FISH.
FISH & RICHARDSON

Street Address
Fish & Richardson P.C.
3200 RBC Plaza
60 South Sixth Street
Minneapolis, MN 55402

Mail Address
P.O. Box 1022
Minneapolis, MN 55440-1022

612 335 5070 main
877 769 7945 fax

May 16, 2019

Attorney Docket No.: 47706-0004006

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

Presented for filing is a new continuation patent application for prioritized examination of:

Inventor(s): MARK S. CHEE

Title: SPATIALLY ENCODED BIOLOGICAL ASSAYS

Enclosed are the following papers, including those required to receive a filing date under 37 CFR 1.53(b):

	Pages
Certification and Request for Prioritized Examination (Track I)	2
Application Data Sheet	9
Specification	43
Claims	1
Abstract	1
Drawing(s)	5
Declaration	1
Power of Attorney	3

The applicant claims small entity status under 37 CFR 1.27.

Basic Filing Fee			$75
Search Fee			$330
Examination Fee			$380
Publication fee			$0
Track I processing fee			$70
Track I prioritized examination fee			$2000
Total Claims 1	over 20	**0 x $50**	$0
Independent Claims 1	over 3	**0 x $230**	$0
Fee for Multiple Dependent claims			$0
Application size fee for each 50 pages over 100 Total Sheets: 50 x .75 - 100/50 = 0 x			$0
Total Filing fee			**$2855**

Please apply any necessary charges or credits to Deposit Account 06-1050, referencing the attorney docket number shown above.

I hereby authorize the USPTO to communicate in response to email communications from the undersigned and practitioners under Customer No. 159367 in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via email. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03).

If this application is considered to be incomplete, or if a telephone conference would otherwise be helpful, call the undersigned at (612) 335-5070.

Send all correspondence to:

159367
Customer Number

Respectfully submitted,

/Cameron Luitjens/

Cameron M. Luitjens, Ph.D., J.D.
Registration No. 58,674

Enclosures

CVL/jxw
61921765.doc

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-14)

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

First Named Inventor:	Mark S. Chee	Non provisional Application Number (if known):	
Title of Invention:	Spatially Encoded Biological Assays		

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

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims.

3. The applicable box is checked below:

I. ☒ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

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

---OR---

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

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

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

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

Signature /Cameron Luitjens/	Date May 16, 2019
Name (Print/Typed) Cameron M. Luitjens, Ph.D., J.D.	Practitioner Registration Number 58,674

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

☐ *Total of _____ forms are submitted.

61921259.doc

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	47706-0004006
	Application Number	
Title of Invention	Spatially Encoded Biological Assays	

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
	Mark	S.	CHEE	

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

City	State/Province	Country of Residence
San Diego	CA	US

Mailing Address of Inventor:

Address 1	11125 Flintkote Avenue
Address 2	Suite A

City	State/Province	Postal Code	Country
San Diego	CA	92121	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	159367		
Email Address	apsi@fr.com	Add Email	Remove Email

Application Information:

Title of the Invention	Spatially Encoded Biological Assays		
Attorney Docket Number	47706-0004006	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	**Suggested Figure for Publication (if any)**	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	47706-0004006
	Application Number	
Title of Invention	Spatially Encoded Biological Assays	

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.

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	159367		

Domestic Benefit/National Stage Information:

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

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	16402098	2019-05-02

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	47706-0004006
	Application Number	
Title of Invention	Spatially Encoded Biological Assays	

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16402098	Continuation of	16276235	2019-02-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16276235	Continuation of	15187661	2016-06-20
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15187661	Continuation of	13080616	2011-04-05	9371598	2016-06-21

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13080616	Claims benefit of provisional	61321124	2010-04-05

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

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[j] (if applicable)

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

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	47706-0004006
	Application Number	
Title of Invention	Spatially Encoded Biological Assays	

☐ 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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	47706-0004006
	Application Number	
Title of Invention	Spatially Encoded Biological Assays	

Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	47706-0004006
	Application Number	
Title of Invention	Spatially Encoded Biological Assays	

Applicant Information:

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

Applicant 1 — Remove

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Prognosys Biosciences, Inc.		
Mailing Address Information For Applicant:			
Address 1	11125 Flintkote Avenue		
Address 2	Suite A		
City	San Diego	**State/Province**	CA
Country	US	Postal Code	92121
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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

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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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	47706-0004006
	Application Number	
Title of Invention	Spatially Encoded Biological Assays	

Assignee 1

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

Remove

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

Organization Name	

Mailing Address Information For Assignee including Non-Applicant Assignee:

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

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

Signature:

Remove

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

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

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

Signature	/Cameron Luitjens/			Date (YYYY-MM-DD)	2019-05-16
First Name	Cameron	Last Name	Luitjens	Registration Number	58674

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	47706-0004006
	Application Number	
Title of Invention	Spatially Encoded Biological Assays	

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.

SPATIALLY ENCODED BIOLOGICAL ASSAYS

Abstract of the Disclosure

The present invention provides assays and assay systems for use in spatially encoded biological assays. The invention provides an assay system comprising an assay capable of high levels of multiplexing where reagents are provided to a biological sample in defined spatial patterns; instrumentation capable of controlled delivery of reagents according to the spatial patterns; and a decoding scheme providing a readout that is digital in nature.

Curio EX1056-p. 14
Curio v Prognosys

I claim:

l. An assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample, wherein the assay system performs the following steps:
providing a sample affixed to a support;
delivering encoded probes for the multiple biological targets to the multiple sites in the sample in a known spatial pattern, wherein each encoded probe comprises a probe region that may interact with the biological targets and a coding tag that identifies a location of the site to which the encoded probe was delivered;
allowing the encoded probes to interact with the biological targets;
separating encoded probes that interact with the biological targets from encoded probes that do not interact with the biological targets;
determining all or a portion of a sequence of the encoded probes, and
associating the abundance or activity or both of the multiple biological targets to the locations of the sites in the sample.

SPATIALLY ENCODED BIOLOGICAL ASSAYS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Patent Application No. 16/402,098 filed May 2, 2019, which is a continuation of U.S. Patent Application No. 16/276,235 filed February 14, 2019, which is a continuation application of U.S. Patent Application No. 15/187,661 filed June 20, 2016, which is a continuation of 13/080,616 filed April 5, 2011, which claims the benefit of United States Provisional Patent Application No. 61/321,124, filed April 5, 2010 and is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] This invention relates to assays of biological molecules, and more particularly to assays for determining spatial distributions of a large number of biological molecules in a solid sample simultaneously.

BACKGROUND OF THE INVENTION

[0003] In the following discussion certain articles and methods will be described for background and introductory purposes. Nothing contained herein is to be construed as an "admission" of prior art. Applicant expressly reserves the right to demonstrate, where appropriate, that the articles and methods referenced herein do not constitute prior art under the applicable statutory provisions.

[0004] Comprehensive gene expression analysis and protein analysis have been useful tools in understanding mechanisms of biology. Use of these tools has allowed the identification of genes and proteins involved in development and in various diseases such as cancer and autoimmune disease. Conventional methods such as *in situ* hybridization and other multiplexed detection of different transcripts have revealed spatial patterns of gene expression and have helped shed light on the molecular basis of development and disease. Other technologies that have enabled the quantitative analysis of many RNA sequences per sample include microarrays (see Shi, et al., Nature Biotechnology, 24(9):1151-61 (2006); and Slonim and Yanai, Plos Computational Biology, 5(10):e1000543 (2009)); serial analysis of gene expression (SAGE) (see Velculescu, et al, Science, 270(5235):484-87 (1995)), high-throughput implementations of qPCR (see Spurgeon, et al., Plos ONE, 3(2):e1662 (2008)) and *in situ* PCR (see Nuovo, Genome Res., 4:151-67 (1995)). As useful as these

methods are, however, they do not enable simultaneous measurement of the expression of many genes or the presence and/or activity of multiple proteins at many spatial locations in a sample. Laser capture microdissection has permitted the analysis of many genes at a small number of locations, but it is very expensive, laborious, and does not scale well. Certain PCR assays in a 2D format preserve spatial information (see Armani, et al., Lab on a Chip, 9(24): 3526-34 (2009)), but these methods have low spatial resolution because they rely on physical transference of tissue into wells, which also prevents random access to tissue samples and high levels of multiplexing.

[0005] At present, no practical method exists to analyze at high resolution the spatial expression patterns of large numbers of genes, proteins, or other biologically active molecules simultaneously. There is thus a need for reproducible, high-resolution spatial maps of biological molecules in tissues. The present invention addresses this need.

SUMMARY OF THE INVENTION

[0006] This Summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This Summary is not intended to identify key or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter. Other features, details, utilities, and advantages of the claimed subject matter will be apparent from the following written Detailed Description including those aspects illustrated in the accompanying drawings and defined in the appended claims.

[0007] The invention encompasses assay systems that provide high-resolution spatial maps of biological activity in tissues. The assay system comprises an assay capable of high levels of multiplexing where encoded probes are provided to a biological sample in defined spatial patterns; instrumentation capable of controlled delivery of reagents according to the spatial patterns; and a decoding scheme providing a readout that is digital in nature. In short, the present invention provides the ability to look at many biological targets in many locations, providing the resolution of in situ hybridization with the highly- parallel data analysis of sequencing.

[0008] Thus, in some embodiments, the invention provides an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample, where the assay system performs the following steps: providing a sample affixed to a support; delivering encoded probes for the multiple biological targets to the multiple sites in the sample in a known spatial pattern, where each encoded probe comprises a probe region that may interact with the biological targets and a coding tag that identifies a location of the site to which the encoded probe was delivered; allowing the encoded probes to interact with the biological targets; separating encoded probes that interact with the biological targets from encoded probes that do not interact with the

biological targets; determining all or a portion of a sequence of the encoded probes, and associating the abundance or activity or both of the multiple biological targets to the locations of the sites in the sample.

[0009] In particular aspects of the invention the biological targets comprise nucleic acids and the encoded probes are oligonucleotides, and in some aspects, there are two encoded probes for each of the multiple nucleic acid targets. In some aspects, the multiple biological targets comprise proteins, the probe regions of the encoding probes are proteins and the coding tags comprise oligonucleotides. In some aspects the multiple biological targets comprise enzymes. In some aspects the probe regions of the encoded probes comprise antibodies, aptamers or small molecules.

[0010] Some aspects of the assay system further comprise an amplification step between the separating step and the determining step. In some aspects, the determining step is performed by nucleic acid sequencing, and in preferred aspects, the sequencing is high- throughput digital nucleic acid sequencing.

[0011] In some aspects of the invention, the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20, in some aspects product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 50, in some aspects the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 75, 100, 150, 500, 750, 1,000, 5,000, 10,000, 25,000, 50,000, 100,000, 500,000, or 1,000,000 or more. In other aspects, the sequence of at least fifty thousand encoding probes are determined in parallel, in other aspects the sequence of at least one hundred thousand encoding probes are determined in parallel, in some aspects the sequence of at least five hundred thousand encoding probes are determined in parallel, and in some aspects the sequence of at least one million, ten million, one hundred million, one billion, ten billion, one hundred billion or more encoding probes are determined in parallel.

[0012] In some aspects, the known spatial pattern is determined by histological features of the sample. Also in some aspects, software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step and the associating step.

[0013] In some aspects, the probe regions of the encoded probes are proteins and the separating step is accomplished by encoded probes that interact with the biological targets being captured by an affinity capture agent. In some aspects the probe regions of the encoding probes are nucleic acids and the separating step is accomplished by a washing of the sample.

[0014] In other embodiments there is provided an assay system to determine spatial patterns of abundance or activity or both of multiple nucleic acid targets at multiple sites in a sample, where the assay system performs the following steps: providing a sample affixed to a support; delivering

oligonucleotide probes for multiple nucleic acid targets to the multiple sites in the sample in a known spatial pattern; allowing the oligonucleotide probes to hybridize with the nucleic acid targets; washing unhybridized encoded oligonucleotide probes from the sample; delivering one or more encoding agents to locations of the multiple sites in the sample according to a known spatial pattern, where the combination of encoding agents delivered to each site is different; coupling the encoding agents and the oligonucleotide probes to form encoded probes; determining all or a portion of a sequence of the encoded probes using high-throughput sequencing, and associating the abundance or activity or both of multiple biological targets to the locations of multiple sites in the sample.

[0015] Other embodiments of the invention provide an assay system to determine spatial patterns of abundance or activity or both of multiple protein targets at multiple sites in a sample, where the assay system performs the following steps: providing a sample affixed to a support; delivering encoded probes for the multiple protein targets to the multiple sites in the sample in a known spatial pattern, where each encoded probe comprises a protein probe region that may interact with the protein targets and a coding tag that identifies a location of the site to which the encoded probe was delivered and the protein probe region of the encoding probe of which the coding tag is part; allowing the encoded probes to interact with the protein targets; separating encoded probes that interact with the protein targets from encoded probes that do not interact with the protein targets; determining all or a portion of a sequence of the encoded probes by high throughput sequencing, and associating the abundance or activity or both of the multiple protein targets to the locations of the multiple sites in the sample.

[0016] Other embodiments provide an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample, where the assay system performs the following steps: providing a sample affixed to a support; delivering encoded probes for the multiple biological targets to the multiple sites in the sample in a known spatial pattern, where each encoded probe comprises a probe region that may interact with the biological targets and a coding tag that identifies a location of the site to which the encoded probe was delivered and identifies the biological target; allowing the encoded probes to interact with the biological targets; determining all or a portion of a sequence of the encoded probes, and associating the abundance or activity or both of the multiple biological targets to the locations of the sites in the sample.

[0017] The assay system of the invention can utilize various detection mechanisms, based on the molecules to be detected and the reagents needed for such detection system. Exemplary methods that can be used with the assay systems of the invention are described in more detail below.

DESCRIPTION OF THE FIGURES

[0018] Figure 1 provides a simplified overview of the assay system of the present invention.

[0019] Figure 2 provides a simplified overview of one embodiment of the assay system of the present invention for detecting nucleic acids.

[0020] Figure 3 is a representational depiction of one embodiment of the assay overviewed in Figure 2.

[0021] Figure 4A-C illustrates a general mechanism for one embodiment of a combinatorial encoding scheme of the assay systems of the invention. Figure 4A shows two target-specific/encoding oligonucleotide constructs specifically bound to a target nucleic acid of interest in a sample. Figure 4B shows a scheme for delivering twenty different coding tags, a1 through a10 and b1 through b10, to a sample to form a 10x10 coding tag grid. Figure 4C shows a tissue section sample to which the coding tags are delivered, forming the coding tag grid in the sample.

[0022] Figure 5 provides a simplified, specific example of the embodiment of a combinatorial encoding scheme shown in Figure 4.

DEFINITIONS

[0023] The terms used herein are intended to have the plain and ordinary meaning as understood by those of ordinary skill in the art. The following definitions are intended to aid the reader in understanding the present invention, but are not intended to vary or otherwise limit the meaning of such terms unless specifically indicated.

[0024] The term "antibody" as used herein is intended to refer to an entire immunoglobulin or antibody or any functional fragment of an immunoglobulin molecule which is capable of specific binding to an antigen (antibodies and antigens are "binding partners" as defined herein). "Antibody" as used herein is meant to include the entire antibody as well as any antibody fragments capable of binding the antigen or antigenic fragment of interest. Examples of such peptides include complete antibody molecules, antibody fragments, such as Fab, F(ab')2, CDRS, VL, VH, and any other portion of an antibody which is capable of specifically binding to an antigen. Antibodies for assays of the invention are immunoreactive or immunospecific for, and therefore specifically and selectively bind to, proteins either detected *(i.e.,* biological targets) or used for detection *(i.e.,* probes) in the assays of the invention.

[0025] The term "binding agent" as used herein refers to any agent that specifically binds to a biological molecule of interest

[0026] "Complementary" or "substantially complementary" refers to the hybridization or base

pairing or the formation of a duplex between nucleotides or nucleic acids, such as, for instance, between the two strands of a double-stranded DNA molecule or between an oligonucleotide primer and a primer binding site on a single-stranded nucleic acid. Complementary nucleotides are, generally, A and T (or A and U), or C and G. Two single-stranded RNA or DNA molecules are said to be substantially complementary when the nucleotides of one strand, optimally aligned and compared and with appropriate nucleotide insertions or deletions, pair with at least about 80% of the other strand, usually at least about 90% to about 95%, and even about 98% to about 100%).

[0027] "Hybridization" refers to the process in which two single-stranded polynucleotides bind non-covalently to form a stable double-stranded polynucleotide, The resulting (usually) double-stranded polynucleotide is a "hybrid" or "duplex," "Hybridization conditions" will typically include salt concentrations of approximately less than 1M, often less than about 500 mM and may be less than about 200 mM. A "hybridization buffer" is a buffered salt solution such as 5% SSPE, or other such buffers known in the art. Hybridization temperatures can be as low as 5°C, but are typically greater than 22°C, and more typically greater than about 30°C, and typically in excess of 37°C. Hybridizations are often performed under stringent conditions, *i.e.,* conditions under which a primer will hybridize to its target subsequence but will not hybridize to the other, non-complementary sequences. Stringent conditions are sequence-dependent and are different in different circumstances. For example, longer fragments may require higher hybridization temperatures for specific hybridization than short fragments. As other factors may affect the stringency of hybridization, including base composition and length of the complementary strands, presence of organic solvents, and the extent of base mismatching, the combination of parameters is more important than the absolute measure of any one parameter alone. Generally stringent conditions are selected to be about 5°C lower than the T_m for the specific sequence at a defined ionic strength and pH. Exemplary stringent conditions include a salt concentration of at least 0.01 M to no more than 1M sodium ion concentration (or other salt) at a pH of about 7.0 to about 8.3 and a temperature of at least 25°C. For example, conditions of 5xSSPE (750 mM NaCl, 50 mM sodium phosphate, 5 mM EDTA at pH 7.4) and a temperature of approximately 30°C are suitable for allele-specific hybridizations, though a suitable temperature depends on the length and/or GC content of the region hybridized.

[0028] "Ligation" means to form a covalent bond or linkage between the termini of two or more nucleic acids, *e.g.,* oligonucleotides and/or polynucleotides, in a template-driven reaction. The nature of the bond or linkage may vary widely and the ligation may be carried out enzymatically or chemically. As used herein, ligations are usually carried out enzymatically to form a phosphodiester linkage between a 5' carbon terminal nucleotide of one oligonucleotide with a 3' carbon of another nucleotide.

[0029] "Nucleic acid", "oligonucleotide", "oligo" or grammatical equivalents used herein refers

generally to at least two nucleotides covalently linked together. A nucleic acid generally will contain phosphodiester bonds, although in some cases nucleic acid analogs may be included that have alternative backbones such as phosphoramidite, phosphorodithioate, or methylphophoroamidite linkages; or peptide nucleic acid backbones and linkages. Other analog nucleic acids include those with bicyclic structures including locked nucleic acids, positive backbones, non-ionic backbones and non-ribose backbones. Modifications of the ribose-phosphate backbone may be done to increase the stability of the molecules; for example, PNA:DNA hybrids can exhibit higher stability in some environments.

[0030] "Primer" means an oligonucleotide, either natural or synthetic, that is capable, upon forming a duplex with a polynucleotide template, of acting as a point of initiation of nucleic acid synthesis and being extended from its 3' end along the template so that an extended duplex is formed. The sequence of nucleotides added during the extension process is determined by the sequence of the template polynucleotide. Primers usually are extended by a DNA polymerase.

