	2013-01-01
C12Q	/	2563	/	159	I	3	5	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	15	
/STEPHANIE K MUMMERT/ Primary Examiner, Art Unit 1637	18 December 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20211218

NeoGenomics
Exhibit 1003 Page 206

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	**Art Unit**
	STEPHANIE K MUMMERT	1637

INTERNATIONAL CLASSIFICATION					
CLAIMED					
C12Q	/	1	/	68	
NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
435	6.12

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					
435	91.2					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 15	
/STEPHANIE K MUMMERT/ Primary Examiner, Art Unit 1637 (Primary Examiner)	18 December 2021 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office — Part of Paper No.: 20211218

NeoGenomics
Exhibit 1003 Page 207

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/934,407	RABINOWITZ et al.
	Examiner	Art Unit
	STEPHANIE K MUMMERT	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:	
(Assistant Examiner)	(Date)	15	
/STEPHANIE K MUMMERT/ Primary Examiner, Art Unit 1637	18 December 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20211218

NeoGenomics
Exhibit 1003 Page 208

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 12/18/2021

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
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 contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	16934407
Filing Date	2020-07-21
First Named Inventor	Matthew RABINOWITZ
Art Unit	1637
Examiner Name	Stephanie Kane Mummert
Attorney Docket Number	N.012.US.32

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
	1	5952170	A	1999-09-14	STROUN, et al.	
	2	6329179	B1	2001-12-11	KOPRESKI	
	3	7741463	B2	2010-06-22	GORMLEY, et al.	
	4	9228234	B2	2016-01-05	RABINOWITZ, et al.	
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	1	2009/105531	WO	A1	2009-08-27	GENE SECURITY NETWORK, INC.		

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That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2021-08-23
Name/Print	Tianran Yan	Registration Number	67162

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L2	85	(multiplex SAME tagg$3 SAME barcode SAME universal SAME sequenc$3)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:07 AM
L3	0	(multiplex SAME tagg$3 SAME barcode SAME universal SAME sequenc$3 SAME "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:08 AM
L4	85	(multiplex SAME tagg$3 SAME barcode SAME universal SAME sequenc$3),clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:08 AM
L5	0	(multiplex SAME tagg$3 SAME barcode SAME (universal NEAR tail) SAME sequenc$3)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:09 AM
L6	0	(multiplex SAME tagg$3 SAME barcode SAME (universal NEAR tail)) AND sequenc$3	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:09 AM
L7	0	(multiplex SAME tagged SAME barcode) AND (universal NEAR tail) AND sequenc$3	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:11 AM
L8	0	(multiplex SAME tagged SAME barcode) AND (universal NEAR tail) AND sequencing	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:11 AM
L9	3	(multiplex SAME (universal NEAR tail)) AND tagged AND barcode AND sequencing	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/08/31 10:12 AM
L10	3711884	(universal adaptor) multiplex AND sequencing AND "cell free" AND tagging AND	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT;	OR	ON	ON	2020/09/02 10:54 PM

		barcode	IBM_TDB)				
L11	527	(universal SAME adaptor) AND multiplex AND sequencing AND "cell free" AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 10:56 PM
L12	91	(universal SAME adaptor) AND (multiplex SAME sequencing SAME "cell free") AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 10:57 PM
L13	0	(universal SAME adaptor) AND (multiplex NEAR sequencing NEAR "cell free") AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:02 PM
L14	91	(universal SAME adaptor) AND (multiplex SAME sequencing SAME "cell free") AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:02 PM
L15	91	(universal SAME adaptor) AND (multiplex SAME sequencing SAME "cell free") AND tagging	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:11 PM
L16	12948	"L19" NOT L14	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:11 PM
L17	26547	"L15" NOT L14	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:11 PM
L18	0	L15 NOT L14	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:12 PM
L19	472	(universal SAME adaptor) AND (multiplex SAME sequencing) AND "cell free" AND tagging	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/02 11:12 PM
L20	580	(universal SAME adaptor) AND (sequencing) AND "cell free" AND tagging AND barcode	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2020/09/03 09:11 PM
L21	22	((universal SAME adaptor) SAME	(US-PGPUB; USPAT; USOCR; FIT (CN, FR,	OR	ON	ON	2020/09/03 09:11 PM

		sequencing SAME "cell free") AND tagging AND barcode	WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L22	9	("universal tail" SAME "SNP" AND "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:56 PM
L23	0	("universal tail" SAME "SNP" SAME "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:56 PM
L24	107	("universal tail" AND "SNP" AND "cell free")	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:56 PM
L25	107	("universal tail" AND "SNP" AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 04:57 PM
L26	67	(L25) AND @ay<2010	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:04 PM
L27	1	("universal tail" AND ("SNP" NEAR (plurality OR multiplex)) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:54 PM
L28	197	(((tail OR adaptor) NEAR universal) AND ("SNP" NEAR (plurality OR multiplex)) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:55 PM
L29	8	((((tail OR adaptor) NEAR universal) SAME ("SNP" NEAR (plurality OR multiplex))) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:56 PM
L30	8	((((tail OR adaptor) NEAR universal) SAME (("SNP" OR polymorphism) NEAR (plurality OR multiplex))) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 05:57 PM
L31	2	((tagged SAME (("SNP" OR polymorphism)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR,	OR	ON	ON	2021/01/01 06:52 PM

		NEAR (plurality OR multiplex))) AND "cell free" AND sequencing)	WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L32	170	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 06:53 PM
L33	16	(L32) AND @ay<2010	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 06:53 PM
L34	0	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 07:07 PM
L35	0	(((tail OR adaptor) NEAR universal) AND ("SNP" NEAR (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/01/01 07:07 PM
L36	0	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/03/26 07:04 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	0	((tagged SAME ("SNP" OR polymorphism) SAME (plurality OR multiplex)) AND "cell free" AND sequencing).clm.	(US-PGPUB; USPAT)	OR	ON	ON	2021/12/18 10:18 PM

UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/934,407	**01/05/2022 06:19:33 PM ET**	**N.012.US.32**

Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2396	FILED BY	Angela McGowan
PATENT CENTER #	60474197	FILING DATE	07/21/2020
CUSTOMER #	110711	FIRST NAMED INVENTOR	Matthew RABINOWITZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Anton Bokal

Documents

TOTAL DOCUMENTS: 20

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
WO2007100911A2.pdf	20	Foreign Reference	1993 KB
WO2007117039A1.pdf	69	Foreign Reference	2877 KB
WO2007140417A2.pdf	20	Foreign Reference	1683 KB
WO2007145612A1.pdf	108	Foreign Reference	4356 KB
WO2007147079A2.pdf	99	Foreign Reference	2707 KB
WO2008056937A1.pdf	30	Foreign Reference	1054 KB
WO2008079374A2.pdf	20	Foreign Reference	4819 KB

WO2008084405A2.pdf	199	Foreign Reference	4143 KB
WO2008115427A2.pdf	20	Foreign Reference	1842 KB
WO2008118988A1.pdf	55	Foreign Reference	2437 KB
WO2009017784A2.pdf	20	Foreign Reference	1814 KB
WO2009049889A1.pdf	46	Foreign Reference	3041 KB
WO2009064897A2.pdf	51	Foreign Reference	3194 KB
WO2005003375A2.pdf	200	Foreign Reference	3088 KB
WO2005023091A2.pdf	20	Foreign Reference	1562 KB
WO2005030999A1.pdf	393	Foreign Reference	4444 KB
WO2006110855A2.pdf	76	Foreign Reference	4325 KB
WO2007070280A2.pdf	167	Foreign Reference	3819 KB
WO2007075836A2.pdf	20	Foreign Reference	2322 KB
WO2007086935A2.pdf	278	Foreign Reference	4475 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
WO2007100911A2.pdf	B2D11B681BCF88900ACBCEB0984666162D462FA7E346A1362A051BBC5B9EC9FA02319F06A7662C1AB9686FAA4E2BF4726A4511A0E7F7FBD51701A57308799769
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WO2007140417A2.pdf	F2895DF73238BAFE1C4AD80DFF6959EEC7F21906CBCD992B B2B5BFEC18D47B3C9363C0D0245E6826F97B0F3BF8CC87B2 C9643BE7A6AA8AABA1F1A695E727D3A9
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WO2008115427A2.pdf	CE35936667DC24E5F3913E55845E384D14AC9CCDE0556561D 375188F34BD5F6DDB9B5F445511BB4FD6938763E7F1DFACF5 FBEACD58C155248B976A67E1E23A00
WO2008118988A1.pdf	8E725C681E3FEF8B6D3A3821807CB521A4DA68FA1C3919FBC 10FEACED55F178C8B4698C384423A3BE8300F447D1E6FE9AF 60F7BFA09A44A0D096360438F3234B
WO2009017784A2.pdf	70F7654EF939FBB9E275B81C7A05867DC116AB2A7C95084306 3A850BA585C1DA557FA5BF6B3CDBA941774CFB180403721FA 922357B46302704AE08C5335F003A
WO2009049889A1.pdf	CEEB2BED0426172C479652767 6B0DF9BC674033BD7D87910E 4FE22AD859B15C25A3100DA0507516AE5A1EF1963760403E6A 137B2A26597AB9C95355E8FE17AEB

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WO2005023091A2.pdf	50A923477C64E0DA419C0E6B5725492B27D2C17D596CBDD0C3529A82E55C1E4E4E6FBF1FB093FE1093798B7C75EFBB8D13491C1E967A89DB69930D64C056140
WO2005030999A1.pdf	578B12833ED3A038081D3BF0A48CA68591FC441A20D45F6F36F76380D700ADA433F7049C8B52AD880F1526C8AA8271AAC6CA934109B2F91D3CBB58C04B616641
WO2006110855A2.pdf	1975C15AD564A7F733678CA8B4A943E81748150E484A669E36D260BEB72D6756C8AC0C92CF8EF62EAB77DCD50274BC4914C33B9F38B907FC479F14222FFF3A56
WO2007070280A2.pdf	A694B51663330C623B167659A86EB1837DF624B408C37D3EE36DB07923025E3EC31F59EB8285CA905B14630D1030B26996FE13A18356C78737D917368B5E7C8B
WO2007075836A2.pdf	83F8A0164E28793F3972C08C6B9E387ADB4077DB85070DF1C81D2D31FB19FE75BE212B0F41D7CA4A9823C637DCD72CE431B5A1F5E6A677DFDD33162921A2FA5B
WO2007086935A2.pdf	6A08E0BC6622217F8686EF63902901D33BCF66BE681BE4518FAA6A35EE2473D90D1EF41F6978591F02CBD111ACDF7CF2B99BF9E4433C1B497B73464ED8326DA7

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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.

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

U.S. PATENTS						
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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	Attorney Docket Number	N.012.US.32

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	Examiner Name	Stephanie Kane Mummert
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	Attorney Docket Number	N.012.US.32

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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	Attorney Docket Number	N.012.US.32

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

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☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2022-01-05
Name/Print	Tianran Yan	Registration Number	67,162

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Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2396	FILED BY	Angela McGowan
PATENT CENTER #	60474207	FILING DATE	07/21/2020
CUSTOMER #	110711	FIRST NAMED INVENTOR	Matthew RABINOWITZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Anton Bokal

Documents

TOTAL DOCUMENTS: 7

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
WO2020106987A1.pdf	173	Foreign Reference	18833 KB
WO2021243045A1.pdf	100	Foreign Reference	4500 KB
WONG_2013_p7.11.1_NPL.pdf	12	Non Patent Literature	1434 KB
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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/934,407	**01/05/2022 06:24:04 PM ET**	**N.012.US.32**

Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2396	FILED BY	Angela McGowan
PATENT CENTER #	60474202	FILING DATE	07/21/2020
CUSTOMER #	110711	FIRST NAMED INVENTOR	Matthew RABINOWITZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Anton Bokal

Documents

TOTAL DOCUMENTS: 20

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
WO2010033578A2.pdf	20	Foreign Reference	1602 KB
WO2010042831A2.pdf	55	Foreign Reference	2946 KB
WO2010045617A2.pdf	20	Foreign Reference	2134 KB
WO2010115016A2.pdf	20	Foreign Reference	1515 KB
WO2010115154A1.pdf	20	Foreign Reference	1569 KB
WO2010118016A2.pdf	46	Foreign Reference	1898 KB
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WO2009117122A2.pdf	400	Foreign Reference	6511 KB
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PATENT CENTER #	60474184	FILING DATE	07/21/2020
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URBANOVA_2010_p242_NPL.pdf	18	Non Patent Literature	1002 KB
VALLONE_2008_p42_NPL.pdf	4	Non Patent Literature	536 KB
VANNESTE_2020_16pgs_NPL.pdf	16	Non Patent Literature	1450 KB
VLAMINCK_2014_26pgs_NPL.pdf	26	Non Patent Literature	5367 KB
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WITHERSPOON_2010_15pgs_NPL.pdf	15	Non Patent Literature	1530 KB
WO1995001796A1.pdf	62	Foreign Reference	1810 KB
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THOMPSON_2016_p5772_NPL.pdf	12	Non Patent Literature	1149 KB
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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.

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/934,407	**01/05/2022 05:56:02 PM ET**	**N.012.US.32**

Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2396	FILED BY	Angela McGowan
PATENT CENTER #	60474147	FILING DATE	07/21/2020
CUSTOMER #	110711	FIRST NAMED INVENTOR	Matthew RABINOWITZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Anton Bokal

Documents

TOTAL DOCUMENTS: 20

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
GO_2011_p372_NPL.pdf	11	Non Patent Literature	1486 KB
GWEE_2003_5_NPL.pdf	5	Non Patent Literature	4645 KB
HAHN_2001_p1577_NPL.pdf	2	Non Patent Literature	142 KB
HALFORD_1999_p835_NPL.pdf	1	Non Patent Literature	2084 KB
HANDLEY_2010_p581_NPL.pdf	12	Non Patent Literature	2012 KB
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New Applications Under 35 U.S.C. 111

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16/934,407	**01/05/2022 06:07:09 PM ET**	**N.012.US.32**

Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2396	FILED BY	Angela McGowan
PATENT CENTER #	60474169	FILING DATE	07/21/2020
CUSTOMER #	110711	FIRST NAMED INVENTOR	Matthew RABINOWITZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Anton Bokal

Documents

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DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
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PFAFFL_2004_p87_NPL.pdf	26	Non Patent Literature	2049 KB
QIAGEN_2003_68pgs_NPL.pdf	68	Non Patent Literature	3572 KB
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New Applications Under 35 U.S.C. 111

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

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/934,407	**01/05/2022 05:49:54 PM ET**	**N.012.US.32**

Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2396	FILED BY	Angela McGowan
PATENT CENTER #	60474133	FILING DATE	07/21/2020
CUSTOMER #	110711	FIRST NAMED INVENTOR	Matthew RABINOWITZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Anton Bokal

Documents

TOTAL DOCUMENTS: 20

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
BARTLETT_2003_NPL.pdf	5	Non Patent Literature	2017 KB
BENJAMINI_1995_p289_NPL.pdf	13	Non Patent Literature	1323 KB
BRASTIANOS_2015_p1164_NPL.pdf	15	Non Patent Literature	2445 KB
CHAVALI_2005_p3918_NPL.pdf	8	Non Patent Literature	935 KB
CHEN_2002_NPL.pdf	11	Non Patent Literature	3943 KB
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CUNNINGHAM_2006_p121_NPL.pdf	9	Non Patent Literature	686 KB
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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/934,407	**01/05/2022 06:02:52 PM ET**	**N.012.US.32**

Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2396	FILED BY	Angela McGowan
PATENT CENTER #	60474159	FILING DATE	07/21/2020
CUSTOMER #	110711	FIRST NAMED INVENTOR	Matthew RABINOWITZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Anton Bokal

Documents

TOTAL DOCUMENTS: 20

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
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KANE_2006_p694_NPL.pdf	3	Non Patent Literature	2375 KB
KENNEDY_2014_p2586_NPL.pdf	40	Non Patent Literature	1314 KB
KIBBE_2007_pW43_NPL.pdf	4	Non Patent Literature	5032 KB
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MARGUILES_2005_p376_NPL.pdf	67	Non Patent Literature	2984 KB
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JP2002300894_US2002182622A1.pdf	101	Foreign Reference	3351 KB
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Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	11098366
CONFIRMATION #	2396	FILED BY	Angela McGowan
PATENT CENTER #	60289284	FILING DATE	07/21/2020
CUSTOMER #	110711	FIRST NAMED INVENTOR	Matthew RABINOWITZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Anton Bokal

Documents

TOTAL DOCUMENTS: 57

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Trout_1992_p9823_NPL.pdf	3	Non Patent Literature	136 KB
Tufan_2005_p85_NPL.pdf	8	Non Patent Literature	77 KB
WO2009105531A1.pdf	61	Foreign Reference	593 KB
WO2011023078A1.pdf	27	Foreign Reference	579 KB
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NAWROZ_1996_p1035_NPL.pdf	3	Non Patent Literature	787 KB
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Digest

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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

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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.

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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.

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	16934407	Filing Date	2020-07-21	Docket Number (if applicable)	N.012.US.32	Art Unit	1637
First Named Inventor	Matthew RABINOWITZ			Examiner Name	Stephanie Mummert		

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

SUBMISSION REQUIRED UNDER 37 CFR 1.114

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

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

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

☐ Other _____

☑ Enclosed

☐ Amendment/Reply

☑ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

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

☐ Other _____

FEES

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

☑ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 506075

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

✓ Patent Practitioner Signature

Applicant Signature

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PTO/SB/30EFS (02-18)
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Signature of Registered U.S. Patent Practitioner			
Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2021-08-23
Name	Tianran Yan	Registration Number	67162

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

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

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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.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	16934407
Filing Date	2020-07-21
First Named Inventor	Matthew RABINOWITZ
Art Unit	1637
Examiner Name	Stephanie Kane Mummert
Attorney Docket Number	N.012.US.32

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	2	6329179	B1	2001-12-11	KOPRESKI	
	3	7741463	B2	2010-06-22	GORMLEY, et al.	
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	6	9453257	B2	2016-09-27	HOYAL-WRIGHTSON, et al.	
	7	10017810	B2	2018-07-10	IAFRATE, et al.	
	8	10227652	B2	2019-03-12	RABINOWITZ, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
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	9	10240202	B2	2019-03-26	RABINOWITZ, et al.	
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	5	20150211050	A1	2015-07-30	IAFRATE, et al.	
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	1	2009/105531	WO	A1	2009-08-27	GENE SECURITY NETWORK, INC.		

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	Attorney Docket Number	N.012.US.32

	2	2011/023078	WO	A1	2011-03-03	BEIGJING NMC CO., LTD.			
	3	2012042374	WO	A2	2012-04-05				
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	Attorney Docket Number	N.012.US.32

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2021-08-23
Name/Print	Tianran Yan	Registration Number	67162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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Electronic Patent Application Fee Transmittal

Application Number:	16934407
Filing Date:	21-Jul-2020
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Filer:	Anton John Bokal/Angela McGowan
Attorney Docket Number:	N.012.US.32

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Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
PETITION FEE- 37 CFR 1.17(H) (GROUP III)	1464	1	140	140
RCE- 1ST REQUEST	1801	1	1360	1360
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

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Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1500**

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Decision Date : August 23, 2021

In re Application of :

Matthew RABINOWITZ

DECISION ON PETITION
UNDER CFR 1.313(c)(2)

Application No : 16934407

Filed : 21-Jul-2020

Attorney Docket No : N.012.US.32

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed August 23, 2021 , to withdraw the above-identified application from issue after payment of the issue fee.

The petition is **GRANTED.**

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

Telephone inquiries concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

This application file is being referred to Technology Center AU 1637 for processing of the request for continuing examination under 37 CFR 1.114 .

Office of Petitions

Electronic Acknowledgement Receipt

EFS ID:	43578347
Application Number:	16934407
International Application Number:	
Confirmation Number:	2396
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Customer Number:	110711
Filer:	Anton John Bokal/Angela McGowan
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Receipt Date:	23-AUG-2021
Filing Date:	21-JUL-2020
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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.

Doc Code: PET.AUTO Document Description: Petition automatically granted by EFS-Web	PTO/SB/140 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)**
Application Number	16934407
Filing Date	21-Jul-2020
First Named Inventor	Matthew RABINOWITZ
Art Unit	1637
Examiner Name	
Attorney Docket Number	N.012.US.32
Title	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:
(1) Petition fee; and
(2) One of the following reasons:
(a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Petition Fee

- ○ Small Entity
- ○ Micro Entity
- ◉ Regular Undiscounted

Reason for withdrawal from issue

◯ One or more claims are unpatentable ◉ Consideration of a request for continued examination (RCE) (List of Required Documents and Fees) ◯ Applicant hereby expressly abandons the instant application (any attorney/agent signing for this reason must have power of attorney pursuant to 37 CFR 1.32(b)).
RCE request,submission, and fee. ☐ I certify, in accordance with 37 CFR 1.4(d)(4) that : The RCE request ,submission, and fee have already been filed in the above-identified application on ☒ Are attached.
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application. ◯ An attorney or agent registered to practice before the Patent and Trademark Office, acting in a representative capacity. ◯ A sole inventor ◯ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ◯ A joint inventor; all of whom are signing this e-petition

Signature	/Anton Bokal/
Name	Anton Bokal
Registration Number	51243

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.
16/934,407	08/24/2021	11098366	N.012.US.32	2396

110711 7590 08/04/2021

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

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):

Natera, Inc., San Carlos, CA;
Matthew RABINOWITZ, San Francisco, CA;
Matthew Micah HILL, Belmont, CA;
Bernhard ZIMMERMANN, Manteca, CA;
Johan BANER, San Francisco, CA;
George GEMELOS, Portland, OR;
Milena BANJEVIC, Los Altos Hills, CA;
Allison RYAN, Belmont, CA;
Styrmir SIGURJONSSON, San Jose, CA;
Zachary DEMKO, San Francisco, CA;

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.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32

CONFIRMATION NO. 2396

110711
Natera, Inc.
201 Industrial Road
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37 CFR 1.48(f)
ACKNOWLEDGEMENT LETTER

OC000000126914161

Date Mailed: 07/13/2021

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(f)

This is in response to the applicant's request under 37 CFR 1.48(f) submitted on 06/03/2021.

The request under 37 CFR 1.48(f) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

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**.

/byemane/

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/934,407	07/21/2020	1637	3720	N.012.US.32	15	1

CONFIRMATION NO. 2396

UPDATED FILING RECEIPT

110711
Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

OC000000128914159

Date Mailed: 07/13/2021

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)

Matthew RABINOWITZ, San Francisco, CA;
Matthew Micah HILL, Belmont, CA;
Bernhard ZIMMERMANN, Manteca, CA;
Johan BANER, San Francisco, CA;
George GEMELOS, Portland, OR;
Milena BANJEVIC, Los Altos Hills, CA;
Allison RYAN, Belmont, CA;
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Zachary DEMKO, San Francisco, CA;

Applicant(s)

Natera, Inc., San Carlos, CA;

Assignment For Published Patent Application

Natera, Inc., San Carlos, CA

Power of Attorney: The patent practitioners associated with Customer Number 110711

Domestic Priority data as claimed by applicant

This application is a CON of 16/743,724 01/15/2020 PAT 10731220
which is a CON of 16/399,268 04/30/2019 PAT 10538814
which is a CON of 16/140,298 09/24/2018
which is a CON of 14/918,544 10/20/2015 PAT 10316362
which is a CIP of 14/877,925 10/07/2015 ABN
and is a CIP of 14/692,703 04/21/2015 PAT 10179937

and is a CIP of 14/538,982 11/24/2014 PAT 9677118
and claims benefit of 62/148,173 04/15/2015
and claims benefit of 62/147,377 04/14/2015
and claims benefit of 62/146,188 04/10/2015
and claims benefit of 62/066,514 10/21/2014
and said 14/877,925 10/07/2015
is a CIP of 14/225,356 03/25/2014 ABN
and is a CIP of 13/780,022 02/28/2013 ABN
and is a CON of 13/683,604 11/21/2012 ABN
and said 14/692,703 04/21/2015
claims benefit of 62/148,173 04/15/2015
and claims benefit of 62/147,377 04/14/2015
and claims benefit of 62/146,188 04/10/2015
and claims benefit of 62/066,514 10/21/2014
and claims benefit of 61/994,791 05/16/2014
and claims benefit of 61/987,407 05/01/2014
and claims benefit of 61/982,245 04/21/2014
and said 14/538,982 11/24/2014
claims benefit of 62/066,514 10/21/2014
and claims benefit of 61/994,791 05/16/2014
and claims benefit of 61/987,407 05/01/2014
and claims benefit of 61/982,245 04/21/2014
and said 14/225,356 03/25/2014
is a CON of PCT/US2012/058578 10/03/2012
and said 13/780,022 02/28/2013
is a CIP of 13/683,604 11/21/2012 ABN
and is a CIP of PCT/US2012/058578 10/03/2012
and is a CIP of 13/335,043 12/22/2011 PAT 10113196
which is a CIP of 13/300,235 11/18/2011 PAT 10017812
which is a CIP of 13/110,685 05/18/2011 PAT 8825412
and said 13/780,022 02/28/2013
claims benefit of 61/634,431 02/29/2012
and said 13/683,604 11/21/2012
is a CIP of 13/300,235 11/18/2011 PAT 10017812
and is a CIP of 13/110,685 05/18/2011 PAT 8825412
and claims benefit of 61/675,020 07/24/2012
and said PCT/US2012/058578 10/03/2012
is a CIP of 13/300,235 11/18/2011 PAT 10017812
and claims benefit of 61/683,331 08/15/2012
and claims benefit of 61/542,508 10/03/2011
and said 13/335,043 12/22/2011
is a CIP of 13/300,235 11/18/2011 PAT 10017812
and is a CIP of 13/110,685 05/18/2011 PAT 8825412
and claims benefit of 61/426,208 12/22/2010
and said 13/300,235 11/18/2011
is a CIP of 13/110,685 05/18/2011 PAT 8825412
and claims benefit of 61/542,508 10/03/2011
and claims benefit of 61/571,248 06/23/2011
and said 13/110,685 05/18/2011
claims benefit of 61/516,996 04/12/2011
and claims benefit of 61/448,547 03/02/2011

and claims benefit of 61/448,547 03/02/2011
and claims benefit of 61/462,972 02/09/2011
and claims benefit of 61/398,159 06/21/2010
and claims benefit of 61/395,850 05/18/2010

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.

Projected Publication Date: Not Applicable
Non-Publication Request: No
Early Publication Request: No
Title

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

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.

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :C46910

Sale Accounting Date:07/12/2021

Sale Item Reference Number	Effective Date
16934407	06/03/2021

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20217BC59560716	1830	PROCESSING FEE, EXCEPT PROV. APPLS.	$140.00	Deposit Account

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :C46910

Sale Adjustment Accounting Date:07/12/2021

Effective Date	Sale Accounting Date	Sale Item Reference Number
06/03/2021	07/12/2021	16934407

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20217BC57540682	1464	PETITION FEE- 37 CFR 1.17(H) (GROUP III)	$140.00	DA

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :C46910

Refund Accounting Date:07/12/2021

Effective Date	Sale Item Reference Number	Refund Total
06/03/2021	16934407	$140.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I20217BC57540682	1464	PETITION FEE- 37 CFR 1.17(H) (GROUP III)	$140.00	DA	506075

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32	2396

110711 7590 07/09/2021

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

EXAMINER
MUMMERT, STEPHANIE KANE

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
07/09/2021	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@natera.com

Corrected ***Notice of Allowability***	**Application No.** 16/934,407	**Applicant(s)** RABINOWITZ et al.	
	Examiner STEPHANIE K MUMMERT	**Art Unit** 1637	**AIA (FITF) Status** Yes

-- 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 3/3/21.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3. ☑ The allowed claim(s) is/are 1-15 . 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 6/3/21.
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 _____.

/STEPHANIE K MUMMERT/
Primary Examiner, Art Unit 1637

CORRECTED DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Applicant's response filed on March 3, 2021 is acknowledged and has been entered. Claims 1-15 are pending. Claim 1 is amended.

Claims 1-15 are discussed in this Office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on January 5, 2021, March 3, 2021 April 16, 2021 and June 3, 2021 were filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Allowable Subject Matter

Claims 1-15 are allowed.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: The amendment to the claim requires the claimed method excludes samples of cell free nucleic acid obtained from a pregnant female and that the plural 25-2000 loci are associated with cancer. The amendment is sufficient to overcome the rejection of record and over any other references in the prior art which are focused on multiplex amplification and sequencing of 25 to 2000 SNP targets in a sample.

The prior art which is focused on combined amplification and sequencing of cell-free or circulating nucleic acid targets neither teach or suggest each of the claimed features of the method. It is noted that references such as Su et al. (J of Molec Diagn, 2011, 13(1):74-84), as cited in an attached IDS, may appear relevant but there are substantial differences between Su and the method as claimed. Su does not antedate the priority dates of the instant application, the SNaPshot format of multiplex is not applied to cell free nucleic acid and the multiplex format of Su does not include simultaneous amplification and analysis of plural SNP loci, as claimed. Instead, the panel of SNP loci of Su are analyzed in grouped panels of four or six mutations instead of all separate loci together. Therefore, the claims are novel and non-obvious over the prior art.

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

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE KANE MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F 9:00-5:30.

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.

/STEPHANIE K MUMMERT/
Primary Examiner, Art Unit 1637

Notice of References Cited	Application/Control No. 16/934,407	Applicant(s)/Patent Under Reexamination RABINOWITZ et al.	
	Examiner STEPHANIE K MUMMERT	Art Unit 1637	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
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Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

U.S. PATENTS

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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		2007/011903	WO	A3	2007-01-25	LAO, K. Q., et al.		
		2012/058488	WO	A1	2012- 05-03	ZHANG, D. Y., et al.		

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
		COURAUD, S. et al., "Noninvasive Diagnosis of Actionable Mutations by Deep Sequencing of Circulating Free DNA in lung Cancer from Never-Smokers: A Proof-of-Concept Study from BioCAST / IFCT-1002", Clinical Cancer Research, Vol. 20, No. 17, 10 JUL 2014, 4613-4624	

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EXAMINER SIGNATURE

Examiner Signature	/STEPHANIE K MUMMERT/	Date Considered	07/06/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

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☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

The submission of this Information Disclosure Statement does not constitute an admission that a search was made, does not constitute an admission that any information cited is prior art, and does not constitute an admission that no other or better art exists.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2021-06-03
Name/Print	Tianran Yan	Registration Number	67,162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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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		98/39474	WO		1998-09-11	LO, Y.M.D. et al.		

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 07/06/2021

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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	Art Unit	1637
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EXAMINER SIGNATURE

Examiner Signature	/STEPHANIE K MUMMERT/	Date Considered	07/06/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 07/06/2021

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Attorney Docket Number	N.012.US.32

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PTO/SB/08a (01-10)
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	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

OR

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

The submission of this Information Disclosure Statement does not constitute an admission that a search was made, does not constitute an admission that any information cited is prior art, and does not constitute an admission that no other or better art exists.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2021-06-03
Name/Print	Tianran Yan	Registration Number	67,162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/934,407	06/03/2021 03:59:55 PM ET	N.012.US.32

Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2396	FILED BY	Angela McGowan
PATENT CENTER #	60207559	AUTHORIZED BY	Anton Bokal
CUSTOMER #	110711	FILING DATE	07/21/2020
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Matthew RABINOWITZ

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 506075	E202163G00221732	Angela McGowan

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	260.00	1	260.00
1501	UTILITY ISSUE FEE	1200.00	1	1200.00
			TOTAL AMOUNT:	$1,460.00

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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

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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.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/934,407	**06/03/2021 03:59:55 PM ET**	**N.012.US.32**

Title of Invention

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

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PATENT CENTER #	60207559	FILING DATE	07/21/2020
CUSTOMER #	110711	FIRST NAMED INVENTOR	Matthew RABINOWITZ
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Anton Bokal

Documents

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Doc Code: R48.REQ
Document Description: Request under Rule 48 correcting inventorship

PTO/AIA/40 (04-18)
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REQUEST FOR CORRECTION IN A PATENT APPLICATION RELATING TO INVENTORSHIP OR AN INVENTOR NAME, OR ORDER OF NAMES, OTHER THAN IN A REISSUE APPLICATION (37 CFR 1.48)

Application Number	16/934,407
Filing Date	07-21-2020
First Named Inventor	Matthew RABINOWITZ
Art Unit	1637
Examiner Name	MUMMERT, STEPHANIE KANE
Practitioner Docket Number	N.012.US.32

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

Applicant hereby **requests that the inventorship be corrected or changed, or that the name of the inventor or a joint inventor, or the order of the names of joint inventors, be changed,** in the above-identified application. **Note:** 37 CFR 1.48 applies to any request to correct inventorship filed on or after September 16, 2012, regardless of the application filing date. **Do not submit this form after payment of the issue fee or if the application has been patented.** See 37 CFR 1.324 for correction of inventorship in a patent.

Please check the applicable box(es) below.

For a nonprovisional application:

☐ 1. This request is to correct or change the inventorship in a **nonprovisional** application (**under 37 CFR 1.48(a)**) and includes:

☐ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). See the Manual of Patent Examining Procedure (MPEP) section 601.05(a) for information about filing an ADS in an application filed on/after September 16, 2012. For information about filing a Supplemental ADS in an application filed before September 16, 2012, see MPEP 601.05(b).

☐ The processing fee set forth in 37 CFR 1.17(i). $ _____

☐ An inventor is being added. An inventor's oath or declaration by any actual inventor who has not yet executed an oath or declaration is required (see 37 CFR 1.48(b)). See MPEP 602.01(a) for information about an inventor's oath or declaration for an application filed on/after September 16, 2012 (*e.g.*, form **PTO/AIA/01**). For information about an inventor's oath or declaration for an application filed before September 16, 2012 (*e.g.*, form **PTO/SB/01**), see MPEP 602.01(b).

☐ This request is being filed after the first Office action on the merits has been given or mailed (see 37 CFR 1.48(c) and 1.17(d)). Check one of the following:

☐ This request to correct or change the inventorship is due solely to the cancellation of claims in the application.