[0031] The term "SNP" or "single nucleotide polymorphism" refers to a genetic variation between individuals; *e.g.,* a single nitrogenous base position in the DNA of organisms that is variable. SNPs are found across the genome; much of the genetic variation between individuals is due to variation at SNP loci, and often this genetic variation results in phenotypic variation between individuals. SNPs for use in the present invention and their respective alleles may be derived from any number of sources, such as public databases (U.C. Santa Cruz Human Genome Browser Gateway (http://genome.ucsc.edu/cgi-bin/hgGateway) or the NCBI dbSNP website (http://www.ncbi.nlm.nih.gov/SNP/), or may be experimentally determined as described in U.S. Pat No. 6,969,589; and US Pub. No. 2006/0188875 entitled "Human Genomic Polymorphisms." Although the use of SNPs is described in some of the embodiments presented herein, it will be understood that other biallelic or multi-allelic genetic markers may also be used. A biallelic genetic marker is one that has two polymorphic forms, or alleles. As mentioned above, for a biallelic genetic marker that is associated with a trait, the allele that is more abundant in the genetic composition of a case group as compared to a control group is termed the "associated allele," and the other allele may be referred to as the "unassociated allele." Thus, for each biallelic polymorphism that is associated with a given trait *(e.g.,* a disease or drug response), there is a corresponding associated allele. Other biallelic polymorphisms that may be used with the methods presented herein include, but are not limited to multinucleotide changes, insertions, deletions, and translocations. It will be further appreciated that references to DNA herein may include genomic DNA, mitochondrial DNA, episomal DNA, and/or derivatives of DNA such as amplicons, RNA transcripts, cDNA, DNA analogs, etc. The polymorphic loci that are screened in an association study may be in a diploid or a haploid state and, ideally, would

be from sites across the genome.

[0032] The term "selectively binds", "selective binding" and the like as used herein, when referring to a binding partner *(e.g.*. protein, nucleic acid, antibody or other affinity capture agent, etc.), refers to a binding reaction of two or more binding partners with high affinity and/or complementarity to ensure selective hybridization under designated assay conditions. Typically, specific binding will be at least three times the standard deviation of the background signal. Thus, under designated conditions the binding partner binds to its particular "target" molecule and does not bind in a significant amount to other molecules present in the sample.

[0033] "Sequencing", "sequence determination" and the like means determination of information relating to the nucleotide base sequence of a nucleic acid. Such information may include the identification or determination of partial as well as full sequence information of the nucleic acid. Sequence information may be determined "with varying degrees of statistical reliability or confidence. In one aspect, the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, "High throughput digital sequencing" or "next generation sequencing" means sequence determination using methods that determine many (typically thousands to billions) of nucleic acid sequences in an intrinsically parallel manner, *i.e.* where DNA templates are prepared for sequencing not one at a time, but in a bulk process, and where many sequences are read out preferably in parallel, or alternatively using an ultra-high throughput serial process that itself may be parallelized. Such methods include but are not limited to pyrosequencing (for example, as commercialized by 454 Life Sciences, Inc., Branford, CT); sequencing by ligation (for example, as commercialized in the SOLiD™ technology, Life Technology, Inc., Carlsbad, CA); sequencing by synthesis using modified nucleotides (such as commercialized in TruSeq™ and HiSeq™ technology by Illumina, Inc., San Diego, CA, HeliScope™ by Helicos Biosciences Corporation, Cambridge, MA, and PacBio RS by Pacific Biosciences of California, Inc., Menlo Park, CA), sequencing by ion detection technologies (Ion Torrent, Inc., South San Francisco, CA); sequencing of DNA nanoballs (Complete Genomics, Inc., Mountain View, CA); nanopore-based sequencing technologies (for example, as developed by Oxford Nanopore Technologies, LTD, Oxford, UK), and like highly parallelized sequencing methods.

[0034] The term "T_m" is used in reference to the "melting temperature." The melting temperature is the temperature at which a population of double-stranded nucleic acid molecules becomes half dissociated into single strands. Several equations for calculating the T_m of nucleic acids are well known in the art. As indicated by standard references, a simple estimate of the T_m value may be calculated by the equation, T_m=81.5+0.41 (% G+C), when a nucleic acid is in aqueous solution at 1M NaCl (see *e.g.*, Anderson and Young, Quantitative Filter Hybridization, in *Nucleic Acid Hybridization* (1985)). Other

references *(e.g.,* Allawi and SantaLucia, Jr., Biochemistry, 36:10581-94 (1997)) include alternative methods of computation which take structural and environmental, as well as sequence characteristics into account for the calculation of T_m.

DETAILED DESCRIPTION OF THE INVENTION

[0035] The practice of the techniques described herein may employ, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and sequencing technology, which are within the skill of those who practice in the art. Such conventional techniques include polymer array synthesis, hybridization and ligation of polynucleotides, and detection of hybridization using a label. Specific illustrations of suitable techniques can be had by reference to the examples herein. However, other equivalent conventional procedures can, of course, also be used. Such conventional techniques and descriptions can be found in standard laboratory manuals such as Green, et al., Eds., *Genome Analysis: A Laboratory Manual Series* (Vols. I-IV) (1999); Weiner, Gabriel, Stephens, Eds., *Genetic Variation: A Laboratory Manual* (2007); Dieffenbach, Dveksler, Eds., *PCR Primer: A Laboratory Manual* (2003); Bowtell and Sambrook, *DNA Microarrays: A Molecular Cloning Manual* (2003); Mount, *Bioinformatics: Sequence and Genome Analysis* (2004); Sambrook and Russell, *Condensed Protocols from Molecular Cloning: A Laboratory Manual* (2006); and Sambrook and Russell, *Molecular Cloning: A Laboratory Manual* (2002) (all from Cold Spring Harbor Laboratory Press); Stryer, *Biochemistry* (4th Ed.) (1995) W.H, Freeman, New York N.Y.; Gait, *"Oligonucleotide Synthesis: A Practical Approach"* (2002) IRL Press, London; Nelson and Cox, *Lehninger, Principles of Biochemistry* (2000) 3rd Ed., W. H. Freeman Pub., New York, N.Y,; and Berg, et al., *Biochemistry* (2002) 5th Ed., W. H. Freeman Pub., New York, N.Y., all of which are herein incorporated in their entirety by reference for all purposes.

[0036] Note that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a nucleic acid" refers to one or more nucleic acids, and reference to "the assay" includes reference to equivalent steps and methods known to those skilled in the art, and so forth.

[0037] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications mentioned herein are incorporated by reference for the purpose of describing and disclosing devices, formulations and methodologies that may be used in connection with the presently described invention.

[0038] Where a range of values is provided, it is understood that each intervening value, between the

upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention,

[0039] In the following description, numerous specific details are set forth to provide a more thorough understanding of the present invention. However, it will be apparent to one of skill in the art that the present invention may be practiced without one or more of these specific details. In other instances, well-known features and procedures well known to those skilled in the art have not been described in order to avoid obscuring the invention.

The Invention in General

[0040] The assay systems of the invention provide spatially-encoded, multiplexed assays comprising 1) an assay capable of high levels of multiplexing with an efficient spatial encoding scheme; 2) instrumentation capable of delivering reagents according to a spatial pattern; and 3) decoding determined by a readout that is digital in nature. The assay systems of the invention detect the presence or absence and relative amount of a biological target or biological activity indicative of a biological target, as well as the location of the biological target or activity in a biological sample, *e.g.*, a tissue section or other biological structure disposed upon a support such as a microscope slide or culture dish.

[0041] The assay system further provides instrumentation with an ability to deliver reagents in a spatially-defined pattern. This instrumentation, together "with software, reagents and protocols, provides a key component of the highly innovative assay system of the invention, allowing for measurement of numerous biological targets or activities in a meaningful spatial environment, including gene expression and peptide localization, An encoding scheme used in these assay systems allows one to determine the location of biological targets or activity (or lack thereof) in the biological samples after the products of the multiplexed assay are removed from the biological sample and pooled for analysis. Decoding of the encoding scheme can be performed by, *e.g.*, next-generation sequencing, which easily provides millions to trillions of data points at low cost. The assay results such as the amount or activity of biological targets can then be mapped back to specific location in the biological sample. The assay systems open a new analytical window into the complex spatial patterns of cellular function and regulation in biological samples.

[0042] A simplified overview of the assay system 100 of the present invention is provided at Figure 1, At step 110, a biological sample affixed to a support is provided. The biological sample contains biological targets of interest. Biological targets can include any molecule of interest, such as nucleic acids (including, *e.g,* RNA transcripts, genomic DNA sequences, cDNAs, amplicons, or other nucleic acid sequences) and proteins, enzymes and the like. At step 120, encoded probes are delivered to the biological sample according to a known spatial pattern. Encoded probes comprise probes, which can interact "with biological targets of interest, and coding tags, which identify the positions in the sample of the biological targets being assayed, and thus can be used to link assay results back to locations in the sample. Coding tags in most embodiments are oligonucleotides. However, coding tags may also be mass tags, fluorescent labels, or other moieties.

[0043] In some embodiments, the probe and coding tag portions of the encoded probe are pre-coupled before being delivered to the biological sample, For example, in the case where the encoded probes are oligonucleotides, both the probe and coding tag sequence can be synthesized as a single oligonucleotide. Alternatively, the probe and coding tag portions of the encoding probes can be synthesized or obtained separately and combined before delivery to the biological sample *(e.g.,* two separate oligonucleotides can be synthesized and coupled by, *e.g.,* ligation; or an antibody and an oligonucleotide can be prepared separately and conjugated before delivery to the biological sample). Also, as is described in Figures 2-5, the probes and the coding tags (in encoding oligonucleotides) are synthesized separately, and are delivered to the biological sample at different steps (*e.g.,* probes first and coding tags thereafter, or vice versa) in the assay.

[0044] At step 130, the encoded probes are allowed to react or interact with the biological targets, *i.e.,* conditions are provided to allow *e.g.,* oligonucleotides to hybridize to nucleic acid targets, enzymes to catalyze reactions with protein targets, antibodies to bind epitopes, etc. In the case where the biological targets are nucleic acids, the encoded probes are typically oligonucleotides and hybridize to the target nucleic acids. In the case that the biological targets are proteins, the encoded probes typically are aptamers, small molecules, or oligonucleotide-conjugated proteins that interact with target proteins by binding to them or by reacting with them (that is, one of the proteins is a substrate for the other). Encoding oligonucleotides may be coupled to the probes (proteins) by conjugation, chemical or photo-crosslinking via suitable groups and the like.

[0045] Once encoded probes interact with the biological targets, the encoded probes that interacted with the biological targets must be separated from the encoded probes that did not interact with the biological targets at step 140. In the case where the biological targets are nucleic acids and the encoded probes are oligonucleotides, the separation can be accomplished by, *e.g.,* washing the unhybridized encoded probes from the sample. Similarly, for other assays that are based on affinity

binding, including those using aptamer, small molecule, and protein probes, washing steps can be used to remove low affinity binders. In the case where the probe is transformed via interaction with the target, *e.g.,* in the case of a peptide, *e.g.,* via cleavage by a protease or phosphorylation by a kinase, it is convenient to collect, all encoded probes--both encoded probes that interacted with the biological targets and were transformed and encoded probes that were not transformed. After collection or pooling, an antibody or other affinity capture agent can be used to capture probes that were transformed by addition of a moiety (*e.g.,* a phosphate group). In cases where probes have been transformed via cleavage, the transformed probes can be separated, *e.g.,* by capturing the non-transformed probes via a tag that is removed from the transformed probes during the transformation *(e.g.,* by cleavage), or by adding a new tag at the site of cleavage.

[0046] Once the reacted (transformed) or interacted encoded probes are separated from the unreacted or un-interacted encoded probes, the sequence of the reacted and/or interacted encoded probes is determined at step 150 by, preferably, sequencing. The sequence of the encoded probes allows the mapping of the assay results at step 160 back to locations in the biological sample.

[0047] Figure 2 provides a simplified overview of an assay system 200 of the present invention embodying an efficient implementation of a combinatorial coding scheme for the encoding of spatial information. For purposes of this overview, the probes are oligonucleotides, but as explained elsewhere, other types of probes can also be used. In step 210, a biological sample affixed to a support, *e.g.,* a tissue sample or other biological structure, is provided. In step 220, one or more oligonucleotide probes are delivered to the biological sample, where the oligonucleotide probes are capable of hybridizing with biological targets in the biological sample. In step 230, the oligonucleotide probes are allowed to interact with (hybridize to) the nucleic acid targets; that is, appropriate conditions are provided where oligonucleotide probes can hybridize to the target nucleic acids.

[0048] In step 240, the oligonucleotide probes that did not hybridize to target nucleic acids are removed, and thereby separated from oligonucleotide probes that did hybridize to target nucleic acids. In this embodiment, separation can be accomplished by, *e.g.,* washing the sample to remove unhybridized oligonucleotide probes. Next, in step 250, encoding oligonucleotides (the encoding agents) are delivered to the biological sample according to a chosen spatial pattern, where the encoding oligonucleotides comprise coding tags that are used to encode the location of biological targets in the biological sample. Note that in contrast to the assay system of Figure 1, here the probes and encoding agents (encoding oligonucleotides) are delivered in separate steps. In step 260, the encoding oligonucleotides are coupled to the oligonucleotide probes to create

encoded probes. In this case where the probes are oligonucleotides, the encoding oligonucleotides may be coupled to the oligonucleotides probes by, *e.g.,* ligation. Alternatively, the information in the encoding oligonucleotides can be transferred by using a DNA polymerase to extend a probe oligonucleotide that acts as a primer, and thereby copy and incorporate the sequence of the encoding oligonucleotides.

[0049] In step 270, the sequence of the coding tags in the encoded probes as well as the sequence or a portion of the sequence of the probe itself is determined, and in step 280, the target nucleic acids are mapped back to the biological sample. In some embodiments, the abundance of sequences reveals the relative quantity of biological targets at the location. Although this embodiment shows the individual steps in a particular order, so as to better explain the invention, the precise order of the steps can be varied. For example, steps 220 and 250 can be combined, so that a mixture of the probes and encoding oligonucleotides is delivered according to a chosen spatial pattern. Coupling step 260 can then be carried out immediately after the combined steps 220 and 250, or concomitantly with them. In this case, step 240 would then occur after step 260. It can therefore be appreciated that the two key results of this series of steps, *i.e.,* the location-specific encoding of probe molecules and the separation of probe molecules based on their ability to interact with corresponding target molecules, can be accomplished with some flexibility in the implementation of the particular steps. Similarly, there is considerable flexibility in the design of the coding scheme. As described *infra,* the assays of the invention are particularly amenable to combinatorial methods.

[0050] Thus, the present invention provides an ability to look at many different biological targets in many locations, providing the resolution of in situ hybridization with the highly-parallel data analysis of sequencing. In some embodiments, the sum of the multiple biological targets being assayed and the multiple sites in the biological sample is greater than 20, in other embodiments, the sum of the multiple biological targets being assayed and the multiple sites in the biological sample is greater than 50, in other embodiments, the sum of the multiple biological targets being assayed and the multiple sites in the biological sample is greater than 100, greater than 500, 1,000, 10,000, 25,000, 100,000, 500,000, 1,000,000. It will be appreciated that, due to the spatial encoding dimension of the invention, even much larger numbers can be contemplated. For example, assaying l 0,000 targets per location x 10,000 locations would generate $1O^{8}$ different assays, and even larger numbers than these can easily be contemplated, particularly if spatial locations with resolution on the order of that of single cells are utilized. Further, in embodiments where high-throughput digital sequencing is employed, the sequences of at least

1,000 encoding probes are typically determined in parallel. More typically, using a digital readout, it is desirable to obtain multiple sequence reads for each assay (defined by a probe and a spatial location code). It is desirable to obtain an average of at least 3 copies per assay, and more typically at least 10 or at least 30 copies per assay, depending on the design of the experiment and requirements of the assay. For a quantitative readout with suitable dynamic range, it may be desirable to obtain at least 1,000 reads per assay. Therefore, if 1,000,000 assays are carried out, the number of sequence reads may be 1 billion or more. With high-throughput digital sequencing, and allowing for redundancy, the sequence of at least 10,000 encoding probes are determined in parallel, or the sequence of at least 100,000, 500,000, 1,000,000, 10,000,000, 100,000,000, 1,000,000,000 or more encoding probes are determined in parallel.

Assays

[0051] The assay portion of the assay systems of the present invention comprise the following general steps: delivering probes and encoding agents where the encoding agents (in some embodiments pre-coupled to the probes) are delivered to the sample according to a known spatial pattern, allowing the probes to interact or react with biological targets in the sample, and, if the probes and encoding agents have not been pre- coupled, coupling the encoding agents to probes.

[0052] The samples of the present invention include virtually any biological sample or samples that can be affixed to a support or provided essentially in a two-dimensional manner, where the ability to tie an assayed biological target or activity back to the location within the biological sample is important. Exemplary biological samples include tissue sections (e.g., including whole animal sectioning and tissue biopsies), cell populations on slides or culture dishes, and the like. The assay systems of the invention are particularly advantageous in that they are compatible with numerous biological sample types, including fresh samples, such as primary tissue sections, and preserved samples including but not limited to frozen samples and paraformalin-fixed, paraffin-embedded (FFPE) samples. An important aspect of the assay systems of the invention is that the biological samples are immobilized on a substrate surface having discrete, independently measurable areas.

[0053] The biological targets to be detected can be any biological molecules including but not limited to proteins, nucleic acids, lipids, carbohydrates, ions, or multicomponent complexes containing any of the above. Examples of subcellular targets include organelles, e.g., mitochondria, Golgi apparatus, endoplasmic reticulum, chloroplasts, endocytic vesicles, exocytic vesicles, vacuoles, lysosomes, etc.

[0054] In some particular embodiments, the assay system is used to analyze nucleic acids, *e.g.,* by

genotyping, quantitation of DNA copy number or RNA transcripts, localization of particular transcripts within samples, and the like. Figure 3 illustrates an overall scheme for an exemplary assay for, *e.g.,* detecting single nucleotide polymorphisms (SNPs) that can be used with the assay system of the invention. In Figure 3, two oligonucleotide probes are provided. Each oligonucleotide probe comprises a target-specific region (located on either side of the SNP to be analyzed) seen at 305 and 307, and ligation regions, seen at 301 and 303, The oligonucleotide probes are allowed to hybridize to a target nucleic acid (not shown) in the biological sample. At step 302, one of the oligonucleotide probes is extended to incorporate the SNP sequence and ligated to the other probe to form an extended probe comprising target nucleic acid region 309 and ligation regions 301 and 303.

[0055] Two encoding agents, both comprising a coding tag (seen at 315 and 317), a ligation region (seen at 311 and 313), and a primer region (seen at 319 and 321) are combined with and ligated to the extended probe at step 304 to form an encoded target- specific oligonucleotide. Again, in contrast with Figure 1, the probes and encoding agents are delivered at separate steps. Doing so allows use of the combinatorial embodiments described *infra.* In preferred embodiments, the encoding oligonucleotides within a pair of encoding oligonucleotides ligate specifically to one side of the target sequence or the other *(i.e., 5'* or 3' of the target sequence) in step 306. Also, typically, the ligation and primer regions of the encoding oligonucleotides and probes are universal; that is, the set of ligation and primer regions used in constructing the probes and encoding oligonucleotides are constant, and only the target-specific regions of the probes and the coding tags of the encoding oligonucleotides differ. However, again in alternative embodiments, the ligation and primer regions are not universal and differ between probes and encoding agents.