OR

☐ The fee set forth in 37 CFR 1.17(d) is due (in addition to the fee set forth in 37 CFR 1.17(i)). $ _____

This collection of information is required by 37 CFR 1.48. 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 hour 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.**

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

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REQUEST FOR CORRECTION IN A PATENT APPLICATION RELATING TO INVENTORSHIP OR AN INVENTOR NAME, OR ORDER OF NAMES, OTHER THAN IN A REISSUE APPLICATION (37 CFR 1.48)

☒ 2. This request is to correct or update the name of the inventor or a joint inventor, or the order of names of joint inventors, in a **nonprovisional** application (**under 37 CFR 1.48(f)**) and includes:

☒ An application data sheet in accordance with 37 CFR 1.76(c) identifying the complete inventive entity, including the corrected or updated name of the inventor, or the new order of names shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). See the MPEP 601.05(a) for information about filing an ADS in an application filed on/after September 16, 2012. For information about filing a Supplemental ADS in an application filed before September 16, 2012, see MPEP 601.05(b).

☒ The processing fee set forth in 37 CFR 1.17(i). $ 140.00

For a provisional application:

☐ This request is to change or correct the inventorship, or correct or update the name of the inventor or a joint inventor, in a **provisional** application (**under 37 CFR 1.48(d)**) and includes:

☐ **Attached hereto** is a document that is signed by a party set forth in 37 CFR 1.33(b) and identifies each inventor by his or her legal name, in the preferred order. Note: the document may be an application data sheet in accordance with 37 CFR 1.76(c) that identifies the changes with markings (underlining for insertions, strikethrough for deletions).

☐ The processing fee set forth in 37 CFR 1.17(q). $ _____

Fee Payment Information:

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 506075.

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WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ Applicant*

☒ attorney or agent of record
Registration number 67162

☐ attorney or agent acting under 37 CFR 1.34
Registration number _____

Signature /Tianran Yan/

Typed or printed name Tianran Yan

Date 6-3-2021

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. *Juristic entities must be represented by a patent practitioner (See 37 CFR 1.31, applicable to any paper filed on or after September 16, 2012 that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below**.

☒ ** Total of 1 forms are submitted.

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
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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.

Electronic Patent Application Fee Transmittal

Application Number:	16934407
Filing Date:	21-Jul-2020
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Filer:	Anton John Bokal/Angela McGowan
Attorney Docket Number:	N.012.US.32

Filed as Large 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:				
PETITION FEE- 37 CFR 1.17(H) (GROUP III)	1464	1	140	140
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**140**

Electronic Acknowledgement Receipt

EFS ID:	42892086
Application Number:	16934407
International Application Number:	
Confirmation Number:	2396
Title of Invention:	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI
First Named Inventor/Applicant Name:	Matthew RABINOWITZ
Customer Number:	110711
Filer:	Anton John Bokal/Angela McGowan
Filer Authorized By:	Anton John Bokal
Attorney Docket Number:	N.012.US.32
Receipt Date:	03-JUN-2021
Filing Date:	21-JUL-2020
Time Stamp:	15:46:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$140
RAM confirmation Number	E202163F46531426
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	02_N012US32_ADS_SIGNED.pdf	180202 11eb8094c7638e6d9e6bea06d1e62723a42088d3	no	11
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2	Oath or Declaration filed	03_N012US32_Declaration_ZIMMERMANN.pdf	339606 57dce17fe0854561adaa56eb2c298e8472f2eb1d	no	2
Warnings:					
Information:					
3	Request under Rule 48 correcting inventorship	01_N012US32_Request_for_Correction_Relating_to_Inventorship_SIGNED.pdf	173888 cce9b59546945fd7b056b97afe50e37529ac2e99	no	3
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30582 873c197c48d97af7406976cbc9c07b8aca2e6971	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	724278		

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.

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SUPPLEMENTAL Application Data Sheet 37 CFR 1.76	Attorney Docket Number	N.012.US.32
	Application Number	16934407
Title of Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI	

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
	Matthew		RABINOWITZ	

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

City	San Francisco	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	201 Industrial Road		
Address 2	Suite 410		
City	San Carlos	State/Province	CA
Postal Code	94070	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Matthew	Micah	HILL	

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

City	Belmont	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	201 Industrial Road		
Address 2	Suite 410		
City	San Carlos	State/Province	CA
Postal Code	94070	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bernhard		~~EUBANK~~ ZIMMERMANN	

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

SUPPLEMENTAL Application Data Sheet 37 CFR 1.76	Attorney Docket Number	N.012.US.32
	Application Number	16934407
Title of Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI	

City	Manteca	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	201 Industrial Road		
Address 2	Suite 410		
City	San Carlos	State/Province	CA
Postal Code	94070	Country	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Johan		BANER	

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

City	San Francisco	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	201 Industrial Road		
Address 2	Suite 410		
City	San Carlos	State/Province	CA
Postal Code	94070	Country	US

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
Mr.	George		GEMELOS	

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

City	Portland	State/Province	OR	Country of Residence	US

Mailing Address of Inventor:

Address 1	201 Industrial Road		
Address 2	Suite 410		
City	San Carlos	State/Province	CA
Postal Code	94070	Country	US

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Milena		BANJEVIC	

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

City	Los Altos Hills	State/Province	CA	Country of Residence	US

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SUPPLEMENTAL Application Data Sheet 37 CFR 1.76	Attorney Docket Number	N.012.US.32
	Application Number	16934407
Title of Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI	

Mailing Address of Inventor:

Address 1	201 Industrial Road		
Address 2	Suite 410		
City	San Carlos	**State/Province**	CA
Postal Code	94070	**Country**	US

Inventor 7 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Allison		RYAN	

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

City	Belmont	**State/Province**	CA	**Country of Residence**	US

Mailing Address of Inventor:

Address 1	201 Industrial Road		
Address 2	Suite 410		
City	San Carlos	**State/Province**	CA
Postal Code	94070	**Country**	US

Inventor 8 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Styrmir		SIGURJONSSON	

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

City	San Jose	**State/Province**	CA	**Country of Residence**	US

Mailing Address of Inventor:

Address 1	201 Industrial Road		
Address 2	Suite 410		
City	San Carlos	**State/Province**	CA
Postal Code	94070	**Country**	US

Inventor 9 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Zachary		DEMKO	

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

City	San Francisco	**State/Province**	CA	**Country of Residence**	US

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SUPPLEMENTAL Application Data Sheet 37 CFR 1.76	Attorney Docket Number	N.012.US.32
	Application Number	16934407
Title of Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI	

Mailing Address of Inventor:			
Address 1	201 Industrial Road		
Address 2	Suite 410		
City	San Carlos	State/Province	CA
Postal Code	94070	Country i	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	110711		
Email Address	IP@Natera.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI		
Attorney Docket Number	N.012.US.32	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		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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SUPPLEMENTAL Application Data Sheet 37 CFR 1.76	Attorney Docket Number	N.012.US.32
	Application Number	16934407
Title of Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI	

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	110711		

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			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

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

Foreign Priority Information:

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.

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SUPPLEMENTAL Application Data Sheet 37 CFR 1.76	Attorney Docket Number	N.012.US.32
	Application Number	16934407
Title of Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI	

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.

SUPPLEMENTAL Application Data Sheet 37 CFR 1.76	Attorney Docket Number	N.012.US.32
	Application Number	16934407
Title of Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI	

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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SUPPLEMENTAL Application Data Sheet 37 CFR 1.76	Attorney Docket Number	N.012.US.32
	Application Number	16934407
Title of Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI	

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

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. ☐

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

Mailing Address Information For Applicant:

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

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

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.

SUPPLEMENTAL Application Data Sheet 37 CFR 1.76	Attorney Docket Number	N.012.US.32
	Application Number	16934407
Title of Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI	

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.

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.

Signature:

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	/Tianran Yan/			Date (YYYY-MM-DD)	2021-06-03
First Name	Tianran	Last Name	Yan	Registration Number	67162

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

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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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SUPPLEMENTAL Application Data Sheet 37 CFR 1.76	Attorney Docket Number	N.012.US.32
	Application Number	16934407
Title of Invention	METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI	

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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.**

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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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	DETECTING MUTATIONS AND PLOIDY IN CHROMOSOMAL SEGMENTS

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 14/692,703

filed on April 21, 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.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Bernhard Zimmermann Date (Optional): _____

Signature: Bernhard Zimmermann

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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	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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EXAMINER SIGNATURE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	16/934,407
Filing Date	Jul 21, 2020
First Named Inventor	Matthew RABINOWITZ
Art Unit	1637
Examiner Name	Stephanie Kane Mummert
Attorney Docket Number	N.012.US.32

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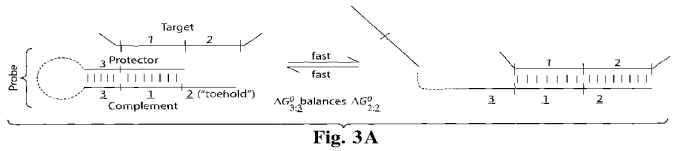


Fig. 3A

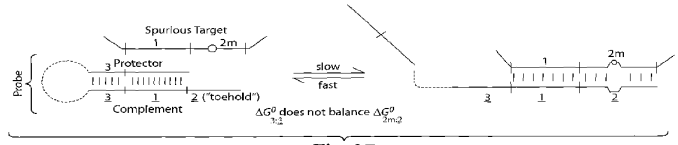


Fig. 3B

(57) Abstract: Provided herein are primers and primer systems having improved specificity and kinetics over existing primers, and methods of use thereof.

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COMPOSITIONS OF TOEHOLD PRIMER DUPLEXES AND METHODS OF USE

RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119(e) from U.S. provisional application serial number 61/407,291, filed October 27, 2010, the entire contents of which are incorporated by reference herein.

FIELD OF INVENTION

The embodiments described herein relate to partially double-stranded nucleic acid primers and their use in, for example, nucleic acid synthesis methods.

BACKGROUND OF INVENTION

Nucleic acids are vital information carriers of biology, and the detection, amplification, and identification of nucleic acids has formed the basis for a vast sector of biotechnology. In particular, methods such as the polymerase chain reaction (PCR) (Saiki *et al. Science* 239, 487-491 (1988)) have been used all over the world as a reliable means of amplifying DNA, while reverse transcriptase methods have been used to probe the transcriptome. The operation of DNA polymerase, RNA polymerase, and reverse transcriptase typically uses a short oligonucleotide fragment known as a primer to direct the portion of a long target to be replicated or transcribed.

Although the specificity of nucleic acid hybridization is frequently sufficient to direct enzymatic activity for most target sequences, targets with repetitive sequence, secondary structure, and high G/C content are difficult to amplify with high yield. Furthermore, high backgrounds of other nucleic acids can frequently lead to incorrect amplification, such as in the case of single copy human genome amplification. Finally, multiplexed amplification, such as from a DNA chip pool, can be difficult to achieve due to the large number of orthogonal amplification reactions that must occur simultaneously. Similar problems exist for transcription and for reverse transcription.

SUMMARY OF INVENTION

The hybridization of nucleic acids is specific at the single nucleotide level. For example, cytosine preferentially binds to guanine, and adenine preferentially binds to thymine or uracil.

However, for nucleic acid molecules composed of many nucleotides, the specificity of hybridization is reduced, and nucleic acids with near complementary sequences will bind almost as strongly as perfect complementary sequences. Given a heterogeneous mixture of target nucleic acid of interest ("targets") and nucleic acids with sequences that differ from the target by, for example, one nucleotide ("spurious targets"), a significant portion of primers complementary to the target will hybridize instead to spurious targets.

Because the correct targets bind with a slightly higher affinity to a primer having a complementary sequence, given enough time, correct targets will eventually displace spurious targets in binding to a complementary primer. Though, this process is very slow, and would take months at the nanomolar concentrations typical of many experimental systems.

In order to mitigate the propensity of complementary primers binding to spurious targets it is often necessary to operate nucleic acid primer-based experimental systems near the melting temperature of the primer/target complex. Because this melting temperature is generally much higher than the temperature at which most biological systems naturally operate, this high temperature requirement precludes the experimental system from operating under normal biological conditions. Additionally, because the melting temperature will vary from target to target, the requisite narrow temperature range for such experimental systems restricts the simultaneous use of multiple primers to detect a plurality of targets.

Provided herein are primers *(e.g.,* primer duplexes and hairpin primer duplexes) that, in embodiments, are able to rapidly bind to nucleic acid targets with high specificity at a broad range of temperatures. These primers may be used, for example, in nucleic acid synthesis reactions *(e.g.,* PCR), microarray analyses, imaging methods, and single nucleotide polymorphism (SNP) analyses. The primers may also be used in nucleic acid detection assays where they function primarily as "probes". Accordingly, regardless of the application, the primers of the invention may be referred herein to interchangeably as "probes". Regardless of the application (or method of use), the primers of the invention overcome problems commonly experienced when specific hybridization is required in the presence of spurious targets, and more particularly when such spurious targets are present in excess.

The primers provided herein possess several unique properties that facilitate their use in combination with enzymes that act upon nucleic acids. First, the primers are thermodynamically designed to bind with high specificity to only their intended targets, and they show high

NeoGenomics
Exhibit 1003 Page 395

discrimination against even single-nucleotide changes. Second, the specificity of the primers enables PCR, transcription, and reverse transcription of traditionally difficult targets, such as those having significant sequence repetition, secondary structure, and/or high G/C content. The high degree of specificity that can be achieved with these primers further enables accurate processing even in high nucleic acid backgrounds such as single-copy human genome amplification. Third, the partially double-stranded nature of the primers means that they are unlikely to interact with each other, and consequently they are amenable to highly multiplexed replication, transcription, and/or reverse transcription reactions. Finally, the hybridization of these primers to targets is relatively robust to temperature and salinity, and therefore the primers may be of significantly greater length than standard primers, which in turn provides further enhanced specificity and primer design flexibility.

In some embodiments, the nucleic acid primers discussed here are rationally designed so that the standard free energy for hybridization *(e.g.,* theoretical standard free energy) between the specific target nucleic acid molecule and the primer is close to zero, while the standard free energy for hybridization between a spurious target (even one differing from the specific (actual) target by as little as a single nucleotide) and the primer is high enough to make their binding unfavorable by comparison. The inventors accomplished this by designing a primer having (a) a "toehold" single-stranded target specific region, (b) a "branch migration" double -stranded target specific region, and (c) a "balance" double -stranded target non-specific region.

In some embodiments, the primer may be comprised of a single strand that self hybridizes to form double-stranded regions. In some embodiments, the primer may be comprised of two strands. As an example of the latter embodiment, the primers is comprised of a first or complement strand and a second or protector strand. The complement strand, as its name implies, is partially complementary to the target of interest and will hybridize to the target. The protector strand, on the other hand, is designed to not hybridize to the target and rather to compete with the target (or spurious target) for binding of the complement.

The "toehold" region is present in the complement strand, is complementary to a target sequence and not complementary to a protector region. The "balance" region in the complement strand (i.e., the complement balance region) is complementary to part of the protector (i.e., to the protector balance region) and not complementary to target sequence. The hybridization energy of toehold to target is matched or nearly matched to the hybridization energy of complement

NeoGenomics
Exhibit 1003 Page 396

balance region to protector balance region (adjusting for various other thermodynamic considerations). The sequence of the balance region is rationally designed to achieve this matching under desired conditions of temperature and primer concentration. As a result, the equilibrium for the actual target and primer rapidly approaches 50% target:primer::protector:primer (or whatever ratio is desired), while equilibrium for the spurious target and primer greatly favors protectonprimer. The abundant free primer in the presence of specific target facilitates its highly sensitive and specific detection.

In some embodiments, the nucleic acid primers discussed here are designed so that the concentration-adjusted free energy for hybridization between the specific target nucleic acid molecule and the primer is close to zero, while the concentration-adjusted standard free energy for hybridization between a spurious target and the primer is high enough to make their binding unfavorable by comparison. "Concentration-adjusted free energy," as used herein, refers to AG^0 + (An)R Tln(c), where R is the universal gas constant, Tis temperature in Kelvins, c is concentration of the primer, and $\Delta\eta$ is the change in the number of molecules through the course of the reaction ($\Delta\eta = -1$ for standard hybridization, $\Delta\eta = 0$ for two-stranded primer hybridization.

Aspects of the invention therefore provide the primer compositions comprising the primers, compositions comprising the complement and protector strands (for example in kits), methods of making the primers, and methods of using the primers in assays or reactions including without limitation nucleic acid synthesis and /or detection assays or reactions.

Thus, in one aspect, the invention provides a partially double-stranded primer comprised of (a) first nucleic acid strand (also referred to herein as a complement strand) and second nucleic acid strand (also referred to herein as a protector strand), wherein the first and second strands when hybridized to each other are arranged into (1) a double-stranded target-non-specific (balance) region, (2) a double-stranded target-specific (branch migration) region, and (3) a single-stranded target-specific (toehold) region contributed to by the first nucleic acid strand, wherein the double-stranded target-non-specific region has a standard free energy approximately equal to the standard free energy for the single-stranded target-specific region bound to a target nucleic acid. The partially double-stranded primer may comprise one or more double-stranded target-non-specific regions, one or more double-stranded target-specific regions, and/or one or more single-stranded target-specific regions. In some embodiments, the partially double-stranded primer may comprise one or two double-stranded target-non-specific (balance) regions,

NeoGenomics
Exhibit 1003 Page 397

one or more double-stranded target-specific (branch migration) regions, and/or one or more single-stranded target-specific (toehold) regions.

In some embodiments, the second nucleic acid strand comprises a non-extendable nucleotide at its 3' end and/or the first nucleic acid strand comprises a non-natural nucleotide at or near the 3' end of its target-non-specific region. In some embodiments, the non-extendable nucleotide is a non-natural nucleotide or a dideoxy nucleotide. In some embodiments, the non-natural nucleotide is iso-C, iso-G or deoxyuridine. These examples are intended as non-limiting.

In some embodiments, the double-stranded target non-specific region is about 4-20 nucleotides in length. The double-stranded target non-specific region may be longer than 20 nucleotides, such as for example 4-21 nucleotides in length. In some embodiments, it may be about 12-192 nucleotides in length.

In some embodiments, the single stranded target specific region is about 4-20 nucleotides in length. The single stranded target specific region may be longer than 20 nucleotides, such as for example 4-21 nucleotides in length. In some embodiments, it may be about 12-192 nucleotides in length.

In some embodiments, the double-stranded target non-specific region and the single stranded target specific region have similar or identical proportions of A/T nucleotides (and typically similar or identical proportions of G/C nucleotides). In some embodiments, the first and second nucleic acid strands are comprised of DNA or RNA or a combination thereof.

In another aspect, the invention provides a single-stranded primer that partially self-hybridizes to form (1) a double-stranded target-non-specific region, (2) a double-stranded target-specific region, (3) single-stranded target-specific region, and (4) a hairpin loop region, wherein the one or more double-stranded target-non-specific region has a concentration-adjusted standard free energy approximately equal to the concentration-adjusted standard free energy for the one or more single-stranded target-specific region bound to a target nucleic acid.

In another aspect, the invention provides a composition comprising the any of the afore-mentioned primers. The composition may further comprise a carrier such as a buffer, optionally comprising a preservative, one or more salts, etc. The composition may also comprise an excess of single-stranded protector strands, wherein each protector strand comprises a protector balance region and a protector branch migration region. The single stranded protector strands may each comprise a non-extendable and/or non-naturally occurring nucleotide, preferably at its 3' end.

NeoGenomics
Exhibit 1003 Page 398

In another aspect, the invention provides a system comprising a nucleic acid target, a polymerase, and any of the foregoing primers. In some embodiments, the primer is a partially double-stranded primer comprising a first and a second nucleic acid strand arranged into (1) a double-stranded target-non-specific region, (2) a double-stranded target-specific region, and (3) a single-stranded target-specific region contributed to by the first nucleic acid strand.

In some embodiments, the nucleic acid target is a single-stranded. In some embodiments, the nucleic acid target is DNA or RNA. In some embodiments, the nucleic acid target comprises repetitive sequence, secondary structure and/or high GC content. In some embodiments, the nucleic acid target is present in a plurality of different nucleic acids. In some embodiments, the nucleic acid target is present as a single copy or in low copy (e.g., less than 0.001%, less than 0.01%, less than 0.1%, or less than 1%) in a plurality of different nucleic acids.

In some embodiments, the system comprises a plurality of any of the foregoing primers such as a plurality of different partially double-stranded primers. In some embodiments, the system comprises at least two of the foregoing primers, such as at least two partially double-stranded primers, which together can be used to amplify a region of the nucleic acid target.

In another aspect, the invention provides a composition comprising the any of the afore-mentioned systems. The composition may further comprise a carrier such as a buffer, optionally comprising a preservative, one or more salts, one or more enzymes such as a polymerase, nucleotides suitable for nucleic acid synthesis, etc. The composition may also comprise an excess of single-stranded protector strands, wherein each protector strand comprises a protector balance region and a protector branch migration region. The single stranded protector strands may each comprise a non-extendable and/or non-naturally occurring nucleotide, preferably at its 3' end.

In another aspect, the invention provides a method comprising contacting any of the foregoing primers, including any of the foregoing partially double-stranded primers to a sample, and detecting hybridization of the primer to a target in the sample.

In some embodiments, the primer such as the partially double-stranded primer is labeled with a detectable moiety. In some embodiments, the detectable moiety comprises a fluorophore or a radioisotope.

The target will typically be a nucleic acid. In some embodiments, the target is a single-stranded nucleic acid. In some embodiments, the target is DNA or RNA. In some embodiments,

NeoGenomics
Exhibit 1003 Page 399

the target is a nucleic acid that comprises repetitive sequence, secondary structure and/or high GC content. In some embodiments, the target is present in a plurality of different nucleic acids. In some embodiments, the target is present as a single copy or in low copy (e.g., less than 0.001%, less than 0.01%, less than 0.1%, or less than 1%) in a plurality of different nucleic acids.

In some embodiments, this and other methods described herein are performed at a temperature below the melting temperature of the complement strand-target complex. In some embodiments, this and other methods described herein are performed at a temperature between and including room temperature up to and including 50°C, or up to and including 40°C, or up to and including 30°C. In some embodiments, this and other methods described herein are performed at about 37 °C. In some embodiments, this and other methods described herein are performed in an excess of protector strand that comprises a protector balance region and a protector branch migration region and that is identical to the protector strand in the partially double-stranded primer. In this and other methods described herein, the primer may be any of the foregoing primers including the partially double-stranded primers.

In another aspect, the invention provides a method comprising hybridizing a single-stranded target-specific (toehold) region of a first (complement) strand of any of the foregoing partially double-stranded primers to a nucleic acid target, thereby dissociating the first strand of the primer from the second (protector) strand of the primer, and extending the first strand at its 3' end, in a target-complementary manner, in the presence of a polymerase.

In another aspect, the invention provides a method comprising performing a nucleic acid synthesis reaction in the presence of a nucleic acid target, a polymerase, and one or more of the foregoing partially double-stranded primers.

In some embodiments, the nucleic acid synthesis reaction is a nucleic acid amplification reaction. In some embodiments, the nucleic acid amplification reaction is polymerase chain reaction (PCR). In some embodiments, the nucleic acid synthesis reaction is a transcription reaction. In some embodiments, the transcription reaction is a reverse transcription reaction.

In some embodiments, two partially double-stranded primers are used.

In another aspect, the invention provides a method of performing a multiplexed nucleic acid amplification reaction comprising amplifying multiple unique nucleic acid molecules using any of the foregoing primers including the partially double-stranded primer.

NeoGenomics
Exhibit 1003 Page 400

In another aspect, the invention provides a kit comprising one or more (including a plurality) of any of the foregoing partially double-stranded primers, and one or more nucleic acid synthesis reagents such as enzymes, nucleotides, salts, EDTA, a buffer, etc.

In some embodiments, the one or more nucleic acid synthesis reagents is selected from the group consisting of a buffer, nucleotides, and a polymerase.

In some embodiments, the kit further comprises an excess of protector strand that is identical to the protector strand comprised in the primer.

In some embodiments, the kit further comprises instructions for use.

In another aspect, the invention provides a kit comprising a first single-stranded (complement) nucleic acid in a first container, and a second single-stranded (protector) nucleic acid that is complementary to a region of the first single-stranded nucleic acid, in a second container, wherein, when the first and second single-stranded nucleic acids are hybridized to each other, a partially double-stranded nucleic acid is formed that comprises (1) a double-stranded target-non-specific region, (2) a double-stranded target-specific region, and (3) a single-stranded target-specific region contributed to by the first nucleic acid, wherein the first single-stranded nucleic acid comprises a non-natural nucleotide and/or the second single-stranded nucleic acid comprises a non-extendable nucleotide at its 3' end.

In some embodiments, the kit further comprises instructions for use. In some embodiments, the kit further comprises one or more nucleic acid synthesis reagents such as those recited above. In some embodiments, the one or more nucleic acid synthesis reagents is selected from the group consisting of a buffer, nucleotides, and a polymerase.

In some embodiments, the protector strand is provided in the kit in an amount (e.g., a molar amount) that is greater than the amount (e.g., a molar amount) of complement strand in the kit.

In some embodiments of the foregoing aspects and inventions, particularly those relating to two strand primers, the nucleotide sequence of the primer is selected such that: $|\Delta G_1^\circ - AG_2^\circ - \Delta G_3^\circ| \leq \Delta G_R^\circ$, wherein: AG_1'' is the standard free energy of hybridization of the protector balance region to the complement balance region; $AG^\wedge$ is the standard free energy of hybridization of the protector balance region to the sequence immediately adjacent in the first direction to the target nucleic acid sequence, if any; AG_3° is the standard free energy of

NeoGenomics
Exhibit 1003 Page 401

hybridization of the toehold region to the second target nucleic acid sequence; andAG^ is 3.5 kcal/mol.

In one aspect, provided herein is a primer duplex system comprising a complement strand and a protector strand, wherein the protector strand comprises a nucleic acid having: a protector branch migration region having a first end, a second end, and a sequence that corresponds to a first target nucleic acid sequence having a first end and a second end, wherein the first end of the protector branch migration region and the first end of the first target nucleic acid sequence are either both 5' or else both 3´; and a protector balance region immediately adjacent to the first end of the protector branch migration region having a sequence that does not correspond to sequence immediately adjacent to the first end of the first target nucleic acid sequence, if any; and the complement primer comprises a nucleic acid having: a complement branch migration region having a first end and a second end, and a sequence that is complementary to the protector branch migration region, wherein the first end of the complement branch migration region and the first end of the first target nucleic acid sequence are either both 5' or else both 3'; a toehold region that is: immediately adjacent to the first end of the complement branch migration region; and complementary to a second target nucleic acid sequence that is immediately adjacent to the second end of the first target nucleic acid sequence; and a complement balance region that: is immediately adjacent to the second end of the complement branch migration region; is complementary to the protector balance region; and has a sequence such that: $|\Delta G_1^\circ - \Delta G_2^\circ - \Delta G_3^\circ| \leq \Delta G_R^\circ$, wherein: AG''_1 is the standard free energy of hybridization of the protector balance region to the complement balance region; $AG^\wedge$ is the standard free energy of hybridization of the protector balance region to the sequence immediately adjacent in the first direction to the target nucleic acid sequence, if any; AG_3° is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence; andAG^ is 3.5 kcal/mol.

In another aspect, provided herein is a primer duplex system comprising a nucleic acid having a protector strand, a hairpin region and a complement strand, wherein: the protector strand comprises a protector branch migration region and a protector balance region, wherein: the protector branch migration region has: a first end; a second end; and a sequence that corresponds to a first target nucleic acid sequence having a first end and a second end, wherein

NeoGenomics
Exhibit 1003 Page 402

the first end of the protector branch migration region and the first end of the first target nucleic acid sequence are either both 5' or else both 3´; and the protector balance region has: a first end; a second end immediately adjacent to the first end of the protector branch migration region; and a sequence that does not correspond to sequence immediately adjacent to the first end of the first target nucleic acid sequence, if any; the hairpin region comprises: a first end; and a second end immediately adjacent to the first end of the protector balance region; and the complement strand comprises a complement balance region, a complement branch migration region, and a toehold region, wherein: the complement balance region has: a first end; a second end immediately adjacent to the first end of the hairpin region; and a sequence that is complementary to the protector balance region; the complement branch migration region has: a first end; a second end immediately adjacent to the first end of the complement balance region; and a sequence that is complementary to the protector branch migration region, wherein the first end of the complement branch migration region and the first end of the first target nucleic acid sequence are either both 5' or else both 3´; the toehold region is: immediately adjacent to the first end of the complement branch migration region; and complementary to a second target nucleic acid sequence that is immediately adjacent to the second end of the first target nucleic acid sequence; and the complement balance region has a sequence such that: $\left|\Delta G_1^\circ - AG_2^\circ - AG_3^\circ + AG_4^\circ + RT\ln(c)\right| \leq AG_R^\circ$, wherein: AG_1° is the standard free energy of hybridization of the protector balance region to the complement balance region; AG_2° is the standard free energy of hybridization of the protector balance region to the sequence immediately adjacent in the first direction to the target nucleic acid sequence, if any; and AG_3° is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence; AG_4° is the standard free energy of confinement of the hairpin region; R is the ideal gas constant; T is the temperature at which the primer duplex system is to be used; c is the concentration at which the primer duplex system is to be used; and AG_R° is 3.5 kcal/mol.

In yet another aspect, provided herein system having, in 3' to 5' order, a first protector strand, a first hairpin region, a complement strand, a second hairpin region and a second protector strand, wherein: the first protector strand comprises: a first protector branch migration region having a sequence that corresponds to a first target nucleic acid sequence; and a first protector balance region that: is immediately 5' to the first protector branch migration region; and

NeoGenomics
Exhibit 1003 Page 403

has a sequence that does not correspond to sequence immediately 5' to the first target nucleic acid sequence, if any; the first hairpin region is immediately 5' to the first protector balance region; the complement strand comprises: a first complement balance region that: is immediately 5' to the first hairpin region; and has a sequence complementary to the sequence of the first protector balance region; a first complement branch migration region that: is immediately 5' to the first complement balance region; and has a sequence complementary to a first protector branch migration region; a toehold region that: is immediately 5' to the first complement branch migration region; and has a sequence that is complementary to a second target nucleic acid sequence that is immediately 3' to the first target nucleic acid sequence; a second complement branch migration region that: is immediately 5' to the toehold region; and has a sequence complementary to a third target nucleic acid sequence that is immediately 3' to the second target nucleic acid sequence; a second complement balance region that: is immediately 5' to the second complement branch migration region; has a sequence that is not complementary to sequence immediately 3' to the third target nucleic acid sequence, if any; the second hairpin region is immediately 5' to the second complement balance region; and the second protector strand comprises: a second protector balance region that: is immediately 5' to the second hairpin region; and has a sequence complementary to the second complement balance region; and a second protector branch migration region that: is immediately 5' to the second protector balance region; and has a sequence complementary to the second complement branch migration region;

wherein the first complement balance region and the second complement balance region have sequences such that: $\left|\Delta G_1^o - AG_2^\circ + AG_3^\circ - AG_4^\circ - AG_5^\circ + AG_6^\circ + AG_7^o + RT\ln(c)\right| \leq AG_R^\circ$,

wherein: AG_1'' is the standard free energy of hybridization of the first protector balance region to the first complement balance region; $AG^\wedge$ is the standard free energy of hybridization of the first complement balance region to the sequence immediately 5' to the first target nucleic acid sequence, if any; AG_3° is the standard free energy of hybridization of the second protector balance region to the second complement balance region; AG_4° is the standard free energy of hybridization of the second complement balance region to the sequence immediately 3' to the third target nucleic acid sequence, if any; AG_5° is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence; AG_6^o is the standard free energy of

NeoGenomics
Exhibit 1003 Page 404

confinement of the first hairpin region; $AG^{\wedge}$ is the standard free energy of confinement of the second hairpin region; R is the ideal gas constant; Tis the temperature at which the primer duplex system is to be used; and c is the concentration at which the primer duplex system is to be used; andAG^ is 3.5 kcal/mol.

In still another aspect, provided herein is a primer duplex system comprising a hairpin primer and a protector strand, wherein: the hairpin primer comprises a nucleic acid having: a first protector strand having: a first protector branch migration region having a sequence that corresponds to a first target nucleic acid sequence; and a first protector balance region that: is immediately 5' to the first protector branch migration region; and has a sequence that does not correspond to sequence immediately 5' to the first target nucleic acid sequence, if any; a hairpin region immediately 5' to the first protector balance region; a complement strand having: a first complement balance region that: is immediately 5' to the first hairpin region; and has a sequence complementary to the sequence of the first protector balance region; a first complement branch migration region that: is immediately 5' to the first complement balance region; and has a sequence complementary to a first protector branch migration region; a toehold region that: is immediately 5' to the first complement branch migration region; and has a sequence that is complementary to a second target nucleic acid sequence that is immediately 3' to the first target nucleic acid sequence; a second complement branch migration region that: is immediately 5' to the toehold region; and has a sequence complementary to a third target nucleic acid sequence that is immediately 3' to the second target nucleic acid sequence; a second complement balance region that: is immediately 5' to the second complement branch migration region; has a sequence that is not complementary to sequence immediately 3' to the third target nucleic acid sequence, if any; and the protector comprises a nucleic acid having: a second protector strand having: a second protector balance region that has a sequence complementary to the second complement balance region; and a second protector branch migration region that: is immediately 5' to the second protector balance region; and has a sequence complementary to the second complement branch migration region; wherein the first complement balance region and the second complement balance region have sequences such that:

$\backslash AG^{\circ} - AG_2^{\circ} + AG_3^{\circ} - AG_4^{\circ} - AG_5^{\circ} + AG_6^{\circ} \mathbf{K} AG_R^{\circ}$, wherein: AG_{1}° is the standard free energy of hybridization of the first protector balance region to the first complement balance region; AG_2 is

NeoGenomics
Exhibit 1003 Page 405

the standard free energy of hybridization of the first complement balance region to the sequence immediately 5' to the first target nucleic acid sequence, if any; AG_3° is the standard free energy of hybridization of the second protector balance region to the second complement balance region; ΔG_4° is the standard free energy of hybridization of the second complement balance region to the sequence immediately 3' to the third target nucleic acid sequence, if any; AG_5° is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence; ΔG_6° is the standard free energy of confinement of the hairpin region; and AG_R° is 3.5 kcal/mol.

In a further aspect, provided herein is a primer duplex system comprising a protector strand and a hairpin primer, wherein: the protector strand comprises a nucleic acid having: a first protector strand having: a first protector branch migration region having a sequence that corresponds to a first target nucleic acid sequence; and a first protector balance region that: is immediately 5' to the first protector branch migration region; and has a sequence that does not correspond to sequence immediately 5' to the first target nucleic acid sequence, if any; the hairpin primer comprises a nucleic acid having: a complement strand having: a first complement balance region that has a sequence complementary to the sequence of the first protector balance region; a first complement branch migration region that: is immediately 5' to the first complement balance region; and has a sequence complementary to a first protector branch migration region; a toehold region that: is immediately 5' to the first complement branch migration region; and has a sequence that is complementary to a second target nucleic acid sequence that is immediately 3' to the first target nucleic acid sequence; a second complement branch migration region that: is immediately 5' to the toehold region; and has a sequence complementary to a third target nucleic acid sequence that is immediately 3' to the second target nucleic acid sequence; a second complement balance region that: is immediately 5' to the second complement branch migration region; has a sequence that is not complementary to sequence immediately 3' to the third target nucleic acid sequence, if any; a hairpin region immediately 5' to the second complement balance region; and a second protector strand having: a second protector balance region that: is immediately 5' to the second hairpin region; and has a sequence complementary to the second complement balance region; and a second protector branch migration region that: is immediately 5' to the second protector balance region; and has a

NeoGenomics
Exhibit 1003 Page 406

sequence complementary to the second complement branch migration region; wherein the first complement balance region and the second complement balance region have sequences such that: $|\Delta G_1^\circ - AG_2^\circ + AG_3^\circ - AG_4^\circ - AG_5^\circ + AG_6^\circ| \leq AG_R^\circ$, wherein: AG_1'' is the standard free energy of hybridization of the first protector balance region to the first complement balance region; AG_2 is the standard free energy of hybridization of the first complement balance region to the sequence immediately 5' to the first target nucleic acid sequence, if any; AG_3° is the standard free energy of hybridization of the second protector balance region to the second complement balance region; AG_4° is the standard free energy of hybridization of the second complement balance region to the sequence immediately 3' to the third target nucleic acid sequence, if any; and AG_5° is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence; $AG^\wedge$ is the standard free energy of confinement of the hairpin region; and AG_R° is 3.5 kcal/mol.

In another aspect, provided herein is a primer duplex system comprising a first protector strand, a complement strand and a second protector strand, wherein: the first protector strand comprises a nucleic acid having: a first protector branch migration region having a sequence that corresponds to a first target nucleic acid sequence; and a first protector balance region that: is immediately 5' to the first protector branch migration region; and has a sequence that does not correspond to sequence immediately 5' to the first target nucleic acid sequence, if any; the complement strand comprises a nucleic acid having: a first complement balance region that: is immediately 5' to the first hairpin region; and has a sequence complementary to the sequence of the first protector balance region; a first complement branch migration region that: is immediately 5' to the first complement balance region; and has a sequence complementary to a first protector branch migration region; a toehold region that: is immediately 5' to the first complement branch migration region; and has a sequence that is complementary to a second target nucleic acid sequence that is immediately 3' to the first target nucleic acid sequence; a second complement branch migration region that: is immediately 5' to the toehold region; and has a sequence complementary to a third target nucleic acid sequence that is immediately 3' to the second target nucleic acid sequence; a second complement balance region that: is immediately 5' to the second complement branch migration region; has a sequence that is not

NeoGenomics
Exhibit 1003 Page 407

complementary to sequence immediately 3' to the third target nucleic acid sequence, if any; and the second protector strand comprises: a second protector balance region that has a sequence complementary to the second complement balance region; and a second protector branch migration region that: is immediately 5' to the second protector balance region; and has a sequence complementary to the second complement branch migration region; wherein the first complement balance region and the second complement balance region have sequences such that: $|\Delta G_1^\circ - AG_2^\circ + AG_3^\circ - AG_4^\circ - AG_5^\circ - RT\ln(c)| \leq AG_R^\circ$, wherein: AG_i° is the standard free energy of hybridization of the first protector balance region to the first complement balance region; AG_2° is the standard free energy of hybridization of the first complement balance region to the sequence immediately 5' to the first target nucleic acid sequence, if any; AG_3° is the standard free energy of hybridization of the second protector balance region to the second complement balance region; AG_4° is the standard free energy of hybridization of the second complement balance region to the sequence immediately 3' to the third target nucleic acid sequence, if any; and AG_5° is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence; R is the ideal gas constant; Tis the temperature at which the primer duplex system is to be used; c is the concentration at which the primer duplex system is to be used; and AG_R° is 3.5 kcal/mol.

In yet another aspect, provided herein is a primer duplex system comprising, in 3' to 5' order, a first protector strand, a first hairpin region, a complement strand, a second hairpin region and a second protector strand, wherein: the first protector strand has a sequence that corresponds to a first target nucleic acid sequence; the first hairpin region is immediately 5' of the first protector strand; the complement strand comprises: a first complement branch migration region that: is immediately 5' of the first hairpin region; and has a sequence complementary to the sequence of the first protector strand; a toehold region that: is immediately 5' of the first complement branch migration region; and has a sequence complementary to a second target nucleic acid sequence that is immediately 3' of the first target nucleic acid sequence; and a second complement branch migration region that: is immediately 5' of the toehold region; and has a sequence complementary to a third target nucleic acid sequence that is immediately 3' of the second nucleic acid sequence; the second hairpin region is immediately 5' of the second

NeoGenomics
Exhibit 1003 Page 408

complement branch migration region; and the second protector strand has a sequence that is complementary to the sequence of the second complement branch migration region.

In any one of the foregoing aspects , ΔG_R^o may be 2.0 kcal/mol, 1.0 kcal/mol, or 0.5 kcal/mol; and/or c may be about 10 nM; and/or T may be about 293 K or about 338 K; and/or the toehold region may be between 4 and 20 nucleotides in length, between about 4 and 15 nucleotides in length, or between about 4 and 10 nucleotides in length; and/or the first end of the protector branch migration region may be 5′ or 3'; and/or the primer duplex system may further comprise a functionalized fluorescent group or dye; and/or the primer duplex system may be immobilized on a solid support; and/or the hairpin region may be no greater than 20 nucleotides in length or no greater than 10 nucleotides in length; and/or the sequence of the hairpin region may be selected from the group consisting of a poly-adenosine sequence, poly-deoxyadenosine sequence, a poly-5'-methyluridine sequence, a poly-thymidine sequence, a poly-guanosine sequence, a poly-deoxyguanosine sequence, a poly-cytidine sequence, a poly-deoxycytidine sequence, a poly-uridine sequence, and a poly-deoxyuridine sequence; and/or the first target nucleic acid sequence and/or the second target nucleic acid sequence may be sequences that naturally occur in an organism or a virus; and/or the first target nucleic acid sequence and/or the second target nucleic acid sequence may be sequences that naturally occur in a micro-RNA.

In one aspect, provided herein is a method of detecting a target nucleic acid in a sample comprising: contacting a target nucleic acid with a primer duplex system of any one of the embodiments described herein; and detecting the formation of a complex between the target nucleic acid and at least a part of the primer duplex system. In some embodiments, the primer duplex system further comprises a functionalized fluorescent group or dye. In some embodiments, the primer duplex system is immobilized on a solid support. In some embodiments, the contacting occurs in a cell. In some embodiments, the target nucleic acid is a nucleic acid that naturally occurs in an organism or a virus. In some embodiments, the target nucleic acid is a micro-RNA.

In another aspect, provided herein is a method of amplifying a sequence contained within a target nucleic acid comprising: forming a solution comprising: a target nucleic acid; a primer duplex system of any one of the embodiments described herein; and reagents for performing an amplification reaction; and incubating the solution under conditions such that a sequence

NeoGenomics
Exhibit 1003 Page 409

contained within the target nucleic acid is amplified. In some embodiments, the target nucleic acid is a nucleic acid that naturally occurs in an organism or a virus.

These and other aspects and embodiments of the invention will be explained in greater detail herein.

BRIEF DESCRIPTION OF DRAWINGS

FIGS. 1A, IB, 2A, 2B, 3A, 3B, 4-8, 9A, and 9B depict exemplary nucleic acid probe systems.

FIGS. 10, 11, 12A, 12B, 13, and 14 depict exemplary methods of using nucleic acid probe systems.

FIGS. 15A and 15B depict highly specific polymerase chain reaction (PCR) using the primer duplexes provided herein.

FIGS. 16A-16D show experimental demonstrations of primer hybridization with single nucleotide discrimination.

FIGS. 17A-17D show additional experimental results and statistics on the single-base discrimination abilities of primer duplexes.

FIGS. 18A-18B show experimental results using duplex primers to improve the PCR yield of a quasi-repetitive target.

DETAILED DESCRIPTION OF INVENTION

A significant challenge in probe-based nucleic acid assays is that nucleic acids having sequences similar to that of a target will hybridize to the target's complement with strong thermodynamics and fast kinetics. However, as described herein, the kinetics and thermodynamics of strand displacement reactions can be partially decoupled, so that reactions that are only slightly thermodynamically favorable or even unfavorable can nonetheless have kinetics as fast as the hybridization of two complementary strands. The compositions and methods described herein take advantage of this decoupling mechanism to provide nucleic acid probe systems with improved specificity and kinetics.

Provided herein are highly specific nucleic acid probe systems and methods of using such probe systems. In certain embodiments, the nucleic acid probe systems described herein comprise complement probes having regions complementary to a target sequence that are

NeoGenomics
Exhibit 1003 Page 410

protected from hybridization to spurious targets by protector regions complementary to a portion of the complement probes. The free energy of the binding reaction between the target and the protected probe is finely controlled via the rationally designed bases of one or more balancing regions, which have sequences that do not correspond to the target nucleic acid sequence or its complement. In certain embodiments, a protector and a complement probe form regions on a single nucleic acid molecule and are separated from one another by one or more nucleic acid hairpins.

The methods and compositions described herein possess several unique properties that facilitate their use in hybridization assays. First, the nucleic acid probe systems described herein reliably convert small sequence differences between targets and spurious targets into large differences in binding affinity and reaction rates between hybridization of the target vs. spurious target with the probe. Second, the nucleic acid probe systems described herein can be designed to operate at any of a wide range of temperatures and salt concentrations, and can therefore function reliably under many different experimental conditions. Third, use of the nucleic acid probe systems described herein can result in hybridization reactions that are kinetically fast even at room temperature, which facilitates rapid and high-throughput analysis of nucleic acids. Fourth, the nucleic acid probe systems described herein are rationally designed, and therefore are unlikely to interact unfavorably or in unexpected ways with other biomolecules.

Accordingly, provided herein are primer compositions, methods of making such compositions, and methods of their use. The embodiments described herein are premised in part on the discovery that primer *(e.g.,* a pair of partially hybridized primers, or a single self-hybridizing primer) that are partially double-stranded and partially single-stranded, when used in a nucleic acid synthesis reaction for example, are able to discriminate between fully complementary targets and those having one or more mismatches *(i.e.,* spurious targets). As demonstrated herein, the primer duplexes described herein are superior to standard primers in, for example, PCR reactions using spurious targets such as those having quasi-repetitive sequences.

The primer duplexes herein comprise a single-stranded region referred to herein as a "toehold" from which the primer duplex initiates binding to a target, a double-stranded "balance region" which spontaneously dissociates so that a single primer strand does not complete hybridization (along the full length of the primer) to the target, and a double-stranded branch

NeoGenomics
Exhibit 1003 Page 411

migration region, in between the toehold and balance regions, which is fully complementary to a target nucleic acid sequence. Mechanistically, it is thought that hybridization to a target begins at the toehold and continues along the length of the complement strand until the primer is no longer "double-stranded". This assumes complementarity between the target and the branch region as well. As used herein, a nucleic acid "region" or "domain" is a consecutive stretch of nucleotides of any length. When nucleotide mismatches exist between the "target" and the complement strand, displacement of the second strand *(i.e.,* the protector strand) is thermodynamically unfavorable and the association between the complement strand and the "target" is reversed. It is to be understood that in this latter description, the "target" is actually a spurious target since it comprises nucleotide differences or mismatches from the complement strand.

Because the standard free energy favors a complete match (fully complementary) between the target sequence of the nucleic acid and branch migration plus toehold regions of the primer rather than a mismatch *(e.g.,* single nucleotide change), the first (complement) strand of the primer will bind stably to a target in the absence of a mismatch but not in the presence of a mismatch. If a mismatch exists between the first (complement) strand of the primer and the target, the primer duplex prefers to reform via newly exposed single-stranded balance regions. In this way, the frequency of beginning a nucleic acid synthesis reaction at an incorrect position in a target (or in a sample, for that matter) is reduced. This type of discrimination is typically not possible using the standard single-stranded primers of the prior art because in those reactions there is no competing nucleic acid strand (such as the protector strand) to which a mismatched primer strand would prefer to bind. In some embodiments, the primers described herein may be significantly longer than conventional primers *(e.g.,* those used for polymerase chain reaction (PCR) amplification) because the instant primers rely on the presence of a competing, protector strand for specificity rather than on melting temperature to discriminate between complementary and mismatched sequences. Accordingly, the instant primers may be selected and used in a manner that is temperature independent.

The primer duplexes described herein therefore improve specificity of for example nucleic acid synthesis reactions and, in some embodiments, allow for a greater degree of multiplexing of primers. Preliminary experiments, the results of which are provided herein, show that the PCR yield of quasi-repetitive targets can be significantly improved using the

NeoGenomics
Exhibit 1003 Page 412

primer duplexes provided herein as compared to standard primers *(e.g.,* 75% vs. 30%). The primer duplexes described herein also provide for specific nucleic acid detection and amplification from a heterogeneous population of nucleic acids, such as for example, detecting and amplifying a bacterial DNA from a sample comprised of human DNA, which has broad applicability in detection of rare organisms such as biowarfare agents.

Primer Duplexes

As used herein, the primers of the invention may be referred to as "primer duplexes" to covey that they may be provided and/or exist in a conformation in which they comprise double-stranded regions. Accordingly, the terms "primer" and "primer duplex" may be used interchangeably.

The primer duplexes provide improved specificity and kinetics over existing primers. A "primer duplex" herein refers to a primer comprising a first strand (referred to herein as a "complement strand") and a second strand (referred to herein as a "protector strand") partially complementary to the first strand. In some embodiments, the complement strand and the protector strand are separate single-stranded nucleic acid molecules (FIGS. 1A and IB). In other embodiments, the complement strand and the protector strand are connected to each other and separated by a hairpin region to form contiguous regions of a single nucleic acid molecule (FIGS. *2A* and 2B). As used herein, a "hairpin region" is a single-stranded loop of nucleotides connecting two double-stranded regions of a nucleic acid. The general structure of exemplary primer duplexes is illustrated in the Figures and described herein. It is to be understood that, in most instances, when reference is made to a complement region or a protector region (or vice versa), each region is typically within a single "primer duplex" (or a single primer system). For example, a complement balance region in a primer of the invention is complementary to a protector balance region in the same primer such that a complement balance region of one primer of the invention does not hybridize to a protector balance region of different physically separate primer.

In embodiments in which the primer of the invention consists of only a single strand, the complement "strand" may be referred to as the complement region, and the protector "strand" may be referred to as the protector region.

NeoGenomics
Exhibit 1003 Page 413

In certain embodiments, the complement strand (or region) comprises a toehold region, a complement branch migration region, and a complement balance region, while the protector strand (or region) comprises a protector branch migration region and a protector balance region. As used herein, a nucleic acid "region" is a consecutive stretch of nucleotides of any length. Toehold and branch migration regions are each designed to be complementary to, and thus "base-pair" with *(e.g.,* hybridize to), adjacent regions in a target nucleic acid. A region of a complement strand that base-pairs with a region in a target nucleic acid is referred to as a "target-specific" region. Balance regions are designed to be not complementary to, and thus to not base-pair with, a target nucleic acid. Balance regions therefore are referred to as "target-non-specific" regions. In certain aspects, when the complement strand (or region) and the protector strand (or region) are hybridized to each other (are double-stranded), a primer duplex is formed. Thus, in some aspects, a primer duplex comprises a target-specific single-stranded toehold region, a target-specific double-stranded branch migration region, and a target-non-specific double-stranded balance region (FIGS. 1A and IB). In some instances, the primer duplex may also comprise a hairpin loop, as described in greater detail below.

The primer duplexes described herein may be designed to hybridize specifically with a target nucleic acid. The efficacy of a primer, for example, in a nucleic acid amplification reaction, depends on the specificity, efficiency, and fidelity of the primer. Typical nucleic acid primers often bind to spurious targets with a thermodynamic and kinetic profile comparable to that of the same primer binding to its intended, specific target nucleic acid, except between the melting temperatures of the mismatched duplex and the perfectly hybridized duplex. Accordingly, mismatched and perfect duplexes can be distinguished by their melting temperatures. The primers of the invention, in contrast, distinguish between spurious and true target in a relatively temperature-independent manner.

A "spurious target" herein refers to a nucleic acid molecule that differs from a target nucleic acid molecule by at least one nucleotide within the region hybridizing to the complement strand. For example, TCGACGGGG is a spurious target, if the target is TCGAAGGGG. In certain embodiments, a spurious target comprises at least 2, at least 3, at least 4, or more nucleotide changes relative to the target. Primer binding to spurious targets reduces the fidelity (accuracy) of, *e.g.,* nucleic acid amplification. The primer duplexes presented herein are designed to alter the standard free energy of strand displacement with spurious targets,

NeoGenomics
Exhibit 1003 Page 414

permitting discrimination between correct targets and spurious targets, including spurious targets that differ from a correct target by only one nucleotide. As described herein, the protector strand is responsible for altering the standard free energy to allow the complement strand to discriminate between correct and spurious targets.

The primers described herein are rationally designed to facilitate strand displacement reactions with finely tuned kinetics and thermodynamics such that kinetics and thermodynamics of strand displacement reactions are partially decoupled. As a result of this decoupling, reactions only slightly thermodynamically favorable or even unfavorable can nonetheless have kinetics as fast as the hybridization of two complementary strands.

For example, at 37° C and 1 M Na^+, the concentration-adjusted standard free energy for hybridization of a primer to a perfectly complementary (correct or specific) target *(i.e.,* 100% nucleotide match) is between 1.9 kcal/mol and 6.6 kcal/mol more favorable than the concentration-adjusted standard free energy for hybridization of the same primer to a spurious target for every nucleotide that the spurious target differs from the intended target. In certain embodiments, the present primer duplexes use toehold exchange strand displacement reactions to translate this 1.9 to 6.6 kcal/mol difference in concentration-adjusted standard free energy to an optimal discrimination between the target and spurious targets. An example of the thermodynamics/kinetics of primer duplex binding to a target nucleic acid is described as follows in reference to FIGS 3A and 3B.

For purposes of this example, the target nucleic acid has at least two regions, (1) and (2). In certain embodiments, region (1) may be about 10 to about 200 (including 14-200 or 20-200) nucleotides long, while region 2 may be smaller, for example, about 4 to about 20 nucleotides long. As used herein, the terms "nucleotide" and "bases" are used interchangeably. The protector strand includes a protector branch migration region adjacent to a protector balance region (3). The protector branch migration region corresponds to target region 1, while the protector balance region (3) does not correspond to region (1) or region (2) or any region immediately 5' of the target regions. A nucleic acid sequence, domain or region is "immediately adjacent to", "immediately 5'" or "immediately 3'" to another sequence if the two sequences are part of the same nucleic acid molecule and if no bases separate the two sequences. The complement strand includes a complement balance region (3), a complement branch migration region (1), and a toehold region (2). The complement balance region (3) is complementary to the

NeoGenomics
Exhibit 1003 Page 415

protector balance region (3), the complement branch migration region (1) is complementary to the protector branch migration region and target region (1) (i.e., the protector branch migration region and the target region (1) are identical in sequence and this both bind to the complement branch migration region (1), and the toehold region (2) is complementary to target region (2).

In certain embodiments, the balance region is designed so that its concentration-adjusted standard free energy ($\Delta G^{\circ}_{3:3}$) is the same or about the same as the concentration-adjusted standard free energy for the toehold region bound to target region (2) ($\Delta G^{\circ}_{2:2}$). In some instances, for a 10 nanomolar (nM) primer used in a reaction at 37 °C, $|\Delta G^{\circ}_{2:2}|$ and $|\Delta G^{\circ}_{3:3}|$ (the vertical bars denoting absolute value) should each be less than about 11.3 kcal/mol to ensure dissociation of the full protector strand from the target .

In some embodiments, when the primer duplex interacts with a specific (correct) target nucleic acid molecule (FIG. 3A), the dissociation of (3):(3) and the association of (2):(2) balance one another, and the (1):(1) hybridization thermodynamics are identical for the target nucleic acid and for the protector strand interacting with the complement strand. The total free energy change between the two states is relatively small *(e.g.,* about 1 kcal/mol), and the reaction quickly *(e.g.,* less than a minute) reaches an equilibrium of about 50:50. In certain embodiments, the balance region may be designed to have standard free energy very close to that of the toehold region binding to target region 2, so that the equilibrium balance is, for example, 60:40 or 70:30. In some embodiments, the design of the balance region may also take into account other contributors to free energy change during the reaction, such as hybridization between the protector balance region and upstream target sequences (which in some instances is negligible), confinement of a hairpin (if present), intended temperature of use, and intended primer concentration.

In some embodiments, when the primer duplex instead interacts with a spurious target nucleic acid molecule (FIG. 3B), the dissociation of (3):(3) and the association of (2m):(2) are not balanced because spurious target region *(2m)* is not fully complementary to the toehold region. The equilibrium is consequently shifted to the state in which the primer duplex does not bind the spurious target.

Explained another way, in some instances, the free energy of the complement strand bound to the protector strand is $\Delta G^{\circ}_{3:3} + \Delta G^{\circ}_{-}$ (ignoring contribution from the optional hairpin

NeoGenomics
Exhibit 1003 Page 416

region and other considerations), which balances the free energy of the complement strand bound to specific target, $AG^{\wedge}_{-} + AG^{\wedge}_{-}$. In this example, this is because the balance region (3) of the primer duplex has been designed to have a concentration-adjusted standard free energy equal to (or approximately equal to) that of target region (2). When the primer duplex interacts with a spurious target having a single-nucleotide (base) change in target region (2m), the system's free energy $AG^{\circ}_{2m:\underline{2}} + \Delta G^{\circ}_{\underline{1}:\underline{1}}$ is less negative than that of the primer duplex, and therefore disfavored in equilibrium.

As used herein, the term "approximately equal to" in reference to standard free energy means that the first referenced free energy is within 10% of the second referenced free energy. In some embodiments, a first free energy that is approximately equal to a second free energy is within about +3 kcal/mol to about -3 kcal/mol of the second free energy. It is to be understood that the differences between the first and second true energies may be less than or about 1 kcal/mol, less than or about 2 kcal/mol, less than or about 3 kcal/mol, less than or about 3.5 kcal/mol, or more, in some embodiments.

Although FIG. 3B illustrates a single nucleotide change corresponding to region (2)/(2m) of a target nucleic acid molecule, the present primer duplexes can also discriminate between a specific target and a spurious target having a nucleotide change in region (1). When the spurious target has a single-base change in target region 1, then the primer duplex's standard free energy after binding becomes $AG^{\circ}_{\underline{2}:\underline{2}} + AG^{\circ}_{\underline{1}m:\underline{1}}$, where $AG^{\circ}_{\underline{1}m:\underline{1}}$ is the standard free energy of the mismatched target region (1) binding to the primer duplex's complement region **(1).** Because of the single-base change, the primer duplex's free energy is less negative than $\Delta G^{\circ}_{\underline{3}:\underline{3}} + AG^{\wedge}_{-}$ (free energy of complement primer bound to protector), so equilibrium is shifted to the state in which the primer duplex does not bind the spurious target region. Standard free energies can be calculated theoretically based on the knowledge in the art and the teachings provided herein.

Complement and Protector Strands, Regions or Domains

The complement domains of the nucleic acid probe systems described herein each include a plurality of regions, including a toehold region and one or more complement target regions. Both the toehold region and the one or more complement target regions have nucleic acid sequences that are complementary to nucleic acid sequences of the target nucleic acid. The

NeoGenomics
Exhibit 1003 Page 417

toehold region and the complement target region are therefore able to base-pair with and therefore form a complex with a sequence of a target nucleic acid when the nucleic acid probe system is contacted with a target nucleic acid under appropriate hybridization conditions. The complement domains may also include one or more complement balance regions. The one or more complement balance regions are rationally designed. Thus, the sequences of the one or more complement balance regions are not designed to be complementary to a target nucleic acid sequence.

A toehold region is complementary to (and thus hybridizes to) a sequence in the target nucleic acid molecule; however, a toehold region does not hybridize to a protector strand. Thus, when the complement strand is hybridized to the target nucleic acid molecule, the toehold region is also hybridized to the target nucleic acid molecule, but when the complement strand is hybridized to the protector strand, the toehold region remains single-stranded. A toehold region may be positioned at the 3' end or the 5' end of the complement strand *(e.g.,* is an extension of the 3' end or 5' end of the complement strand).

In certain embodiments, a toehold region is about 4 nucleotides to about 20 nucleotides in length, about 4 nucleotides to about 15 nucleotides in length, or about 4 nucleotides to about 10 nucleotides in length. In some embodiments, a toehold region is 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length. In some embodiments, the toehold region is greater than 20 nucleotides in length, including for example less than or about 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more nucleotides.

The complement branch migration region is complementary to a sequence in the target nucleic acid molecule and to the protector branch migration region . Thus, when the complement strand hybridizes to a target nucleic acid molecule, the complement branch migration region hybridizes to the target nucleic acid. When the complement strand hybridizes to its protector strand, the complement branch migration region hybridizes to the protector branch migration region.

In certain embodiments, a branch migration region is no more than 200, 100, 75, 50, 40, 30, 25 or 20 nucleotides in length. In some embodiments, a branch migration region is about 10 nucleotides to about 200 nucleotides in length. In certain embodiments, a branch migration region is about 10 nucleotides to about 150 nucleotides, about 10 nucleotides to about 100 nucleotides, or about 10 nucleotides to about 50 nucleotides in length. In particular

NeoGenomics
Exhibit 1003 Page 418

embodiments, a branch migration region is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, or 200 nucleotides in length. In particular embodiments, a branch migration region may be more than 200 nucleotides in length, depending on the target nucleic acid molecule of interest.

The balance regions of a complement strand and a protector strand are complementary to each other *(i.e.,* form a double-stranded nucleic acid) but are non-complementary to the target of interest *(i.e.,* neither forms a double-stranded nucleic acid with the target). Thus, when a complement strand hybridizes to a target nucleic acid molecule, the complement balance region does not hybridize to the target nucleic acid molecule. When the complement strand hybridizes to its protector strand, the complement balance region hybridizes to the protector balance region.

The design of the balance region is dependent on the design of the toehold region. In some embodiments, the balance region is designed such that the thermodynamic profile of the balance region is comparable to that of the toehold region. In some embodiments, the thermodynamic profile is based on a theoretic model, using for example, Mfold software available at the bioinfo website of RPI. The number and/or nature of nucleotides within a balance region is comparable to that of the toehold region. For example, if a toehold region is comprised of 40% A and T nucleotides and 60% G and C nucleotides, then the balance region should also be comprised of 40% A and T nucleotides and 60 % G and C nucleotides. In embodiments, the balance region is designed such that no more than three consecutive nucleotides are complementary to a sequence on the target nucleic acid to avoid binding of the balance region to the target nucleic acid.

In some embodiments, the length of a balance region is short enough so that the complement and protector spontaneously dissociate from each other. In some embodiments, a

NeoGenomics
Exhibit 1003 Page 419

balance region is about 4 nucleotides to about 20 nucleotides in length, about 4 nucleotides to about 15 nucleotides in length, or about 4 nucleotides to about 10 nucleotides in length. In some embodiments, a balance region is 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length. In some embodiments, a balance region is greater than 20 nucleotides, including for example less than about 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more nucleotides. In some embodiments, the number of consecutive nucleotides that are complementary to a nucleotide sequence within the target nucleic acid may be greater than three provided that the balance region does not bind to the target nucleic acid.

In some embodiments, for example those where the primer duplex contains two separate nucleic acid strands, the design of a balance region does not depend on the concentration of the primer duplex or the temperature at which the primer duplex is formed/used. In some embodiments, a balance region is designed such that the standard free energy for the reaction in which the protector strand is displaced from the complement strand by the target nucleic acid molecule is close to zero kcal/mol. As used herein, "close to zero" means the standard free energy for the reaction is within 3.5 kcal/mol from 0 kcal/mol. In certain embodiments, the standard free energy of this displacement reaction is within 3.5, 3.0, 2.5, 2.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1 kcal/mol of zero kcal/mol.

In other embodiments, for example those where the primer duplexes is formed by a single nucleic acid molecule *(e.g.,* a hairpin region separating the complement strand (or region or domain) and the protector strand (or region or domain)), the design of a balance region will be dependent on the primer duplex concentration as well as reaction temperature. In such embodiments, a balance region is designed so that the standard free energy for the reaction in which the protector strand is displaced from the complement strand by the target nucleic acid plus $R\,T\ln(c)$ is close to zero kcal/mol, where R is the universal gas constant (0.0019858775(34) kcal/mol•K), Tis the temperature at which the primer duplex is used, and c is the concentration at which primer duplex is used. In some embodiments, the temperature at which the primer duplexes are used is about 273 K (0°C), 277 K, 283 K, 288 K, 293K, 298 K, 303 K, 308 K, 313 K, 318 K, 323 K, 328 K, 333 K, 338 K, 343 K, 348 K, 353 K, 358 K or 363 K (90°C). In some embodiments the concentration (c) at which the primer duplexes are used is about 1 nM, 2 nM, 3 nM, 4 nM, 5 nM, 10 nM, 15 nM, 20 nM, 25 nM, 30 nM, 35 nM,. 40 nM, 45 nM,. 50 nM, 55 nM, 60 nM, 65 nM, 70 nM, 75 nM, 80 nM, 85 nM, 90 nM, 95 nM, 100 nM, 125 nM, 150 nM, 175

NeoGenomics
Exhibit 1003 Page 420

nM, 200 nM, 225 nM, 250 nM, 300 nM, 350 nM, 400 nM, 450 nM, 500 nM, 600 nM, 700 nM, 800 nM, 900 nM or 1 μM. In certain embodiments, the standard free energy of this displacement reaction plus $R71n(c)$ is within 3.5, 3.0, 2.5, 2.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1 kcal/mol of zero kcal/mol.

In some embodiments, a primer duplex may include one or more hairpin regions that connect the complement strand to the protector strand. In certain embodiments, the hairpin region of a primer duplex can be of any length. In some embodiments, the hairpin region is more than 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4 or 3 nucleotides in length. In some embodiments, the sequence of the hairpin is not complementary to a sequence of the target nucleic acid molecule.

In certain embodiments, the hairpin region has a poly-mononucleotide sequence, such as a poly-adenosine sequence, poly-deoxyadenosine sequence, a poly-5'-methyluridine sequence, a poly-thymidine sequence, a poly-guanosine sequence, a poly-deoxyguanosine sequence, a poly-cytidine sequence, a poly-deoxycytidine sequence, a poly-uridine sequence or a poly-deoxyuridine sequence.

The primer duplex described herein may be one of at least two orientations. For example, in one orientation, the toehold region is located at the 5' end, immediately adjacent to the complement branch migration region *(i.e.,* no intervening nucleotides between the two regions), and the complement balance region is located at the 3' end, immediately adjacent to the complement branch migration region. In this orientation, the protector balance region is at the 5' end of the protector strand, immediately adjacent to the protector branch migration region (FIG. 1A). In another orientation, the toehold region is located at the 3' end, immediately adjacent to the complement branch migration region, and the complement balance region is located at the 5' end, immediately adjacent to the complement branch migration region. In this orientation, the protector balance region is at the 3' end of the protector strand, immediately adjacent to the protector branch migration region (FIG. IB).

Regardless of orientation, the sequence of the complement balance region is such that such that:

$$\left|\Delta G_1^o - \Delta G_2^o - \Delta G_3^o\right| \leq \Delta G_R^o,$$

where:

NeoGenomics
Exhibit 1003 Page 421

AG''_1 is the standard free energy of hybridization of the protector balance region to the complement balance region;

$AG^{\wedge}$ is the standard free energy of hybridization of the protector balance region to the sequence immediately adjacent in the first direction to the target nucleic acid sequence, if any;

AG_3° is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence; and

AG_R° is 3.5 kcal/mol.

In some embodiments, a primer duplex comprises a complement strand longer than the protector, the difference in length being dependent on the length of the toehold region of the complement strand. The lengths of the primers are designed such that hybridization of the complement to the target of interest has a standard free energy (AG^0) close to zero. Release of the protector strand (from the primer duplex) ensures that this hybridization reaction is entropically neutral and robust to concentration. As a result, in some embodiments, this reaction at room temperature *(e.g.,* about 25 °C or about 298 K) parallels the specificity of hybridization achieved at near melting temperature across many conditions .

As intended herein, a AG^0 (change in standard free energy) "close to zero" refers to an absolute value (amount) less than or about 1 kcal/mol, less than or about 2 kcal/mol, less than or about 3 kcal/mol, or less than or about 3.5 kcal/mol. In some embodiments, the standard free energy of a balance region or toehold region is >-1 kcal/mol to < 1 kcal/mol >-3 kcal/mol to <3 kcal/mol or >-3.5 kcal/mol to <3.5 kcal/mol.

The primer duplexes may be prepared at a ratio of protector strand to complement strand of about 2:1 to about 5:1. In some embodiments, the ratio of protector strand to complement strand is about 2:1, about 3:1, about 4:1, or about 5:1. In some embodiments, the ratio of protector strand to complement strand is 2:1, 2.1:1, 2.2:1, 2.3:1, 2.4:1, 2.5:1, 2.6:1, 2.7:1, 2.8:1, 2.9:1, 3:1, 3.1:1, 3.2:1, 3.3:1, 3.4:1, 3.5:1, 3.6:1, 3.7:1, 3.8:1, 3.9:1, 4:1, 4.2:1, 4.3:1, 4.4:1, 4.5:1, 4.6:1, 4.7:1, 4.8:1, 4.9:1, or 5:1. The primer duplexes may also be used together with excess protector strand in any of the assays or reactions described herein. The protector strand may be

NeoGenomics
Exhibit 1003 Page 422

in about equal to or more than 2-, 5-, 10-, 20-, 50-, 100-, or 500-fold molar excess relative to the primer.