[0056] Following ligation, the encoded probes are eluted, pooled, and, optionally, sequencing adapters are added to the encoded probes via PCR. In alternative embodiments, sequencing primers may be ligated to the encoding oligonucleotides, or sequencing primer sequences can be included as part of the encoding oligonucleotide. As seen in Figure 3, each sequencing adapter comprises primer region 319 or 321, compatible with the primer regions 319 and 321 on the encoded probes. The final construct comprising first adapter 327, first primer region 319, first coding tag 315, ligation regions 311 and 301, target region 309, ligation regions 313 and 303, second coding tag 317, second primer region 325 and second adapter 329 is now ready for input into a digital high-throughput sequencing process.

[0057] A combination of extension and ligation reactions are exemplified in Figure 3, but it should be appreciated that a variety of reactions may be used to couple the encoding oligonucleotides to the target-specific oligonucleotides, including ligation only (e.g., for oligonucleotides that hybridize to contiguous portions of the target nucleic acid sequence). Alternatively, an assay utilizing an additional

oligonucleotide, such as in the GOLDENGATE® assay (see Fan, et al., Cold Spring Symp. Quant. Biol., 68:69-78 (2003); (Ilumina, Inc., San Diego, CA)), may be employed.

[0058] In other embodiments, the assay system of the invention also can be used to analyze peptides or proteins, the presence of antibodies, enzymatic and other protein activities, posttranslational modifications, active and non-active forms of peptides, as well as peptide isoforms in a biological sample. Accordingly, the probes may comprise an active region of an enzyme, a binding domain of an immunoglobulin, defined domains of proteins, whole proteins, synthetic peptides, peptides with introduced mutations, aptamers and the like.

[0059] In certain aspects, the probes are substrates for enzymes or proenzymes, *e.g.,* kinases, phosphatases, zymogens, proteases, or fragments thereof. In certain aspects, the probes are phosphorylation substrates used to detect proteins involved in one or more signal transduction pathways, *e.g.,* a kinase or a phosphatase. In another specific aspect of the invention, the probes are specific protease substrates that associate only with individual proteases or classes of proteases. In other aspects, the probes are different processed forms, isoforms and/or domains of an enzyme. Protein-based probes are typically conjugated or otherwise linked to oligonucleotide encoding agents. The oligonucleotide encoding agents in this case would also include a nucleotide sequence component that allows for identification of the protein probe.

[0060] In certain aspects, the present invention provides assays for evaluating differences in the amount and/or activity of biological targets between different locations in a sample and/or between samples. The method includes determining a plurality of encoded results from the biological sample and evaluating the differences in quantity of the biological targets at each location in the biological sample.

Combinatorial Embodiments

[0061] To maximize the efficiency of encoding, a combinatorial approach using pairs of coding tags in the encoding oligonucleotides can be used. By de-coupling the target-specific information and the coding tags, the number of oligonucleotides required is dramatically reduced, with a concomitant decrease in cost.

[0062] Figure 4 illustrates a general mechanism for one embodiment of a combinatorial encoding scheme of the assay systems of the invention, where nucleic acids in a representative tissue section (shown at 416) are assayed. Figure 4 at A shows two target-specific/encoding oligonucleotide constructs 420 and 422 *(e.g.,* formed between steps 302 and 304 of Figure 3) specifically bound to a target nucleic acid 402 of interest, The first encoded probe 420 comprises coding tag 408, associated with, *e.g.,* a universal priming site for amplification of the assay products or an adapter to enable

identification of the coding identifiers using sequencing technologies 404. The second encoded probe 422 comprises coding tag 406, associated with, *e.g.,* a universal priming site for amplification of the assay products or an adapter to enable identification of the coding identifiers using sequencing technologies 410.

[0063] Figure 4 at B shows the spatial pattern that may be used for twenty different coding tags, al through a10 (coding tag 406 on encoded probe 420) and b1 through b10 (coding tag 408 encoded probe 422). Coding tag al., for example, is deposited on the biological sample in ten discrete areas or spots (shown as the first horizontal line of spots in 412). Coding tag a2 is deposited on the biological sample in ten spots on the second horizontal line in 412. Coding tag a3 is deposited on the biological sample in ten spots on the third horizontal line in 412, and so on. Whereas the "a" tags are deposited in ten horizontal rows, the "b" tags are deposited in ten vertical rows as shown in 414. For example, coding tag b1 is deposited on the biological sample in ten discrete spots in the first vertical row of 414, coding tag b2 is deposited on the biological sample in ten discrete spots in the second vertical row of 414, and so on. Using such a configuration allows for twenty coding tags to uniquely define 100 different locations on the biological sample.

[0064] Figure 4 at C shows a representative tissue section 416 coincident with coding tag grid 418. The arrows show how the "a" coding tags and the "b" coding tags are deposited on grid 418 that is coincident with tissue section 416. If, once sequenced, coding tags al and b4, *e.g.,* are associated with a target nucleic acid sequence, then that target nucleic acid sequence *(i.e.,* biological target) was present in the tissue section at location al, b4.

[0065] Figure 5 provides a simplified, specific example of the encoding scheme of the assay systems of the invention. Figure 5 shows encoding oligonucleotides 510, comprising al, a2, a3, a4 and b1, b3, b3 and b4. Target-specific oligonucleotides (TSOs) (probes) 1 and 2 are shown at 520. A deposit or dispensing scheme is shown at 530. Like the grid exemplified in Figure 4, encoding oligonucleotides al through a4 are deposited in spots in a pattern (here, in a vertical pattern), and encoding oligonucleotides bl through b4 are deposited in spots in a pattern (here, a horizontal pattern). The grid though shown as a square with spots is actually a deposition pattern on a biological sample (not shown) such as tissue section 416 shown in Figure 4.

[0066] The target-specific oligonucleotides are delivered to the biological sample, where the target-specific oligonucleotides hybridize to target nucleic acids in the biological sample if target nucleic acids are present. Unhybridized target-specific oligonucleotides are then removed, *e.g.,* by washing. The encoding oligonucleotides are then delivered to the biological sample according to the spatial pattern shown at 530. The encoding oligonucleotides are ligated (or, *e.g.,* extended and ligated) to any target-specific oligonucleotides that hybridized to the target nucleic acid in the biological sample, the

ligated constructs are then eluted from the biological sample, pooled, and sequencing adapters are added through, *e.g.,* PCR or ligation, if the sequences were not previously included in the encoding oligonucleotides. The ligated constructs are sequenced by, *e.g.,* high throughput or "next generation" sequencing.

[0067] The pool of resulting sequences is shown at 540. A sequence readout was obtained for target-specific oligonucleotide 1 only at a4bl, a4b2, alb3, a2b3, a3b3, a4b3 and a4b4 (positions shown with horizontal lines). A sequence readout was obtained for target-specific oligonucleotide 2 only at a1b1 (position shown with vertical lines). A sequence readout was obtained for both target-specific oligonucleotides 1 and 2 at positions a2b1, a3b1, a1b2, a2b2, and a3b2 (positions shown with cross-hatching). No sequence readout was obtained for either target-specific oligonucleotides at alb4, a2b4 or a3b4 (positions shown without shading). Thus, in the biological sample on which the assay took place the first target nucleic acid was detected in a large portion of the left side and at the bottom of the biological sample, the second target nucleic acid was detected only in the upper left portion of the biological sample, and neither target nucleic acid was detected in the upper right portion of the biological sample. The differential expression of the two target nucleic acids now can be mapped back to the biological sample and to the biological structures or cell types in these locations in the biological sample, as shown in 550.

[0068] In addition to location information, information relating to relative abundance of the encoded tags can be obtained. For example, if it is found that there are ten times as many a4T1b1 sequences occurring in the data set as compared to a4T1b2 sequences, this would indicate that target nucleic acid sequence 1 is ten times more abundant at the a4T1b1 location than at the a4T1b2 location.

[0069] In the case of nucleotide analysis as shown in Figure 3, by ligating the coding tags directly to target-specific oligonucleotides, only 2n target-specific oligonucleotides are needed for n targets. For example, using the combinatorial approach outlined in Figure 2, assaying 100 different targets at 10,000 spatial locations would require 2 x 100 target-specific oligonucleotides and 2 x 100 encoding oligonucleotides. The total count of assay oligonucleotides would be only 400 (200 target-specific and 200 encoding), not counting universal primers. In contrast, if the coding oligonucleotides were not decoupled from the target-specific o1igonucleotides, (n x X positional codes) + (n x Y positional codes) would be needed, or in the above example, 20,000 oligonucleotides, not counting universal primer sequences. Moreover, though the embodiments shown in Figures 2- 5 depict a combinatorial scheme using two encoding agents (coding tags), three, four or more encoding agents and coding tags may be used, and attached to the probe or one another by varying means and in varying combinations of steps.

[0070] Due to the spatial encoding aspect of the assay system of the invention, a large amount of

information can be generated with even a modest number of assays. For example, five or more biological targets assayed at five or more positions in the sample generates 25 or more combinations. Using digital sequencing as a readout, the optimum number of sequence reads per combination depends on the sensitivity and dynamic range required, and can be adjusted, For example, if for each combination on average 100 reads are sampled, the total for 25 combination is 25,000 reads. If 1,000 targets are assayed at 1,000 locations with an average sampling depth of 1,000, then 10^9 reads are required. These numbers, although large, are within the capacity of intrinsically parallel digital sequencing methods, which can generate datasets of billions or even trillions of reads in a reasonable timeframe and at a very low cost per read. Therefore, by varying the numbers of positions interrogated or biological targets assayed, or both, and using digital sequencing, large amounts of information can be obtained. In specific aspects, multiple locations are interrogated for two or more biological molecules.

Reagent Delivery Systems

[0071] The reagent delivery system of the invention includes instrumentation that allows the delivery of reagents to discrete portions of the biological sample, maintaining the integrity of the spatial patterns of the encoding scheme. Reagent delivery systems of the assay systems of the invention comprise optional imaging means, reagent delivery hardware and control software. Reagent delivery can be achieved in a number of different ways. It should be noted that reagent delivery may be to many different biological samples at one time. A single tissue section has been exemplified herein; however, multiple biological samples may be affixed and analyzed simultaneously. For example, pions of a tissue sample can be analyzed in parallel and the data combined to build a 3D map.

[0072] Integral to the assay system of the invention is instrumentation that allows for spatial patterning of reagents onto the biological sample. Technologies for formulating and delivering both biological molecules *(e.g.* oligonucleotides or antibodies) and chemical reagents (e.g., small molecules or dNTPs) are known in the art, and uses of these instrument systems are known to one skilled in the art and easily adaptable to the assay systems of the invention. One example of a suitable reagent delivery system is the Labcyte™ Echo acoustic liquid handier, which can he used to deliver nanoliter scale droplets containing biological molecules with high precision and reproducibility. One skilled in the art could incorporate this reagent delivery device into the overall system, using software to specify the locations to which reagents should be delivered.

[0073] Other instruments that can be used for the deposition of agents and/or coding identifiers

onto biological samples include, but are not limited to, ink jet spotting; mechanical spotting by means of pin, pen or capillary; micro contact printing; photochemical or photolithographic methods; and the like. For several applications, it may be preferred to segment or sequester certain areas of the biological samples into one or more assay areas for different reagent distributions and/or biological target determination. The assay areas may be physically separated using barriers or channels.

[0074] In one exemplary aspect, the reagent delivery system may be a flow-based system. The flow-based systems for reagent delivery in the present invention can include instrumentation such as one or more pumps, valves, fluid reservoirs, channels, and/or reagent storage cells. Reagent delivery systems are configured to move fluid to contact a discrete section of the biological sample. Movement of the reagents can be driven by a pump disposed, for example, downstream of the fluid reagents. The pump can drive each fluid reagent to (and past) the reaction compartment. Alternatively, reagents may be driven through the fluid by gravity. US Pub. Nos. 20070166725 and 20050239192 disclose certain general-purpose fluidics tools that can be used with the assay systems of the invention, allowing for the precise manipulation of gases, liquids and solids to accomplish very complex analytical manipulations with relatively simple hardware.

[0075] In a more specific example, one or more flow-cells can be attached to the substrate-affixed biological sample from above. The flow-cell can include inlet and outlet tubes connected thereto and optionally an external pump is used to deliver reagents to the flow-cell and across the biological sample. The flow cells are configured to deliver reagents only to certain portions of the biological sample, restricting the amount and type of reagent delivered to any specific section of the biological sample.

[0076] In another aspect, a microfluidic system can be integrated into the substrate upon which the biological sample is disposed or externally attached on top of the substrate. Microfluidic passages for holding and carrying fluid may be formed on and/or above the planar substrate by a fluidics layer abutted to the substrate. Fluid reagents can be selected and delivered according to selective opening and closing of valves disposed between reagent reservoirs.

[0077] Pumps generally include any mechanism for moving fluid and/or reagents disposed in fluid. In some examples, the pump can be configured to move fluid and/or reagents through passages with small volumes *(i.e.,* microfluidic structures). The pump can operate mechanically by exerting a positive or negative pressure on fluid and/or on a structure carrying fluid, electrically by appropriate application of an electric field(s), or both, among other means. Exemplary mechanical pumps may include syringe pumps, peristaltic pumps, rotary pumps, pressurized gas, pipettors, etc. Mechanical pumps may be micromachined, molded, etc. Exemplary electrical pumps may include electrodes and

may operate by electrophoresis, electroendoosmosis, electrocapillarity, dielectrophoresis (including traveling wave forms thereof), and/or the like.

[0078] Valves generally include any mechanism for regulating the passage of fluid through a channel. Valves can include, for example, deformable members that can be selectively deformed to partially or completely close a channel, a movable projection that can be selectively extended into a channel to partially or completely block a channel, an electrocapillary structure, and/or the like.

[0079] An open gasket can be attached to the top of the biological sample and the sample and reagents can be injected into the gasket. Suitable gasket materials include, but are not limited to, neoprene, nitrile, and silicone rubber. Alternatively, a watertight reaction chamber may be formed by a gasket sandwiched between the biological sample on the substrate and a chemically inert, water resistant material such as, but not limited to, black-anodized aluminum, thermoplastics *(e.g.,* polystyrene, polycarbonate, etc), glass, etc.

[0080] In an optional embodiment, the assay system comprises imaging means to determine features and organization of the biological sample of interest. The images obtained, *e.g.,* may be used to design the deposition pattern of the reagents, Imaging means are optional, as an individual can instead view the biological sample using, *e.g.,* a microscope, analyze the organization of the biological sample, and specify a spatial pattern for delivery assay reagents. If included, the delivery system can comprise a microcircuit arrangement including an imager, such as a CCD or IGFET-based *(e.g.,* CMOS-based) imager and an ultrasonic sprayer for reagent delivery such as described in US Pub. No. 20090197326, which is incorporated herein by reference. Also, it should be noted that although Figures 4 and 5 illustrate using a x,y grid configuration, other configurations can be used, such as, *e.g.,* following the topology of a tissue sample; targeting certain groups of cells, cell layers and/or cell types in a tissue, and the like.

[0081] In yet another alternative, the reagent delivery system controls the delivery of reagents to specific patterns on a biological sample surface using semiconductor techniques such as masking and spraying. Specific areas of a biological sample can be protected from exposure to reagents through use of a mask to protect specific areas from exposure. The reagents may be introduced to the biological sample using conventional techniques such as spraying or fluid flow. The use of masked delivery results in a patterned delivery scheme on the substrate surface.

[0082] In a preferred aspect of the invention, the reagent delivery instrumentation is based on inkjet printing technology. There are a variety of different ink-jetting mechanisms (*e.g.,* thermal, piezoelectric) and compatibility has been shown with aqueous and organic ink formulations. Sets of independently actuated nozzles can be used to deliver multiple reagents at the same time, and very high resolutions are be achieved.

[0083] In order to target specific sites of interest, an informative image of the biological sample to be assayed may be used to assist in the reagent delivery methods and associated encoding scheme. Sample regions of the biological sample can be identified using image processing (e.g., images of cell types differentiated by immunohistochemistry or other staining chemistries) integrated with other features of the assay system. In some aspects, software is used to automatically translate image information into a reagent delivery pattern. A mechanism to register and align very precisely the biological sample for reagent delivery is thus an important component of the assay systems of the invention. Mechanisms such as the use of fiducial markers on slides and/or other very accurate physical positioning systems can be adapted to this purpose.

[0084] The invention preferably comprises a complete suite of software tailored to the assay system. Optionally, oligonucleotide design software is used to design the encoding nucleotides (and in embodiments where nucleic acids are assayed, the target-specific oligonucleotides) for the specific assay to be run, and may be integrated as a part of the system. Also optionally, algorithms and software for reagent delivery and data analysis (i.e., sequence analysis) may be integrated to determine assay results. Integrated data analysis is particularly useful, as the type of dataset that is generated may be massive as a consequence of scale. Algorithms and software tools that are specifically designed for analysis of the spatially-associated data generated by the assay systems, including pattern-analysis software and visualization tools, enhance the value of the data generated by the assay systems.

[0085] In certain aspects, the assay system comprises processes for making and carrying out the quality control of reagents, *e.g.,* the integrity and sequence fidelity of oligonucleotide pools. In particular, reagents are formulated according to factors such as volatility, stability at key temperatures, and chemical compatibility for compatibility with the reagent delivery instrumentation and may be analyzed by instrumentation integrated within the assay system.

Sequencing

[0086] Numerous methods can be used to identify the coding tags and probe sequences in the encoded probes of the assay systems of the invention. The coding tags can be detected using techniques such as mass spectroscopy *(e.g.,* Maldi-T of, LC-MS/MS), nuclear magnetic resonance imaging, or, preferably, nucleic acid sequencing. Examples of techniques for decoding the coding tags of the present invention can be found, for example, in US Pub. No. 20080220434, which is incorporated herein by reference. For example, the coding tags may be oligonucleotide mass tags (OMTs or massTags). Such tags are described, *e.g.,* in US Pub. No. 20090305237, which is incorporated by reference in its entirety. In yet another alternative, the encoded probes can be

amplified and hybridized to a microarray. This would require separate amplification reactions to be carried out, in which each amplification is specific to a particular spatial code or subset of codes, accomplished by using code-specific primers. Each amplification would also incorporate a different resolvable label (e.g. fluorophor). Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can he determined by the relative abundances of the resolvable labels.

[0087] In one particularly preferred aspect, the resulting coding tags according to the assay system are substrates for high-throughput, next-generation sequencing, and highly parallel next-generation sequencing methods are used to confirm the sequence of the coding tags, for example, with SOLiD™ technology (Life Technologies, Inc.) or Genome Ananlyzer (Illumina, Inc.). Such next-generation sequencing methods can be carried out, for example, using a one pass sequencing method or using paired-end sequencing. Next generation sequencing methods include, but are not limited to, hybridization-based methods, such as disclosed in *e.g.,* Drmanac, U.S. Pat. Nos. 6,864,052; 6,309,824; and 6,401,267; and Drmanac et al, U.S. patent publication 2005/0191656; sequencing-by-synthesis methods, *e.g.,* U.S. Pat Nos. 6,210,891; 6,828,100; 6,969,488; 6,897,023; 6,833,246; 6,911,345; 6,787,308; 7,297,518; 7,462,449 and 7,501,245; US Publication Application Nos. 20110059436; 20040106110; 20030064398; and 20030022207; Ronaghi, et al, Science, 281: 363-365 (1998); and Li, et al, Proc. Natl. Acad. Sci., 100: 414-419 (2003); ligation-based methods, *e.g.,* U.S, Patent Nos. 5,912,148 and 6,130,073; and U.S. Pat. Appln Nos. 20100105052, 20070207482 and 20090018024; nanopore sequencing *e.g.,* U.S. Pat. Appln Nos. 20070036511; 20080032301; 20080128627; 20090082212; and Soni and Meller, Clin Chem 53: 1996-2001 (2007)), as well as other methods, *e.g.,* U.S. Pat. Appln Nos. 20110033854; 20090264299; 20090155781; and 20090005252; also, see, McKernan, et al., Genome Res., 19:1527-41 (2009) and Bentley, et al., Nature 456:53-59 (2008), all of which are incorporated herein in their entirety for all purposes.