Hairpin Primer Duplex Systems (e.g., Single-Stranded Systems)

In certain embodiments, a primer duplex includes a single nucleic acid that comprises a complement region or domain , a hairpin region, and a protector region or domain . In some embodiments, the complement domain hybridizes to the protector domain, forming a primer duplex having in intervening hairpin-loop region. Like other primer systems disclosed here, such hairpin primer systems are designed to specifically hybridize to a target nucleic acid molecule. Herein, a "hairpin primer duplex system" or a "hairpin system" includes a complement balance region, a complement branch migration region, a toehold region, a protector balance region, and a protector branch migration region. As described above, a complement balance region is complementary to a protector balance region ; a complement branch migration region is complementary to a protector branch migration region and a target nucleic acid region; and a toe hold region is complementary to a target nucleic acid region. A protector branch migration region corresponds to a target nucleic acid region and is complementary to a complement branch migration region. Because the hairpin primer duplex systems described herein are formed by a single nucleic acid molecule, the design of the complement balance region will be dependent on the temperature and concentration at which the primer system is to be used, as described herein. It is to be understood that though the sequence of the target nucleic acid molecule may be used to describe the characteristics of the primer systems, in some embodiments, the target nucleic acid itself may or may not be a component of the primer system *(e.g.,* two-stranded or single-stranded systems).

For primer duplexes having a hairpin region, the standard free energy of the confinement of the hairpin region may be considered when determining the standard free energy for the reaction in which the protector strand is displaced from the complement strand by the target nucleic acid. Approximate values for the standard free energy of hairpin confinement for hairpins of various sizes are provided in Table 1 (from SantaLucia and Hicks, *Annu. Rev. Biophys. Biomol. Struct.,* 33:414-440, (2004)).

NeoGenomics
Exhibit 1003 Page 423

Hairpin Size	ΔG° of Hairpin Confinement
3 nt	3.5 kcal/mol
4 nt	3.5 kcal/mol
5 nt	3.3 kcal/mol
6 nt	4.0 kcal/mol
7 nt	4.2 kcal/mol
8 nt	4.3 kcal/mol
9 nt	4.5 kcal/mol
10 nt	4.6 kcal/mol
12 nt	5.0 kcal/mol
14 nt	5.1 kcal/mol
16 nt	5.3 kcal/mol
18 nt	5.5 kcal/mol
20 nt	5.7 kcal/mol
25 nt	6.1 kcal/mol
30 nt	6.3 kcal/mol

The standard free energy of the confinement of the hairpin regions having lengths not provided in Table 1 *(e.g.,* a length of n) can be estimated using the following equation:

$$AG^{\circ}(\text{loop - } n) = AG^{\circ}(\text{loop - } x) + 2.AART \ln(n / x)$$

where AG°(loop - *n)* is the unknown standard free energy of the confinement of a hairpin region of n nucleotides in length, AG°(loop - *x)* is the known standard free energy of the confinement of a hairpin region of n nucleotides in length *(e.g.,* as provided in Table 1), *R* is the ideal gas constant, and *T* is the temperature at which the primer duplex is to be used. Additional information on the calculation of standard free energies of hairpin region confinement is provided in SantaLucia and Hicks, *id.,* which is hereby incorporated by reference in its entirety.

The hairpin primer duplex systems described herein may be one of at least two orientations. For example, in one orientation shown in FIG. 2A, the toehold region is located at the 5' end of the nucleic acid molecule. The 5' end of the complement branch migration region is immediately adjacent to the 3'end of the toehold region; the 5' end of the complement balance region is immediately adjacent to the 3' end of the complement branch migration region; the 5' end of the hairpin region is immediately adjacent to the 3' end of the complement balance region; the 5' end of the protector balance region is immediately adjacent to the 3' end of the

NeoGenomics
Exhibit 1003 Page 424

hairpin region; and the 5' end of the protector branch migration region is immediately adjacent to the 3' end of the protector balance region. In this orientation, when the nucleic acid molecule is subjected to conditions that permit annealing, the hairpin region forms a loop that extends from the complement balance region and the protector balance region. In another orientation shown in FIG. 2B, the toehold region is located at the 3' end of the nucleic acid molecule. The 3' end of the complement branch migration region is immediately adjacent to the 5'end of the toehold region; the 3' end of the complement balance region is immediately adjacent to the 5' end of the complement branch migration region; the 3' end of the hairpin region is immediately adjacent to the 5' end of the complement balance region; the 3' end of the protector balance region is immediately adjacent to the 5' end of the hairpin region; and the 3' end of the protector branch migration region is immediately adjacent to the 5' end of the protector balance region.

Regardless of orientation, the complement balance region of the hairpin primer duplex system has a sequence such that:

$$\left|\Delta G_1^o - AG_{\sim}'' - AG_3^\circ + AG_4^\circ + RT \ln(c)\right| \leq AG_R^\circ,$$

where:

$AG_{\sim}''$ is the standard free energy of hybridization of the protector balance region to the complement balance region;

AG_2^o is the standard free energy of hybridization of the protector balance region to the sequence immediately adjacent in the first direction to the target nucleic acid sequence, if any; and

AG_3° is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence;

AG_4° is the standard free energy of confinement of the hairpin region;

R is the ideal gas constant;

T is the temperature at which the primer system is to be used;

c is the concentration at which the primer system is to be used; and

AG_R^o is 3.5 kcal/mol.

NeoGenomics
Exhibit 1003 Page 425

Other Primer Systems

Additional primer systems are depicted in FIGS. 4-7. Each of these primer systems include a complement domain and two protector domains. The complement domain has a single toehold region that is flanked by two complement branch migration regions and two complement balance regions. Each of the protector domains include a protector branch migration region that has a sequence complementary to the sequence of one of the complement branch migration regions, and a protector balance region that has a sequence that is complementary to the sequence of one of the complement balance regions. The difference between the primer systems of FIGS. 4-7 is in the number and location of the hairpin regions, which in turn affects the design of the complement balance regions. Like the other primer systems disclosed here, these primer systems are designed to specifically hybridize to a target nucleic acid. Though the sequence of the target nucleic acid is used to describe the characteristics of a primer system, in some embodiments, the target nucleic acid is not a component of a primer system.

As depicted in FIG. 4, a primer system may have, in 3' to 5' order, a first protector domain, a first hairpin region, a complement domain, a second hairpin region and a second protector domain.

In such embodiments, the first protector domain includes a first protector branch migration region and a first protector balance region. The first protector branch migration region has a sequence that corresponds to a first target nucleic acid sequence. The first protector balance region is immediately 5' to the first protector branch migration region and has a sequence that does not correspond to sequence immediately 5' to the first target nucleic acid sequence, if any, on the target nucleic acid.

In this embodiment, the first hairpin region is immediately 5' to the first protector balance region.

The complement domain of such target nucleic acids comprises a first complement balance region, a first complement branch migration region, a toehold region, a second complement branch migration region and a second complement balance region. The first complement balance region is immediately 5' to the first hairpin region and has a sequence complementary to the sequence of the first protector balance region. The first complement branch migration region is immediately 5' to the first complement balance region and has a sequence complementary to a first protector branch migration region. The toehold region is

NeoGenomics
Exhibit 1003 Page 426

immediately 5' to the first complement branch migration region and has a sequence that is complementary to a second target nucleic acid sequence that is immediately 3' to the first target nucleic acid sequence on the target nucleic acid. The second complement branch migration region is immediately 5' to the toehold region and has a sequence complementary to a third target nucleic acid sequence that is immediately 3' to the second target nucleic acid sequence on the target nucleic acid. The second complement balance region is immediately 5' to the second complement branch migration region and has a sequence that is not complementary to sequence immediately 3' to the third target nucleic acid sequence, if any, on the target nucleic acid.

In such embodiments, the second hairpin region is immediately 5' to the second complement balance region.

In this embodiment the second protector domain includes a second protector balance region and a second protector branch migration region. The second protector balance region is immediately 5' to the second hairpin region and has a sequence complementary to the second complement balance region. The second protector branch migration region is immediately 5' to the second protector balance region and has a sequence complementary to the second complement branch migration region.

According to this embodiment, the first complement balance region and the second complement balance region have sequences such that:

$$\left|\Delta G_1^o - \Delta G_2^o + \Delta G_3^o - \Delta G_4^o - \Delta G_5^o + \Delta G_6^o + \Delta G_7^o + RT\ln(c)\right| \le AG_R^\circ,$$

where:

AG_1'' is the standard free energy of hybridization of the first protector balance region to the first complement balance region;

AG_2^o is the standard free energy of hybridization of the first complement balance region to the sequence immediately 5' to the first target nucleic acid sequence, if any;

AG_3° is the standard free energy of hybridization of the second protector balance region to the second complement balance region;

AG_4° is the standard free energy of hybridization of the second complement balance region to the sequence immediately 3' to the third target nucleic acid sequence, if any;

NeoGenomics
Exhibit 1003 Page 427

AG_5° is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence;

ΔG_6° is the standard free energy of confinement of the first hairpin region;

ΔG_7° is the standard free energy of confinement of the second hairpin region;

R is the ideal gas constant;

T is the temperature at which the primer system is to be used; and

c is the concentration at which the primer system is to be used; and

AG_R° is 3.5 kcal/mol.

As depicted in FIG. 5, in certain embodiments, a primer system may have a hairpin primer and a protector, where the hairpin primer is a nucleic acid that includes a first protector domain, a first hairpin region, a complement domain and the protector is a nucleic acid that includes a second protector domain.

In such embodiments, the first protector domain includes a first protector branch migration region and a first protector balance region. The first protector branch migration region has a sequence that corresponds to a first target nucleic acid sequence. The first protector balance region is immediately 5' to the first protector branch migration region and has a sequence that does not correspond to sequence immediately 5' to the first target nucleic acid sequence, if any, on the target nucleic acid.

In this embodiment, the hairpin region is immediately 5' to the first protector balance region.

The complement domain of such target nucleic acids comprises a first complement balance region, a first complement branch migration region, a toehold region, a second complement branch migration region and a second complement balance region. The first complement balance region is immediately 5' to the hairpin region and has a sequence complementary to the sequence of the first protector balance region. The first complement branch migration region is immediately 5' to the first complement balance region and has a sequence complementary to a first protector branch migration region. The toehold region is immediately 5' to the first complement branch migration region and has a sequence that is complementary to a second target nucleic acid sequence that is immediately 3' to the first target nucleic acid sequence on the target nucleic acid. The second complement branch migration

NeoGenomics
Exhibit 1003 Page 428

region is immediately 5' to the toehold region and has a sequence complementary to a third target nucleic acid sequence that is immediately 3' to the second target nucleic acid sequence on the target nucleic acid. The second complement balance region is immediately 5' to the second complement branch migration region and has a sequence that is not complementary to sequence immediately 3' to the third target nucleic acid sequence, if any, on the target nucleic acid.

In this embodiment, the second protector domain includes a second protector balance region and a second protector branch migration region. The second protector balance region has a sequence complementary to the second complement balance region. The second protector branch migration region is immediately 5' to the second protector balance region and has a sequence complementary to the second complement branch migration region.

According to this embodiment, the first complement balance region and the second complement balance region have sequences such that:

$$\left|\Delta G'' - \Delta G''_{2} + \Delta G^{\circ}_{3} - \Delta G^{\circ}_{4} - \Delta G^{\circ}_{5} + \Delta G''_{6}\right| \leq \Delta G^{\circ}_{R},$$

where:

$\Delta G''_{1}$ is the standard free energy of hybridization of the first protector balance region to the first complement balance region;

ΔG°_{2} is the standard free energy of hybridization of the first complement balance region to the sequence immediately 5' to the first target nucleic acid sequence, if any;

ΔG°_{3} is the standard free energy of hybridization of the second protector balance region to the second complement balance region;

$\Delta G''_{4}$ is the standard free energy of hybridization of the second complement balance region to the sequence immediately 3' to the third target nucleic acid sequence, if any;

ΔG°_{5} is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence;

ΔG°_{6} is the standard free energy of confinement of the hairpin region; and

$\Delta G''_{R}$ is 3.5 kcal/mol.

As depicted in FIG. 6, in certain embodiments a primer system may have a protector and a hairpin primer, where the protector is a nucleic acid that includes a first protector domain and

NeoGenomics
Exhibit 1003 Page 429

the hairpin primer is a nucleic acid that includes a complement domain, hairpin region and a second protector domain.

In such embodiments, the first protector domain includes a first protector branch migration region and a first protector balance region. The first protector branch migration region has a sequence that corresponds to a first target nucleic acid sequence. The first protector balance region is immediately 5' to the first protector branch migration region and has a sequence that does not correspond to sequence immediately 5' to the first target nucleic acid sequence, if any, on the target nucleic acid.

The complement domain of such target nucleic acids comprises a first complement balance region, a first complement branch migration region, a toehold region, a second complement branch migration region and a second complement balance region. The first complement balance region has a sequence complementary to the sequence of the first protector balance region. The first complement branch migration region is immediately 5' to the first complement balance region and has a sequence complementary to a first protector branch migration region. The toehold region is immediately 5' to the first complement branch migration region and has a sequence that is complementary to a second target nucleic acid sequence that is immediately 3' to the first target nucleic acid sequence on the target nucleic acid. The second complement branch migration region is immediately 5' to the toehold region and has a sequence complementary to a third target nucleic acid sequence that is immediately 3' to the second target nucleic acid sequence on the target nucleic acid. The second complement balance region is immediately 5' to the second complement branch migration region and has a sequence that is not complementary to sequence immediately 3' to the third target nucleic acid sequence, if any, on the target nucleic acid.

According to such embodiments, the hairpin region is immediately 5' to the second complement balance region.

In this embodiment the second protector domain includes a second protector balance region and a second protector branch migration region. The second protector balance region is immediately 5' to the hairpin region and has a sequence complementary to the second complement balance region. The second protector branch migration region is immediately 5' to the second protector balance region and has a sequence complementary to the second complement branch migration region.

NeoGenomics
Exhibit 1003 Page 430

According to this embodiment, the first complement balance region and the second complement balance region have sequences such that:

$$\left|\Delta G'' - \Delta G''_{2} + \Delta G^{\circ}_{3} - \Delta G^{\circ}_{4} - \Delta G^{\circ}_{5} + \Delta G''_{6}\right| \leq \Delta G^{\circ}_{R},$$

where:

$\Delta G''_{1}$ is the standard free energy of hybridization of the first protector balance region to the first complement balance region;

ΔG^{o}_{2} is the standard free energy of hybridization of the first complement balance region to the sequence immediately 5' to the first target nucleic acid sequence, if any;

ΔG°_{3} is the standard free energy of hybridization of the second protector balance region to the second complement balance region;

$\Delta G''_{4}$ is the standard free energy of hybridization of the second complement balance region to the sequence immediately 3' to the third target nucleic acid sequence, if any; and

ΔG°_{5} is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence;

ΔG°_{6} is the standard free energy of confinement of the hairpin region; and

$\Delta G''_{R}$ is 3.5 kcal/mol.

As depicted in FIG. 7, in certain embodiments a primer system may have a first protector, a complement primer and a second protector, where the first protector is a nucleic acid that includes a first protector domain, the complement primer is a nucleic acid that includes a complement domain, and the second protector is a nucleic acid that includes a second protector domain.

In such embodiments, the first protector domain includes a first protector branch migration region and a first protector balance region. The first protector branch migration region has a sequence that corresponds to a first target nucleic acid sequence. The first protector balance region is immediately 5' to the first protector branch migration region and has a sequence that does not correspond to sequence immediately 5' to the first target nucleic acid sequence, if any, on the target nucleic acid.

NeoGenomics
Exhibit 1003 Page 431

The complement domain of such target nucleic acids comprises a first complement balance region, a first complement branch migration region, a toehold region, a second complement branch migration region and a second complement balance region. The first complement balance region has a sequence complementary to the sequence of the first protector balance region. The first complement branch migration region is immediately 5' to the first complement balance region and has a sequence complementary to a first protector branch migration region. The toehold region is immediately 5' to the first complement branch migration region and has a sequence that is complementary to a second target nucleic acid sequence that is immediately 3' to the first target nucleic acid sequence on the target nucleic acid. The second complement branch migration region is immediately 5' to the toehold region and has a sequence complementary to a third target nucleic acid sequence that is immediately 3' to the second target nucleic acid sequence on the target nucleic acid. The second complement balance region is immediately 5' to the second complement branch migration region and has a sequence that is not complementary to sequence immediately 3' to the third target nucleic acid sequence, if any, on the target nucleic acid.

In this embodiment the second protector domain includes a second protector balance region and a second protector branch migration region. The second protector balance region has a sequence complementary to the second complement balance region. The second protector branch migration region is immediately 5' to the second protector balance region and has a sequence complementary to the second complement branch migration region.

According to this embodiment, the first complement balance region and the second complement balance region have sequences such that:

$$\left|\Delta G_{1}^{o} - AG_{2}'' + AG_{3}^{\circ} - AG_{4}^{\circ} - AG_{5}^{\circ} - RT\ln(c)\right| \leq AG_{R}^{\circ},$$

where:

AG_{1}'' is the standard free energy of hybridization of the first protector balance region to the first complement balance region;

AG_{2}^{o} is the standard free energy of hybridization of the first complement balance region to the sequence immediately 5' to the first target nucleic acid sequence, if any;

AG_{3}° is the standard free energy of hybridization of the second protector balance region to the second complement balance region;

NeoGenomics
Exhibit 1003 Page 432

ΔG_4^o is the standard free energy of hybridization of the second complement balance region to the sequence immediately 3' to the third target nucleic acid sequence, if any; and

AG_5° is the standard free energy of hybridization of the toehold region to the second target nucleic acid sequence;

R is the ideal gas constant;

T is the temperature at which the primer system is to be used;

c is the concentration at which the primer system is to be used; and

AG_R° is 3.5 kcal/mol.

Primer Duplex Systems Lacking Balance Domains

In some embodiments, primer systems may lack balance domains. Such nucleic acids will hybridize with a target nucleic acid with fast kinetics if the target nucleic acid has a sequence complementary to the sequence of the toehold region of the primer system, but with slow kinetics if the target nucleic is mutated so that it does not contain a sequence complementary to the toehold region of the primer system. Such primer systems are therefore useful, for example, for locating difference and/or mutations in nucleic acid targets using kinetic discrimination.

As depicted in FIG. 8, in certain embodiments a primer system may include a nucleic acid having, in 3' to 5' order, a first protector domain, a first hairpin region, a complement domain, a second hairpin region and a second protector domain. The first protector domain of such primer systems has a sequence that corresponds to a first target nucleic acid sequence. The first hairpin region is immediately 5' of the first protector domain. The complement domain has a first complement branch migration region, a toehold region and a second complement branch migration region. The first complement branch migration region is immediately 5' of the first hairpin region and has a sequence complementary to the branch migration sequence of the first protector domain. The toehold region is immediately 5' of the first complement branch migration region and has a sequence complementary to a second target nucleic acid sequence that is immediately 3' of the first target nucleic acid sequence on the target nucleic acid molecule. The second complement branch migration region is immediately 5' of the toehold region and has a sequence complementary to a third target nucleic acid sequence that is

NeoGenomics
Exhibit 1003 Page 433

immediately 3' of the second nucleic acid sequence. The second hairpin region is immediately 5' of the second complement branch migration region. The second protector domain has a sequence that is complementary to the sequence of the second complement branch migration region.

Primer Modifications Generally

Each primer described herein may be comprised of DNA, RNA, or analogs thereof, and/or combinations thereof. In certain embodiments, a primer comprises one or more non-natural nucleotides. The incorporation of non-natural nucleotides in the primers can further augment the performance of the primer duplexes. In particular, the protector strand, while not intended to serve to initiate transcription, may happen to be complementary to other regions of the target or other background molecules, and may spuriously initiate replication/transcription. To prevent this, the use of a non-natural nucleotide or a dideoxy nucleotide at the 3' end of the second protector strand may serve to prevent unintended priming by that strand. Examples of non-natural nucleotides include, but are not limited to, iso-C, iso-G, deoxyuridine (see also Krueger *et al. Chem Biol.* 16:242-48 (2009), the teachings which relating to non-natural nucleotides are incorporated by reference herein).

In some embodiments, for example, in a polymerase chain reaction (PCR) where a repeated primed enzymatic function is used, the extended complement strand can become a target for subsequent primer hybridization. To preserve the specificity of primer hybridization for subsequent rounds of amplification, a balance region of a primer cannot be replicated. Introducing a non-natural nucleotide at the interface between the branch migration and balance regions of the complement strand, for example, may prevent the balance region from being replicated.

In certain embodiments, the primers described herein serve as starting points for polymerase extensions. To facilitate analysis of amplified (nucleic acid) fragments, labeled primers can also be used in PCR reactions. Labeled primers are those that are coupled (or conjugated) to a detectable moiety. Examples include fluorescent dyes, radioactive labels, and identifiable metals, nucleic acid sequences, and proteins. When a reaction is carried out with fluorescently labeled primers, amplicons (nucleic acid products) with a fluorescent label may be generated.

NeoGenomics
Exhibit 1003 Page 434

The primers described herein can be synthesized by any method known in the art (see, *e.g.,* Ogilvie *et al. J. Amer. Chem. Soc.* 99 (23): 7741-7743; Reese, C. B. *Tetrahedron* 34(21): 3143 (1978); Efimov *et al. Nucleic Acids Res.* 11(23): 8369-8387 (1983); Garegg *et al. Tetrahedron Lett.* 27(34): 4051 (1986); Beaucage *et al. Tetrahedron* 48(12): 2223 (1992); Efimov *et al. Nucleosides, Nucleotides & Nucleic Acids* 26 (8-9): 1087-93 (2007), incorporated herein by reference).

Target Nucleic Acid Molecules

A "target" can be a single-stranded (ss) or double-stranded (ss) nucleic acid. Target nucleic acids can be, for example, DNA, RNA, or the DNA product of RNA subjected to reverse transcription. In some embodiments, a target may be a mixture (chimera) of DNA and RNA. In other embodiments, a target comprises artificial nucleic acid analogs, for example, peptide nucleic acids (Nielsen *et al. Science* 254(5037): 1497-500 (1991)) or locked nucleic acids (Alexei *et al. Tetrahedron* 54(14): 3607-30 (1998)). In some embodiments, a target may be naturally occurring *(e.g.,* genomic DNA) or it may be synthetic *(e.g.,* from a genomic library). As used herein, a "naturally occurring" nucleic acid sequence is a sequence that is present in nucleic acid molecules of organisms or viruses that exist in nature in the absence of human intervention. In some embodiments, a target is genomic DNA, messenger RNA, ribosomal RNA, micro-RNA, pre-micro-RNA, pro-micro-RNA, viral DNA, viral RNA or piwi-RNA. In certain embodiments, a target nucleic acid is a nucleic acid that naturally occurs in an organism or virus. In some embodiments, a target nucleic is the nucleic acid of a pathogenic organism or virus. In certain embodiments the presence or absence of a target nucleic acid in a subject is indicative that the subject has a disease or disorder or is predisposed to acquire a disease or disorder. In certain embodiments the presence or absence of a target nucleic acid in a subject is indicative that the subject will respond well or poorly to a treatment, such as a drug, to treat a disease or disorder.

The terms "polynucleotide," "nucleic acid" and "nucleic acid molecule" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci

NeoGenomics
Exhibit 1003 Page 435

(locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. A polynucleotide may be further modified, such as by conjugation with a labeling component. The term "recombinant" polynucleotide means a polynucleotide of genomic, cDNA, semi-synthetic, or synthetic origin which either does not occur in nature or is linked to another polynucleotide in a non-natural arrangement. The term "isolated nucleic acid" refers to a polynucleotide of natural or synthetic origin or some combination thereof, which (1) is not associated with the cell in which the "isolated nucleic acid" is found in nature, and/or (2) is operably linked to a polynucleotide to which it is not linked in nature.

A nucleic acid may also encompass single- and double-stranded DNA and RNA, as well as any and all forms of alternative nucleic acid containing modified bases, sugars, and backbones. The term "nucleic acid" thus will be understood to include, but not be limited to, single- or double-stranded DNA or RNA (and forms thereof that can be partially single-stranded or partially double-stranded), cDNA, aptamers, peptide nucleic acids ("PNA"), 2'-5' DNA (a synthetic material with a shortened backbone that has a base-spacing that matches the A conformation of DNA; 2'-5' DNA will not normally hybridize with DNA in the B form, but it will hybridize readily with RNA), and locked nucleic acids ("LNA"). Nucleic acid analogues include known analogues of natural nucleotides that have similar or improved binding, hybridization of base-pairing properties. "Analogous" forms of purines and pyrimidines are well known in the art, and include, but are not limited to aziridinylcytosine, 4-acetylcytosine, 5-fluorouracil, 5-bromouracil, 5-carboxymethylaminomethyl-2-thiouracil, 5-carboxymethylaminomethyluracil, inosine, N6-isopentenyladenine, 1-methyladenine, 1-methylpseudouracil, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N.sup.6-methyladenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5-methoxyuracil, 2-methylthio- N6-isopentenyladenine, uracil-5-oxyacetic acid methylester, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-

NeoGenomics
Exhibit 1003 Page 436

thiouracil, 5-methyluracil, uracil-5-oxyacetic acid, and 2,6-diaminopurine. DNA backbone analogues provided herein include phosphodiester, phosphorothioate, phosphorodithioate, methylphosphonate, phosphoramidate, alkyl phosphotriester, sulfamate, 3'-thioacetal, methylene(methylimino), 3'-N-carbamate, morpholino carbamate, and peptide nucleic acids (PNAs), methylphosphonate linkages or alternating methylphosphonate and phosphodiester linkages (Strauss-Soukup, 1997, Biochemistry 36:8692-8698), and benzylphosphonate linkages, as discussed in U.S. Pat. No. 6,664,057; see also OLIGONUCLEOTIDES AND ANALOGUES, A PRACTICAL APPROACH, edited by F. Eckstein, IRL Press at Oxford University Press (1991); Antisense Strategies, Annals of the New York Academy of Sciences, Volume 600, Eds. Baserga and Denhardt (NYAS 1992); Milligan, 1993, *J. Med. Chem.* 36:1923-1937; Antisense Research and Applications (1993, CRC Press). The nucleic acids herein can be extracted from cells or synthetically prepared according to any means known to those skilled in the art; for example, the nucleic acids can be chemically synthesized or transcribed or reverse transcribed from cDNA or mRNA, among other sources.

As used herein, two nucleic acids or nucleic acid regions "correspond" to one another if they are both complementary to the same nucleic acid sequence. Two nucleic acids or nucleic acid regions are "complementary" to one another if they base-pair with each other to form a double-stranded nucleic acid molecule.

A target nucleic acids utilized herein can be any nucleic acid, for example, human nucleic acids, bacterial nucleic acids, or viral nucleic acids. A target nucleic acid sample can be, for example, a nucleic acid sample from one or more cells, tissues, or bodily fluids. Target samples can be derived from any source including, but not limited to, eukaryotes, plants, animals, vertebrates, fish, mammals, humans, non-humans, bacteria, microbes, viruses, biological sources, serum, plasma, blood, urine, semen, lymphatic fluid, cerebrospinal fluid, amniotic fluid, biopsies, needle aspiration biopsies, cancers, tumors, tissues, cells, cell lysates, crude cell lysates, tissue lysates, tissue culture cells, buccal swabs, mouthwashes, stool, mummified tissue, forensic sources, autopsies, archeological sources, infections, nosocomial infections, production sources, drug preparations, biological molecule productions, protein preparations, lipid preparations, carbohydrate preparations, inanimate objects, air, soil, sap, metal, fossils, excavated materials, and/or other terrestrial or extra-terrestrial materials and sources. The sample may also contain mixtures of material from one source or different sources. For example, nucleic acids of an

NeoGenomics
Exhibit 1003 Page 437

infecting bacterium or virus can be amplified along with human nucleic acids when nucleic acids from such infected cells or tissues are amplified using the disclosed methods. Types of useful target samples include eukaryotic samples, plant samples, animal samples, vertebrate samples, fish samples, mammalian samples, human samples, non-human samples, bacterial samples, microbial samples, viral samples, biological samples, serum samples, plasma samples, blood samples, urine samples, semen samples, lymphatic fluid samples, cerebrospinal fluid samples, amniotic fluid samples, biopsy samples, needle aspiration biopsy samples, cancer samples, tumor samples, tissue samples, cell samples, cell lysate samples, crude cell lysate samples, tissue lysate samples, tissue culture cell samples, buccal swab samples, mouthwash samples, stool samples, mummified tissue samples, autopsy samples, archeological samples, infection samples, nosocomial infection samples, production samples, drug preparation samples, biological molecule production samples, protein preparation samples, lipid preparation samples, carbohydrate preparation samples, inanimate object samples, air samples, soil samples, sap samples, metal samples, fossil samples, excavated material samples, and/or other terrestrial or extra-terrestrial samples.

In some embodiments, a target nucleic acids utilized herein comprise repetitive sequence, secondary structure, and/or a high G/C content.

In certain embodiments, a target nucleic acid molecule of interest is about 100 to about 1,000,000 nucleotides (nt) in length. In some embodiments, the target is about 100 to about 1000, about 1000 to about 10,000, about 10,000 to about 100,000, or about 100,000 to about 1,000,000 nucleotides in length. In some embodiments, the target is about 100, about 200, about 300, about 400, about 500, about 600, about 700, about 800, about 900, about 1,000, about 2,000, about 3,000, about 4,000, about 5,000, about 6,000, about 7,000, about 8,000, about 9000, about 10,000, about 20,000, about 30,000, about 40,000, about 50,000, about 60,000, about 70,000, about 80,000, about 90,000, about 100,000, about 200,000, about 300,000, about 400,000, about 500,000, about 600,000, about 700,000, about 800,000, about 900,000, or about 1,000,000 nucleotides in length. It is to be understood that the target nucleic acid may be provided in the context of a longer nucleic acid (e.g., such as a coding sequence or gene within a chromosome or a chromosome fragment).

In certain embodiments, a target of interest is linear, while in other embodiments, a target is circular *(e.g.,* plasmid DNA, mitochondrial DNA, or plastid DNA).

NeoGenomics
Exhibit 1003 Page 438

Combined Primer-Target Systems

In some embodiments, provided herein are primer-target systems. A primer-target system comprises one or more nucleic acid targets, a polymerase, and one or more primers *(e.g.,* primer duplex and/or hairpin primer duplex). The term "primer" encompasses any one of the primers or primer systems described herein *(e.g.,* single-stranded primers, double-stranded primer duplexes, and hairpin primer duplexes). In certain embodiments, the primer-target systems described herein comprise a plurality of different primers. In some embodiments, a primer-target system can comprise at least two primers, which can be used to identify and, for example amplify, a target nucleic acid molecule. A target nucleic acid molecule may be present amongst a plurality of non-target nucleic acid molecules, for example, as a single copy or in low copy number. Any one of the primer-target systems described herein may comprises conditions similar to those used in nucleic acid amplification or sequencing reactions *(e.g.,* similar reagents, reaction temperature, *etc.).*

Methods of Use

The primer systems described herein are able to discriminate a specific target from spurious targets either through a thermodynamic mechanism or through a kinetic mechanism. In distinguishing the target from spurious targets using a thermodynamic mechanism (described below), the strand displacement reaction is run to completion and the target is distinguished from the spurious targets based on differences in equilibrium binding affinity. To distinguish the target from spurious targets using a kinetic mechanism (described below), the strand displacement reaction is stopped before reaching equilibrium, and the differential rate in reaction completion is used to distinguish the targets from spurious targets.

Thermodynamic separation

The general strategy for both the thermodynamic and the kinetic mechanism is to use toehold exchange strand displacement reactions. In general, toehold exchange involves extending a target's complement with an additional region that is not complementary to the target, and pre-hybridizing a protector strand to this extended complement strand and a large number of bases adjacent to the extended region, but not to a single-stranded toehold region.

NeoGenomics
Exhibit 1003 Page 439

FIG. 9 depicts one implementation of toehold exchange. In this implementation, a two-stranded primer duplex system (as described above and depicted in FIG. 1A) is used to distinguish between a target nucleic acid and a spurious target. The complement branch migration region and the toehold region of the complement strand have sequences that correspond to a first target sequence and a second target sequence, respectively. A complement balance region was designed to be the same length and nucleotide base distribution as the toehold region. In this way, the standard free energy of the strand displacement reaction shown in FIG. 9A between the correct target and the protected complement is roughly AG° = 0 kcal/mol.

The strand displacement reaction can be written as:

$$\text{Target} + \text{Complement/Protector} \Leftrightarrow \text{Target/Complement} + \text{Protector}$$

AG° relates to the equilibrium constant K_{eq} by the following relation:

$$AG° = R71n(K_{eq}).$$

For a reaction with AG° = 0, the equilibrium constant (K_{eq}) is 1. The equilibrium constant also relates to the equilibrium; for this reaction, K_{eq} = [TC] [P] / [T] [PC] = 1. For an assay where [PC] and [P] and are in excess of [T], [TC] / [T] = 1, meaning that exactly half of all target molecules are hybridized at equilibrium. In the example shown in FIG. 9A, AG° = +0.1 kcal/mol, corresponding to a K_{eq} = 0.85, which means that 46% of the target molecules are hybridized at equilibrium.

The protector strand correspondingly changes the standard free energy of the strand displacement reaction with spurious targets. In the example shown in FIG. 9B, the spurious target differs from the correct target by a single base, which results in the strand displacement reaction with the same two-stranded nucleic acid primer system having a AG° of +3.7 kcal/mol, which corresponds to $K_{eq} = 1.9 * 10^{-3}$. At equilibrium, only 0.19% of the spurious target will be hybridized to the complement. Thus, the exemplary nucleic acid primer system depicted in FIG. 8 preferentially binds to its target versus a spurious target having only a single nucleotide mismatch by more than 200-fold.

FIG. 10 is a plot of the equilibrium binding affinity as a function of the standard free energy of the reaction. When the standard free energy of the reaction is very negative (as in the case in a pure hybridization reaction), both the target and the spurious targets bind very strongly,

NeoGenomics
Exhibit 1003 Page 440

and it is difficult to distinguish between the two, leading to false positives. On the other hand, when the standard free energy of the reaction is very positive, the primer binds to the target very weakly, leading to false negatives. Designing a primer duplex system to have a standard free energy of near zero results in an optimal discrimination between targets and spurious targets, thereby minimizing false positives and false negatives.

Kinetic Separation

Kinetic separation relies on the differential kinetics of toehold exchange. The kinetics of the toehold exchange reaction depend on the binding strengths of the toeholds regions. Each kcal/mol of difference in toehold binding energy can affect kinetics by a factor of 5.4 (Figure 11), so the +3.6 kcal/mol mismatch shown in FIG. 9B would yield a kinetic slowdown of 434.

Unlike in thermodynamic discrimination, kinetic discrimination occurs only when the mismatch is in the toehold region. Spurious targets differing from the correct target at a position complementary to the complement branch migration region are unlikely to yield significantly different reaction kinetics. As a consequence, methods that use the kinetic mechanism of distinguishing target from spurious target are useful in conjunction with thermodynamic separation as a means of pinpointing the locations of target/primer mismatches.

Significantly, primer duplex systems lacking complement balance regions, such as the primer systems depicted in FIG. 8, can be used in methods that exploit the kinetic mechanism to pinpoint the location of target/primer mismatches.

Microarrays

Nucleic acid microarrays are often used for high-throughput nucleic acid detection, but often are unable to distinguish between closely related nucleic acid sequences. In some embodiments, the primer duplex systems described herein can be used in nucleic acid microarrays in order to, for example, improve the specificity of microarray analysis. In some instance, microarrays assays can be performed using methods well known in the art, with the exception that the primer duplex systems described herein can be used in place of conventional nucleic acid primers.

For example, as depicted in FIG. 12A, in certain embodiments, a hairpin primer duplex system from can be directly synthesized or immobilized on a microarray chip using standard

NeoGenomics
Exhibit 1003 Page 441

techniques. In other embodiments, a two-stranded primer duplex system can be used in a nucleic acid microarray. In some embodiment, hairpin structures including two photocleavable bases at predefined positions can be synthesized as in FIG. 12A. Subsequent exposure to light cleaves the hairpin, yielding the two-stranded complexes functionalized to the array surface (FIG. 12B). Other methods, such as use of nicking or restriction enzymes, can also be used to prepare two-stranded complexes.

Nucleic Acid Synthesis Reactions, Including Amplification Reactions

Primer duplexes and systems disclosed here can be used in some embodiments to improve the specificity of a primer-based amplification reaction, including polymerase chain reaction (PCR), strand displacement amplification, or transcription mediated amplification, by substituting a primer duplex system described herein for the nucleic acid primers in a primer based amplification reaction known in the art.

For example, as depicted in FIG. 13, by using as PCR primers the hairpin primer duplex systems of the type depicted in FIG. 4, it is possible to improve the specificity of PCR for a variety of *(e.g.,* biotechnological) applications. In this example, a target nucleic acid sequence is amplified by forming a solution comprising a primer duplex system with the target nucleic acid and standard reagents for performing an amplification reaction and incubating the solution under conditions such that an amplification reaction occurs. In certain embodiments, non-natural bases are incorporated into a hairpin primer duplex primer systems in order to prevent replication of the hairpin itself.

In some embodiments, the primer duplexes described herein can be adapted for use in amplifying target nucleic acids that typically require amplification by any one or more of the following PCR methods: allele-specific PCR, assembly PCR, asymmetric PCR, helicase-dependent amplification, inter sequence-specific PCR (ISSR), inverse PCR, ligation-mediated PCR, methylation-specific PCR (MSP), miniprimer PCR, multiplex PCR, nested PCR, overlap-extension PCR, quantitative PCR (Q-PCR), reverse transcription PCR (RT-PCR), solid phase PCR, thermal asymmetric interlaced PCR (TAIL-PCR), or touchdown PCR. In some instances, the primer duplexes and methods described herein may be used or adapted for use in any one of the foregoing PCR methods or may substitute (used instead of) any one of the foregoing PCR methods. A brief description of each of the foregoing PCR methods is presented below.

NeoGenomics
Exhibit 1003 Page 442

Allele-specific PCR is a diagnostic or cloning technique based on single-nucleotide polymorphisms (SNPs) (single-base differences in DNA). It typically requires prior knowledge of a DNA sequence, including differences between alleles.

Assembly PCR or polymerase cycling assembly (PCA) is an artificial synthesis of long DNA sequences by performing PCR on a pool of long oligonucleotides with short overlapping segments. The oligonucleotides alternate between sense and antisense directions, and the overlapping segments determine the order of the PCR fragments, thereby selectively producing the final long DNA product (Stemmer *et al. Gene* 164(1): 49-53 (1995)).

Asymmetric PCR preferentially amplifies one DNA strand in a double-stranded DNA target. It can be used in sequencing and hybridization probing where amplification of only one of the two complementary strands is required (Innis et al. Proc. Natl. Acad. Sci. USA 85(24): 9436-40 (1988)).

Helicase-dependent amplification is similar to traditional PCR, but typically uses a constant temperature rather than cycling through denaturation and annealing/extension cycles. DNA helicase, an enzyme that unwinds DNA, is used in place of thermal denaturation (Vincent *et al. EMBO Reports* 5(8): 795-800 (2004)).

Intersequence-specific PCR (ISSR) is a PCR method for DNA fingerprinting that amplifies regions between simple sequence repeats to produce a unique fingerprint of amplified fragment lengths (Zietkiewicz *et al. Genomics* 20(2): 176-83 (1994)).

Inverse PCR is commonly used to identify the flanking sequences around genomic inserts. It involves a series of DNA digestions and self-ligation, resulting in known sequences at either end of the unknown sequence (Ochman *et al. Genetics* 120 (3): 621-623 (1988)).

Ligation-mediated PCR uses small DNA linkers ligated to the DNA of interest and multiple primers annealing to the DNA linkers; it has been used for DNA sequencing, genome walking, and DNA footprinting (Mueller *et al. Science* 246(4931): 780-786 (1988)).

Methylation-specific PCR (MSP) is used to detect methylation of CpG islands in genomic DNA. DNA is first treated with sodium bisulfite, which converts unmethylated cytosine bases to uracil, which is recognized by primers as thymine.

Miniprimer PCR uses a thermostable polymerase (S-Tbr) and is used to amplify conserved DNA sequences, such as the 16S (or eukaryotic 18S) rRNA gene (Isenbarger *et al. Applied and Environmental Microbiology* 74(3): 840-9. (2008)).

NeoGenomics
Exhibit 1003 Page 443

Multiplex-PCR targets multiple genes at once, gaining additional information from a single test-run that otherwise would require several times the reagents and more time to perform.

Nested PCR increases the specificity of DNA amplification, by reducing background due to non-specific amplification of DNA. Two sets of primers are used in two successive PCRs. In the first reaction, one pair of primers is used to generate DNA products, which besides the intended target, may still consist of non-specifically amplified DNA fragments. The product(s) are then used in a second PCR with a set of primers whose binding sites are completely or partially different from and located 3' of each of the primers used in the first reaction.

Overlap-extension PCR or splicing by overlap extension (SOE) is a genetic engineering technique that is used to splice together two or more DNA fragments that contain complementary sequences. It is used to join DNA pieces containing genes, regulatory sequences, or mutations; the technique enables creation of specific and long DNA constructs.

Quantitative PCR (Q-PCR) is used to measure the quantity of a PCR product (commonly in real-time). It quantitatively measures starting amounts of DNA, cDNA, or RNA. Q-PCR is commonly used to determine whether a DNA sequence is present in a sample and the number of its copies in the sample.

Reverse Transcription PCR (RT-PCR) is used for amplifying DNA from RNA. Reverse transcriptase reverse transcribes RNA into cDNA, which is then amplified by PCR. RT-PCR is widely used in expression profiling, to determine the expression of a gene or to identify the sequence of an RNA transcript, including transcription start and termination sites. If the genomic DNA sequence of a gene is known, RT-PCR can be used to map the location of exons and introns in the gene. The 5' end of a gene (corresponding to the transcription start site) is typically identified by RACE-PCR (Rapid Amplification of cDNA Ends).

Solid Phase PCR encompasses multiple meanings, including polony amplification (where PCR colonies are derived in a gel matrix, for example), bridge PCR (primers are covalently linked to a solid-support surface), conventional solid phase PCR (where asymmetric PCR is applied in the presence of solid support bearing primer with sequence matching one of the aqueous primers) and enhanced solid phase PCR (where conventional solid phase PCR can be improved by employing high melting temperature (T_m) and nested solid support primer with optional application of a thermal 'step' to favor solid support priming).

NeoGenomics
Exhibit 1003 Page 444

Thermal asymmetric interlaced PCR (TAIL-PCR) is used for isolation of an unknown sequence flanking a known sequence. Within the known sequence, TAIL-PCR uses a nested pair of primers with differing annealing temperatures; a degenerate primer is used to amplify in the other direction from the unknown sequence (Liu *et al. Genomics* 25 (3): 674-81. (1995)).

Touchdown PCR (step-down PCR) is a variant of PCR that aims to reduce nonspecific background by gradually lowering the annealing temperature as PCR cycling progresses. The annealing temperature at the initial cycles is usually a few degrees (3-5°C) above the Tm of the primers used, while at the later cycles, it is a few degrees (3-5°C) below the primer Tm. The higher temperatures give greater specificity for primer binding, and the lower temperatures permit more efficient amplification from the specific products formed during the initial cycles.

The temperature of the reaction solutions may be sequentially cycled between a denaturing state, an annealing state, and an extension state for a predetermined number of cycles. The actual times and temperatures can be enzyme, primer, and target dependent.

For any given reaction, denaturing states can range in certain embodiments from about 75 °C to about 100 °C. The annealing temperature and time can influence the specificity and efficiency of primer binding to a particular locus within a target nucleic acid and may be important for particular PCR reactions.

For any given reaction, annealing states can range in certain embodiments from about 20 °C to about 75 °C. In some embodiments, the annealing state can be performed at about 20 °C to about 25 °C, about 25 °C to about 30 °C, about 30 °C to about 35 °C, or about 35 °C to about 40 °C, about 40 °C to about 45 °C, about 45 °C to about 50 °C. In certain embodiments, the annealing state can be performed at room temperature *{e.g.,* 20 °C or 25 °C). In some embodiments, the annealing state can be performed at a temperature of 20 °C, 21 °C, 22 °C, 23 °C, 24 °C, 25 °C, 26 °C, 27 °C, 28 °C, 29 °C, 30 °C, 31 °C, 32 °C, 33 °C, 34 °C, 35 °C, 36 °C, 37 °C, 38 °C, 39 °C, 40 °C, 41 °C, 42 °C, 43 °C, 44 °C, 45 °C, 46 °C, 47 °C, 48 °C, 49 °C, or 50 °C.

Extension temperature and time may impact the allele product yield and are understood to be an inherent property of the enzyme under study. For a given enzyme, extension states can range in certain embodiments from about 60 °C to about 75 °C.

In any of the foregoing embodiments, any DNA or RNA polymerase (enzyme that catalyzes polymerization of nucleotides into a nucleic acid strand) may be utilized, including

NeoGenomics
Exhibit 1003 Page 445

thermostable polymerases and reverse transcriptases (RTases). Examples include *Bacillus stearothermophilus* pol I, *Thermus aquaticus* (Taq) pol I, *Pyrecoccusfuriosus* (Pfu), *Pyrococcus woesei* (Pwo), *Thermusflavus* (Tfl), *Thermus thermophilus* (Tth), *Thermus litoris* (Tli) and *Thermotoga maritime* (Tma). These enzymes, modified versions of these enzymes, and combination of enzymes, are commercially available from vendors including Roche, Invitrogen, Qiagen, Stratagene, and Applied Biosystems. Representative enzymes include PHUSION® (New England Biolabs, Ipswich, MA), Hot MasterTaq™ (Eppendorf), PHUSION® Mpx (Finnzymes), PyroStart® (Fermentas), KOD (EMD Biosciences), Z-Taq (TAKARA), and CS3 AC/LA (KlenTaq, University City, MO).

Salts and buffers include those familiar to those skilled in the art, including those comprising $MgCl_2$, and Tris-HCl and KC1, respectively. Buffers may contain additives such as surfactants, dimethyl sulfoxide (DMSO), glycerol, bovine serum albumin (BSA) and polyethylene glycol (PEG), as well as others familiar to those skilled in the art. Nucleotides are generally deoxyribonucleoside triphosphates, such as deoxyadenosine triphosphate (dATP), deoxycytidine triphosphate (dCTP), deoxyguanosine triphosphate (dGTP), and deoxythymidine triphosphate (dTTP), and are also added to a reaction adequate amount for amplification of the target nucleic acid.

Also provided herein are methods comprising (1) hybridizing a complement strand of a primer duplex to a target nucleic acid, thereby dissociating the complement strand from its protector strand, and (2) extending the complement strand at its 3' end, in a target-complementary manner, in the presence of a polymerase.

Also provided herein are methods comprising performing a nucleic acid synthesis reaction in the presence of a target nucleic acid, a polymerase, and one or more of the primer duplexes of any one of the embodiments described herein.

A "nucleic acid synthesis reaction" refers to any reaction in which a nucleic acid is synthesized. Examples include nucleic acid amplification reactions such as polymerase chain reaction (PCR) or a variation thereof (described elsewhere herein), a transcription reaction, a reverse transcription reaction, sequencing-by-synthesis, or other primer extension reactions (see also, Lizardi *et al. Nat. Genet.* 19: 225-32 (1998), incorporated by reference).

In some instances, a method is provided that comprises (1) synthesizing a complement strand having a target-non-specific balance region, a target- specific branch migration region, and

NeoGenomics
Exhibit 1003 Page 446

a target-specific toehold region; (2) synthesizing a protector strand having a balance region complementary to the complement strand and a branch migration region complementary to the complement strand; and (3) hybridizing the complement strand to the protector strand to form a primer duplex.

In some instances, a method is provided that comprises (1) providing a complement strand having a target-non-specific balance region, a target-specific branch migration region, and a target-specific toehold region; (2) providing a protector strand having a balance region complementary to the complement strand and a branch migration region complementary to the complement strand; and (3) combining the complement strand to the protector strand to form a primer duplex.

In some instances, a method is provided that comprises (1) providing a plurality of nucleic acid molecules comprising a target nucleic acid; (2) providing at least one primer duplex having (i) a balance region, (ii) a branch migration region complementary to the target nucleic acid, and (iii) a toehold region; and (3) combining in a single reaction the plurality of target nucleic acids, at least one primer duplex, and a polymerase under conditions suitable for nucleic acid hybridization.

Also provided herein are methods of amplifying at least one target nucleic acid of interest, comprising (1) providing a plurality of nucleic acid molecules comprising at least one target nucleic acid, (2) providing at least one primer duplex having (i) a balance region, (ii) a branch migration region, and (iii) a toehold region; and (3) combining in a single reaction the plurality of target nucleic acid molecules, at least one primer duplex, and a polymerase under conditions suitable for amplification of the at least one target nucleic acid. In certain embodiments multiple unique target nucleic acids are amplified in a single reaction or in multiple reactions, for example, in one or more multiplexed PCR amplification reaction. In some embodiments, about 10 to 100, about 100 to about 1000, about 1000 to about 10,000, or about 10,000 to about 100,000 nucleic acid targets are amplified. The number of different primer duplexes in a reaction will depend on the number of desired targets.

In some embodiments, provided herein are methods of discriminating against spurious nucleic acid molecules having one or more nucleotide changes relative to a target nucleic acid molecule, comprising (1) providing a plurality of nucleic acid molecules comprising at least one target nucleic acid, (2) providing at least one primer duplex having (i) a balance region, (ii) a

NeoGenomics
Exhibit 1003 Page 447

branch migration region, and (iii) a toehold region; and (3) combining in a single reaction the plurality of target nucleic acid molecules, at least one primer duplex, and a polymerase under conditions suitable for amplification of the at least one target nucleic acid molecule.

Any one of the methods described herein may further comprise providing or combining in a single reaction one or more of the following reagents: buffer *(e.g.,* KC1, $MgCl_2$, Tris-HCl), dNTPs *(e.g.,* dATP, dCTP, dGTP, dTTP at concentrations of, *e.g.,* about 50 to about 100 μM), polymerase *(e.g.,* at concentrations of about 0.5-2.0 units per 50 μĭ reaction), and/or water. The concentration of each strand of a primer duplex in a single reaction varies depending on, for example, the concentration of target nucleic acid. In some embodiments, about 5 to about 50 pg of plasmid or viral target may be used, or about 50 ng to about 500 ng of genomic target may be used. In such instances, the concentration each primer (the first strand and the second strand) may be, for example, about 0.05 μM to about 1 μM. In particular embodiments, the concentration of each primer is about 1 nM to about 1 μM.

In any one of the embodiments described herein, a single reaction may be subject to cyclic temperature changes such that a dsDNA structure undergoes multiple rounds of denaturation, subsequent primer annealing, and polymerase-based extension, for example, similar to those conditions used for standard PCR. In some embodiments, the temperature range for a denaturation step is about 90 to about 95 °C. In certain embodiments, an initial denaturation step of about 1 to about 5 minutes is required prior to cycling; the exact amount of time may depend on GC content of the nucleic acid target of interest. In certain embodiments, the denaturation step during a cycling reaction is about 15 to about 30 seconds. In some embodiments, the temperature range for an annealing step is about 50 °C to about 60 °C. In some embodiments, the annealing step is about 20 °C to about 40 °C. in particular embodiments, the annealing step is at room temperature (about 20°C or about 25°C). In certain embodiments, the annealing step during a cycling reaction is about 15 to about 30 seconds. In some embodiments, the temperature range for an extension step is about 70 °C to about 75 °C. In certain embodiments, the extension step during a cycling reaction is about 45 to about 60 seconds. The temperature, time of each step, and number of cycles of a cycling reaction may depend on the length of the nucleic acid target(s) of interest as well as the polymerase being used. Longer target may require, for example, longer extension times. One example of cycling conditions for a 500 nucleotide target is set forth in Table 2.

NeoGenomics
Exhibit 1003 Page 448

Table 2

1 cycle	98 °C	2 minutes
25 cycles	98 °C	15 seconds
	30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 55 °C, or 60 °C	15 seconds
	72 °C	45 seconds
1 cycle	72 °C	5 minutes
1 cycle	4 °C	indefinite

In any one of the embodiments described herein, a single reaction *(e.g.,* nucleic acid amplification) may proceed at room temperature *(e.g.,* about 20°C or about 25°C). In certain embodiments, a single reaction proceeds at room temperature for about 1 hour.

In any one of the methods described herein, the second protector strand of a primer duplex may be provided in excess of the first complementary strand or in excess of the annealed primer duplexes. For example, in some embodiments, the second strand is provided at a concentration about 1x to about lOx *(e.g.,* Ix, 2x, 3x, 4x, 5x, 6x, 7x, 8x, 9x, or lOx) the concentration the first strand, or about 1x to about lOx *(e.g.,* lx, 2x, 3x, 4x, 5x, 6x, 7x, 8x, 9x, or lOx) the concentration of the annealed primer duplex. In some embodiments, the first strand is provided at a concentration of about 0.05 μM to about 1 μM, while the second strand is provided at a concentration of about 0.10 μM to about 2 μM, or about 0.15 μM to about 3 μM, about 0.2 μM to about 4 μM, or about 0.25 μM to about 5 μM.

Any one of the methods described herein may comprise a method selected from: allele-specific PCR, assembly PCR, asymmetric PCR, helicase-dependent amplification, intersequence-specific PCR (ISSR), inverse PCR, ligation-mediated PCR, methylation-specific PCR (MSP), miniprimer PCR, multiplex PCR, nested PCR, overlap-extension PCR, quantitative PCR (Q-PCR), reverse transcription PCR (RT-PCR), solid phase PCR, thermal asymmetric interlaced PCR (TAIL-PCR), and touchdown PCR.

In any one of the methods described herein, the yield of amplified nucleic acid target may be about 30% to about 100%. In some embodiments, the yield is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 100%.

NeoGenomics
Exhibit 1003 Page 449

In any one of the methods described herein, the amplified nucleic acid product may be purified. Nucleic acid purification methods are well-known to those of skill in the art and include, phenol extraction, guanidinium isothiocyanate, alcohol precipitation, DEAE (ion exchange), size exclusion chromatography (SEC), cesium chloride, extraction from agarose, silica, and other column-based purification methods.

In any one of the methods described herein, a purified amplified target nucleic acid may be about 30% to about 100% pure. In some embodiments, the purity is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% pure.

Imaging

The primer duplexes and systems described herein can also be used to improve the specificity of *in situ* imaging assays. Nonspecific interactions between biological RNAs and fluorophore-labeled primers are frequently a source of background noise. Thus, as depicted in FIG. 14, the use fluorophore-labeled nucleic acid primer systems described herein in the place of conventional primers, in some embodiments, greatly improves the performance of existing *in situ* imaging techniques. Notably, by labeling the complement strand or domain with a fluorophore and the protector strand or domain with a quencher, the primer duplex system will only produce a detectable signal when it is bound to the target.

Single Nucleotide Polymorphism (SNP) Detection

The accurate detection of the location and identity of single nucleotide polymorphisms (SNPs) is of great interest for both research and therapeutic purposes. The kinetic discrimination methods described herein are therefore useful for the convenient identification SNPs.

Kits

Provided herein are kits comprising (1) at least one complement strand having a balance region, a branch migration region, and a toehold region, and (2) at least one protector strand having a balance region and a branch migration region.

NeoGenomics
Exhibit 1003 Page 450

Provided herein are kits comprising at least one primer duplex comprising (1) at least one complement strand or region having a balance region, a branch migration region, and a toehold region, and (2) at least one protector strand or region having a balance region and a branch migration region.

Any one of the kits described herein may further comprise a polymerase. Any one of the kits provided herein may further comprise one or more agent selected from buffer *(e.g.,* KC1, $MgCl_2$, Tris-HCl), dNTPs *(e.g.,* dATP, dCTP, dGTP, dTTP), and water. Any one of the kits provided herein may comprise protector strand is molar excess of the primer. Any one of the kits provided herein may further comprise instructions or directions for obtaining instructions *(e.g.,* from a website) for using the components of the kits. Any one of the kits provided herein may further comprise at least one reaction tube, well, chamber, or the like.

Any one of the primers or primer systems described herein may be provided in the form of a kit or comprised within a kit.

EXAMPLES

In accordance with the invention, the above limitations of PCR, transcription, and reverse transcription can be overcome through the use of highly specific primer duplexes. The experiments described herein demonstrate that primer duplexes can reliably discriminate against targets with single-base changes (FIG. 16) for both DNA and RNA targets and primers (FIG. 17). The correct target hybridizes to the 7/5 primers with roughly 50% yield, but even a large excess (200x) of targets with a single-base change is insufficient to significantly hybridize. Primer duplexes were designed and tested for multiple different targets, and each primer duplex achieved high discrimination factors versus single-nucleotide changes (FIG. 17). Quantitatively, the median discrimination in hybridization yield to a spurious target with a single-nucleotide change is 26.

The primer duplexes were used for PCR in a proof-of-principle demonstration (FIGS. 18A and 18B). A semi-repetitive target nucleic acid was designed, which is difficult to amplify by traditional PCR (PCR without the use of the instant primer duplexes). The yield of standard 2 1 nucleotide primers and the primer duplexes were calculated. Many different thermal cycling schedules were determined in order to investigate the range of function. Based on the length and nucleotide content of the primer duplexes, standard PCR condition would predict that the

NeoGenomics
Exhibit 1003 Page 451

annealing temperature of the primers would 55 °C. Surprisingly, as an example, even under conditions most unfavorable for primer duplex annealing (35 °C and 40 °C), the fraction (50.2%) of correct-length product amplified using the primer duplexes was higher than the fraction (31.0%) of correct-length product amplified using standard primers under their most favorable PCR conditions (45 °C). Furthermore, in this particular experiment, the primer duplexes were arbitrarily designed (7 nucleotide toehold region and 5 nucleotide balance region), and were not optimized for PCR yield performance. Thus, it is likely that even higher PCR specificity can be achieved through optimization of the instant primer duplexes.

FIG. 15 shows highly specific PCR using the primer duplexes provided herein. In Figure 5A, the primer "PC" is comprised of a complement strand "C" and a protector strand "P". When PC binds to the intended target at the correct position "X", the single-stranded protector oligonucleotide "P" is released as an inert waste product, and the primed target is elongated by the DNA polymerase. In FIG. 5B, when the primer PC binds to an unintended target or to the correct target at an incorrect position (in either case, denoted "Y") , the displacement of the protector from the complementary strand "C" is thermodynamically unfavorable, and kinetically quick to reverse. Consequently, off-target amplification *(e.g.,* amplification of Y rather than X) is expected to be significantly reduced.

FIG. 16. shows an experimental demonstration of primer hybridization with single nucleotide discrimination. In FIG. 16A, short synthetic DNA target "X" or spurious target "Y" is reacted with the primer. (The poly-T tail on the protector strand "P" serves to distinguish products from reactants on a gel.) Shown in red boxes are the positions of single-base changes for spurious target Y. FIG 16B shows native polyacrylamide gel results. The primer "PC" was prepared at a 2:1 ratio of protector P to complement C, and annealed at 1 μM concentration of PC. Either the correct or spurious targets were added to achieve final concentrations of 200 nM target (X or Y), 100 nM PC, and 100 nM P. In some embodiments, a reaction may have an excess of the protector (P) primer. For example, in some embodiments, the protector strand is provided at a concentration of about 1x to about 10x *(e.g.,* 1x, 2x, 3x, 4x, 5x, 6x, 7x, 8x, 9x, or 10x) of the complement strand. All reactions proceeded at room temperature (25 °C) for 1 hour. As an example, the designation "7/4" denotes a primer that possesses 7 nucleotides of single-stranded nucleotides (as a 3' overhang) to initiate hybridization to the target, and the protector spontaneously dissociates 4 nucleotides to be released. FIG. 16C is a plot of hybridization yields

NeoGenomics
Exhibit 1003 Page 452

inferred from data shown in FIG. 16B. Shown as plot "X" is the hybridization of the primer to the correct target X, while the remaining "dotted" plots show the hybridization to the spurious targets Y. The 7/4, 7/5 and 7/6 primers all discriminate in their hybridization yields (χ) between the correct and the spurious targets. The 7/0 target does not. In FIG. 16D, the discrimination factor (Q) is a quantitative measurement of the specificity of the primer, and is calculated as the hybridization yield (χ) of the correct target divided by the hybridization yield (χ) of the spurious target. In 16E, there is little hybridization of the 7/5 primer to a spurious target Y even when such target is present in large excess *(i.e.,* 200-fold).

FIG. 17. shows additional experimental results and statistics on the single-base discrimination abilities of primer duplexes. FIG 17A shows that four additional targets and sets of primers were constructed and tested: two based on naturally occurring microRNA sequences, and two designed to intentionally possess significant secondary structure. FIG. 17B shows a histogram of the discrimination factors (Q) achieved by the 7/5 primers for each target. Due to limitations of the gel scanner, it was not possible to reliably measure discrimination factors above 100, and these were all grouped as "100+." FIG. 17C show RNA target and primer. The target sequence is a synthetic RNA oligonucleotide with sequence identical to the human let7g microRNA. FIG. 17D shows native PAGE results. The PC primer was prepared at a 2:1 ratio of protector P to complement C, and annealed at 3 μM concentration. Either the correct or spurious targets were added to achieve final concentrations of 2 μM X or Y, 1 μM PC, and 1 μM P. The correct target successfully binds to the primer; the hybridization yield of targets with single-nucleotide mismatches is low.

FIG. 18 shows experimental results using duplex primers to improve the PCR yield of a quasi-repetitive target. FIG. 18A shows a quasi-repetitive PCR target (168 nt) that traditional PCR primers struggle to amplify with high yield. Here, a* is the correct target for XI. The remaining sites labeled a*ml (which is Xl-ml7G), a*m2 (which is Xl-m9T), and a*m3 (which is Xl-ml 1G) are not the correct targets. Similarly, b* is the correct target for X2, and b*ml (which is X2-m3T), b*m2 (which is X2-ml 1C), and b*m3 (which is X2-ml8T) are not the correct targets. Thus, the outer-most binding sites are the perfect binding sites for the primers, but there are also 3 additional single-base mismatch primer binding sites between the perfect sites. The primer duplexes bind by 7 nucleotides to the target, and the protector must spontaneously dissociate 5 nucleotides to be released. The primer duplex was designed so that

NeoGenomics
Exhibit 1003 Page 453

its 3' end cannot be extended by the polymerase. The toehold region of the complement strand was designed at the 3' end, instead of the 5' end as in previous designs. In FIG. 18B, primer duplexes show significantly higher yield of correct length product, as compared to standard primers. Each lane is labeled with the primers used as well as the temperature cycling schedule (*e.g.,* "98-40-72" indicates denaturation at 98 °C, annealing at 40 °C, and elongation at 72 °C). The left-most lane shows the synthetic oligonucleotide reference. The lower numbers labeled "% Correct" indicate the relative intensity of band corresponding to the correct length product compared to the integrated intensity of all bands in the lane. The primer duplex PCR product appears as 10 nucleotides longer than the reference and the standard PCR product because of the 5 nucleotide of overhangs (toehold region) on each primer.

EQUIVALENTS

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process. Furthermore, it is to be understood that the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, descriptive terms, etc., from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim.

Where elements are presented as lists, e.g., in Markush group format, it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be

NeoGenomics
Exhibit 1003 Page 454

removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity those embodiments have not been specifically set forth in haec verba herein. It is also noted that the term "comprising" is intended to be open and permits the inclusion of additional elements or steps.

Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

As used herein, the term "about" generally may refer to any value within a range of 10% of the recited value. In some instance, however, "about" may encompasses a range of 20% of the recited value.

In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the methods of the invention can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art. This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing," "involving," and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

Each of the foregoing patents, patent applications and references is hereby incorporated by reference, particularly for the teaching referenced herein.

NeoGenomics
Exhibit 1003 Page 455

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NeoGenomics
Exhibit 1003 Page 456

CLAIMS

1. A partially double-stranded primer comprised of first and second nucleic acid strands arranged into

(1) one double-stranded target-non-specific region,

(2) one double-stranded target-specific region, and

(3) one single-stranded target-specific region contributed to by the first nucleic acid strand,

wherein the double-stranded target-non-specific region has a standard free energy approximately equal to the standard free energy for the single-stranded target-specific region bound to a target nucleic acid.

2. The partially double-stranded primer of claim 1, wherein the second nucleic acid strand comprises a non-extendable nucleotide at its 3' end and/or the first nucleic acid strand comprises a non-natural nucleotide at or near the 3' end of its target-non-specific region.

3. The partially double-stranded primer of claim 2, wherein the non-extendable nucleotide is a non-natural nucleotide or a dideoxy nucleotide.

4. The partially double-stranded primer of claim 3, wherein the non-natural nucleotide is iso-C, iso-G or deoxyuridine.

5. The partially double-stranded primer of any of the foregoing claims, wherein the double-stranded target non-specific region is about 4-21 nucleotides in length.

6. The partially double-stranded primer of any of the foregoing claims, wherein the single-stranded target-specific region is about 4-20 nucleotides in length.

7. The partially double-stranded primer of any of the foregoing claims, wherein the first and second nucleic acid strands are comprised of DNA or RNA.

NeoGenomics
Exhibit 1003 Page 457

8. A system comprising

a nucleic acid target,

a polymerase, and

a partially double-stranded primer comprising a first and a second nucleic acid strand arranged into

(1) one double-stranded target-non-specific region,

(2) one double-stranded target-specific region, and

(3) one single-stranded target-specific region contributed to by the first nucleic acid strand.

9. The system of claim 8, wherein the nucleic acid target is a single-stranded.

10. The system of any one of claims 8 or 9, wherein the nucleic acid target is DNA or RNA.

11. The system of any one of claims 8-10, wherein the system comprises a plurality of different partially double-stranded primers.

12. The system of one of claims 8-11, wherein the system comprises at least two partially double-stranded primers which together can be used to amplify a region of the nucleic acid target.

13. The system of any one of claims 8-12, wherein the nucleic acid target comprises repetitive sequence, secondary structure and/or high GC content.

14. The system of any one of claims 8-13, wherein the nucleic acid target is present in a plurality of different nucleic acid targets.

15. The system of claim 14, wherein the nucleic acid target is present as a single copy or in low copy in a plurality of different nucleic acid targets.

NeoGenomics
Exhibit 1003 Page 458

16. A method comprising

contacting a partially double-stranded primer of claim 1 or 8 to a sample, and detecting hybridization of the primer to a target in the sample.

17. The method of claim 16, wherein the partially double-stranded primer is labeled with a detectable moiety.

18. The method of claim 17, wherein the detectable moiety comprises a fluorophore or a radioisotope.

19. The method of any one of claims 16-18, wherein the target is present as a single copy in the sample.

20. A method comprising

hybridizing a single-stranded target-specific region of a first strand of a partially double-stranded primer of claim 1 or 8 to a nucleic acid target, thereby dissociating the first strand of the primer from a second strand of the primer, and

extending the first strand at its 3' end, in a target-complementary manner, in the presence of a polymerase.

21. A method comprising

performing a nucleic acid synthesis reaction in the presence of a nucleic acid target, a polymerase, and one or more partially double-stranded primers of claim 1 or 8.

22. The method of claim 21, wherein the nucleic acid synthesis reaction is a nucleic acid amplification reaction.

23. The method of claim 22, wherein the nucleic acid amplification reaction is polymerase chain reaction (PCR).

NeoGenomics
Exhibit 1003 Page 459

24. The method of claim 21, wherein the nucleic acid synthesis reaction is a transcription reaction.

25. The method of claim 24, wherein the transcription reaction is a reverse transcription reaction.

26. The method of any one of claims 20-25, wherein two partially double-stranded primers are used.

27. A kit comprising

one or more partially double-stranded primers of claim 1 or 8, and

one or more nucleic acid synthesis reagents.

28. The kit of claim 27, wherein the one or more nucleic acid synthesis reagents is selected from the group consisting of a buffer, nucleotides, and a polymerase.

29. The kit of claim 27 or 28, further comprising instructions for use.

30. A kit comprising

a first single-stranded nucleic acid in a first container, and

a second single-stranded nucleic acid that is complementary to a region of the first single-stranded nucleic acid, in a second container,

wherein, when the first and second single-stranded nucleic acids are hybridized to each other, a partially double-stranded nucleic acid is formed that comprises

(1) a double-stranded target-non-specific region,

(2) a double-stranded target-specific region, and

(3) a single-stranded target-specific region contributed to by the first nucleic acid,

wherein the first single-stranded nucleic acid comprises a non-natural nucleotide and/or the second single-stranded nucleic acid comprises a non-extendable nucleotide at its 3' end.

NeoGenomics
Exhibit 1003 Page 460

31. The kit of claim 30, further comprising instructions for use.

32. The kit of claim 30 or 31, further comprising one or more nucleic acid synthesis reagents.

33. The kit of claim 32, wherein the one or more nucleic acid synthesis reagents is selected from the group consisting of a buffer, nucleotides, and a polymerase.

34. A single stranded primer that partially self-hybridizes to form

(1) one or more double-stranded target-non-specific region,

(2) one or more double-stranded target-specific region,

(3) one or more single-stranded target-specific region, and

(4) one or more hairpin loop regions,

wherein the one or more double-stranded target-non-specific region has a concentration-adjusted standard free energy approximately equal to the concentration-adjusted standard free energy for the one or more single-stranded target-specific region bound to a target nucleic acid.