Applications of Assay System

[0088] It will be apparent to one skilled in the art upon reading the present disclosure that there are numerous important areas of biological research, diagnostics, and drug development that will benefit from a high throughput multiplexed assay system that can measure simultaneously the amount and spatial location of a biological target in a biological sample. For example, combining the ability to estimate the relative abundance of different RNA transcripts with the ability to reconstruct an image of spatial patterns of abundance across many locations, which may be as small as or even smaller than individual cells, in a tissue enables many different areas of basic research. The following are exemplary uses and are

by no means meant to be limiting in scope.

[0089] In one example, 3-dimensional patterns of gene expression are determined by analyzing a series of tissue sections, in a manner analogous to image reconstruction in CT scanning, Such a method can be used to measure changes in gene expression in disease pathology, *e.g.,* in cancerous tissue and/or a tissue upon injury, inflammation or infection. With the assay systems of the invention, more detailed information on gene expression and protein localization in complex tissues is obtained, leading to new insights into the function and regulation both in normal and diseased states, and provides new hypotheses that can be tested. For example, an assay system of the invention may enable some of the insights gained from many individual studies and larger programs like ENCODE (Birney, et al., Nature, 447:799-816 (2007)) and modENCODE to be integrated at the tissue level. The assay systems also aid computational efforts to model interacting networks of gene expression in the field of systems biology.

[0090] The assay systems also provide a novel approach to analysis of somatic variation, *e.g.,* somatic mutations in cancer or variability in response to infectious organisms. For example, tumors are typically highly heterogeneous, containing cancer cells as well as genetically normal cells in an abnormal local environment. Cancer cells undergo mutation and selection, and in this process it is not unusual for local clones to develop. Identifying relatively rare somatic mutations in the context of tumors may enable the study of the role of key mutations in the selection of clonal variants. Transcriptional patterns associated with angiogenesis, inflammation, or other cancer-related processes in both cancer and genetically normal cells can be analyzed for insights into cancer biology and assist in the development of new therapeutic agents for the treatment of cancers. In another example, individuals have varying susceptibility to infectious organisms, and the assay systems of the invention can be used to study the interaction between microbes and tissues or the various cell types within the tissue.

[0091] Importantly, in addition to providing spatially-associated information, the invention allows a great increase in the sensitivity of detecting rare mutations, as signal to noise can he dramatically increased since only a small location is assayed in any given reaction. In a typical assay for rare mutations in a mixed sample, the sample is treated in bulk, *i.e.,* nucleic acids are extracted from many cells into a single pool. Thus, if a mutation is present in one cell in 10,000, it must be detected against a background of normal DNA from ~10,000 cells. In contrast, with the assay systems of the invention many cells can be analyzed, but individual cells or small groups of cells would be identified by the spatial coding system. Therefore, in the assay systems of the present invention, background is reduced by orders of magnitude, greatly increasing sensitivity. Furthermore, the spatial organization of mutant cells can be observed, which may be particularly important in detecting key mutations in tissue

sections in cancer. Already molecular histological analyses are yielding insights into cancer biology and may have potential for use in diagnostics. The technology of the invention promises to greatly increase the power of such approaches.

[0092] The present invention provides assays, assay systems, and methods of using such assays in spatially encoded biological assays. The invention provides an assay system comprising one or more agents provided in defined spatial patterns on a substrate surface, and a detection system for identifying the presence or absence, relative amount, and location of a biological molecule. Such biological molecules include, but are not limited to, nucleic acids, peptides, carbohydrates, cellular components, and the like. The assay system is a novel multiplexing approach, as it allows multiple molecules and their respective multiple locations to be identified in a single system using a unique encoding scheme. This encoding scheme uses both molecule-specific binding agents and coding identifiers to provide a practical and cost-effective determination of information on multiple biological molecules, including specific positional information of such molecules in a biological sample, e.g., a tissue section. The single molecule detection analysis using the encoding system also allows relative amounts of biological molecules to be detected, thus providing information on expression levels, sequestering in specific locales, and the like.

[0093] The assay systems detect the presence or absence, and relative amount, of a biological molecule at more than one spatial location in a sample. In addition, the assays provide methods for doing this for multiple biological molecules simultaneously. The assay systems utilize one or more binding agents that specifically bind to the biological molecule of interest and unique coding identifiers associated with specific binding agents. The detection system utilizes a method for identifying the presence and spatial address of the agent binding based on the positive and/or negative results that are obtained using detection of the agent and identifier and the encoding scheme of the spatial patterns on the substrate surface. In a specific aspect, the encoding scheme employs limited reagent delivery to the spatial patterns on the substrate surface, and access of the coding identifiers and/or binding agents to portions of the sample is controlled through such limited delivery.

[0094] In one aspect, the assay system detects the presence or absence and spatial location of a biological molecule based on the positive and/or negative results that are obtained using limited reagent delivery and the encoding scheme of the spatial patterns on the substrate surface.

[0095] The assay system and methods of the invention are based on relational, solid-state substrates with positions that represent specific spatial locations within a biological sample, e.g., a cell, organelle or tissue. The ability to use encoding features to represent locations allows high-throughput analysis of the presence or absence, and relative amount, of a biological molecule at more than one spatial location in a sample. The encoding features also allow provide assaying of multiple biological

molecules at these multiple locations simultaneously.

[0096] A primary feature of the invention is the preservation of the spatial organization of elements in a sample of interest through the use of an encoding scheme. For example, the assay may be designed to preserve the relative position of cells in a tissue, and the assay may interrogate the individual cells for genomic DNA variation (including epigenetic modifications), and RNA and protein expression.

[0097] In one specific aspect, the encoding scheme of the assay system comprises the use of two or more coding patterns, each comprising regions defined by spatial patterns on the substrate surface. For example, the assay system can utilize an encoding scheme that comprises a 2-dimensional grid format based on the discrete positioning of the binding agents in the substrate surfaces. In another example, the spatial patterns may be based on more randomized cell locations, e.g., the patterns on the substrate surface follow an underlying biological structure rather than a strict, x,y grid pattern. This aspect includes systems with two or more substantially identical spatial patterns using different binding agents and/or coding identifiers, as well as systems having different patterns for different agents and/or coding identifiers. The encoding scheme of the systems can be controlled by delivery of different reagents to discrete regions on the substrate surfaces, which allows different reactions to take place on substantially similar agents of known location on the substrate surfaces.

[0098] In one specific aspect, the invention provides high resolution, high- throughput analysis of nucleic acids and/or expression levels that provides both detection and spatial identification of large numbers of nucleic acids, e.g., DNA or RNA.

[0099] In another specific aspect, the invention provides high resolution, high- throughput analysis of proteins that provides both detection and spatial identification of large numbers of such proteins, e.g., kinases or proteases.

[00100] Numerous reagent delivery systems can be used with the assay system of the invention. The primary criteria of such reagent delivery systems is the ability to direct delivery of specific agents based on spatial patterns on the substrate surface.

[00101] In one preferred aspect, the encoding scheme utilizes a reagent delivery system based on printing and informatics technologies to implement the spatial patterns used for identification and localization of the biological materials. For example, the patterns found in the encoding scheme may be created using ink jet printing technology to provide reagents at specific locations on one or more substrate surfaces. The desired patterns are set out in specific coding patterns on the substrate surface.

[00102] In certain aspects of the invention, the binding agents are immobilized directly to the substrate surface, and the location of the binding agents is known or determined prior to use of the substrate surface in the assay system. In another aspect, the binding agents are immobilized onto beads or other separate structural elements that are then provided in known locations on the substrate

surface. In yet another aspect, the binding agents may be provided in or on features of the substrate surface, e.g., provided in wells or channels.

[00103] In specific aspects of the invention, the binding agents are nucleic acids immobilized directly or indirectly to the substrate surface, e.g., directly through the use of amino groups on the substrate surface or indirectly through the use of a linker. The location of the nucleic acid sequences is known or determined prior to use of the substrate surface in the assay system. In another specific aspect, the nucleic acids may be immobilized directly or indirectly onto beads that are then provided in known locations on the substrate surface. In yet another aspect, the nucleic acids may be provided in or on features of the substrate surface, e.g., provided in wells.

[00104] In these aspects involving nucleic acid agents, any methods of sequence determination can be used, e.g., sequencing, hybridization and the like. In a preferred aspect, nucleic acid sequencing, and preferably next-generation sequencing, is used to decode the spatial encoding scheme in the assay system of the invention. This provides a very wide dynamic range for very large numbers of assays, allowing for efficient multiplexing.

[00105] In some aspects, the assay utilizes two or more oligonucleotides, the oligonucleotides comprising a universal primer region and a region that correlates specifically to a single spatial pattern within the spatial encoding scheme. In a specific aspect, the assay comprises two allele specific oligonucleotides and one locus specific oligonucleotides. These oligonucleotides allow the identification of specific SNPs, indels or mutations within an allele. This is useful in the identification of genetic changes in somatic cells, genotyping of tissues, and the like.

[00106] In other specific aspects of the invention, the binding agents are peptides. In one aspect, these peptides are associated directly or indirectly to known locations on a substrate surface, e.g., using binding protein pairs or through oligonucleotide linkers complementary to oligonucleotides on the substrate surface. In another aspect, the binding agents are peptides are immobilized directly or indirectly onto beads or other separate structural elements that are then provided in known locations on the substrate surface. In yet another aspect, the peptides may be provided in or on features of the substrate surface, e.g., provided in wells.

[00107] In yet other specific aspects of the invention, the binding agents are chemical entities (e.g., small molecules) that are coded, e.g. using sequence tags or mass spectroscopy tags as coding identifiers. In one aspect, these chemical entities can be are immobilized directly to the substrate surface. In another aspect, the binding agents are immobilized onto beads or other separate structural elements that are then provided in known locations on the substrate surface. In yet another aspect, the binding agents may be provided in or on features of the substrate surface, e.g., provided in wells.

[00108] The assay system of the invention can utilize various detection mechanisms, based

on the molecules to be detected and the reagents needed for such detection system. Exemplary methods that can be used with the assay systems of the invention are described in more detail below.

[00109] The Invention in General

[00110] The assay system and methods of the invention are based on relational methods that allow extraction of data to detect the presence or absence and relative amount of a biological molecule, and the location of this molecule in a sample having a distinct structure, *e.g.,* a tissue section or other biological structure with distinct locations of specific biological molecules. The encoding scheme used in these systems corresponds to the structural elements of the sample, and the information obtained using a two-dimensional coding system is indicative of the spatial addresses of these molecules in a sample of interest.

[00111] Integral to the assay system of the invention is a method for spatial patterning of reagents. Technologies for formulating and delivering both biological molecules *(e.g.* DNA or antibodies) and chemical reagents *(e.g.,* small molecules or dNTPs) have already been demonstrated, and use of these systems will be available to one skilled in the art and easily adaptable upon reading this specification.

[00112] The assay design of the invention provides an accurate and easily scalable spatial encoding system. The ability to deliver reagents in a spatially defined pattern together with software, reagents and protocols comprises a novel and highly innovative assay system for spatial analysis of various biological molecules and activities. This allows the assays to measure numerous biological functions in a meaningful spatial environment, including functions such as gene expression and peptide localization. The systems provide the potential to open a new analytical window into the complex spatial patterns of cellular function and regulation in biological systems.

[00113] The biological molecules to be detected can be any biological molecules such as proteins, nucleic acids, lipids, carbohydrates, ions, or multicomponent complexes containing any of the above. Further examples of subcellular objects include organelles, *e.g.,* mitochondria, Golgi apparatus,

endoplasmic reticulum, chloroplast, endocytic vesicle, exocytic vesicles, vacuole, lysosome, etc.

[00114] Fig. 1 illustrates such a target-specific assay system for identification of nucleic acid sequences in a sample. In this system 101, two reagents 120, 122 that specifically bind to a biological molecule of interest are associated with coding identifiers 106, 108 that encode for a spatial location in the sample. These coding identifiers 106, 108 are optionally associated with sites that assist in their identification in the assay format, *e.g.,* universal priming sites 104, 110 for amplification of the assay products or adapters to enable identification of the coding identifiers and the binding agents using sequencing technologies. The sample that is tested, here shown as a tissue section 116 is encoded using the combination of the patterns 112, 114 created using the separate coding identifiers 106, 108 which provide a two dimensional code 118 that shows the location of any positive detection of the biological molecule 102 as well as quantifying the biological molecule 102 at each location assayed in the tissue.

[00115] The assay systems of the invention are particularly advantageous in that they are compatible with numerous samples types, such as fresh samples, such as primary tissue sections, and preserved samples including but not limited to frozen samples and paraformalin-fixed, paraffin-embedded (FFPE) samples. An important aspect of the assay systems of the invention is that the binding agents are immobilized on a substrate surface in discrete, independently measureable areas. These discrete areas can be formed by spatially selective deposition of the binding agents on the substrate surface. Numerous methods can be used for the deposition of the agent and the coding identifiers associates with the agent. For example, the coding identifiers can be delivered together or separately from the agent. If delivered together they can be attached *(e.g.,* synthesized as a single molecule or attached through ligation or a chemical coupling mechanism) or simply mixed together to be attached after delivery to the substrate. In a preferred aspect, the agent and the coding identifier are made separately, mixed together for attachment, and delivered either attached or as a mixture to be attached on the surface. In a specific aspect the binding agents are delivered generally over the substrate surface

and the coding identifiers are delivered in a pattern-specific manner.

[00116] Examples of methods that can be used for deposition of agents and/or coding identifiers onto the substrate surface include, but are not limited to, ink jet spotting, mechanical spotting by means of pin, pen or capillary, micro contact printing, fluidically contacting the measurement areas with the biological or biochemical or synthetic recognition elements upon their supply in parallel or crossed micro channels, upon exposure to pressure differences or to electric or electromagnetic potentials, and photochemical or photolithographic immobilization methods.

[00117] For several applications, it may be preferred to arrange the substrates into segments of one or more measurement areas for reagent distribution and agent determination. These regions may be physically separated using barriers or channels. They may still comprise several additional discrete measurement areas with agents that are different or in different combination from each other.

[00118] In certain aspects, the present invention provides a method, *e.g.,* a machine-based method, for evaluating changes in the presence and/or location of a biological molecule over time. The method includes providing a plurality of encoded array results representative of the biological molecule over time and evaluating the differences in detection and/or localization of the biological molecules.

Nucleic Acid Detection and Localization

[00119] In a particular aspect, the assay system is used to analyze nucleic acids, *e.g* genotyping, gene expression analysis, localization of particular transcripts within samples, and the like.

[00120] Genotyping may be performed using any technique known to those of skill in the art. Preferred techniques permit rapid, accurate determination of multiple variations with a minimum of sample handling. Some examples of suitable techniques involve but are not limited to direct DNA sequencing, capillary electrophoresis, hybridization, allele-specific probes or primers, single-strand conformation polymorphism analysis, nucleic acid arrays, bead arrays, restriction fragment length

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polymorphism analysis, cleavage fragment length polymorphism analysis, random amplified polymorphic DNA, ligase detection reaction, heteroduplex or fragment analysis, differential sequencing with mass spectrometry, atomic force microscopy, pyrosequencing, FRET *(e.g.,* TaqMan (Applied Biosystems, Inc., Foster City, Calif.) and Molecular Beacon (Stratagene, La Jolla, Calif.) assays), and other related techniques. Several methods for DNA sequencing are well known and generally available in the art. See, for example, Sambrook, et al., Molecular Cloning: A Laboratory Manual (Cold Spring Harbor Laboratory, New York) (2001); Ausubel, et al., Current Protocols in Molecular Biology (John Wiley and Sons, New York) (1997), Twyman, et al. (2003) "Techniques Patents for SNP Genotyping", Pharmacogenomics 4(1):67-79; and Kristensen, et al. (2001) "High-Throughput Methods for Detection of Genetic Variation", BioTechniques 30(2):318-332. For details on the use of nucleic acid arrays (DNA chips) for the detection of, for example, SNPs, see U.S. Pat. No. 6,300,063 issued to Lipshultz, et al., and U.S. Pat. No. 5,837,832 to Chee, et al., HuSNP Mapping Assay, reagent kit and user manual, Affymetrix Part No. 90094 (Affymetrix, Santa Clara, Calif.). The molecular inversion probe (MIP) assay format (Hardenbol et al., 2003) is another example of a highly multiplexable assay that may be used with the assay systems of the invention.

[00121] In one exemplary and preferred method for analyzing nucleic acids using the assay system of the invention, the detection of nucleic acids uses two allele- specific oligonucleotides and a locus specific oligonucleotide. The assay methods are carried out according to the strategy outlined in Fig. 2 using next-generation sequencing or another highly parallel nucleic acid assay technology. In this assay, a set of two oligonucleotides is designed to hybridize to each target sequence, with a common oligonucleotide and two unique coding identifiers. The allele can be determined, *e,g,* by primer extension of the locus specific oligonucleotide. Following primer extension and ligation, an amplifiable template is formed with universal primer sequences at either end. Assay oligonucleotides are annealed to a template and enzymatic reactions are used to join the two oligonucleotides only when both are correctly annealed. The detection techniques and read out parameters used in this

system of the invention include a much shorter tag than the oligonucleotides used in the assays that are based on capture by hybridization. These shorter tags are designed to be read out by sequencing or, preferably, used to ligate codes onto both ends of the fragment as illustrated in Fig. 2.

[00122] In Figure 2, two target-specific assay oligonucleotides are ligated together 202 following *in situ* hybridization to target sequences. At the same time, encoding oligonucleotides containing tag sequence sets X and Y are ligated 204 to the target specific oligonucleotides. Oligonucleotides containing X ligate specifically to one side of the targeting construct and oligonucleotides containing Y ligate to the other. The oligonucleotides contain universal primer sites Pl and P2. Following ligation, the constructs are eluted and, optionally, sequencing adapters can be attached 206, *e.g.,* via PCR.

[00123] In one preferred aspect, the final construct created from the assay method is a substrate for next-generation sequencing, and highly parallel next-generation sequencing methods are used to confirm the sequence of constructs. Such sequencing methods can be carried out, for example, using a one pass sequencing method or using paired-end sequencing. Next generation sequencing methods include, but are not limited to, hybridization-based methods, such as disclosed in Drmanac, U.S. Pat. Nos. 6,864,052; 6,309,824; and 6,401,267; and Drmanac et al, U.S. patent publication 2005/0191656, and sequencing by synthesis methods, *e.g.,* Nyren et al, U.S. Pat. No. 6,210,891; Ronaghi, U.S. Pat. No. 6,828,100; Ronaghi et al (1998), Science, 281: 363-365; Balasubramanian, U.S. Pat. No. 6,833,246; Quake, U.S. Pat. No. 6,911,345; Li et al, Proc. Natl. Acad. Sci., 100: 414-419 (2003); Smith et al, PCT publication WO 2006/074351; use of reversible extension terminators, *e.g.,* Turner, U.S. Pat. No. 6,833,246 and Turner, U.S. Pat. No. 6,833,246 and ligation-based methods, *e.g.,* Shendure et al (2005), Science, 309: 1728-1739, Macevicz, U.S. Pat. No. 6,306,597; which references are incorporated by reference. Soddart et al., PNAS U S A. 2009 Apr 20; Xiao et al., Nat Methods. 2009 Mar;6(3):199-201. Epub 2009 Feb 8.