35. A method of performing a multiplexed nucleic acid amplification reaction comprising amplifying multiple unique nucleic acid molecules using a primer of any one of claims 1-8 or 34.

NeoGenomics
Exhibit 1003 Page 461

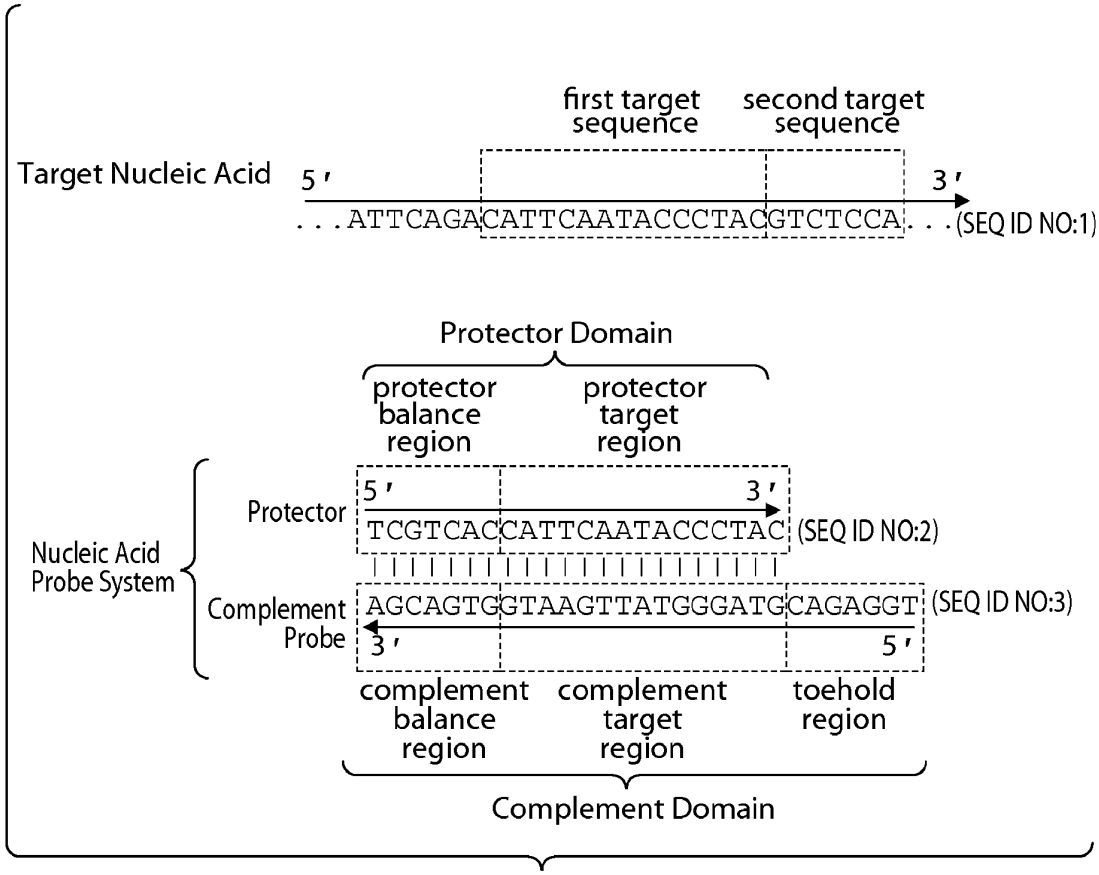


Fig. 1A

NeoGenomics
Exhibit 1003 Page 462

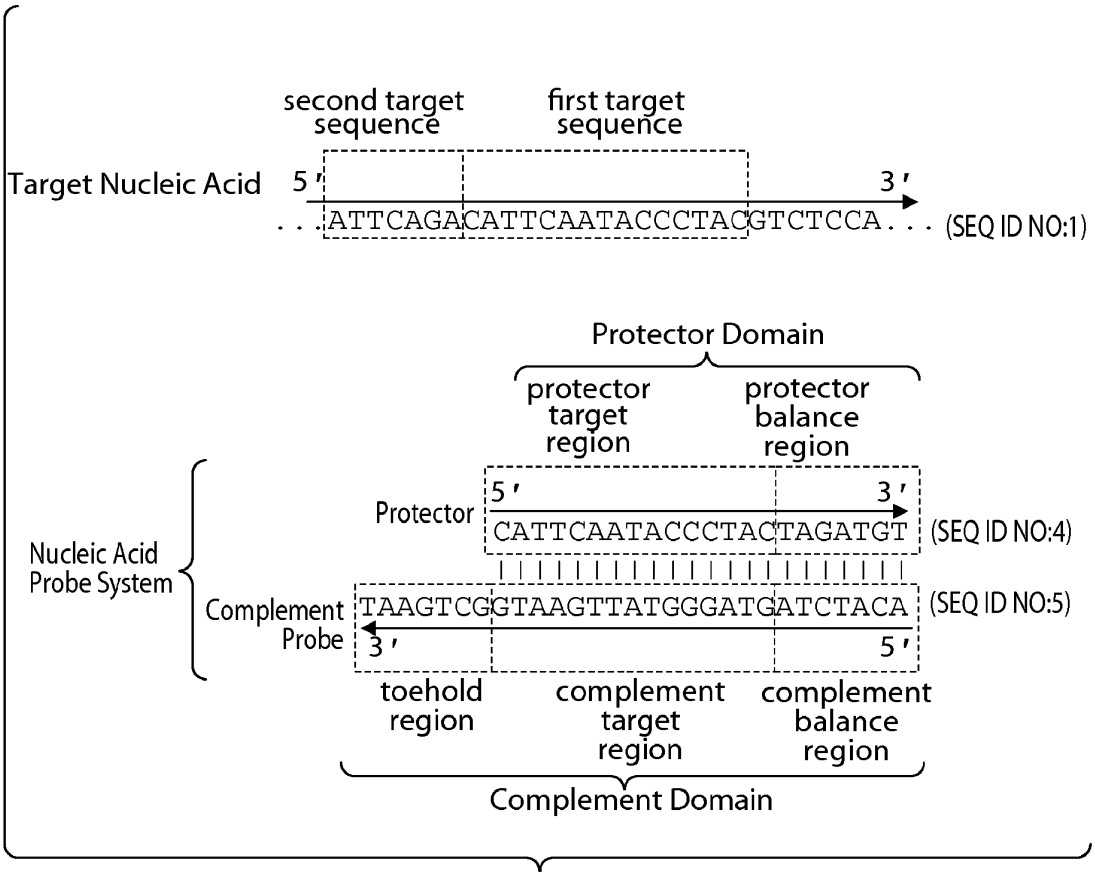


Fig. 1B

NeoGenomics
Exhibit 1003 Page 463

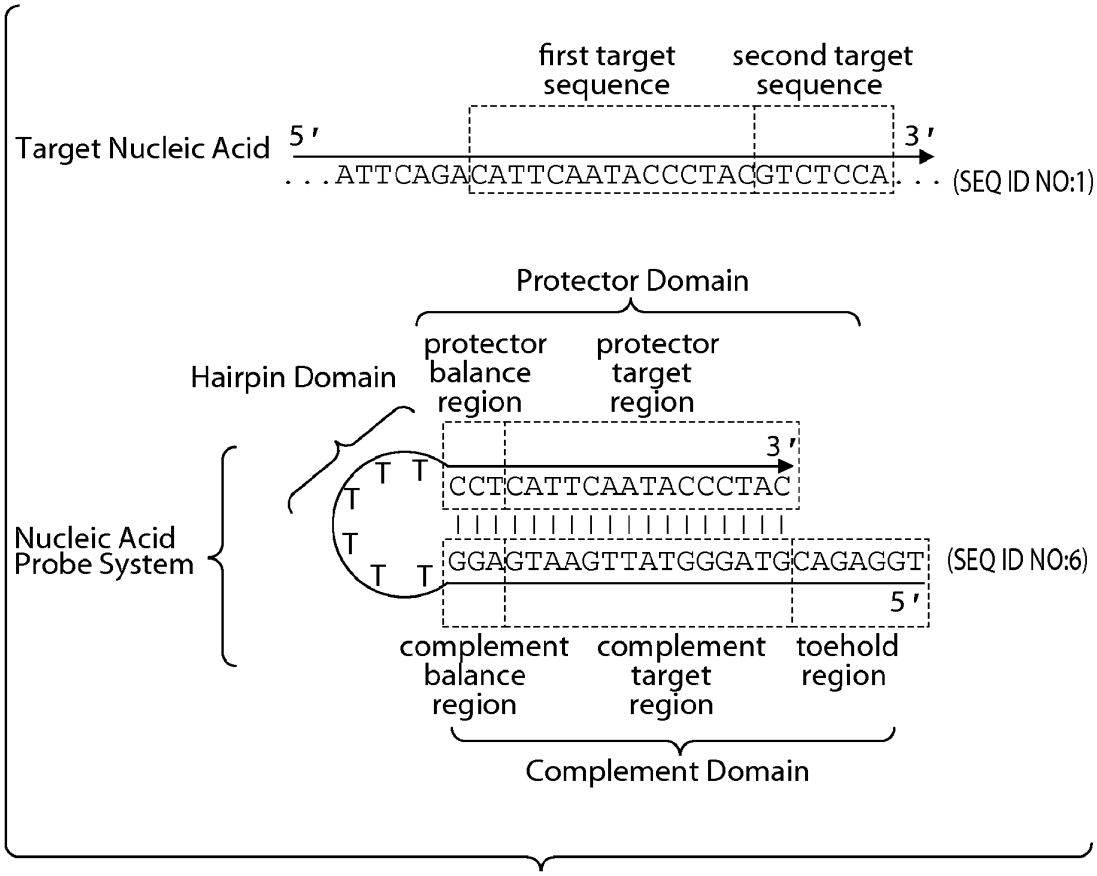


Fig. 2A

NeoGenomics
Exhibit 1003 Page 464

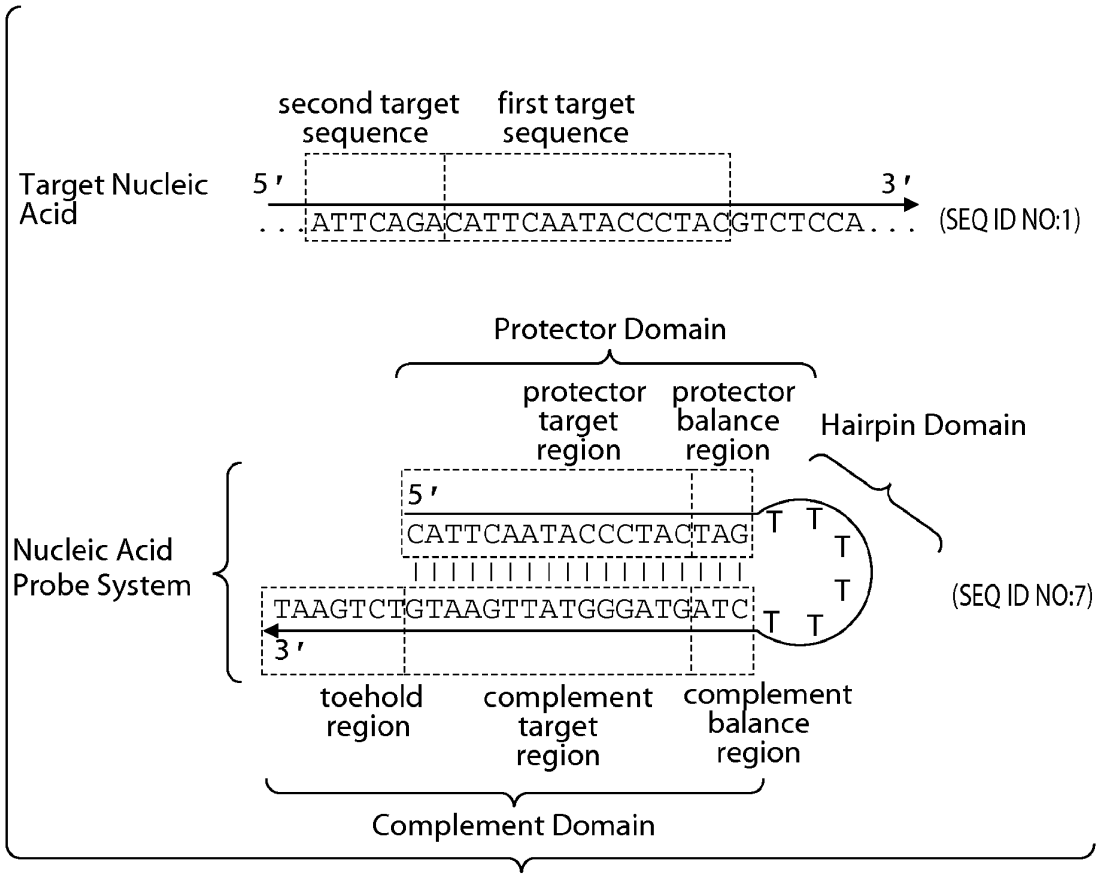

second target sequence
first target sequence
Target Nucleic Acid
5′
3′
. . . ATTCAGACATTCAATACCCTACGTCTCCA . . .
(SEQ ID NO:1)
Protector Domain
protector target region
protector balance region
Hairpin Domain
Nucleic Acid Probe System
5′
CATTCAATACCCTACTAG
T T T T T T
TAAGTCTGTAAGTTATGGGATGATC
3′
(SEQ ID NO:7)
toehold region
complement target region
complement balance region
Complement Domain