[00124] To maximize the efficiency of encoding, a combinatorial approach using pairs of oligonucleotides can be used. For example, with only two sets of 100 codes, a substrate can theoretically encode up to 10,000 locations. The number of assay oligonucleotides required is dramatically reduced, the cost decreased, and the robustness of the approach increased by decoupling the coding sequences from the genome-specific sequences. Alternative assay formats can also be used (e.g. ligation or primer extension followed by ligation).

[00125] By ligating the codes on separately, only 2n target-specific assay oligonucleotides are needed for n targets. For example, assaying 100 different targets at 10,000 spatial locations would require 2 x 100 targeting oligonucleotides and 2 x 100 encoding oligonucleotides, using a combinatorial approach outlined in Fig. 2. The total count of assay oligonucleotides would be only 400 (200 target- specific and 200 encoding), not counting universal primers. In contrast, if the coding oligonucleotides were not decoupled, (n x X positional codes) + (n x Y positional codes) would be needed, or in the above example, 20,000 oligonucleotides, not counting universal primer sequences.

[00126] Due to the matrix system of the invention, a large amount of information can be obtained even using five or more positions interrogated for five or more biological molecules. By varying one or the other of these, large amounts of information can be obtained, both in terms of locations and/or specific biological In specific aspects, multiple locations are interrogated for two or more biological molecules. As an example, for each datapoint ~1,000 reads may be sampled, for a total of -10E9 reads for 10E6 datapoints.

Peptide Detection Systems

[00127] The assay system of the invention can be used to analyze biological molecules using peptide agents that are associated with the substrate surface in a spatial pattern. Such peptides may comprise an active region of an enzyme, a binding domain of an immunoglobulin, defined domains of proteins, whole proteins, synthetic peptides, peptides with introduced mutations, etc.

[00128] The assay system of the invention allows the identification and spatial location of various forms of peptides, including isoforms and peptides that have undergone posttranslational modification. Importantly, certain aspects of the invention allow the identification of active versus non-active forms of such peptides in a sample. This allows the identification of the presence or absence of specific peptide isoforms, and also acts as a proxy for identification of peptide activity in a sample.

[00129] In certain aspects of the invention, the binding agents associated with the substrate surfaces of the assay system include substrates for enzymes or proenzymes, *e.g.,* a kinase, a phosphatase, a zymogen, a protease, or a fragment thereof. In certain aspects, the binding agents associated with the substrate surfaces are phosphorylation substrates used to detect proteins involved with one or more signal transduction pathways, *e.g.,* a kinase or a phosphatase. In another specific aspect of the invention, the binding agents are specific protease substrates that associate only with individual or classes of proteases. In other aspects, the binding agents on the substrate surface are different processed forms, isoforms and/or domains of an enzyme.

Reagent Delivery

[00130] The reagent delivery system of the invention can be any system that allows the delivery of reagents to discrete portions of the array in order to keep the integrity of the defined spatial patterns of the encoding scheme. Such discrete delivery can be achieved in a number of different ways.

[00131] In one exemplary aspect, the reagent delivery system can be a flow-based system. The flow-based systems for reagent delivery in the present invention can include one or more pumps, valves, fluid reservoirs, channels, and/or reagent storage cells. Such a reagent delivery system is configured to move fluid in contact with a discrete section of the substrate surface. Movement of the reagents can be driven through a fluid by a pump disposed, for example, downstream of the fluid reagents. The pump can drive each fluid reagent to (and past) the reaction compartment. Alternatively, the reagents

may be driven through the fluid by gravity.

[00132] US Appln Nos. 20070166725 and 20050239192 disclose certain general- purpose fluidics tools that can be used with the assay systems of the invention. These allow the precise manipulation of gases, liquids and solids to accomplish very complex analytical manipulations with relatively simple hardware.

[00133] In a more specific example, one or more flow-cells can be attached to the substrate from above. The flow-cell can include inlet and outlet tubes connected thereto and optionally an external pump can be used to deliver the sample or reagents to the flow-cell and across the substrate. The flow cell is configured to deliver reagents only to certain portions of the array, restricting the amount and type of reagent delivered to any specific section of the array.

[00134] In another aspect, a microfluidic system can be integrated into the substrate or externally attached on top of the substrate. Microfluidic passages for holding and carrying fluid can be formed on and/or above the planar substrate by a fluidics layer abutted to the substrate. Fluid reagents can be selected according to selective opening and closing of valves disposed between reagent reservoirs.

[00135] Pumps generally include any mechanism for moving fluid and/or reagents disposed in fluid. In some examples, the pump can be configured to move fluid and/or reagents through passages with small volumes (i.e., microfluidic structures). The pump can operate mechanically by exerting a positive or negative pressure on fluid and/or on a structure carrying fluid, electrically by appropriate application of an electric field(s), or both, among others. Exemplary mechanical pumps may include syringe pumps, peristaltic pumps, rotary pumps, pressurized gas, pipettors, etc. The mechanical pumps may be micromachined, molded, etc. Exemplary electrical pumps can include electrodes and may operate by electrophoresis, electroendoosmosis, electrocapillarity, dielectrophoresis (including traveling wave forms thereof), and/or the like.

[00136] Valves generally include any mechanism for regulating the passage of fluid through a

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channel. The valves can include, for example, deformable members that can be selectively deformed to partially or completely close a channel, a movable projection that can be selectively extended into the channel to partially or completely block the channel, an electrocapillary structure, and/or the like.

[00137] In yet another aspect, an open gasket can be attached to the top of the substrate and the sample and reagents can be injected into the gasket. Suitable gasket materials include, but are not limited to, neoprene, nitrile, and silicone rubber. Alternatively, a watertight reaction chamber formed by a gasket sandwiched between the substrate and a chemically inert, water resistant material such as, but not limited to, black-anodized aluminum, thermoplastics (e.g., polystyrene, polycarbonate, etc), glass, etc.

[00138] In a specific aspect of the present invention, the delivery system can compnse a microcircuit arrangement including an imager, such as a CCD or IGFET-based (e.g., CMOS-based) imager and an ultrasonic sprayer for reagent delivery such as described in US Appln No. 20090197326, which is incorporated herein by reference.

[00139] In yet another aspect of the invention, the reagent delivery system controls the delivery of reagents to specific patterns on a substrate surface using semiconductor techniques such as masking and spraying. Specific areas of a substrate surface can be protected from exposure to reagents through use of a mask to protect specific areas from exposure. The reagents may be introduced to the substrate using conventional techniques such as spraying or fluid flow. The use of the masked substrate delivery results in a patterned delivery scheme on the substrate surface.

[00140] In a preferred aspect of the invention, the reagent delivery instrumentation is based on inkjet printing technology. There are a variety of different ink-jetting mechanisms *(e.g.,* thermal, piezoelectric) and compatibility has been shown with aqueous and organic ink formulations. Sets of independently actuated nozzles can be used to deliver multiple reagents at the same time, and very high resolutions can be achieved.

Software for use in the Assay System

[00141] In order to target specific sites of interest, an informative image of the biological section to be analyzed can be used to assist in the reagent delivery methods and associated encoding scheme. Sample regions can be identified using image processing (*e.g.*, images of cell types differentiated by immunohistochemistry or other staining chemistries) integrated with the other features of the assay system. In some aspects, software is used to automatically translate this information into a reagent delivery pattern. A mechanism to register and align very precisely the biological sample in a targeting system is thus a preferred component of the assay systems of the invention. Mechanisms such as the use of fiducial markers on slides and other very accurate physical positioning systems can be adapted to this purpose.

[00142] Additional software components will also be key components that will be part of a complete assay system. The invention thus preferably comprises a complete suite of software tailored to the assay system. Optionally, oligonucleotide design software will be customized for the specific assay to be run, and may be integrated as a part of the system. Also optionally, algorithms and software for data analysis may be integrated to assist in determination of results of the assays. This can be especially useful, as the type of dataset that will be generated will be novel, particularly as a consequence of scale. The ability to provide algorithms and software tools that are specifically designed for analysis of spatially-associated data for significant patterns, including pattern-analysis software and visualization tools, is a novel feature that will enhance the value of the data generated by the assay systems.

[00143] In certain aspects, the assay system will comprise processes for making and carrying out quality control of reagents, *e.g.*, the integrity and sequence fidelity of oligonucleotide pools. In particular, reagents will need to be formulated for compatibility with the reagent delivery instrumentation. Factors such as volatility, stability at key temperatures, and chemical compatibility

can be optimized by those skilled in the art upon reading the present disclosure.

Applications of Assay System

[00144] It will be apparent to one skilled in the art upon reading the present disclosure that there are numerous very important areas of biological research, diagnostics, and drug development that will benefit from a high throughput means to simultaneously measure the presence or absence and spatial location of a biological molecule in a sample. For example, this technology combining the ability to analyze semi-quantitatively the expression of many different genes with the ability to image the spatial organization of expression across many cells in a tissue is enabling for many different areas of basic research. The following are exemplary uses and are by no means meant to be limiting in scope.

[00145] In one example, 3-dimensional patterns of expression can be determined by analyzing a series of tissue sections, in a manner analogous to image reconstruction in CT scanning. This can be used to measure changes in gene expression in disease pathology, *e.g.,* in cancerous tissue and/or a tissue upon injury, inflammation or infection. With the assay systems of the invention, more detailed information on gene expression and protein localization in complex tissues can be obtained. This may lead to new insights into the function and regulation both in normal and diseased states, and is likely to provide new hypotheses that can be tested. For example, a system of the invention may enable some of the insights gained from many individual studies and larger programs like ENCODE (Birney et al., 2007) and modENCODE to be integrated at the tissue level. The assay systems will also aid in computational efforts to model interacting networks of gene expression in the field of systems biology.

[00146] The assay systems also provide a novel approach that enables the analysis of somatic variation, *e.g.,* somatic mutations in cancer or variability in response to infectious organisms. For example, tumors are typically highly heterogeneous, containing cancer cells as well as genetically normal cells in an abnormal local environment. Cancer cells undergo mutation and selection, and in this process it is not unusual for local clones to develop. Identifying relatively rare somatic mutations

in the context of tumors may enable the study of the role of key mutations in the selection of clonal variants. Transcriptional patterns associated with angiogenesis, inflammation, or other cancer related processes in both cancer and genetically normal cells can be analyzed for insights into cancer biology and assist in the development of new therapeutic agents for the treatment of cancers.

[00147] In another example, different people have varying susceptibility to infectious organisms, and much of this may be to underlying genetic differences in individuals and/or populations. Identifying these differences will aid in an understanding of the underlying disease pathologies and assist in the development of vaccines or therapeutics to prevent or ameliorate these disease states.

[00148] Importantly, in addition to providing spatially associated information, the technology of the invention will allow a great increase in the sensitivity of detecting rare mutations. The reason is that signal to noise can be dramatically increased because the approach of the invention assays a small location in any given reaction. In a typical assay for rare mutations in a mixed sample, the sample is treated in bulk, i.e. nucleic acids are extracted from many cells into a single pool. Thus, if a mutation is present in 1 cell in 10,000, it must be detected against a background of normal DNA from ~10,000 cells. In contrast, with the systems of the invention many cells can be analyzed, but individual cells or small groups of cells would be identified by the spatial coding system. Therefore, the background can be reduced by orders of magnitude, greatly increasing sensitivity. Furthermore, the spatial organization of mutant cells can be observed. This may be particularly important in detecting key mutations in tissue sections in cancer. Already, molecular histological analyses are yielding insights into cancer biology and may have potential for use in diagnostics (Choe et al., 2003). The technology of the invention promises to greatly increase the power of such approaches.

EXAMPLES

[00149] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventor regards as his invention, nor are they intended to

represent or imply that the experiments below are all of or the only experiments performed. It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

[00150] Efforts have been made to ensure accuracy with respect to numbers used *(e.g.,* amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees centigrade, and pressure is at or near atmospheric.

EXAMPLE 1: Initial Proof of Concept of Encoding Scheme

[00151] As an initial proof of concept, a model system is developed using a microarray to demonstrate a working single-plex assay. The basic design validates the concept of the assay, and establishes a working assay prior to addressing issues related to the analysis of a more complicated biological sample. Conventional sequencing is used as a readout for this proof of concept.

[00152] A microarray is used as a proxy for a tissue section. The target sequences of the microarray are fully specified, so that the composition of the targets are known and can be varied systematically. Synthetic oligonucleotide templates are attached to a glass slide via a 5' amino modification. Each slide has a single oligonucleotide template sequence, and the assays that are carried out may employ either ligation, or extension followed by ligation as this may be useful in determining certain polymorphisms.

[00153] Once the *in situ* part of the assay is complete, the reaction products are eluted and analyzed by qPCR to determined presence or absence of a product and estimate yield, and by conventional sequencing to determine the structure of the assay products. The single plex assays that are tested include appropriate positive and negative controls, and a single nucleotide variant (SNV) to check ability to discriminate single base variants.

EXAMPLE 2: Scalability

[00154] The complexity of the assay system is increased to establish scalability of the assay for use in high throughput studies. Scalability of both the spatial encoding and assay systems is demonstrated by carrying out a 24-plex x 24-site assay using a microarray model system.

[00155] The amount of biological target, here a DNA target sequence, at each assay location is systematically varied on microarray substrate. For example, in a microarray with 50 micron spot size (center to center), a 1 mm^2 area contains ~400 spots. The region around each site is optionally occupied by a region that is devoid of these spots to allow individual resolvability of the target

sequences. Alternatively, the spots may be clustered, with two or more directly adjacent spots surrounded by or adjacent to a region that is devoid of target sequences.

[00156] In order to demonstrate that spatial encoding is accurate, the sites comprise different target compositions to show that the assay readout matches the expected composition of each site. With 24 target sequences, a simple digital pattern is made with each site having a different set of 12 targets present and 12 targets absent, to make a binary code (0= absent, 1=present). The assay readout is then determined to show that the detected regions match the expected signal after spatial decoding. In this particular example, the code space is large enough (2^{24}) so that even a few errors would not result in different codes being mixed up. Moreover, this design allows identification of errors and allows an estimation not only of accuracy of spatial encoding but also of accuracy calling the presence or absence of target sequences.

In an exemplary aspect, a 4 x 4 arrangement of 16 sequences is used for the array configuration. A white square indicates that the sequence is absent and a black square that it is present, i.e. 8 of the 16 possible sequences are present in this sample. In a different sample, a different pattern of absent and present sequences can be constructed. In this way, unique patterns are associated with spatial locations so that the accuracy of spatial encoding can be measured.

[00157] The ability to detect quantitative differences is evaluated by generating dose-response curves for each of the 24 assays that are carried out at each site in a 24-site assay. This allows estimation of the limit of detection, dynamic range, and power to detect a given fold-change across the range.

[00158] In one aspect, a latin square design is used to represent individual targets at different ratios by varying the number of features for each target. In other words, with multiple spots in a site, the number of spots allocated to each of the 24 target sequences can be varied and each of the 24 sites can have a different composition. A 1 x 3 inch microarray is sufficiently large to permit multiple replicates. This larger set of 24 sequences will require deconvolution, and this is accomplished using high throughput techniques such as next-generation sequencing technologies *(e.g.,* SOLiD™ technology (Life Technologies, Inc., Carlsbad, CA) or Genome Analyzer (Illumina, Inc., San Diego, CA)). The use of the 24-plex assay demonstrates both the accuracy of spatial encoding and decoding, and the quantitative response of the assay system.

EXAMPLE 3: Adaptation of the assay to preserved samples.

[00159] Genomic DNA is assayed as a proof of concept for assaying RNA, as it provides a way to establish a single-copy reference signal. Once a working assay is developed for FFPE samples, it is adapted to an RNA assay. To this end, assay oligonucleotide concentrations are assayed to ensure

compatibility with high multiplexing. Assuming a cell diameter of 10 microns, and delivery of a 10 micron diameter reagent droplet to an individual cell, the volume of the droplet will be ~500 µl and can contain ~3 x 10^{11} molecules at a 1 µM concentration. To assay 1,000 target sequences in 10,000 cells, ~2,000 targeting oligonucleotides would be required in a droplet. Therefore, each droplet could contain ~160 million copies of each assay oligo, a vast excess over the few thousand target sequences in a cell.

[00160] The handling of small absolute numbers of product molecules generated from very small or compromised samples are enhanced to counter the issue of low recovery efficiency; that is, elution is efficient and losses resulting from adsorption of molecules to surfaces are prevented. An approach to addressing the latter issue is to include a carrier material, such as glycogen or carrier nucleic acids.

Example 4: Adapting the Assay to a Biological Sample.

[00161] A control RNA template is immobilized to a solid support in order to create an artificial system. The assay is performed using T4 DNA ligase, which can repair nicks in DNA/RNA hybrids. Assays are carried out on matched slides, or different sections of the same slide, where in one case gDNA is assayed and in the other RNA is assayed. When assaying gDNA the slide can be pretreated with RNase, and when assaying RNA the slide is pretreated with DNase. Results of the assay are confirmed by extracting gDNA or RNA and quantitating the relative amounts by qPCR or RT-qPCR respectively.

[00162] In order make the tissue section RNA assays as informative as possible, pre-existing information on expression levels in specific tissues to target transcripts across a range of abundances are used in the assay design. Both high abundance transcripts, as well as some medium and low abundance transcripts, are targeted to enable an initial assessment of the quantitative performance characteristics of the assay.

[00163] The preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such

equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims. In the claims that follow, unless the term "means" is used, none of the features or elements recited therein should be construed as means-plus-function limitations pursuant to 35 U.S.C. §112, ¶6.