Fig. 2B

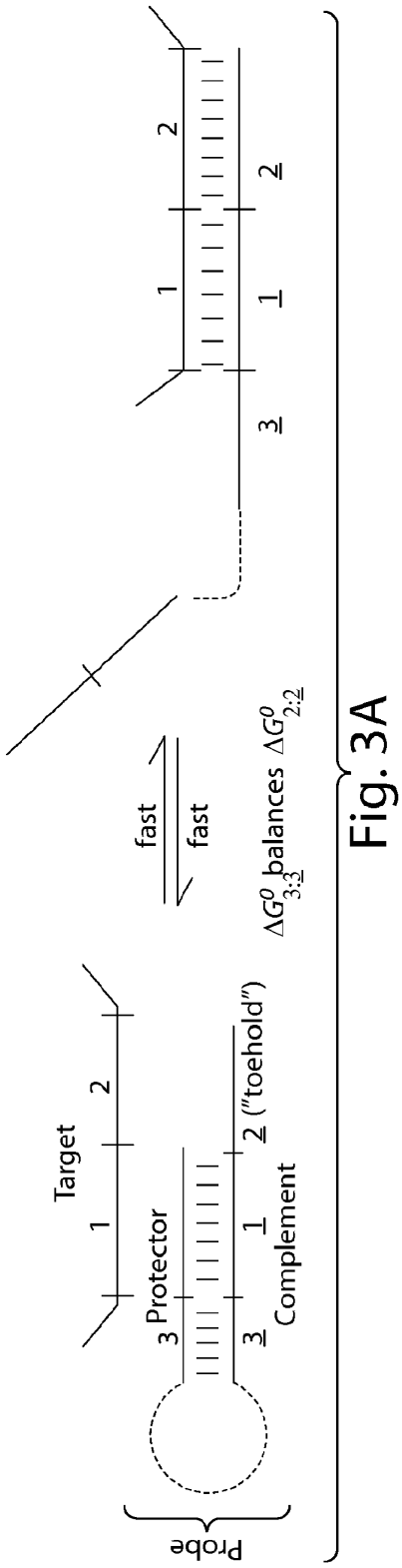


Fig. 3A

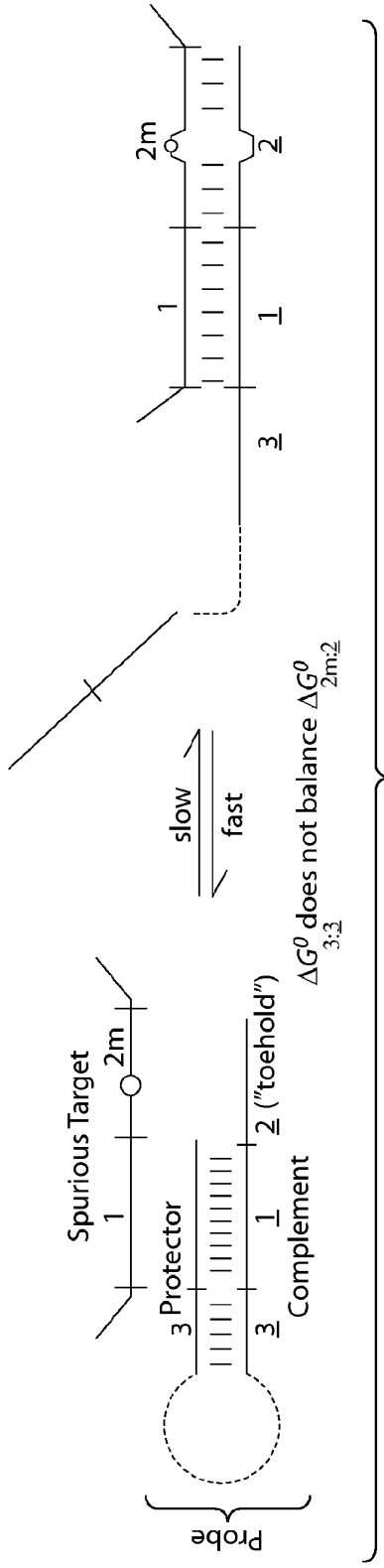


Fig. 3B

NeoGenomics
Exhibit 1003 Page 466

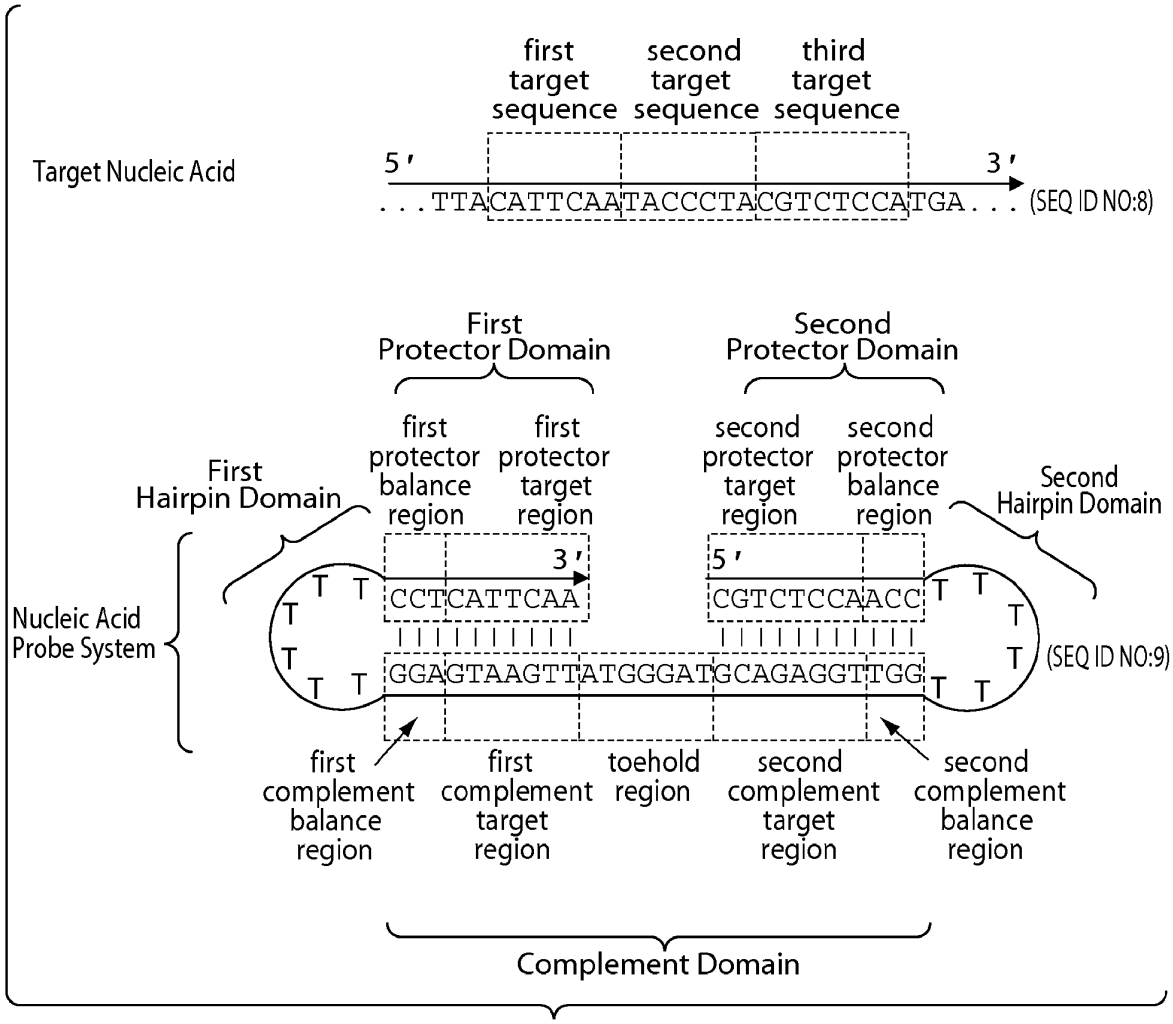


Fig. 4

NeoGenomics
Exhibit 1003 Page 467

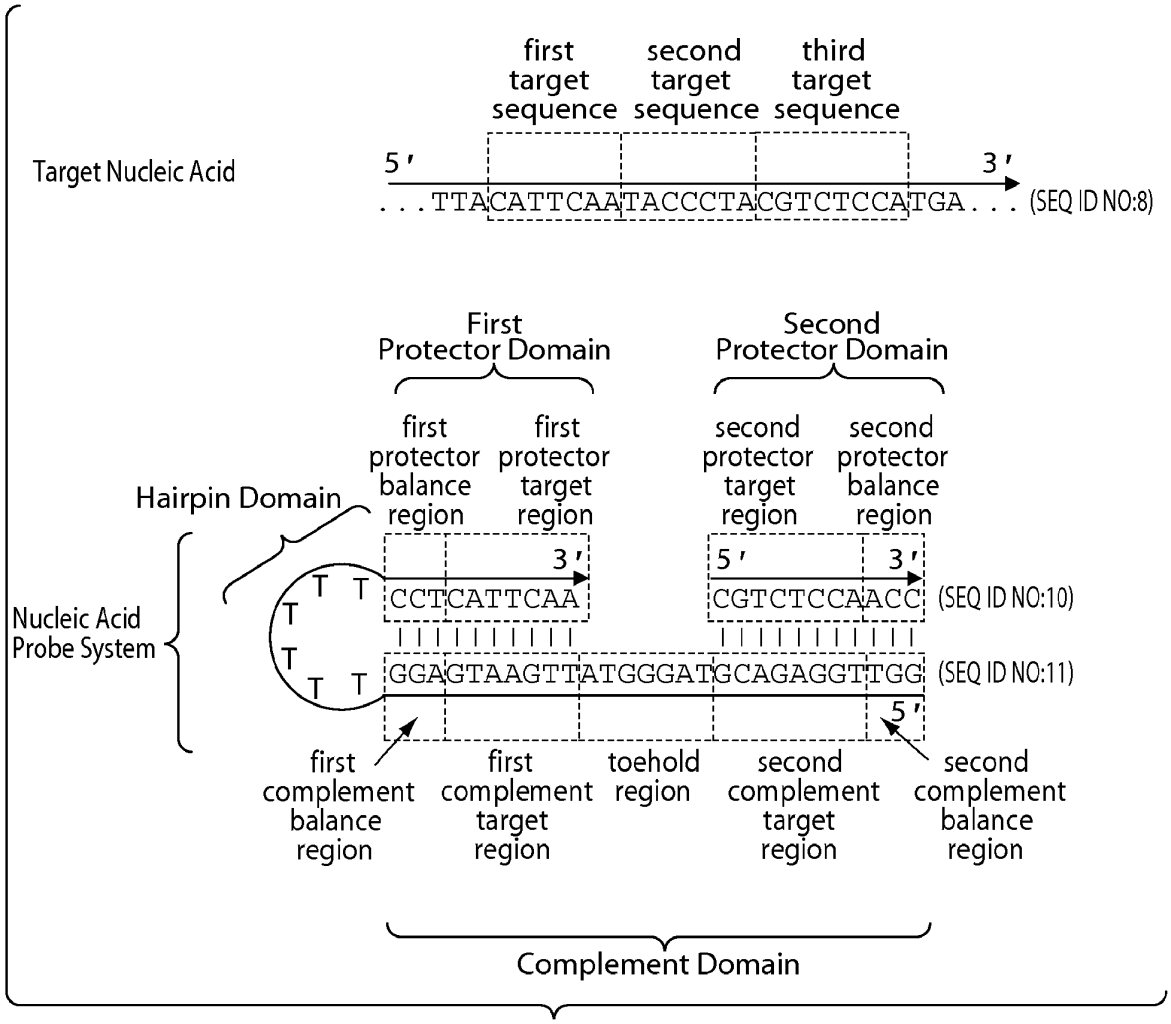


Fig. 5

NeoGenomics
Exhibit 1003 Page 468

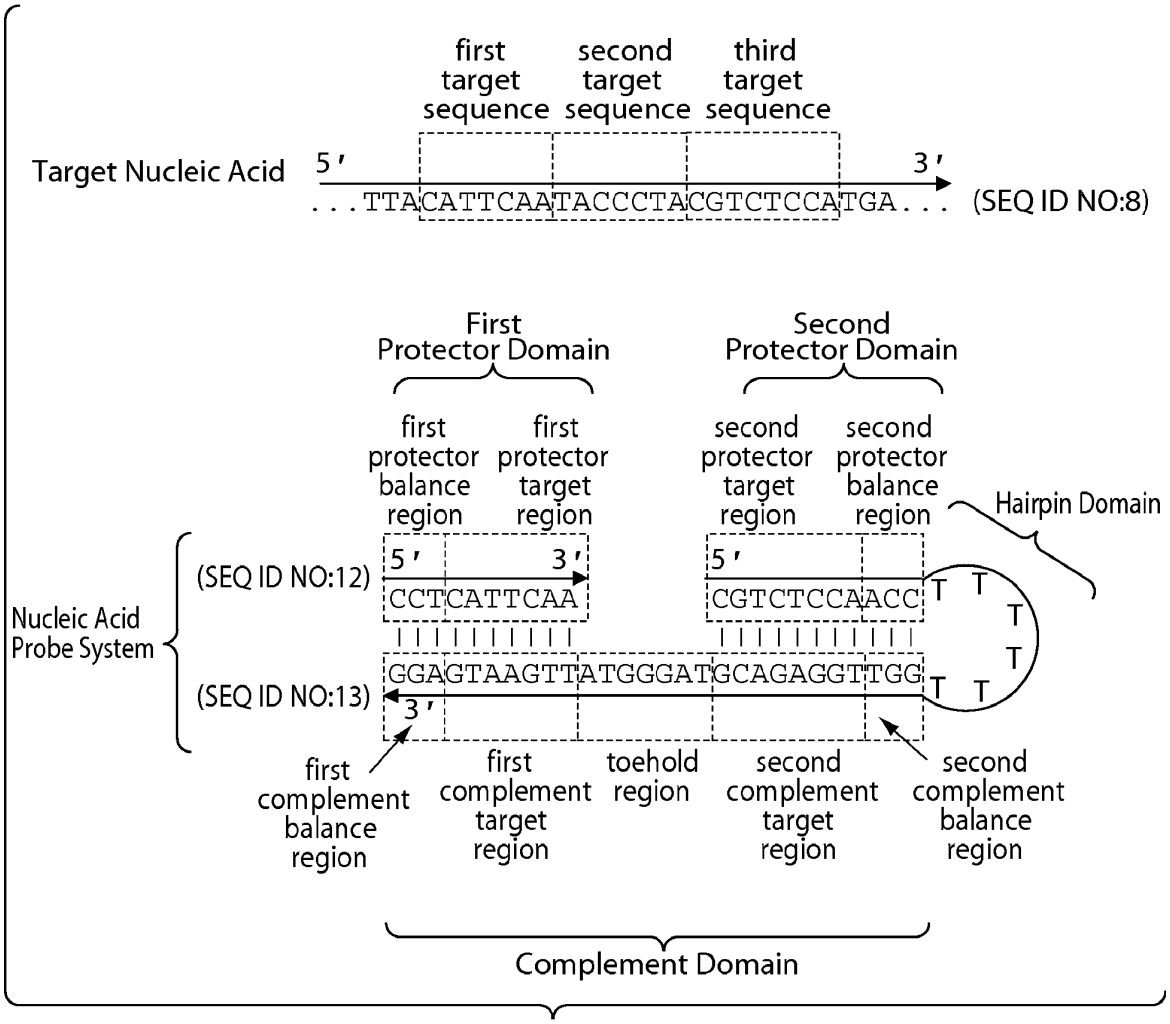


Fig. 6

NeoGenomics
Exhibit 1003 Page 469

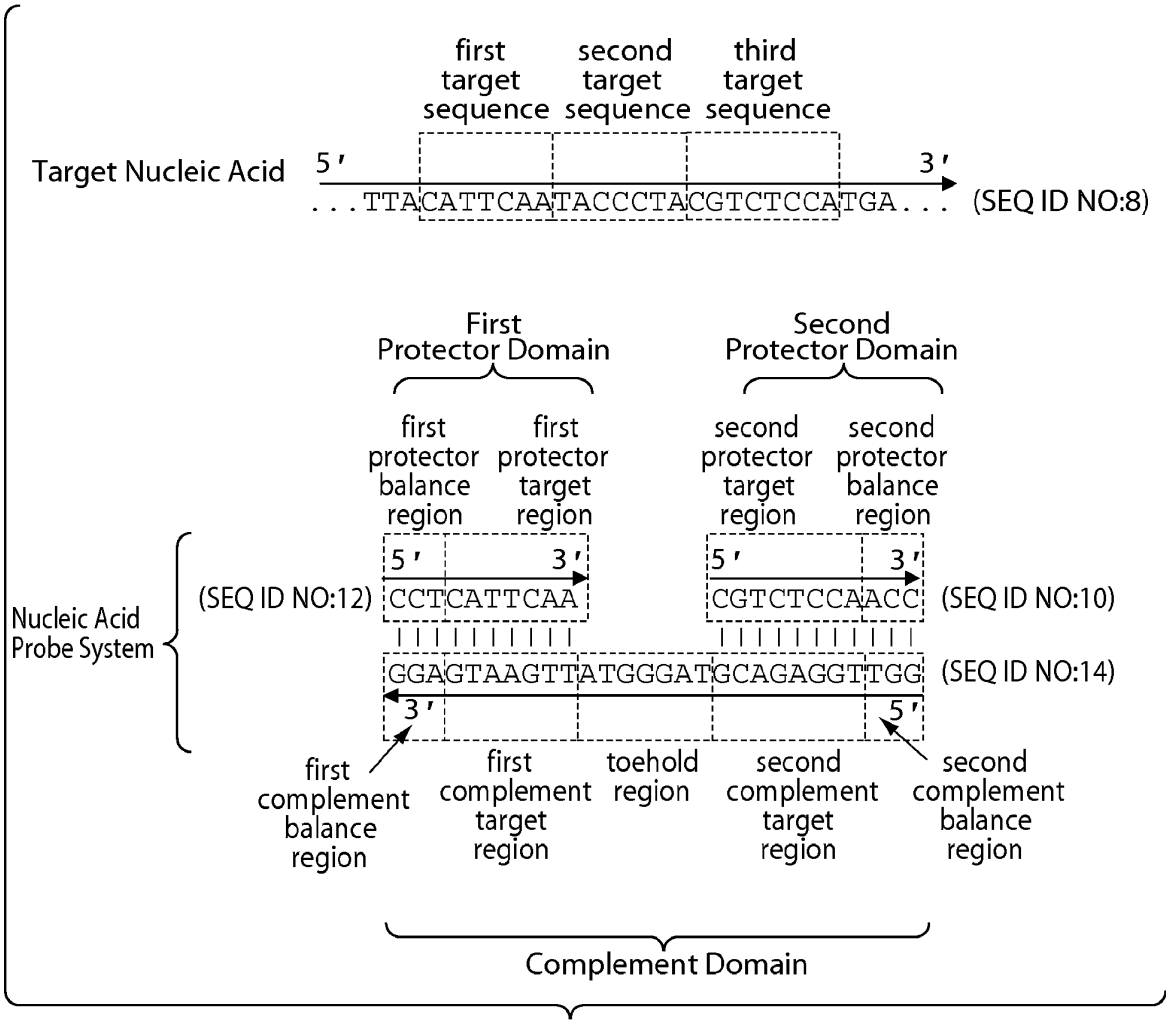


Fig. 7

NeoGenomics
Exhibit 1003 Page 470

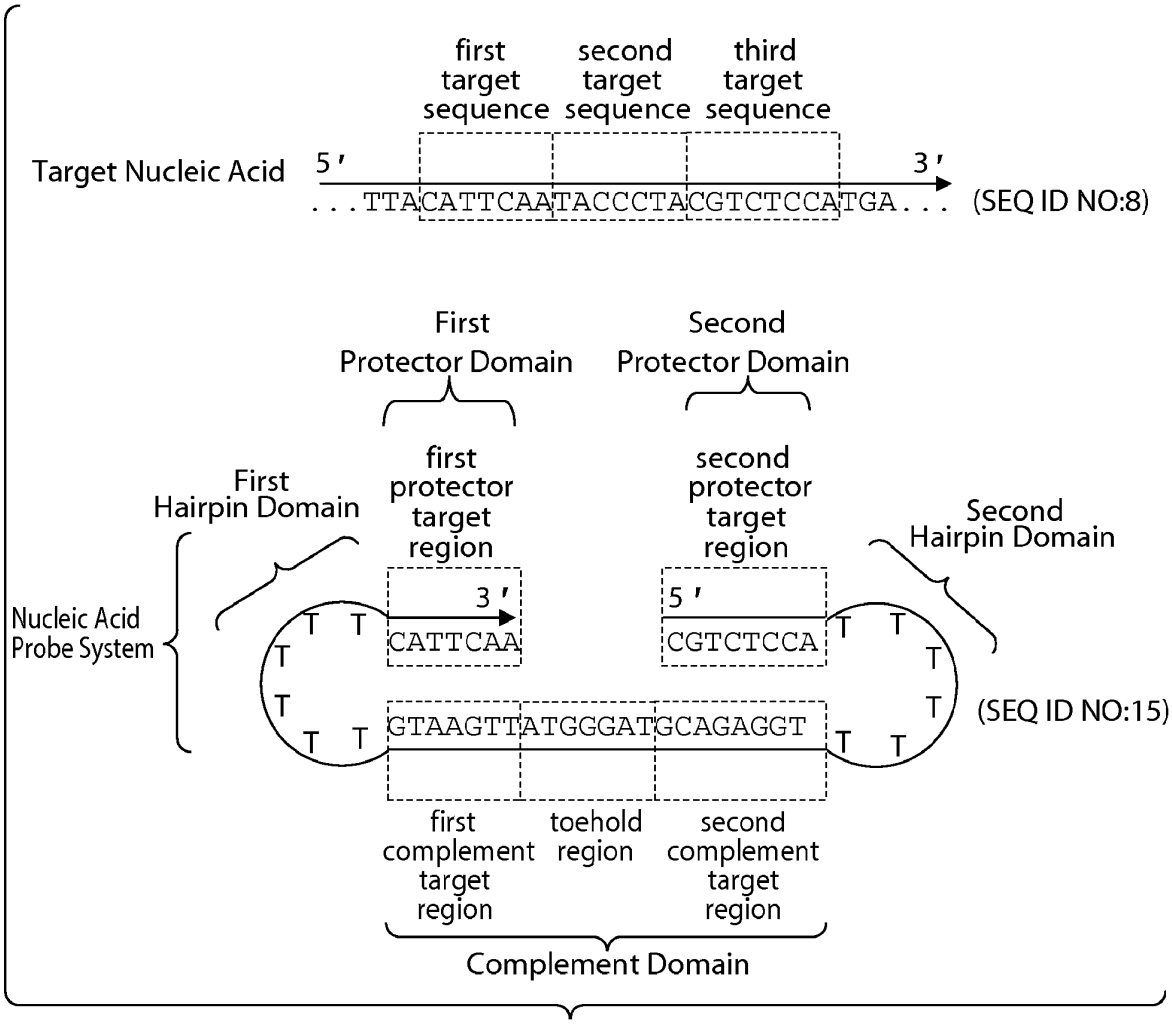


Fig. 8

NeoGenomics
Exhibit 1003 Page 471

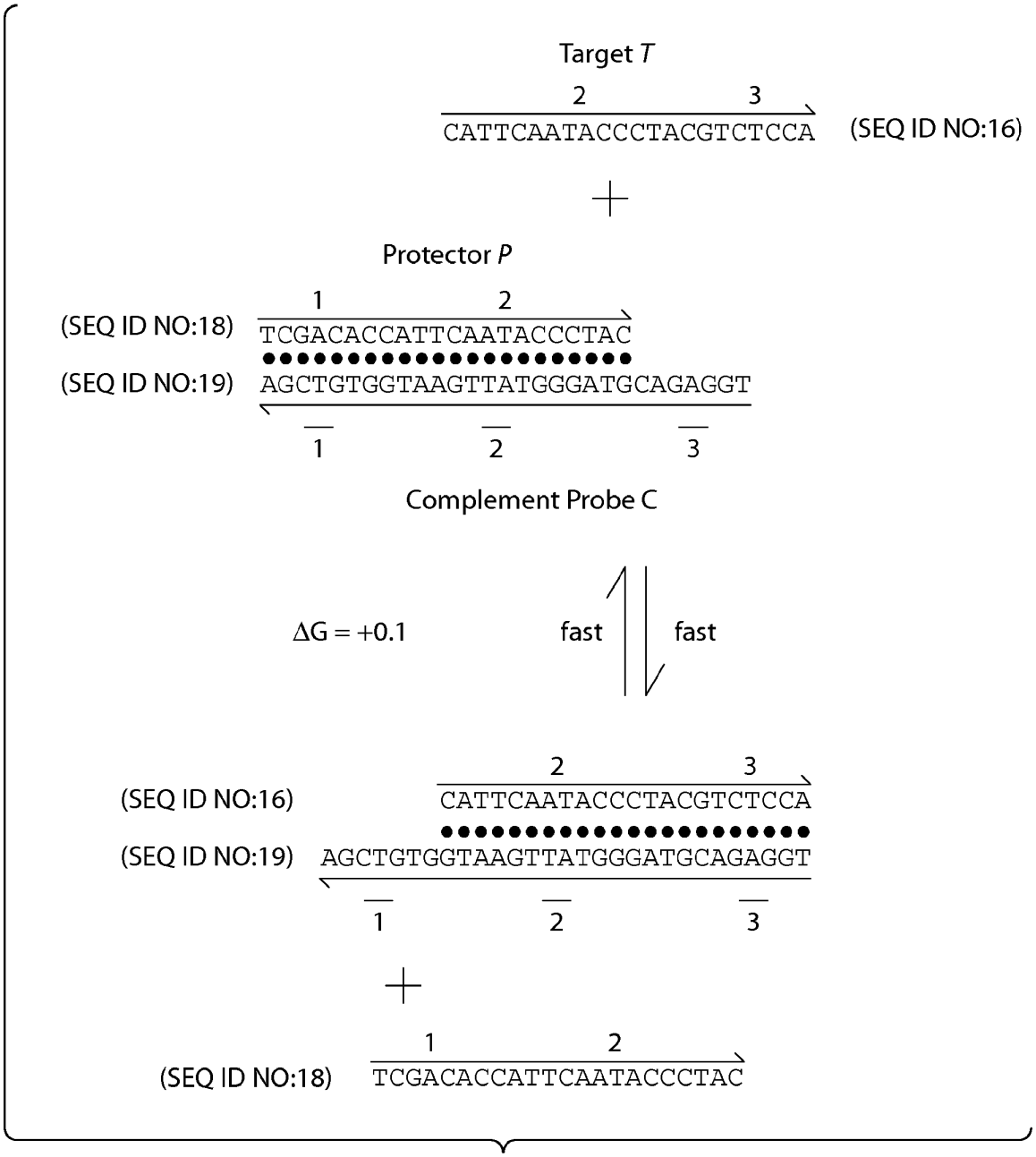


Fig. 9A

NeoGenomics
Exhibit 1003 Page 472

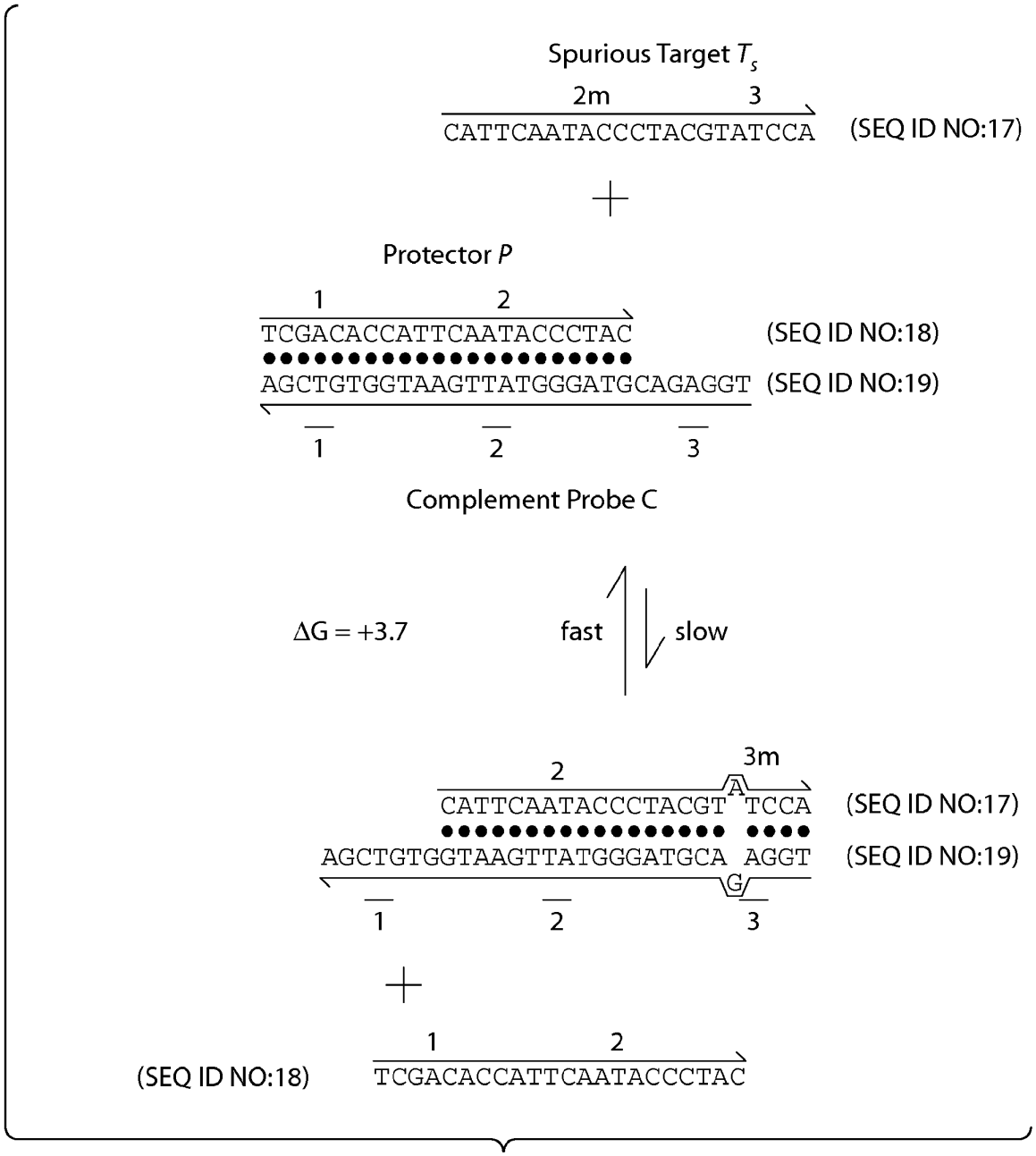

Spurious Target T_s
2m 3
CATTCAATACCCTACGTATCCA (SEQ ID NO:17)
Protector P
1 2
TCGACACCATTCAATACCCTAC (SEQ ID NO:18)
AGCTGTGGTAAGTTATGGGATGCAGAGGT (SEQ ID NO:19)
1 2 3
Complement Probe C
ΔG = +3.7
fast
slow
2 3m
CATTCAATACCCTACGT A TCCA (SEQ ID NO:17)
AGCTGTGGTAAGTTATGGGATGCA AGGT (SEQ ID NO:19)
G
1 2 3
(SEQ ID NO:18) 1 2
TCGACACCATTCAATACCCTAC

Fig. 9B

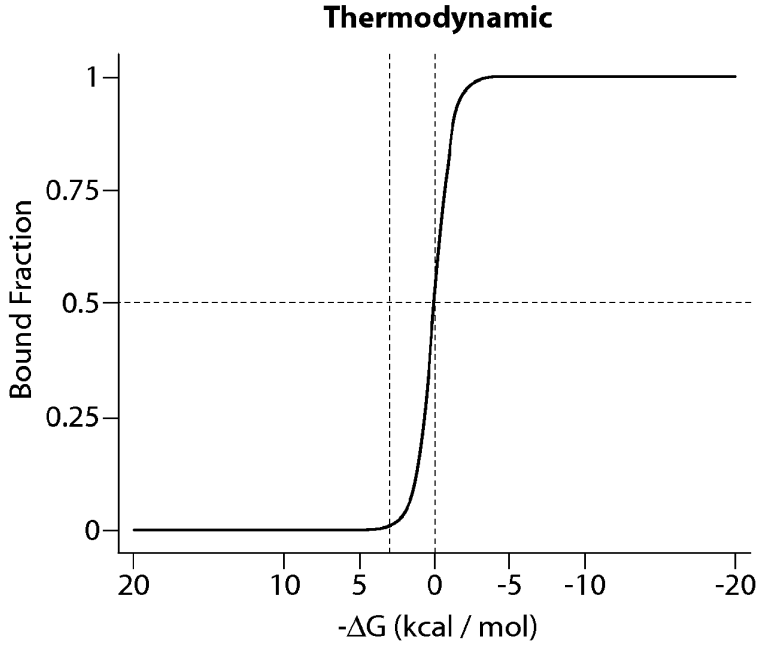

Thermodynamic
Bound Fraction
1
0.75
0.5
0.25
0
20
10
5
0
-5
-10
-20
-ΔG (kcal / mol)

Fig. 10

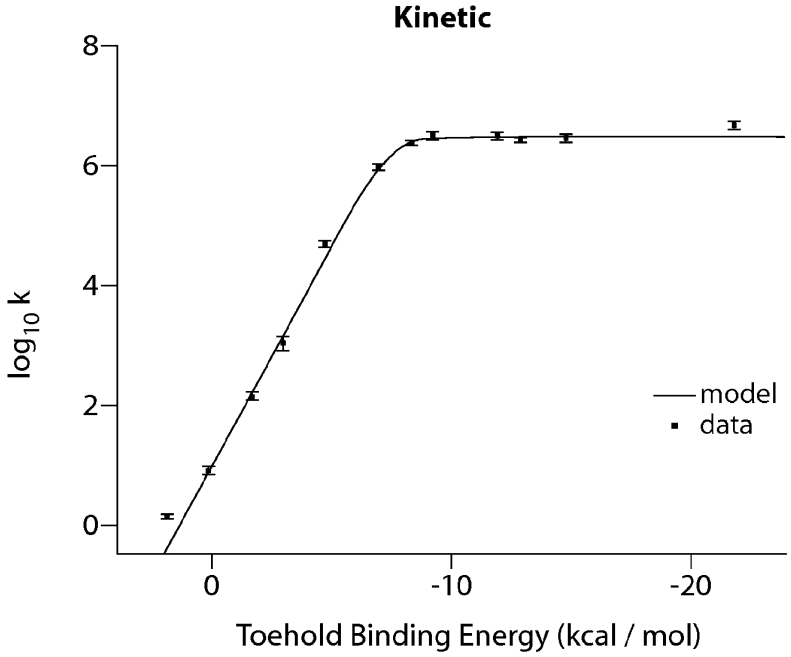

Kinetic
log10 k
8
6
4
2
0
model
data
0
-10
-20
Toehold Binding Energy (kcal / mol)