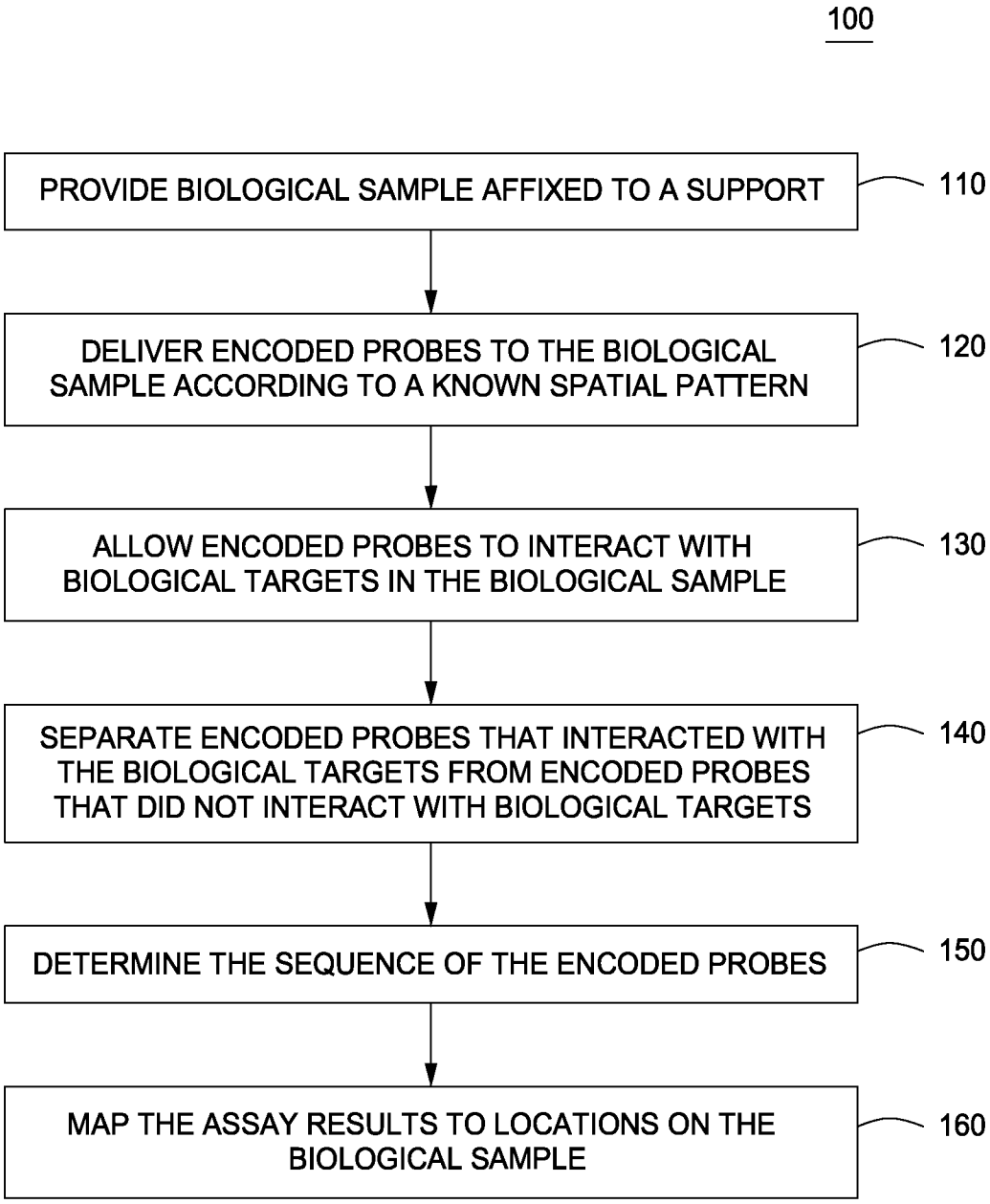

100
PROVIDE BIOLOGICAL SAMPLE AFFIXED TO A SUPPORT
110
DELIVER ENCODED PROBES TO THE BIOLOGICAL SAMPLE ACCORDING TO A KNOWN SPATIAL PATTERN
120
ALLOW ENCODED PROBES TO INTERACT WITH BIOLOGICAL TARGETS IN THE BIOLOGICAL SAMPLE
130
SEPARATE ENCODED PROBES THAT INTERACTED WITH THE BIOLOGICAL TARGETS FROM ENCODED PROBES THAT DID NOT INTERACT WITH BIOLOGICAL TARGETS
140
DETERMINE THE SEQUENCE OF THE ENCODED PROBES
150
MAP THE ASSAY RESULTS TO LOCATIONS ON THE BIOLOGICAL SAMPLE
160

FIG. 1

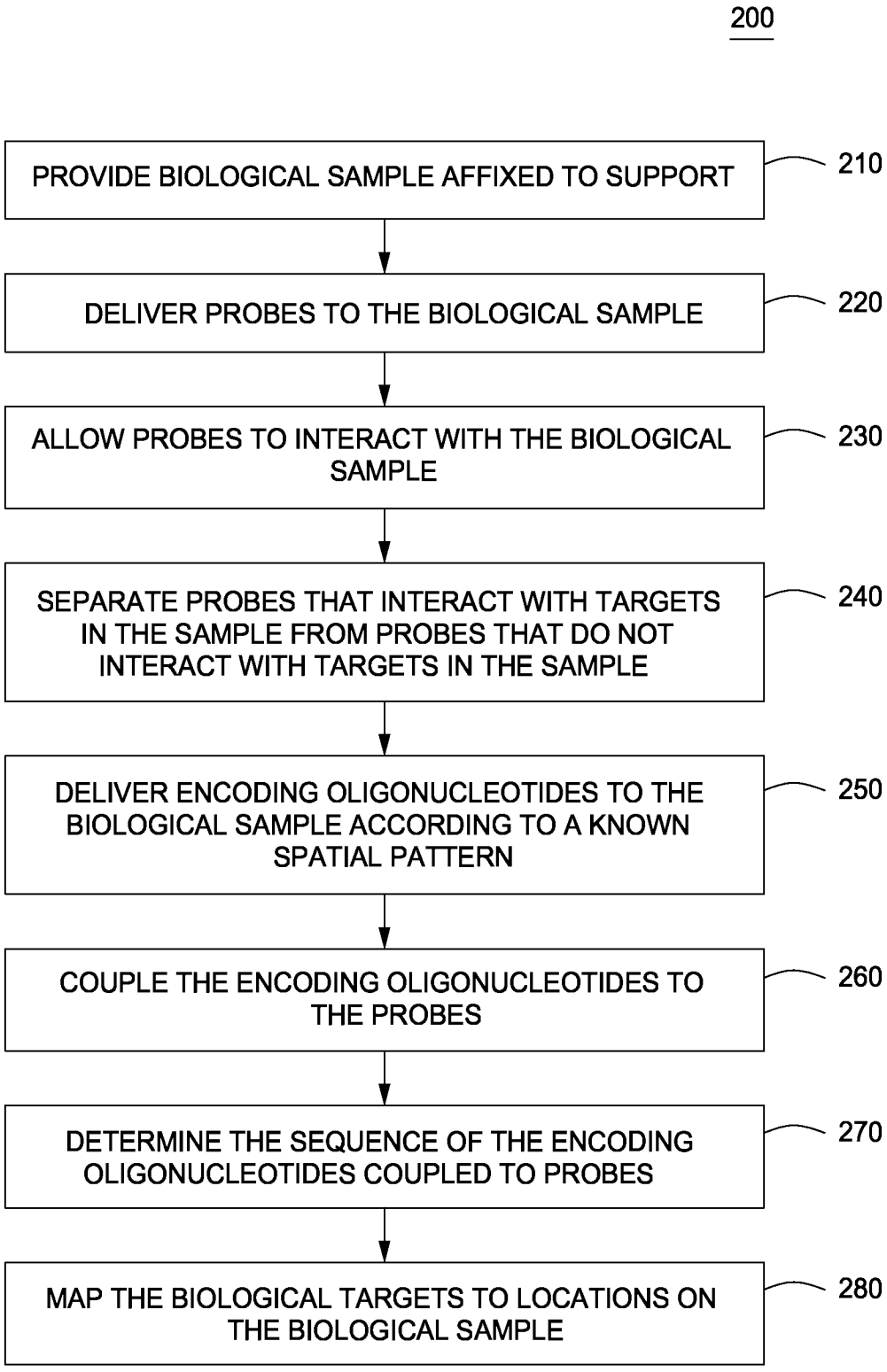

200
PROVIDE BIOLOGICAL SAMPLE AFFIXED TO SUPPORT
210
DELIVER PROBES TO THE BIOLOGICAL SAMPLE
220
ALLOW PROBES TO INTERACT WITH THE BIOLOGICAL SAMPLE
230
SEPARATE PROBES THAT INTERACT WITH TARGETS IN THE SAMPLE FROM PROBES THAT DO NOT INTERACT WITH TARGETS IN THE SAMPLE
240
DELIVER ENCODING OLIGONUCLEOTIDES TO THE BIOLOGICAL SAMPLE ACCORDING TO A KNOWN SPATIAL PATTERN
250
COUPLE THE ENCODING OLIGONUCLEOTIDES TO THE PROBES
260
DETERMINE THE SEQUENCE OF THE ENCODING OLIGONUCLEOTIDES COUPLED TO PROBES
270
MAP THE BIOLOGICAL TARGETS TO LOCATIONS ON THE BIOLOGICAL SAMPLE
280

FIG. 2

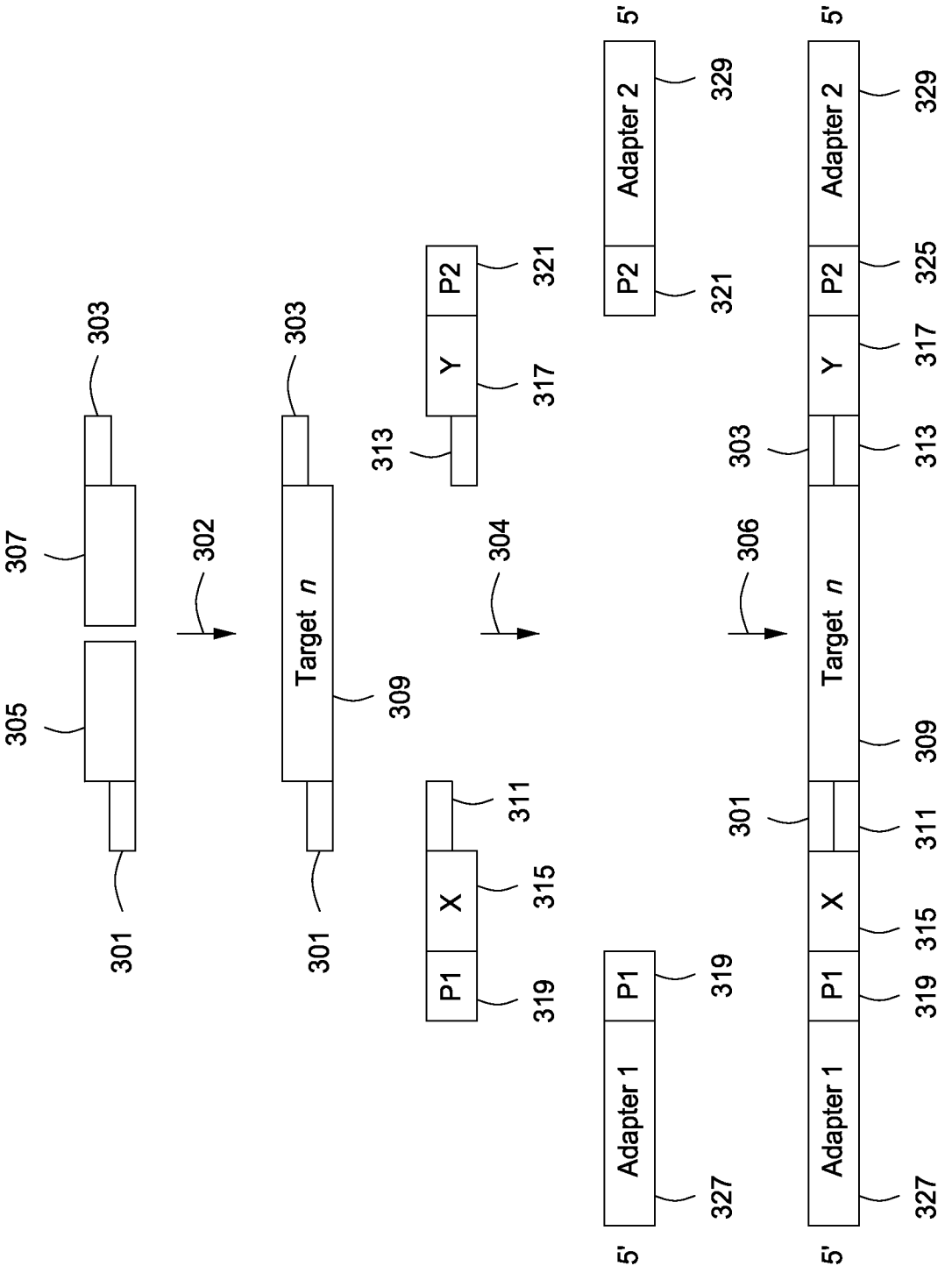

303
307
305
301
302
Target n
309
303
301
313
P2
321
Y
317
304
P1
319
X
315
311
306
5'
Adapter 2
329
P2
321
Adapter 1
327
P1
319
303
313
Y
317
P2
325
301
311
Target n
309
X
315
P1
319
Adapter 1
327
5'

FIG. 3

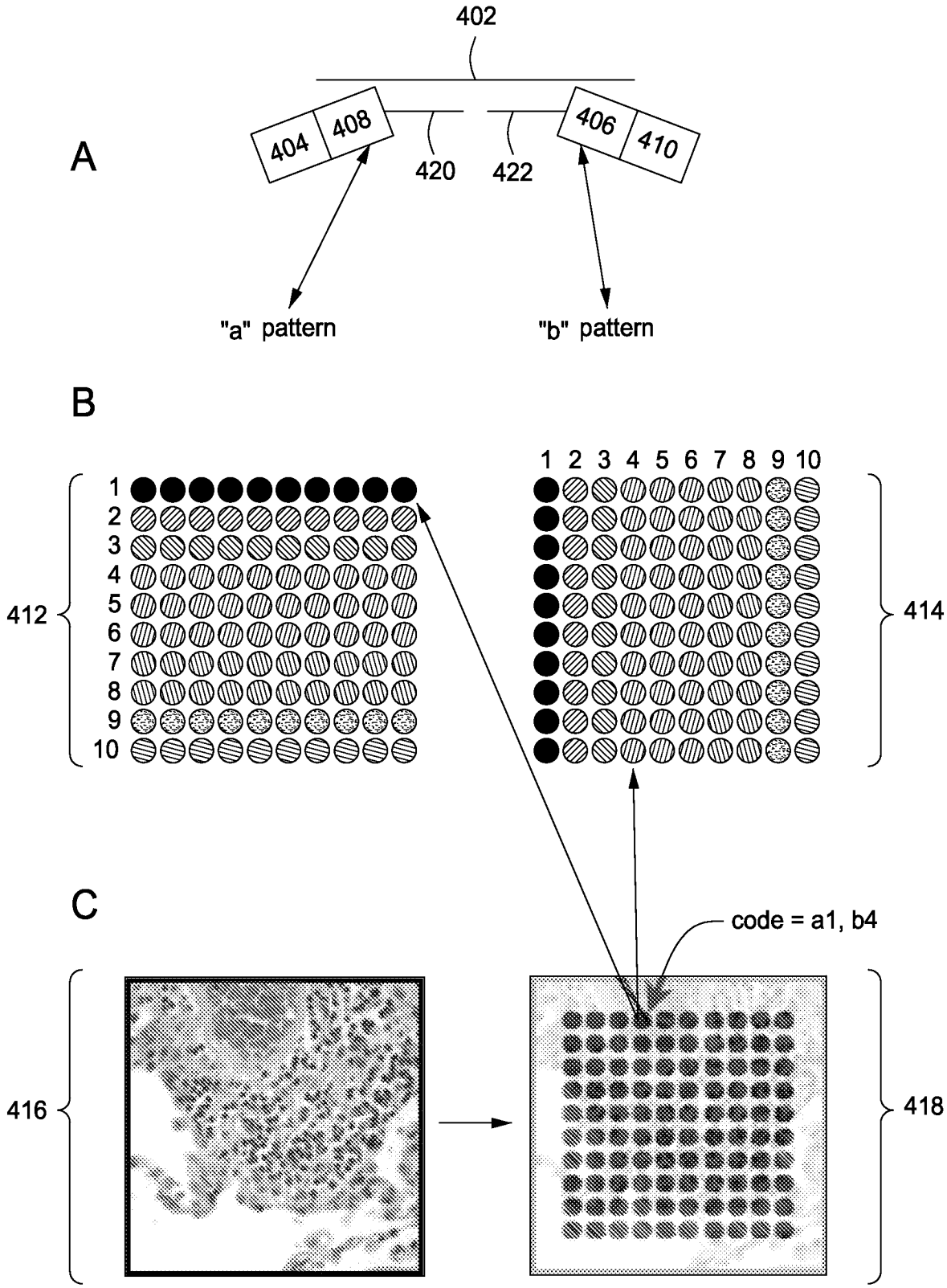

A
402
404
408
420
422
406
410
"a" pattern
"b" pattern
B
1 2 3 4 5 6 7 8 9 10
412
414
C
code = a1, b4
416
418

FIG. 4

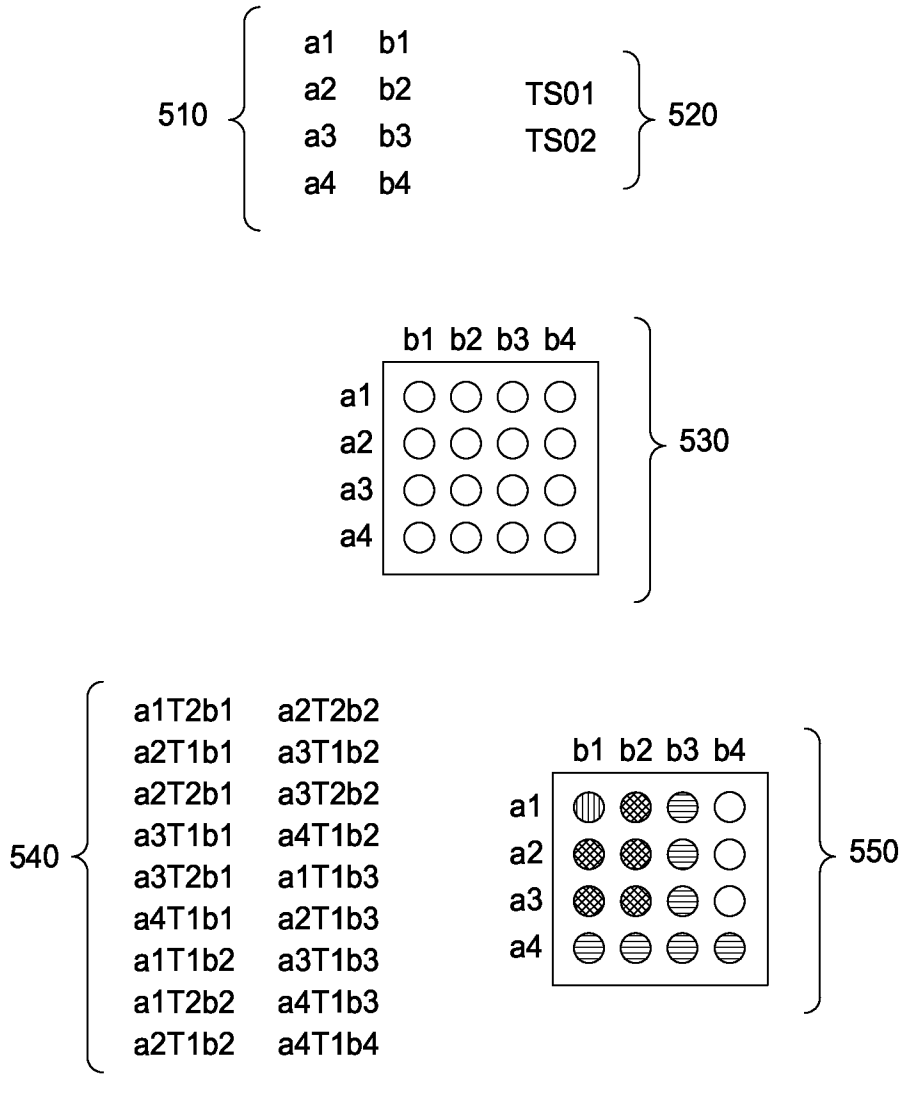

510
a1 b1
a2 b2
a3 b3
a4 b4
TS01
TS02
520
b1 b2 b3 b4
a1
a2
a3
a4
530
540
a1T2b1 a2T2b2
a2T1b1 a3T1b2
a2T2b1 a3T2b2
a3T1b1 a4T1b2
a3T2b1 a1T1b3
a4T1b1 a2T1b3
a1T1b2 a3T1b3
a1T2b2 a4T1b3
a2T1b2 a4T1b4
b1 b2 b3 b4
a1
a2
a3
a4
550

FIG. 5

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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	SPATIALLY ENCODED BIOLOGICAL ASSAYS

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 15/187,661 filed on 06/20/2016 .