Fig. 11

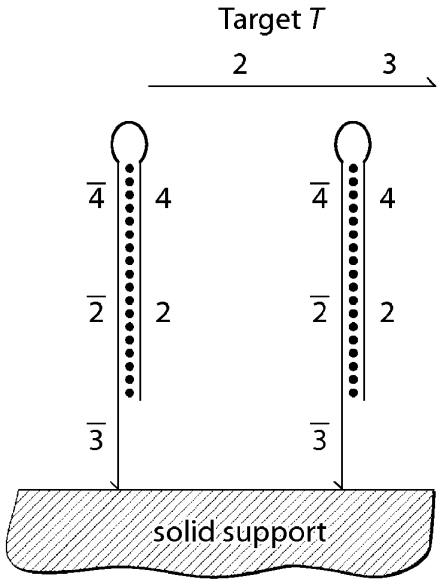


Fig. 12A

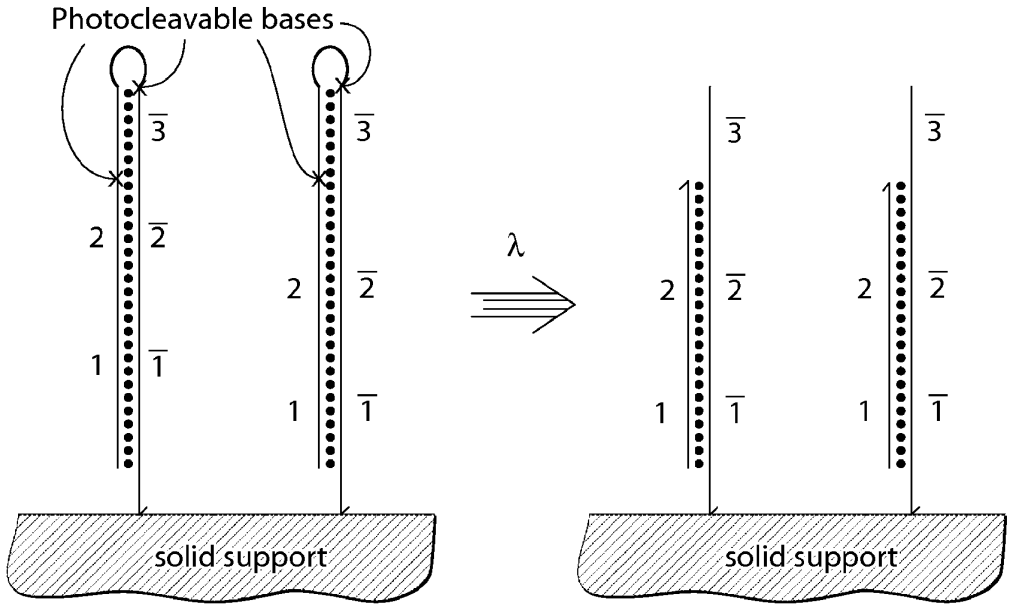


Fig. 12B

NeoGenomics
Exhibit 1003 Page 475

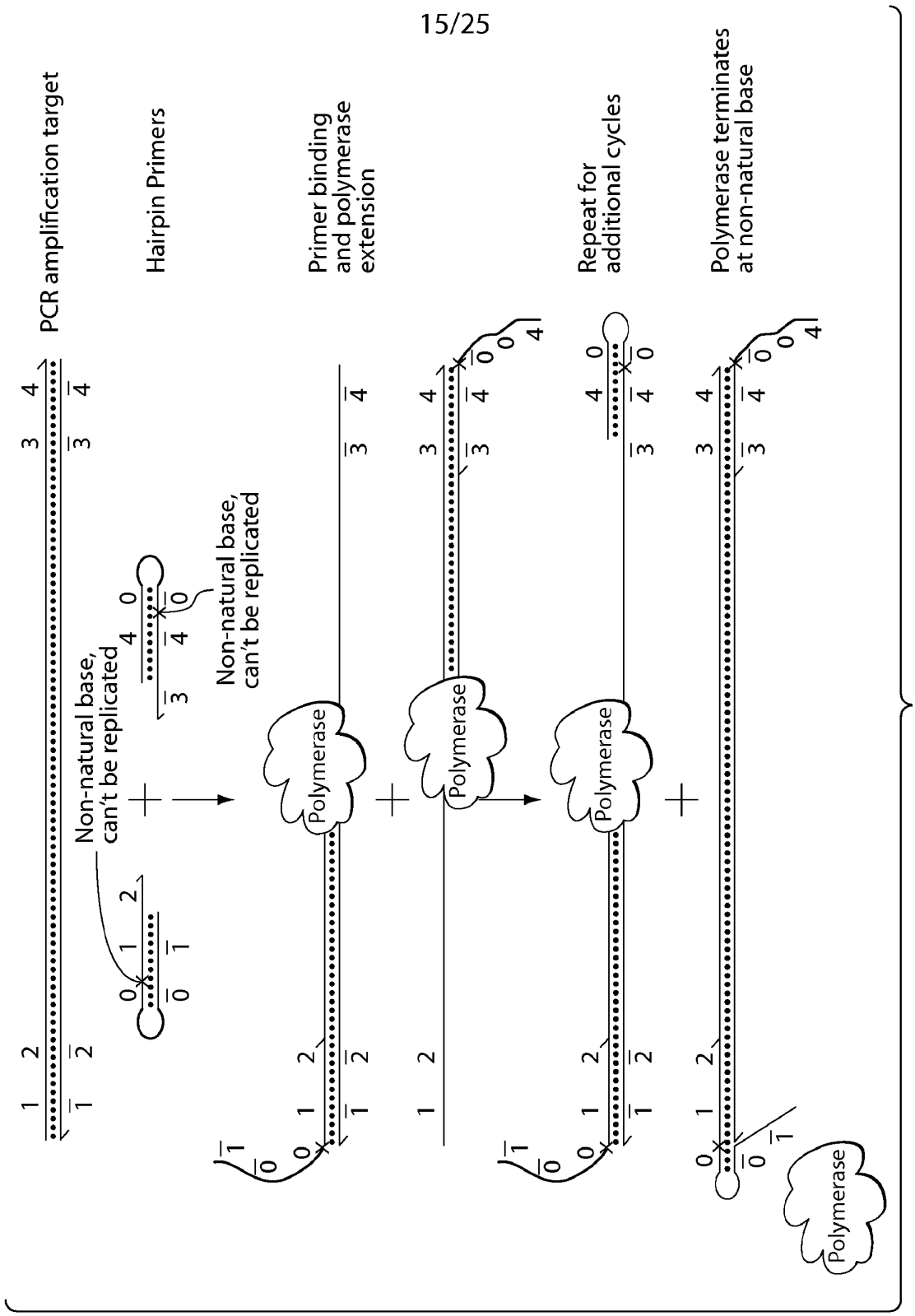


Fig. 13

NeoGenomics
Exhibit 1003 Page 476

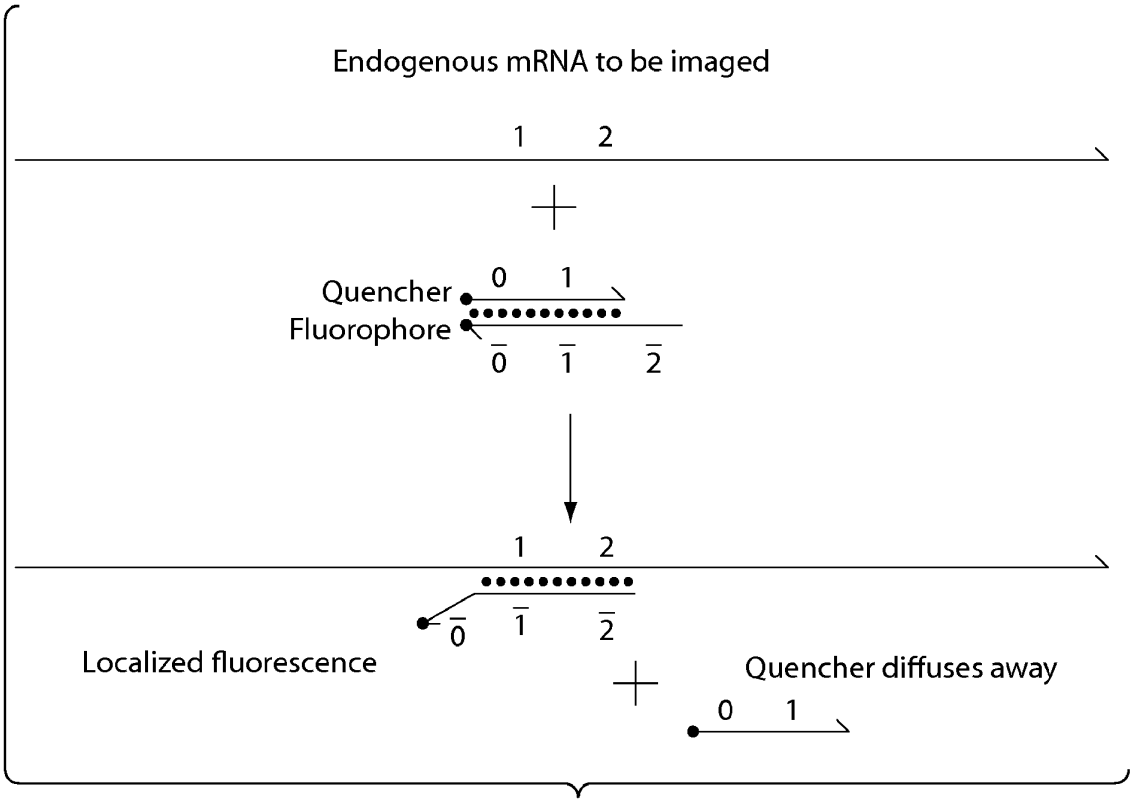


Fig. 14

NeoGenomics
Exhibit 1003 Page 477

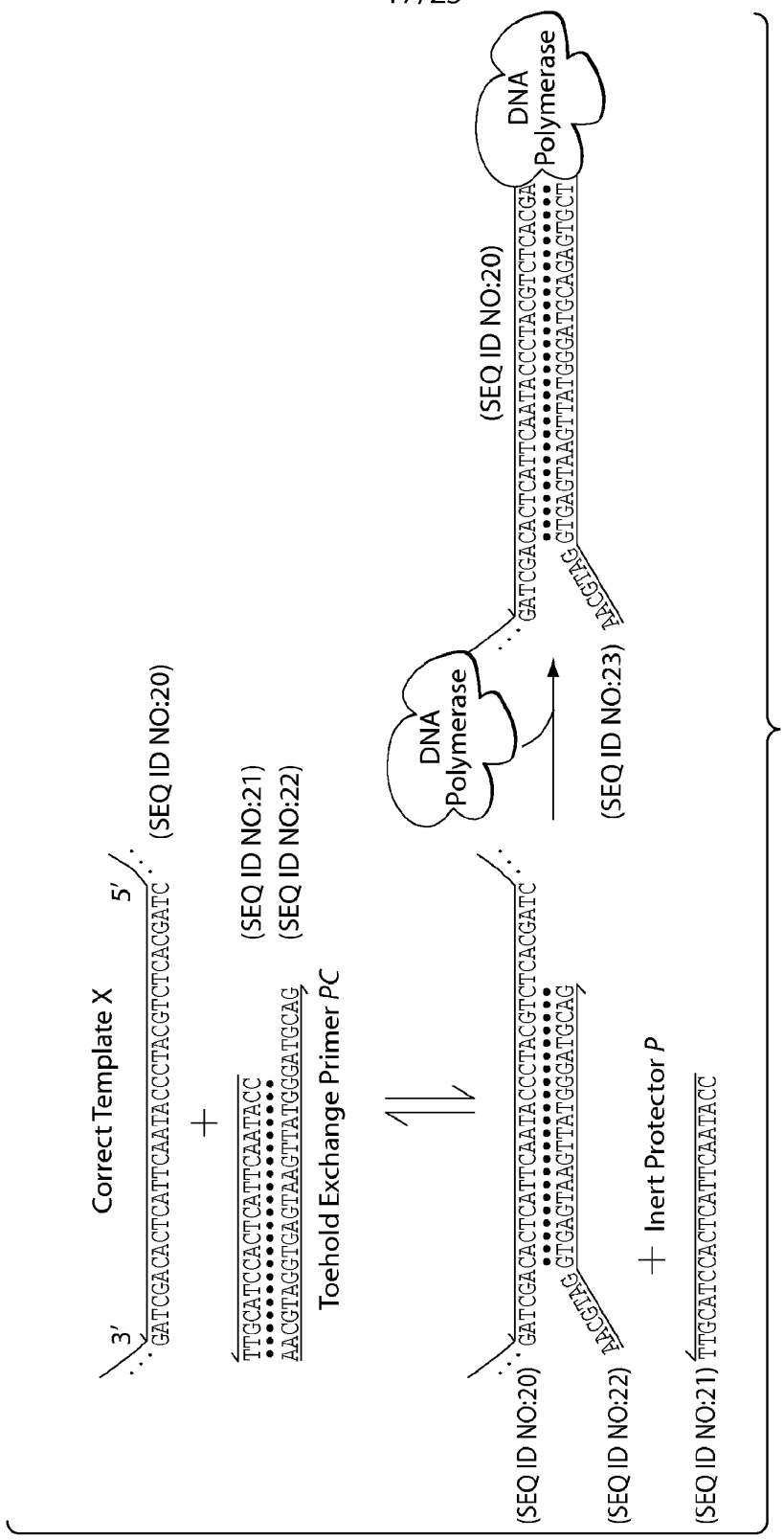


Fig. 15A

NeoGenomics
Exhibit 1003 Page 478

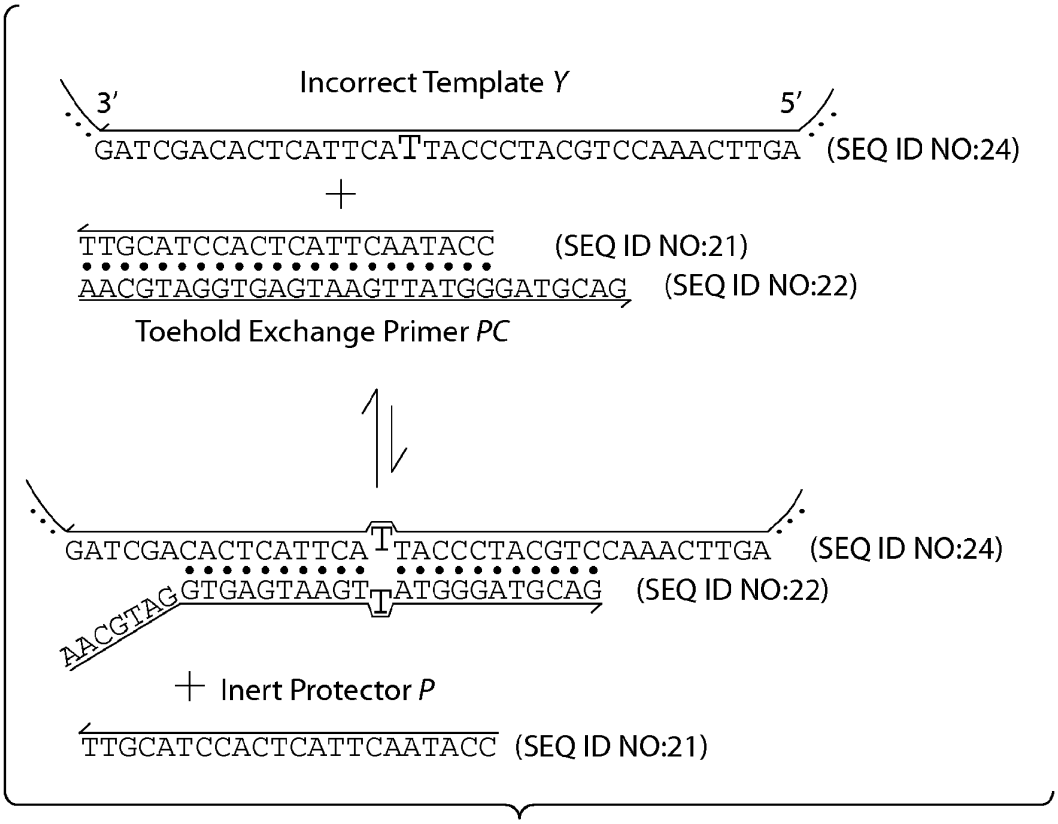


Fig. 15B

NeoGenomics
Exhibit 1003 Page 479

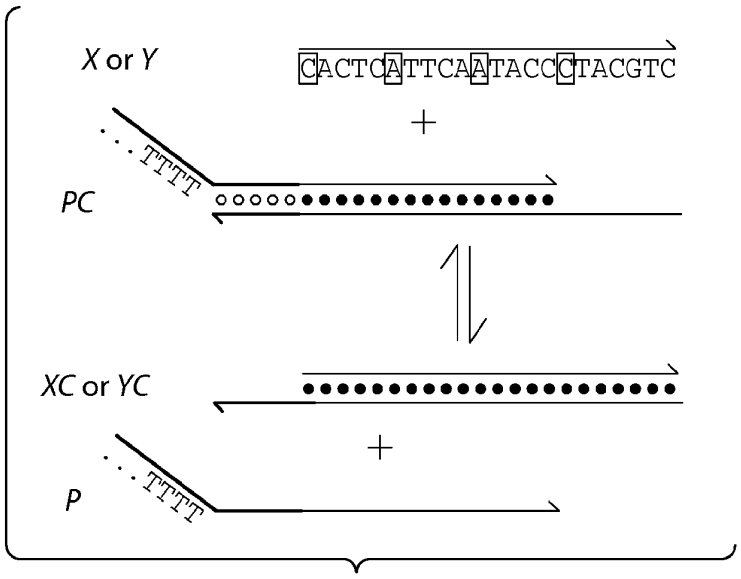


Fig. 16A

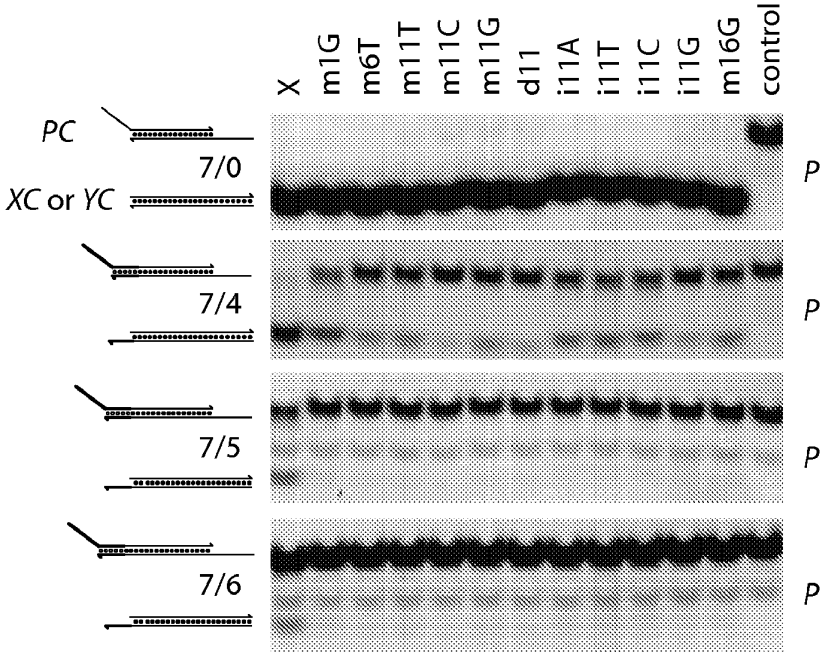


Fig. 16B

NeoGenomics
Exhibit 1003 Page 480

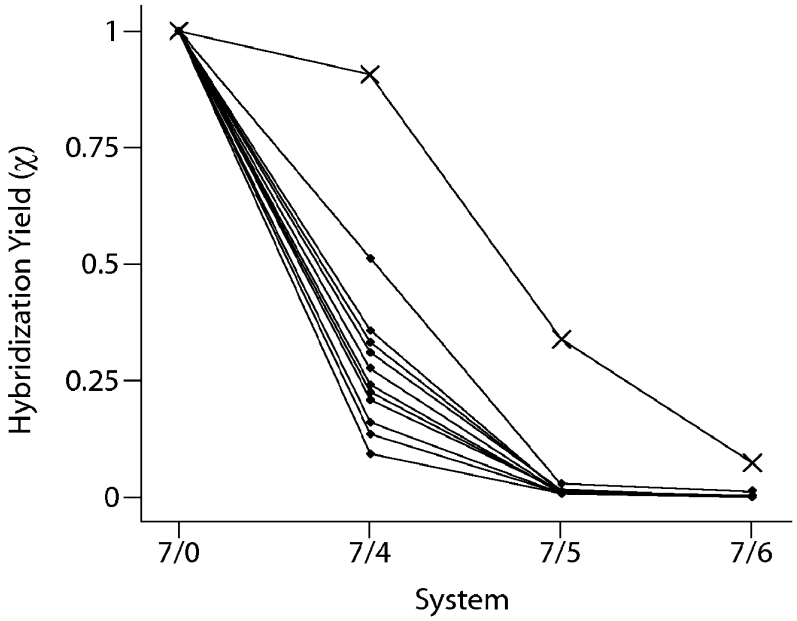


Fig. 16C

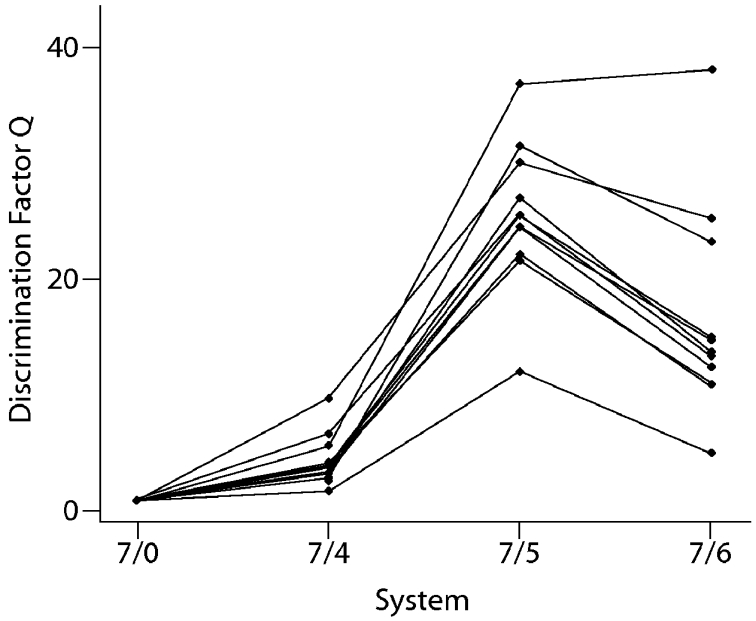


Fig. 16D

NeoGenomics
Exhibit 1003 Page 481

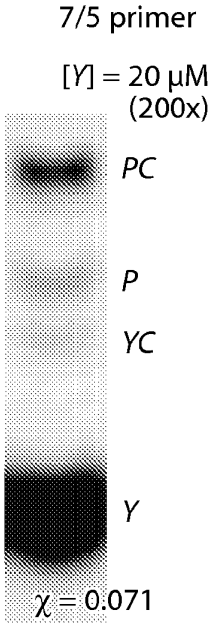


Fig. 16E

NeoGenomics
Exhibit 1003 Page 482

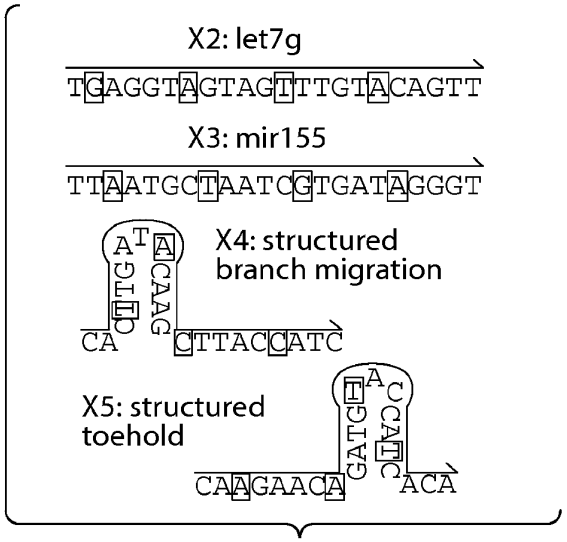


Fig. 17A

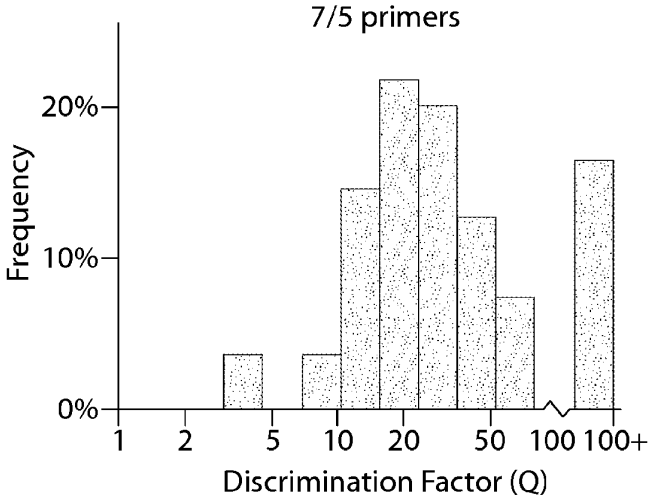


Fig. 17B

NeoGenomics
Exhibit 1003 Page 483

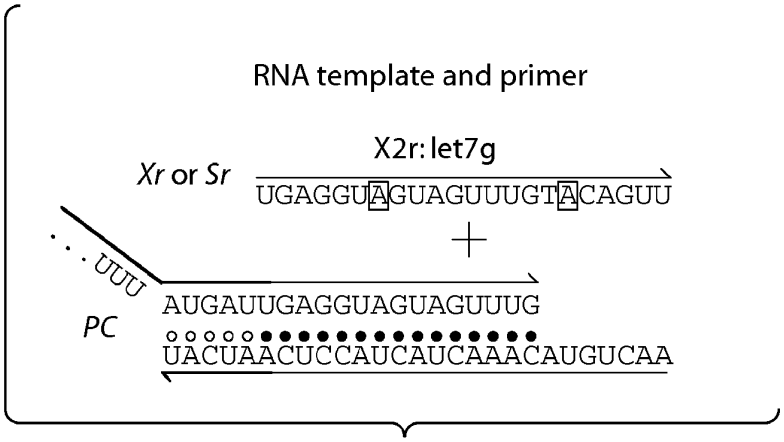


Fig. 17C

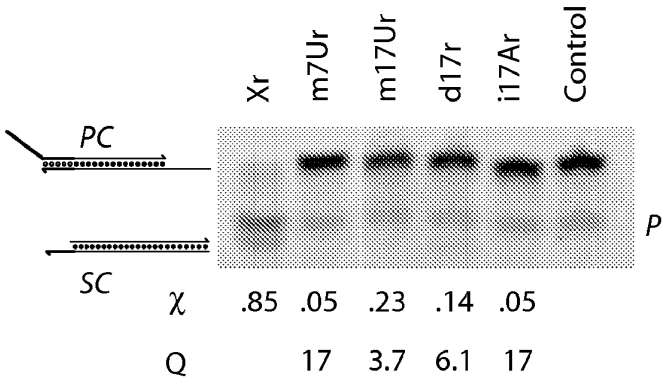


Fig. 17D

NeoGenomics
Exhibit 1003 Page 484

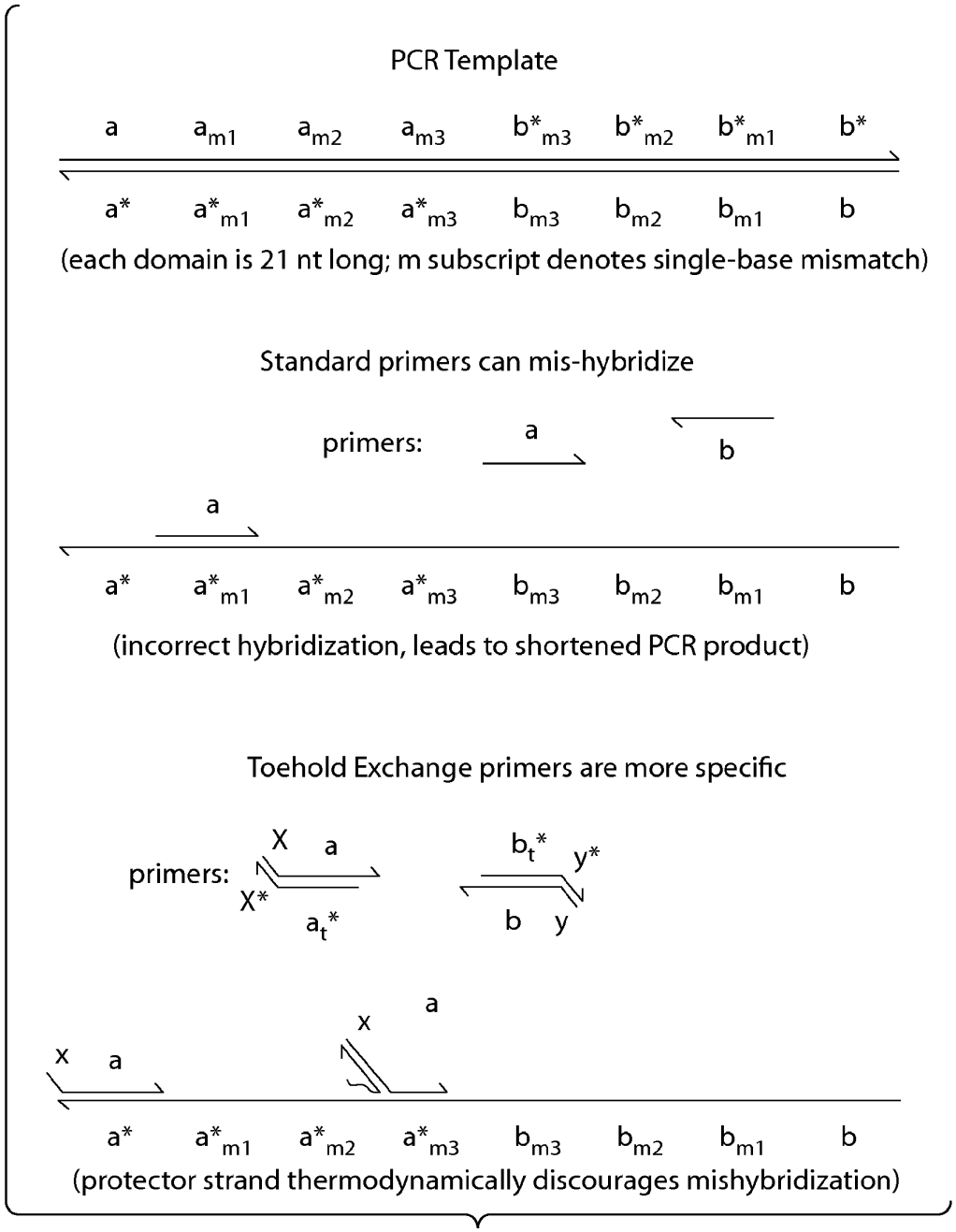
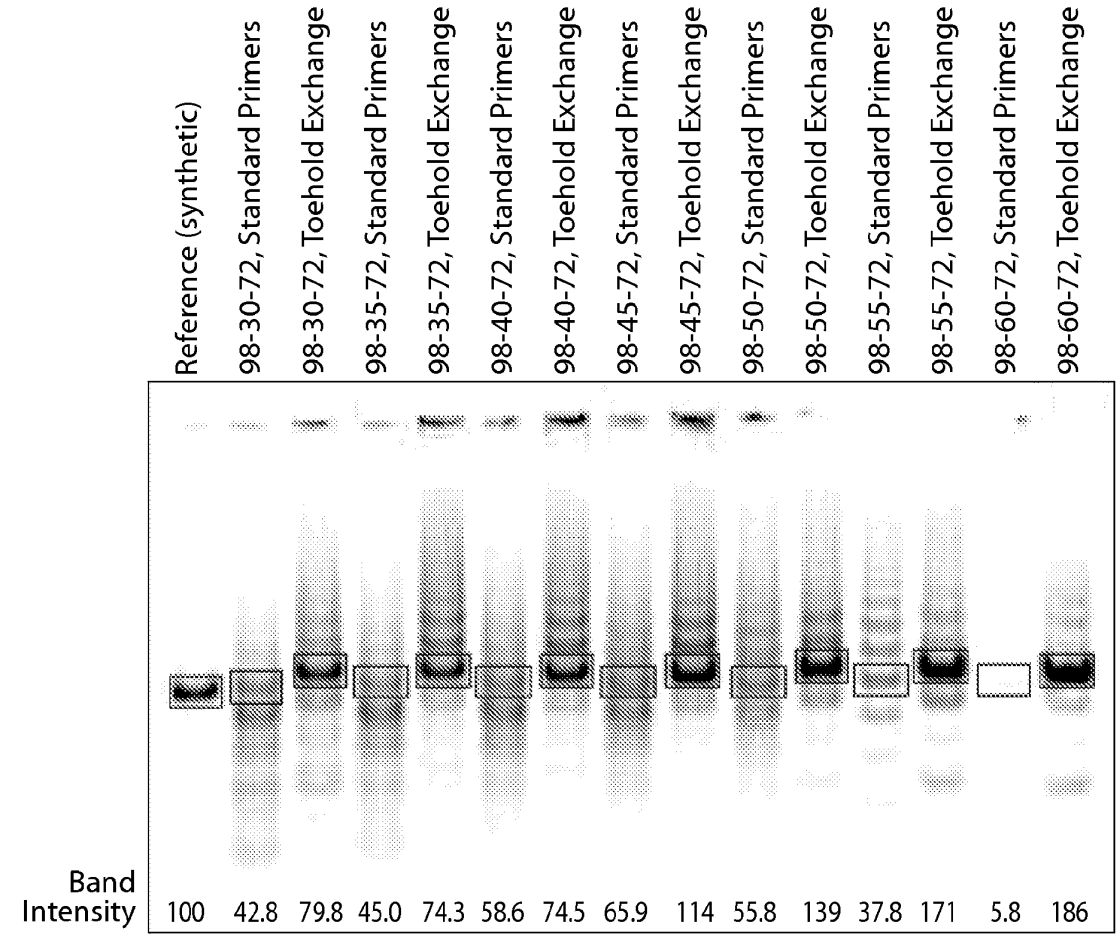


Fig. 18A

NeoGenomics
Exhibit 1003 Page 485



(Toehold exchange product 10nt longer than reference due to 5nt overhangs on each primer)

Fig. 18B

NeoGenomics
Exhibit 1003 Page 486

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/058178

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , BIOSIS, Sequence Search , EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DAVID YU ZHANG ET AL: "Control of DNA Strand Displacement Kinetics Using Toehold Exchange" , JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol . 131 , no. 47 , 2 December 2009 (2009-12-02) , pages 17303-17314, XP55016993, ISSN : 0002-7863, DOI : 10. 1021/ja906987s figures 1, 4 table 2 page 17305, paragraph bridging - page 17306 page 17307, left-hand column , last paragraph page 17310, right-hand column , last paragraph page 17311, left-hand column , last paragraph ----- -/--	1,5-7 , 16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2012	01/02/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ripaud, Leslie

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/058178

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/191546 A1 (ZHANG DAVID [US] ET AL) 30 July 2009 (2009-07-30) figures 3, 5 paragraphs [0036], [0037], [0044], [0055] - [0059] -----	1,5-7,16
X	WO 2010/048002 A1 (UNIV CALIFORNIA [US]; SOH HYONGSOK [US]; XIAO YI [US]) 29 April 2010 (2010-04-29) paragraphs [0102], [0103] table 1 -----	34
X	US 2009/087838 A1 (REIF JOHN H [US] ET AL) 2 April 2009 (2009-04-02) figure 8 paragraphs [0103] - [0106] -----	34
X	BRADLEY HALL ET AL: "Kinetic optimization of a protein-responsive aptamer beacon", BIOTECHNOLOGY AND BIOENGINEERING, vol. 103, no. 6, 15 August 2009 (2009-08-15), pages 1049-1059, XP55016996, ISSN: 0006-3592, DOI: 10.1002/bit.22355 figure 1 table 1 page 1051, right-hand column, paragraph 1st -----	1,5-7,16-18
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-/--

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/058178

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHAO ZHANG ET AL: "A DNA-Ori garni Chi p Pl atform for Label -Free SNP Genotyping Using Toehold-Medi ated Strand Di spl acement" , SMALL, vol . 6 , no. 17, 6 September 2010 (2010-09-06) , pages 1854-1858, XP55017003 , ISSN : 1613-6810, D0l : 10. 1002/sml 1 .201000908 f i gures 1 , 2 page 1854 - page 1857 page 1858, left-hand col umn, paragraph 2nd ful l	1 ,8-17 , 19-33 ,35
X	US 6 033 851 A (YAMANE AKI0 [JP]) 7 March 2000 (2000-03-07) col umn 2 , l ines 57-67 col umns 6-7; example 2	1 ,7-15 , 19-33 ,35
A	BRESLAUER K J ET AL: "PREDICTING DNA DUPLEX STABI LITY FROM THE BASE SEQUENCE", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCI ENCES OF USA, NATIONAL ACADEMY OF SCI ENCE, WASHINGTON, DC; US, vol . 83, 1 June 1986 (1986-06-01) , pages 3746-3750, XP002034050, ISSN : 0027-8424, D0l : 10. 1073/PNAS. 83. 11.3746 abstract	1-35
A	SANTALUCIA J ET AL: "THE THERMODYNAMICS OF DNA STRUCTURAL MOTI FS" , ANNUAL REVI EW OF BIOPHYSICS AND BI0M0LECULAR STRUCTURE, ANNUAL REVI EWS INC. , PALO ALTO, CA, US, vol . 33, 1 January 2004 (2004-01-01) , pages 415-440, XP009053922, ISSN : 1056-8700, DOI : 10. 1146/ANNUREV.BI0PHYS.32. 110601 . 141800 ci ted i n the appl i cati on abstract	1-35

-/--

NeoGenomics
Exhibit 1003 Page 489

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/058178

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MCKEEN C M ET AL: "Synthesi s of f l uorophore and qhencher monomers for use i n scorpi on primers and nuclei c acid structural probes" , ORGANIC & BIOMOLECULAR CHEMISTRY, ROYAL SOCI ETY OF CHEMISTRY, GB, vol . 1, no. 13, 1 January 2003 (2003-01-01) , pages 2267-2275 , XP002578022, ISSN : 1477-0520, D0I : 10. 1039/B301859H [retri eved on 2003-05-28] page 2268, left-hand col umn, paragraph bridgi ng - r i ght-hand col umn ----	1-35
A	T. MANN ET AL: "A thermodynami c approach t o PCR primer desi gn" , NUCLEIC ACIDS RESEARCH, vol . 37, no. 13, 15 June 2009 (2009-06-15) , pages E95-E95, XP55017036, ISSN : 0305-1048, D0I : 10. 1093/nar/gkp443 the whole document ----	1-35

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/058178

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2008097929 A2	14-08-2008
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		WO 9617932 A1	13-06-1996

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PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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Application Number	16/934,407
Filing Date	Jul 21, 2020
First Named Inventor	Matthew RABINOWITZ
Art Unit	1637
Examiner Name	Stephanie Kane Mummert
Attorney Docket Number	N.012.US.32

U.S. PATENTS

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

U.S. PATENT APPLICATION PUBLICATIONS

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
		2007/011903	WO	A3	2007-01-25	LAO, K. Q., et al.		
		2012/058488	WO	A1	2012- 05-03	ZHANG, D. Y., et al.		

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
		COURAUD, S. et al., "Noninvasive Diagnosis of Actionable Mutations by Deep Sequencing of Circulating Free DNA in lung Cancer from Never-Smokers: A Proof-of-Concept Study from BioCAST / IFCT-1002", Clinical Cancer Research, Vol. 20, No. 17, 10 JUL 2014, 4613-4624	

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	Application Number	16/934,407
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	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

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		TAKASHIMA, Y. et al., "Expansion–contraction of photoresponsive artificial muscle regulated by host–guest interactions", Nature Communications, Vol. 3, No. 1270, 11 DEC 2012, 8 pages	

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Examiner Signature		Date Considered	

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	Filing Date	Jul 21, 2020
	First Named Inventor	Matthew RABINOWITZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

The submission of this Information Disclosure Statement does not constitute an admission that a search was made, does not constitute an admission that any information cited is prior art, and does not constitute an admission that no other or better art exists.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2021-06-03
Name/Print	Tianran Yan	Registration Number	67,162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

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
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 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)

110711 7590 04/09/2021

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

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.

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(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/934,407	07/21/2020	Joshua BABIARZ	N.012.US.32	2396

TITLE OF INVENTION: METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/09/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
MUMMERT, STEPHANIE KANE	1637	435-006120

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: Natera, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): San Carlos, California, USA

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. 506075

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 /Tianran Yan/ Date 6-3-2021

Typed or printed name Tianran Yan Registration No. 67162

NeoGenomics
Exhibit 1003 Page 495

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Natera, Inc.
201 Industrial Road
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San Carlos, CA 94070

EXAMINER
MUMMERT, STEPHANIE KANE

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
05/21/2021	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@natera.com

Corrected ***Notice of Allowability***	**Application No.** 16/934,407	**Applicant(s)** RABINOWITZ et al.	
	Examiner STEPHANIE K MUMMERT	**Art Unit** 1637	**AIA (FITF) Status** Yes

-- 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 3/3/21.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3. ☑ The allowed claim(s) is/are 1-15 . 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 4/16/21.
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 _____.

/STEPHANIE K MUMMERT/
Primary Examiner, Art Unit 1637

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 05/18/2021

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Joshua BABIARZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

U.S. PATENTS

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

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		20030232348	A1	2003-12-18	JONES, K. W., et al.	
		20100273219	A1	2010-10-28	MAY, A. et al.	
		20110045462	A1	2011-02-24	FU, X. D., et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
		2007/052006	WO	A1	2007- 05-10	GORMLEY, M. A., et al.		

NON-PATENT LITERATURE DOCUMENTS

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	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
		, "Abstracts for CNAPS III Circulating Nucleic Acids in Plasma and Serum and Serum Proteomics", Clinical Chemistry, Vol. 49, No. 11, 2003, 33 pages	
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EXAMINER SIGNATURE

Examiner Signature	/STEPHANIE K MUMMERT/	Date Considered	05/18/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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OR

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

The submission of this Information Disclosure Statement does not constitute an admission that a search was made, does not constitute an admission that any information cited is prior art, and does not constitute an admission that no other or better art exists.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2021-04-16
Name/Print	Tianran Yan	Registration Number	67,162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 05/18/2021

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. 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 contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Joshua BABIARZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

U.S. PATENTS

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

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		20070059700	A1	2007-03-15	TAO, S. et al.	
		2011064824	A1	2011-03-17	LASCOSTE, C. et al.	
		20110212446	A1	2011-09-01	WANG, D. et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
		01/57269	WO	A2	2001-08-09	FAN, J. B.		
		02/070751	WO	A1	2002-09-12	GODFREY, T. E., et al.		
		2003/521252	JP	A	2003-07-15	FAN, J. B.		
		2008/061213	WO	A2	2008- 05-22	SESHAGIRI, S. et al.		

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 05/18/2021

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	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

		2008/271980	JP	A	2008-11-13	FINKELSTEIN, S. D., et al.		
		2010-509922	JP	A	2010-04-02	SESHAGIRI, S. et al.		
		2011/508662	JP	A	2011-03-17	LASCOSTE, C. et al.		
		2013/123220	WO	A1	2013-08-22	BARANY, F. et al.		
		2013/138510	WO	A1	2013-09-19	PATEL, A. A.		
		2019/118926	WO	A1	2019-06-20	MITCHELL, A. T., et al.		

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
		AGBOR-ENOH, S. et al., "Donor-derived cell-free DNA predicts allograft failure and mortality after lung transplantation", EBioMedicine, Vol. 40, 2019, 541-553	
		KANOU, et al., "Cell-free DNA in human ex vivo lung perfusate as a potential biomarker to predict the risk of primary graft dysfunction in lung transplantation", The Journal of Heart and Lung Transplantation, Vol. 36, No. 45, 2017, S187	
		MARSHUTINA, N. V. et al., "COMPARATIVE CLINICAL AND DIAGNOSTIC SIGNIFICANCE OF SOME SEROLOGICAL TUMOR ASSOCIATED MARKERS FOR DIFFERENT HISTOLOGICAL TYPES OF LUNG CANCER", RUSSIAN ONCOLOGICAL JOURNAL, Vol. 3, 2010, 13-16	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 05/18/2021

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/934,407
	Filing Date	Jul 21, 2020
	First Named Inventor	Joshua BABIARZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

		XU, W. et al., "A Novel Universal Primer-Multiplex-PCR Method with Sequencing Gel Electrophoresis Analysis", PLOS One, Vol. 7, No. 1, 17 JAN 2012, 10 pgs	

EXAMINER SIGNATURE

Examiner Signature	/STEPHANIE K MUMMERT/	Date Considered	05/18/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.K.M/ 05/18/2021

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

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	First Named Inventor	Joshua BABIARZ
	Art Unit	1637
	Examiner Name	Stephanie Kane Mummert
	Attorney Docket Number	N.012.US.32

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e) (2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

The submission of this Information Disclosure Statement does not constitute an admission that a search was made, does not constitute an admission that any information cited is prior art, and does not constitute an admission that no other or better art exists.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Tianran Yan/	Date (YYYY-MM-DD)	2021-04-16
Name/Print	Tianran Yan	Registration Number	67,162

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

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.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32	2396

7590 05/13/2021

Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	PAPER NUMBER
1637	
NOTIFICATION DATE	DELIVERY MODE
05/13/2021	ELECTRONIC

NOTICE REQUIRING INVENTOR'S OATH OR DECLARATION

☐ An inventor's oath or declaration in compliance with 37 CFR 1.63 or substitute statement in compliance with 37 CFR 1.64 executed by or with respect to each inventor has not yet been submitted.

The inventor's oath or declaration or substitute statement dated 7-21-20 is defective. The inventor's oath or declaration does not comply with 37 CFR 1.63 or the substitute statement does not comply with 37 CFR 1.64 because it:

☐ does not include a statement that the person executing the oath or declaration or substitute statement believes the named inventor or joint inventor to be the original inventor or an original joint inventor of a claimed invention in the application for which the oath or declaration is being submitted.

☐ does not state that the application was made or was authorized to be made by the person executing the oath or declaration or substitute statement.

☐ does not acknowledge that any willful false statement made in such oath or declaration or substitute statement is punishable under section 1001 of title 18 by fine or imprisonment of not more than 5 years, or both.

☑ does not identify the person executing the oath or declaration or substitute statement by his or her legal name.

☐ does not identify the application to which the oath or declaration or substitute statement is directed.

☑ Other: Need oath for "Bernhard Eubank".

The substitute statement dated _____ does not comply with 37 CFR 1.64 because it:

☐ does not identify the inventor with respect to whom the statement applies.

☐ does not identify the relationship to the non-signing inventor.

☐ does not identify the circumstances permitting execution of the statement.

☐ was signed by someone other than the applicant.

☐ Other: _____

An oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each inventor MUST be filed **no later than the date on which the issue fee is paid.** See 35 U.S.C. 115(f). Failure to timely comply will result in ABANDONMENT of this application. This period for reply is not extendable under 37 CFR 1.136(a).

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

(571)-272-4200 or 1(888)-786-0101
Patent Publication Branch
Office of Data Management

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/934,407	07/21/2020	Matthew RABINOWITZ	N.012.US.32

CONFIRMATION NO. 2396

110711
Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

37 CFR 1.48 ACKNOWLEDGEMENT LETTER

OC000000125483645

Date Mailed: 05/11/2021

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(a)

This is in response to the applicant's request under 37 CFR 1.48(a) submitted on 05/07/2021.

The request under 37 CFR 1.48(a) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

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**.

/byemane/

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/934,407	07/21/2020	1637	3720	N.012.US.32	15	1

CONFIRMATION NO. 2396

UPDATED FILING RECEIPT

110711
Natera, Inc.
201 Industrial Road
Suite 410
San Carlos, CA 94070

OC000000125483644

Date Mailed: 05/11/2021

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)

Matthew RABINOWITZ, San Francisco, CA;
Matthew Micah HILL, Belmont, CA;
Bernhard EUBANK, Manteca, CA;
Johan BANER, San Francisco, CA;
George GEMELOS, Portland, OR;
Milena BANJEVIC, Los Altos Hills, CA;
Allison RYAN, Belmont, CA;
Styrmir SIGURJONSSON, San Jose, CA;
Zachary DEMKO, San Francisco, CA;

Applicant(s)

Natera, Inc., San Carlos, CA;

Assignment For Published Patent Application

Natera, Inc., San Carlos, CA

Power of Attorney: The patent practitioners associated with Customer Number 110711

Domestic Priority data as claimed by applicant

This application is a CON of 16/743,724 01/15/2020 PAT 10731220
which is a CON of 16/399,268 04/30/2019 PAT 10538814
which is a CON of 16/140,298 09/24/2018
which is a CON of 14/918,544 10/20/2015 PAT 10316362
which is a CIP of 14/877,925 10/07/2015 ABN
and is a CIP of 14/692,703 04/21/2015 PAT 10179937

and is a CIP of 14/538,982 11/24/2014 PAT 9677118
and claims benefit of 62/148,173 04/15/2015
and claims benefit of 62/147,377 04/14/2015
and claims benefit of 62/146,188 04/10/2015
and claims benefit of 62/066,514 10/21/2014
and said 14/877,925 10/07/2015
is a CIP of 14/225,356 03/25/2014 ABN
and is a CIP of 13/780,022 02/28/2013 ABN
and is a CON of 13/683,604 11/21/2012 ABN
and said 14/692,703 04/21/2015
claims benefit of 62/148,173 04/15/2015
and claims benefit of 62/147,377 04/14/2015
and claims benefit of 62/146,188 04/10/2015
and claims benefit of 62/066,514 10/21/2014
and claims benefit of 61/994,791 05/16/2014
and claims benefit of 61/987,407 05/01/2014
and claims benefit of 61/982,245 04/21/2014
and said 14/538,982 11/24/2014
claims benefit of 62/066,514 10/21/2014
and claims benefit of 61/994,791 05/16/2014
and claims benefit of 61/987,407 05/01/2014
and claims benefit of 61/982,245 04/21/2014
and said 14/225,356 03/25/2014
is a CON of PCT/US2012/058578 10/03/2012
and said 13/780,022 02/28/2013
is a CIP of 13/683,604 11/21/2012 ABN
and is a CIP of PCT/US2012/058578 10/03/2012
and is a CIP of 13/335,043 12/22/2011 PAT 10113196
which is a CIP of 13/300,235 11/18/2011 PAT 10017812
which is a CIP of 13/110,685 05/18/2011 PAT 8825412
and said 13/780,022 02/28/2013
claims benefit of 61/634,431 02/29/2012
and said 13/683,604 11/21/2012
is a CIP of 13/300,235 11/18/2011 PAT 10017812
and is a CIP of 13/110,685 05/18/2011 PAT 8825412
and claims benefit of 61/675,020 07/24/2012
and said PCT/US2012/058578 10/03/2012
is a CIP of 13/300,235 11/18/2011 PAT 10017812
and claims benefit of 61/683,331 08/15/2012
and claims benefit of 61/542,508 10/03/2011
and said 13/335,043 12/22/2011
is a CIP of 13/300,235 11/18/2011 PAT 10017812
and is a CIP of 13/110,685 05/18/2011 PAT 8825412
and claims benefit of 61/426,208 12/22/2010
and said 13/300,235 11/18/2011
is a CIP of 13/110,685 05/18/2011 PAT 8825412
and claims benefit of 61/542,508 10/03/2011
and claims benefit of 61/571,248 06/23/2011
and said 13/110,685 05/18/2011
claims benefit of 61/516,996 04/12/2011
and claims benefit of 61/448,547 03/02/2011

and claims benefit of 61/448,547 03/02/2011
and claims benefit of 61/462,972 02/09/2011
and claims benefit of 61/398,159 06/21/2010
and claims benefit of 61/395,850 05/18/2010

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.

Projected Publication Date: Not Applicable
Non-Publication Request: No
Early Publication Request: No
Title

METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

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).

SelectUSA

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.

Doc Code: R48.REQ
Document Description: Request under Rule 48 correcting inventorship

PTO/AIA/40 (04-18)
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.

REQUEST FOR CORRECTION IN A PATENT APPLICATION RELATING TO INVENTORSHIP OR AN INVENTOR NAME, OR ORDER OF NAMES, OTHER THAN IN A REISSUE APPLICATION (37 CFR 1.48)

Application Number	16/934,407
Filing Date	Jul 21, 2020
First Named Inventor	Joshua BABIARZ
Art Unit	1637
Examiner Name	MUMMERT, STEPHANIE KANE
Practitioner Docket Number	N.012.US.32

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

Applicant hereby **requests that the inventorship be corrected or changed, or that the name of the inventor or a joint inventor, or the order of the names of joint inventors, be changed,** in the above-identified application. **Note**: 37 CFR 1.48 applies to any request to correct inventorship filed on or after September 16, 2012, regardless of the application filing date. **Do not submit this form after payment of the issue fee or if the application has been patented.** See 37 CFR 1.324 for correction of inventorship in a patent.

Please check the applicable box(es) below.

For a nonprovisional application:

☒ 1. This request is to correct or change the inventorship in a **nonprovisional** application (**under 37 CFR 1.48(a)**) and includes:

☒ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). See the Manual of Patent Examining Procedure (MPEP) section 601.05(a) for information about filing an ADS in an application filed on/after September 16, 2012. For information about filing a Supplemental ADS in an application filed before September 16, 2012, see MPEP 601.05(b).

☒ The processing fee set forth in 37 CFR 1.17(i). $ 140.00

☒ An inventor is being added. An inventor's oath or declaration by any actual inventor who has not yet executed an oath or declaration is required (see 37 CFR 1.48(b)). See MPEP 602.01(a) for information about an inventor's oath or declaration for an application filed on/after September 16, 2012 (*e.g.*, form **PTO/AIA/01**). For information about an inventor's oath or declaration for an application filed before September 16, 2012 (*e.g.*, form **PTO/SB/01**), see MPEP 602.01(b).

☒ This request is being filed after the first Office action on the merits has been given or mailed (see 37 CFR 1.48(c) and 1.17(d)). Check one of the following:

☐ This request to correct or change the inventorship is due solely to the cancellation of claims in the application.

OR

☒ The fee set forth in 37 CFR 1.17(d) is due (in addition to the fee set forth in 37 CFR 1.17(i)). $ 640.00

This collection of information is required by 37 CFR 1.48. 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 hour 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.**

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