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: Mark S. CHEE Date (Optional) : _____

Signature: Mark S. Chee

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.

699932000201

sd-683655

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	Unknown
Patent No.	:	9,371,598	Examiner	:	Unknown
Issue Date	:	June 21, 2016	Conf. No.	:	2142
Application No.	:	13/080,616			
Filed	:	April 5, 2011			
Title	:	SPATIALLY ENCODED BIOLOGICAL ASSAYS			

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

REVOCATION AND NEW POWER OF ATTORNEY

The undersigned for **10X Genomics, Inc.** ("10X") and **Prognosys Biosciences, Inc.**, ("Prognosys") acting on behalf of **10X** and **Prognosys**, hereby revokes all powers of attorney previously granted in the application.

By virtue of an agreement effective as of November 18, 2018 between **10X** and **Prognosys**, **10X** is authorized to direct prosecution of the above-identified patent application.

The undersigned for **10X** and **Prognosys**, acting on behalf of **10X** and **Prognosys**, hereby appoints **10X**'s attorney(s) and agent(s) at Fish & Richardson P.C. (the "Firm"), which are associated with the Customer Number provided below, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, said appointment to be to the exclusion of the inventor(s) and his/their attorney(s) and agent(s) in accordance with the provisions of 37 CFR §3.71, et seq. of the Patent Office Rules of Practice.

159367

The undersigned also direct all correspondence be addressed to that Customer Number.

PTO Customer Number: 159367

By executing this Power of Attorney, **Prognosys** is allowing the Firm to prosecute the above-referenced patent application and to prosecute any matters that may arise before the U.S. Patent & Trademark Office ("PTO") in the enforceable life of the above-referenced patent. Although this Power of Attorney states that **Prognosys** is appointing the Firm with "power of attorney" for the sole purpose of prosecuting the matters arising before the PTO in connection with the patent and patent application, that appointment is understood solely in light of

Prognosys's ownership interest in the application. So, despite the use of the phrase "power of attorney," the executed Power of Attorney does not create an attorney-client relationship between **Prognosys** and the Firm, or, for that matter, between the Firm and any other person. Moreover, communications between **Prognosys** and the Firm will not be withheld from **10X**.

10X will remain the Firm's sole client with respect to the subject application and patent. Accordingly, the Firm understands, and your signature on the Power of Attorney confirms, that the Firm has no attorney-client relationship with **Prognosys**, despite your execution of this Power of Attorney.

Each undersigned, whose title is supplied below, is empowered to act on behalf of the indicated party.

Respectfully submitted,

Date: April 12, 2019

Printed Name: Eric S. Whitaker
10X Genomics, Inc.

Title: General Counsel

Date: May 3, 2019

Printed Name: MARK CHEE
Prognosys Biosciences, Inc.

Title: CEO

Customer Number 159367
Fish & Richardson P.C.
Telephone: (612) 335-5070
Facsimile: (877) 769-7945

61850684.doc

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. Chee
Filer:	Cameron Mark Luitjens/Judith Witzel
Attorney Docket Number:	47706-0004006

Filed as Small Entity

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	75	75
UTILITY SEARCH FEE	2111	1	330	330
UTILITY EXAMINATION FEE	2311	1	380	380
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2855**

Electronic Acknowledgement Receipt

EFS ID:	36032451
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Geri O'Connor
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	16-MAY-2019
Filing Date:	
Time Stamp:	15:37:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$2855
RAM confirmation Number	051719INTEFSW00015042061050
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	Transmittal of New Application	TransLtr.pdf	109605 e7754e94e7a6d3f305a9d11b763c249845eb445e	no	2
Warnings:					
Information:					
2	TrackOne Request	Track1Req.pdf	147804 449d4882737909d6de56d462576fca1d4b67e7c9	no	2
Warnings:					
Information:					
3	Application Data Sheet	ADS.pdf	1256341 71f75661ab91e180d1b4953e961ea566d98d2f27	no	9
Warnings:					
Information:					
4		Application.pdf	334394 a2c9afed93ecbda9c6d0cb2f663819a344038188	yes	45

Multipart Description/PDF files in .zip description

Document Description	Start	End
Abstract	45	45
Claims	44	44
Specification	1	43

Warnings:					
Information:					
5	Drawings-only black and white line drawings	Drawings.pdf	714456 7a1e12837252c2bc77a8f1e7e97d0dcd0238911a	no	5

Warnings:					
Information:					
6	Oath or Declaration filed	ExecutedDeclaration.pdf	49134 8a78ea1badfc8d530956fa8eca52e1072981fe4e	no	1
Warnings:					
Information:					
7	Power of Attorney	POA_0004001.pdf	180783 48ecdc165cc53fb0e30703629fdbf2459a06c2df	no	3
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	38934 4729885aa006aa2a4f716d2a7cd87ac308d8292e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2831451		

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	Unknown
Application No.	:	16/414,213	Examiner	:	Unknown
Filed	:	May 16, 2019	Conf. No.	:	8760
Title	:	SPATIALLY ENCODED BIOLOGICAL ASSAYS			

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

INFORMATION DISCLOSURE STATEMENT

Please consider the documents listed on the disclosure form submitted with this statement. Copies of the documents are being submitted with this statement to the extent required under 37 C.F.R. § 1.98(a)(2). A copy of a communication from a foreign patent office in a counterpart application is also being submitted.

This statement is being filed within three months of the filing date of the application.

Apply any necessary charges or credits applicable under 37 C.F.R. § 1.17(p) to deposit account 06-1050, referencing the above attorney docket number.

Please contact the undersigned if there are any questions regarding this statement.

Respectfully submitted,

Date: May 23, 2019

/Cameron Luitjens/
Cameron M. Luitjens, Ph.D., J.D.
Reg. No. 58,674

Customer Number 159367
Fish & Richardson P.C.
Telephone: (612) 335-5070
Facsimile: (877) 769-7945

61930063.doc

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 47706-0004006	Application No. 16/414,213
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	1.	4,683,195	7/28/1987	Mullis			
	2.	4,883,867	11/28/1989	Lee			
	3.	5,002,882	3/26/1991	Lunnen			
	4.	5,308,751	5/3/1994	Ohkawa			
	5.	5,455,166	10/3/1995	Walker			
	6.	5,512,439	4/30/1996	Hornes			
	7.	5,512,462	4/30/1996	Cheng			
	8.	5,599,675	2/4/1997	Brenner			
	9.	5,641,658	6/24/1997	Adams			
	10.	5,750,341	5/12/1998	Macevicz			
	11.	5,763,175	6/1/1998	Brenner			
	12.	5,912,148	6/15/1999	Eggerding			
	13.	6,013,440	1/11/2000	Lipshutz			
	14.	6,130,073	10/10/2000	Eggerding			
	15.	6,143,496	11/7/2000	Brown			
	16.	6,153,389	11/28/2000	Haarer			
	17.	6,210,891	4/3/2001	Nyren			
	18.	6,210,894	4/3/2001	Brennan			
	19.	6,214,587	4/10/2001	Dattagupta			
	20.	6,258,558	7/10/2001	Szostak			
	21.	6,258,568	7/10/2001	Nyren			
	22.	6,266,459	7/24/2001	Walt			
	23.	6,281,804	8/28/2001	Haller			
	24.	6,309,824	10/30/2001	Drmanac			
	25.	6,344,316	2/5/2002	Lockhart			
	26.	6,355,431	3/12/2002	Chee			

Examiner Signature	Date Considered

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 47706-0004006	Application No. 16/414,213
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	27.	6,401,267	6/11/2002	Drmanac			
	28.	6,404,907	6/11/2002	Gilchrist			
	29.	6,416,950	7/9/2002	Lohse			
	30.	6,485,982	11/26/2002	Charlton			
	31.	6,579,695	6/17/2003	Lambalot			
	32.	6,632,641	10/14/2003	Brennan			
	33.	6,770,441	8/3/2004	Dickinson			
	34.	6,773,886	8/10/2004	Kaufman			
	35.	6,787,308	9/7/2004	Balasubramanian			
	36.	6,800,453	10/5/2004	Labaer			
	37.	6,828,100	12/7/2004	Ronaghi			
	38.	6,833,246	12/21/2004	Balasubramanian			
	39.	6,878,515	4/12/2005	Landegren			
	40.	6,897,023	5/24/2005	Fu			
	41.	6,911,345	6/28/2005	Quake			
	42.	6,969,488	11/29/2005	Bridgham			
	43.	6,969,589	11/29/2005	Patil			
	44.	6,977,033	12/20/2005	Becker			
	45.	7,052,244	5/30/2006	Fouillet			
	46.	7,057,026	6/6/2006	Barnes			
	47.	7,115,400	10/3/2006	Adessi			
	48.	7,118,883	10/10/2006	Inoue			
	49.	7,163,612	1/16/2007	Sterling			
	50.	7,211,414	5/1/2007	Hardin			
	51.	7,229,769	6/12/2007	Kozlov			
	52.	7,264,929	9/4/2007	Rothberg			

Examiner Signature	Date Considered

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 47706-0004006	Application No. 16/414,213
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	53.	7,297,518	11/20/2007	Quake			
	54.	7,315,019	1/1/2008	Turner			
	55.	7,329,492	2/12/2008	Hardin			
	56.	7,378,242	5/27/2008	Hurt			
	57.	7,393,665	7/1/2008	Brenner			
	58.	7,405,281	7/29/2008	Xu			
	59.	7,407,757	8/5/2008	Brenner			
	60.	7,537,897	5/26/2009	Brenner			
	61.	7,544,473	6/9/2009	Brennan			
	62.	7,579,153	8/25/2009	Brenner			
	63.	7,595,883	9/29/2009	El Gamal			
	64.	7,601,498	10/13/2009	Mao			
	65.	7,635,566	12/22/2009	Brenner			
	66.	7,666,612	2/23/2010	Johnsson			
	67.	7,674,752	3/9/2010	He			
	68.	7,754,429	7/13/2010	Rigatti			
	69.	7,858,321	12/28/2010	Glezer			
	70.	8,092,784	1/10/2012	Mao			
	71.	8,148,068	4/3/2012	Brenner			
	72.	8,148,518	4/3/2012	Buchanan			
	73.	8,288,103	10/16/2012	Oliphant			
	74.	8,337,851	12/25/2012	Aukerman			
	75.	8,343,500	1/1/2013	Wraith			
	76.	8,383,338	2/26/2013	Kitzman			
	77.	8,460,865	6/11/2013	Chee			
	78.	8,481,257	7/9/2013	Van Eijk			

Examiner Signature	Date Considered
EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Substitute Disclosure Form

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 47706-0004006	Application No. 16/414,213
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	79.	8,481,292	7/9/2013	Casbon			
	80.	8,586,310	11/19/2013	Mitra			
	81.	8,614,073	12/24/2013	Van Eijk			
	82.	8,685,889	4/1/2014	Van Eijk			
	83.	8,741,606	6/3/2014	Casbon			
	84.	8,778,849	7/15/2014	Bowen			
	85.	8,785,353	7/22/2014	Van Eijk			
	86.	8,815,512	8/26/2014	Van Eijk			
	87.	8,835,358	9/16/2014	Fodor			
	88.	8,865,410	10/21/2014	Shendure			
	89.	8,895,249	11/25/2014	Shen			
	90.	8,911,945	12/16/2014	Van Eijk			
	91.	8,936,912	1/20/2015	Mitra			
	92.	8,951,781	2/10/2015	Reed			
	93.	9,023,768	5/5/2015	Van Eijk			
	94.	9,062,348	6/23/2015	Van Eijk			
	95.	9,080,210	7/14/2015	Van Eijk			
	96.	9,085,798	7/21/2015	Chee			
	97.	9,121,069	9/1/2015	Lo			
	98.	9,194,001	11/24/2015	Brenner			
	99.	9,290,808	3/22/2016	Fodor			
	100.	9,290,809	3/22/2016	Fodor			
	101.	9,328,383	5/3/2016	Van Eijk			
	102.	9,334,536	5/10/2016	Van Eijk			
	103.	9,340,830	5/17/2016	Lipson			
	104.	9,371,598	6/21/2016	Chee			

Examiner Signature	Date Considered
EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Substitute Disclosure Form

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 47706-0004006	Application No. 16/414,213
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	105.	9,376,716	6/28/2016	Van Eijk			
	106.	9,376,719	6/28/2016	Van Eijk			
	107.	9,404,156	8/2/2016	Hicks			
	108.	9,447,459	9/20/2016	Van Eijk			
	109.	9,453,256	9/27/2016	Van Eijk			
	110.	9,493,820	11/15/2016	Van Eijk			
	111.	9,506,061	11/29/2016	Brown			
	112.	9,574,230	2/21/2017	Van Eijk			
	113.	9,593,365	3/14/2017	Frisen et al.			
	114.	9,657,335	5/23/2017	Van Eijk			
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Substitute Disclosure Form

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 47706-0004006	Application No. 16/414,213
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
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Substitute Disclosure Form

Electronic Acknowledgement Receipt

EFS ID:	36104687
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Kirsten Neuman
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	23-MAY-2019
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Application Type:	Utility under 35 USC 111(a)

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Electronic Acknowledgement Receipt

EFS ID:	36104754
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Kirsten Neuman
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	23-MAY-2019
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Time Stamp:	22:07:25
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	no

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46	Non Patent Literature	Burns_WellLessGel_2001.pdf	8186403 bbb12ac5052a0489294df6df0ed5bf6e3d325f49	no	8
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47	Non Patent Literature	Burton_CoverslipMountedImmersion_1998.pdf	6690451 b3289da982903272a72aebf6d5222efccb27ab6c	no	6
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48	Non Patent Literature	Carlson_FunctionAndStructure_2008.pdf	5372972 fd5c6fe83bc4bc1c6708ea1a2abb5e84da3a31ef	no	9
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49	Non Patent Literature	Carter_StabilizationOfAn_2007.pdf	6965619 32b03b5fbd32e786029f41739f0c26841bfd55af	no	7
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51	Non Patent Literature	Cha_SpecificityEfficiencyAnd_2016.pdf	5019186 72996535a064fc2387a967811f49fb6e746d6b10	no	13
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52	Non Patent Literature	Chandra_CellFreeSynthesis_2010.pdf	6534481 4c0541bac1cd0169040331e492ffd53a85bebdd2	no	14
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53	Non Patent Literature	Chatterjee_MitochondrialDNAMutations2006_flat.pdf	8494708 ab69ed732fc42fe980418761ad20bdca1d4e03e8	no	13
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54	Non Patent Literature	Chatterjee_ProteinMicroarrayOn_2008.pdf	5336621 dd7427a320987ca916c26c8bfda34b0e7a5a7194	no	5
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55	Non Patent Literature	Chen_DNAHybridizationDetection_2008.pdf	5773029 cebd684c41d55b2aaa50a9494c66215880af46cb	no	5
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56	Non Patent Literature	CHENG_SensitiveDetectionOf.pdf	3978228 85d4a8202c3b35791802f53e234b8598863fef3e	no	4
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57	Non Patent Literature	Condina_SensitiveMagneticBead_2009.pdf	5174917 e2a66b7cf58310bf7c0f536e09995f2003dd8e51	no	11
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58	Non Patent Literature	Constantine_1998.pdf	1328671 9f6cd9b34edf49c97591c89ebc82e448efbb9d5c	no	5
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59	Non Patent Literature	Copeland_MitochondrialDNAAlterations_2002.pdf	5818209 0c3a00ede3c207a3229aadbeec0a2557f5c74a72	no	13
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60	Non Patent Literature	Cujec_SelectionOfTyrosine_2002.pdf	6180803 bc3028560a12c89af03506cd21e86de2a00c5f51	no	12
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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

Electronic Acknowledgement Receipt

EFS ID:	36104820
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Kirsten Neuman
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	23-MAY-2019
Filing Date:	16-MAY-2019
Time Stamp:	22:26:58
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	Non Patent Literature	DAHL_CircleToCircle.pdf	8239270 c1e41620faf77b5f78a06d0a3b1aa33327892841	no	6

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2	Non Patent Literature	Darmanis_ProteinSeqHigh_2011.pdf	4939237 cee57e0b343a9f02d4e899594f7361bca3b536cc	no	10
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3	Non Patent Literature	DAUBENDIEK_RollingCircleRNA.pdf	4314025 b7a0e85ea92148178556ab35d87f3cd5453999f1	no	7
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4	Non Patent Literature	DEAN_ComrpehensiveHumanGenome.pdf	8573191 436028db50309f6e1f73b6ab65a37503bd36688a	no	6
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5	Non Patent Literature	Dhindsa_VirtualElectrowettingChannels_2010.pdf	3273974 2658ba07c0bc40984e745689d145c733df834508	no	6
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6	Non Patent Literature	Dressman_TransformingSIngleDNA_2003.pdf	4148180 e6372517708a70717e722a8a697af4c27008dcaf	no	6
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7	Non Patent Literature	Drmanac_AccurateSequencing_1998.pdf	909741 d972a9559604e6186f6f0b10ca444b385635170e	no	5
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9	Non Patent Literature	Duncan_AffinityChromatography_1988.pdf	1082115 3c4806a710df6b2d756de74421e4e9b69de85e44	no	5
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10	Non Patent Literature	Eberwine_AnalysisOfGene_1992.pdf	1607230 d19fe6315a71d73194a33bd455a11c17058f736a	no	5
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11	Non Patent Literature	Eberwine_AmplificationOfmRNA_1996.pdf	7309279 b7ce66c3a2488602fb6d863fd33c065998478106	no	5
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13	Non Patent Literature	Eldridge_AnInVitroSelection_2009.pdf	7360438 5b49aa716798555df26639cca7fa1c034258073e	no	8
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14	Non Patent Literature	Ellington_AntibodybasedProtein_2010.pdf	4958334 174c0bd91d9de15f13bf506107489cf1cd5a2389	no	8
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15	Non Patent Literature	AUOA_ESR_2010278710_2-11-2014.pdf	258338 0d3430d45a95c63f39442aa3003e795cf95af2ef	no	4
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18	Non Patent Literature	AUOA_2014203638_10-1-2015.pdf	199466 0d41bc2e2ae47b73b2c9cdc805c9dfad45f2b4a1	no	2
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20	Non Patent Literature	EPOEESR_11766613_1-15-2014.pdf	198468 33bcc562b6b44928ac44d376c0a6030a99bc0bab	no	4
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21	Non Patent Literature	EPOEESR_12767937_11-18-2014.pdf	342335 686feaabbc541730859545b91b38d8f0ba4e7d81	no	5
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26	Non Patent Literature	Fan_HighlyParallel_2003.pdf	7005844 3786260aedc5558600abab82138881236fd80d60	no	11
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27	Non Patent Literature	Fire_Xu_Rolling_replication_1995.pdf	1474069 309be2730d21dfc78108125e30a6d5a47525b767	no	5
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28	Non Patent Literature	Fodor_LightDirectedSpatially_1995.pdf	2341684 63ad04192aca1e78285cc4b00359af1206f5c9c2	no	7
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29	Non Patent Literature	Fredriksson_ProteinDetection_2002.pdf	3562652 94685812e972e8fc96d2849c5b08f28f2c407219	no	5
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30	Non Patent Literature	Fredriksson_MultiplexedProtein_2007.pdf	2078426 eff0bf544e9a480c22d0c577a130e3aea71fdd77	no	3
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31	Non Patent Literature	Fredriksson_MultiplexedProximityLigation_2008.pdf	4434733 58cf0869434dea5e7603126ce007a94191d4a3e7	no	8
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37	Non Patent Literature	Goldkom_Prockop_ASimple_1986.pdf	10819594 ea115a998ce5e9b7f621595375ca4f4e3b7b6333	no	21
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38	Non Patent Literature	Gunderson_DecodingRandomly_2004.pdf	8471406 4a982aab5e6b1dd295c24bd13255a81efac9a7a6	no	9
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39	Non Patent Literature	Hammond_ProfilingCellularProtein_2012.pdf	6804095 0f556ceed1f0b6372ee29952687d8e3002c59fdc	no	9
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40	Non Patent Literature	Han_3Cand_2018.pdf	977856 07b8385a6ec40ced73ad544441de6aa93f6a7ecc	no	10
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42	Non Patent Literature	He_PrintingProteinArrays_2008.pdf	3694405 4c1ea719e7126023aff5201344aaa1a42f3a456b	no	3
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43	Non Patent Literature	He_CellFreeProteinSynthesis_2008.pdf	7758277 ecdd260080fbe744ca49768d8f20596f980c3a46	no	7
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51	Non Patent Literature	Kanehisa_UseOfSttistical_1984.pdf	4852068 79632c694477c145548d55bb5e49237410cf573f	no	11
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52	Non Patent Literature	Kap_HistologicalAssessment_2011.pdf	3685251 f509d9cc64376665dc20481e1a1dd9b353cfee14	no	10
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53	Non Patent Literature	Kolb_ClickChemistry_2001.pdf	680339 46493a3f85708c4abf7f22017d426274190a1bff	no	18
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58	Non Patent Literature	Kozlov_AMethodFor_2006.pdf	6360146 e95d7f50ea13bad3deea3cb5b7c1b4a78a530462	no	7
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59	Non Patent Literature	Kurz_eDNAProteinFusion_2001.pdf	241735 041a81c4d240ca2ece3c95b3410b1f8c2455ea9f	no	7
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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

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New International Application Filed with the USPTO as a Receiving Office

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Electronic Acknowledgement Receipt

EFS ID:	36104869
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Kirsten Neuman
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	23-MAY-2019
Filing Date:	16-MAY-2019
Time Stamp:	22:47:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

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2	Non Patent Literature	Larman_AutoantigenDiscovery_2011.pdf	8273046 ef69890669747 7f5c912ffa76af6884f38d9607b	no	9
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7	Non Patent Literature	Linnarsson_RecentAdvancesIn_2010.pdf	159323 21918f5bee270d5562319c4b50d726a3ecc2efd0	no	5
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8	Non Patent Literature	Lizardi_MutationDetection_1998.pdf	8288775 3c053b314a5a7ca413f4b704214e27de48f424da	no	8
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9	Non Patent Literature	Lund_AssessmentOfMethod_1988.pdf	10770287 8bc96d868f76c60295dd682290dcb881d4c94668	no	20
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15	Non Patent Literature	MacIntyre_UnmaskingAntigens_2001.pdf	617351 d683a7bdf10ca42e1e0db06559d753103da7fba9	no	7
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21	Non Patent Literature	Mir_SequencingByCyclic_2009.pdf	2836207 28640e41e2b5db23a836e70166a27e158c5845b3	no	8
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22	Non Patent Literature	Mitsuhashi_GeneManipulation_1992.pdf	2964919 d7e312386df859a3603ee26bbad9ec99c3923abc	no	2
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23	Non Patent Literature	Mizusawa_Abacteriophage_1982.pdf	1151029 d2c152798f27ee1ff3d16a9cb15d1027e34a5596	no	6
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26	Non Patent Literature	Ng_MassivelyParallelSequencing_2010.pdf	1959154 7e71f5162a0d765d9e1e0fd14e97f192725e5ac2	no	6
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27	Non Patent Literature	Ng_MultiplexSequencingofPaired-end_2006.pdf	8111648 57f590fe4b6a81d5e60ce45aa48d52107acb1379	no	10
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28	Non Patent Literature	Niemeyer_TheDevelopments_2002.pdf	6624557 d5323ca9fdc1276b2abc540e90012cd5aba68135	no	7
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30	Non Patent Literature	Oleinikov_SelfAssemblingProte_2003x.pdf	3763536 cf521b529742f12ac505946e518cca479250aefb	no	7
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32	Non Patent Literature	OShannessy_DetectionAndQuantitation_1995.pdf	7417488 4cca57e5376e1b8c9902aab5484c8798c6c392c2	no	6
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34	Non Patent Literature	PCTIPRP_pctUS1044134_1-31-2012.pdf	690458 774f165a767ef67ef7f7af6fbc68b601ea10d38e	no	20
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36	Non Patent Literature	PCTIPRP_pctUS11031163_10-9-2012.pdf	417793 0c2495ff20f2e2357a447a755b6c3701458ce992	no	7
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38	Non Patent Literature	PCTIPRP_pctUS1232759_10-8-2013.pdf	1138171 fce580341b39abe8f98506295f1e7d2982ed0758	no	17
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39	Non Patent Literature	PCTISRWO_pctUS1429691_8-19-2014.pdf	1136572 1b20d2e9aaec4246795a5830437ea9fe78448e0d	no	10
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44	Non Patent Literature	PCTISRWO_pctUS1059327_3-29-2011_2.pdf	681150 2b8f6803df5af4527474f508e9a46d286b677fa9	no	10
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49	Non Patent Literature	Perler_InterveningSequencesinanArchaea_1992.pdf	3967779 99ec57b9e5908bb36aa5b75e4b75a208daab02ac	no	5
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50	Non Patent Literature	Petterson_GenerationsofSequencingTechnologies_2008.pdf	1306242 bfdcdb931c8d5aa85fbdbb02a357cf6e392b4ddf	no	7
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51	Non Patent Literature	Polsky-Cynkin_UseOfDNA_1985.pdf	8295610 4414c1672f4536596c2a7af8784395c0ccb35051	no	6
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52	Non Patent Literature	RAMACHANDRAN_Next-generationHigh-Density.pdf	3907142 4ab14ec1b801afe7dddef3a2916c455bf6496511	no	4
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53	Non Patent Literature	Ranki_SandwichHybridization_1983.pdf	1702632 62f45cc370851fced9b582b285d7bcf2e18484ce	no	9
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Information:					
54	Non Patent Literature	Roberts_RNApeptifeFusions_1997.pdf	5201220 ac050f77eeeba22dfe26ecb3eaa5084b3911344a	no	6
Warnings:					
Information:					
55	Non Patent Literature	RONAGHI_ASequencingMethodBased.pdf	2205298 a454bf4393c4504334c53a66fbea476ff6894f32	no	5
Warnings:					
Information:					
56	Non Patent Literature	RONAGHI_Real-timeDNASequencing.pdf	4542113 fae6a3098395ff0d222b44261f6421e06a10d82f	no	6
Warnings:					
Information:					
57	Non Patent Literature	RONAGHI_PyrosequencingShedsLight.pdf	6779360 41bae8415b2af6dc3c108a771500e60824b0544f	no	10
Warnings:					
Information:					

58	Non Patent Literature	ROUILLARD_OligoArray2.pdf	4916105 581cc40f024b88909e9a9a0dea2f881a307939bd	no	6
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Information:					
59	Non Patent Literature	ROUTENBERG_MicrofluidicProbeANewTool.pdf	3848731 b39a6617b1b72830b2898c16f7515e2b14a54cc7	no	5
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Information:					
60	Non Patent Literature	RUBIN_WholegenomereseqeuncingReveals.pdf	7911780 0526feb1127236558f08197d7d8b8ff45f0e1535	no	7
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			Total Files Size (in bytes):	234687445	

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Electronic Acknowledgement Receipt

EFS ID:	36104922
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Kirsten Neuman
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	23-MAY-2019
Filing Date:	16-MAY-2019
Time Stamp:	23:09:13
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	Non Patent Literature	RUSH_NewAldehydeTag.pdf	1819249 6ccc8cbb80a6625fde38d7aa51160fa8c08bd0d7	no	2

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Information:					
2	Non Patent Literature	SCHENA_QuantativeMonitoringofGene.pdf	1853109 d002fa050d64c6e91fe6ba6af8334b392d657c81	no	5
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3	Non Patent Literature	Schena_EnteringThePostgenomeEra.pdf	518794 037b0e729242c620dc859804a448534f2dae7b05	no	3
Warnings:					
Information:					
4	Non Patent Literature	Schlapak_GlassSurfacesGrafted_2006.pdf	486149 8e91d89f0fd60f694b444f65d1d816808fe3736a	no	9
Warnings:					
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5	Non Patent Literature	Schmitt_DetectionOfUltra-Rare.pdf	1457733 97d43f94d22eed92b7416f0faac54ed732d35c1b	no	6
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6	Non Patent Literature	Sergeeva_DisplayTechnologies.pdf	4832814 68a1cffec2b8aaae85843ae054fd04a6d0e2c441	no	42
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7	Non Patent Literature	Seurynck_Servoss_EvaluationOfSurface_2007.pdf	13823746 149c938429ee8afe9e415a8cde9c88a64a0b1d2d	no	19
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8	Non Patent Literature	Shelbourne_FastCopperFree_2011.pdf	4676107 2eefa37011d57f2a48f99c35d9e63734db686842	no	3
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9	Non Patent Literature	Shendure_AccurateMultiplesPolony.pdf	5837042 da1fb0671d0e7568c87b0bba560bd0d3e02471c1	no	6
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10	Non Patent Literature	Shi_TheMicroArrayQualityControl_2006.pdf	4048354 61a24acc723aa97ecadf320e277804e1052cb268	no	23
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13	Non Patent Literature	Shults_AMultiplexedProtein.pdf	5069887 eba2f53d377ffaee4500745b5f0555cf3fd08e58	no	10
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14	Non Patent Literature	SIEVERTZON_TranscriptomeAnalysisinPrimary.pdf	7417889 6241e6dbbcb5ed84d3041cdcfba3555fe2713690	no	13
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18	Non Patent Literature	Spurgeon_HighThroughputGene.pdf	4759399 c791cb1d96baf9c53ec2405426d10ac085f028f7	no	7
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19	Non Patent Literature	SUMMERGILL_FluorescencInSituHybridizationAnalysis.pdf	2185690 34dfed66f9d7923918bd53aab36b6c063cee0f5e	no	35
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21	Non Patent Literature	Takahashi_InVitroSelection_2009.pdf	3214338 102b914a0c97fd72d8a9b483ba769958f66818b6	no	24
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22	Non Patent Literature	TANG_RNA-SeqAnalysis.pdf	4385545 bd9d55ebdfa40055ff3ff296878901a83b673803	no	34
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23	Non Patent Literature	Taniguchi_QuantitativeAnalysis_2009.pdf	912951 7840097c72bdac18aa691fd40aefc7cf0b96e192	no	7
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24	Non Patent Literature	Taylor_MitochondrialDNAMutations_2005.pdf	7944727 ed44abb72f2267a930ff220967e56842459b7747	no	14
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25	Non Patent Literature	Thornton_HighRateThick_1977.pdf	3970648 ddc1ce4aa30a48a02e6ccbb3e6e6496453dd2868	no	23
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26	Non Patent Literature	Tian_AntigenPeptideBased_2009.pdf	4922623 d67be31417fc8129d6df5e4477b12cdaabe57db2	no	8
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27	Non Patent Literature	Tijssen_OverviewOfPrinciples_1993.pdf	7059003 a4b8881d052d20daa7d4f15d971e4056a52548d0	no	65
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28	Non Patent Literature	Tolbert_NewMethods_2002.pdf	144609 5f97d01b71eca6e187fa3e80d02efcdbf4151755	no	4
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29	Non Patent Literature	Valencia_mRNADisplayBased_2008.pdf	5760101 80c2890bb9572bef3245716414c6111e0969f32f	no	9
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30	Non Patent Literature	VanGelder_AmplifiedRNA_1990.pdf	1648446 9258fc1f5374c45aa0198775d67e4fd087bc2b04	no	5
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31	Non Patent Literature	VanNess_AVersatileSolid_1991.pdf	7260883 790a1486bb1fddac8a9f3475679d9a4e27332f7b	no	6
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32	Non Patent Literature	Velculescu_SerialAnalysisOf_1995.pdf	1320828 334662270bf0fc53524920c5982ea8dd0f6c954ca	no	4
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37	Non Patent Literature	Wang_SingleCellAnalysis_2010.pdf	11844370 58b0ba49cd6e943b1f4d7dfced1a7cade086f0a6	no	19
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38	Non Patent Literature	Wang_HighFidelitymRNA_2000.pdf	2298682 deb18753f25658a4d2cdd8aee51a2b337d772ed8	no	3
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39	Non Patent Literature	Weichhart_FunctionalSelectionOf_2003.pdf	5134507 fd2b1f18ed0ae773aef56e5861ba9b476a342bb7	no	9
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40	Non Patent Literature	WILLI-MONNERAT_ComprehensiveSpatiotemporalTranscriptomic.pdf	1774143 07ab1dc14e74c9501cf6ecc05e8c5686bab7f147	no	12
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42	Non Patent Literature	Wong_DirectSiteSelective_2008.pdf	5659730 9a3b5553e359ff55885e70c1773d92b8557314f2	no	9
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43	Non Patent Literature	WOO_AComparisonofcDNA.pdf	5000360 0ba417db3847195e48bd7e47d9c2a3dc5b1b578a	no	9
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45	Non Patent Literature	XIAO_DirectDeterminationOf.pdf	3947956 fc3b35a3bb6808735867a36df373a39b835e51d5	no	3
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48	Non Patent Literature	ZHANG_BindingInducedDNA.pdf	7962744 533abf1b6f934aef3a27b660f4feced11a32f755	no	8
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49	Non Patent Literature	Zheng_OriginsOfHuman_2006.pdf	4685345 791fd86536b7975f1d7cbc94869bdfb45be03375	no	10
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/414,213	05/16/2019	1636	785	47706-0004006	1	1

CONFIRMATION NO. 8760

FILING RECEIPT

159367
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10x Genomics
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022



Date Mailed: 05/28/2019

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.

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Inventor(s)

Mark S. CHEE, San Diego, CA;

Applicant(s)

Prognosys Biosciences, Inc., San Diego, CA;

Power of Attorney: The patent practitioners associated with Customer Number 159367

Domestic Priority data as claimed by applicant

This application is a CON of 16/402,098 05/02/2019
which is a CON of 16/276,235 02/14/2019
which is a CON of 15/187,661 06/20/2016 PAT 10308982
which is a CON of 13/080,616 04/05/2011 PAT 9371598
which claims benefit of 61/321,124 04/05/2010

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.

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Projected Publication Date: 09/05/2019

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

Spatially Encoded Biological Assays

Preliminary Class

435

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

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/414,213

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	75		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	330		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	380		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	1 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 230 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	785		TOTAL	

APPLICATION AS AMENDED - PART II

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/414,213	05/16/2019	Mark S. CHEE	47706-0004006	8760

159367 7590 05/29/2019

FISH & RICHARDSON P.C.
10x Genomics
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
MARTINELL, JAMES	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
05/29/2019	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):

PATDOCTC@fr.com
ipadmin@10xgenomics.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 16/414,213	**Applicant(s)** CHEE, Mark S.	
	Examiner BRIAN W BROWN	**Art Unit** OPET	**AIA (FITF) Status** No

1. THE REQUEST FILED 16 May 2019 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to BRIAN BROWN at (571)272-5338.

In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/BRIAN W BROWN/ Petitions Examiner, OPET	

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

Application Number	16/414,213
Filing Date	May 16, 2019
First Named Inventor	Mark S. Chee
Title	SPATIALLY ENCODED BIOLOGICAL ASSAYS
Art Unit	
Examiner Name	
Attorney Docket Number	47706-0004006

SIGNATURE of Applicant or Patent Practitioner

Signature	/Cameron Luitjens/	Date (Optional)	June 3, 2019
Name	Cameron M. Luitjens, Ph.D., J.D.	Registration Number	58,674
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

61938675.doc

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on the Transmittal.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter, which may be an application filed after the date of this power of attorney, or identified above:

159367

OR

☐ I hereby appoint Practitioner(s) named in the attached list as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter, which may be an application filed after the date of this power of attorney, or identified above.

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

☐ The address associated with the above-mentioned Customer Number

OR

☒ The address associated with Customer Number: **159367**

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Prognosys Biosciences, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Mark Chee	Date (Optional)	
Name	MARK CHEE		
Title	CEO		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

61883609.doc

Electronic Acknowledgement Receipt

EFS ID:	36188565
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Judith Witzel
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	03-JUN-2019
Filing Date:	16-MAY-2019
Time Stamp:	19:00:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	TransPOA.pdf	145602 0422e7a483ee83ae17d2ac9c435a0baf15ad7bb7	no	2

Warnings:

Information:	
Total Files Size (in bytes):	145602

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/414,213	05/16/2019	Mark S. CHEE	47706-0004006

CONFIRMATION NO. 8760

POA ACCEPTANCE LETTER

159367
FISH & RICHARDSON P.C.
10x Genomics
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

OC000000108673345

Date Mailed: 06/05/2019

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/03/2019.

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

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

/vnguyen/

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/25 PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	16414213
Filing Date	16-May-2019
First Named Inventor	Mark CHEE
Attorney Docket Number	47706-0004006
Title of Invention	Spatially Encoded Biological Assays

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Prognosys Biosciences, Inc.	100 %

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

16276235 filed on 02/14/2019

16402098 filed on 05/02/2019

16276260 filed on 02/14/2019

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

10308982

9371598

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

(●) Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

( ) I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

(●) Small Entity

( ) Micro Entity

( ) Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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 is of record in this application

Registration Number 58674

( ) 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 request

Signature	/Cameron Mark Luitjens/
Name	Cameron Mark Luitjens

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16414213
Filing Date:	16-May-2019
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Attorney Docket Number:	47706-0004006

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	2814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16414213

Filing Date: 16-May-2019

Applicant/Patent under Reexamination: CHEE

Electronic Terminal Disclaimer filed on June 6, 2019

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	36223463
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	06-JUN-2019
Filing Date:	16-MAY-2019
Time Stamp:	14:12:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	060719INTEFSW00000459061050
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	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	37915 54186fff56a173573b0380006298ad08abd2300f	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30472 f9f033872a66246d14d7b52d428142a9d215e51c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	68387		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/414,213	05/16/2019	Mark S. CHEE	47706-0004006	8760

159367 7590 06/07/2019

FISH & RICHARDSON P.C.
10x Genomics
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
MARTINELL, JAMES	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
06/07/2019	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):

PATDOCTC@fr.com
ipadmin@10xgenomics.com

Office Action Summary	Application No. 16/414,213	Applicant(s) CHEE, Mark S.	
	Examiner JAMES MARTINELL	Art Unit 1634	AIA (FITF) Status No

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

Period for Reply

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

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

Status

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

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

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

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

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

Disposition of Claims*

5) ☑ Claim(s) 1 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1 is/are rejected.

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

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

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

Application Papers

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

11)☑ The drawing(s) filed on 16 May 2019 is/are: a)☐ accepted or b)☑ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 5/23/19.

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

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

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

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description.

(a) 101, 122, 106, 108, 104, 112, 114, 118, and 102 (e.g. see the instant application at paragraph 00114).

(b) 202, 204, and 206 (e.g., see the instant application at paragraph 00122.

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. The claim is vague and indefinite.

(a) The recitation of "wherein each encoded probe comprises a probe region that may interact with the biological targets" is vague and indefinite because it is not clear whether the encoded probes actually do interact with the biological targets. Hence, it is not clear whether the passage indicated is a claim limitation.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

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

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

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

Claim 1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2, 3, 5-8, 10-26, and 32-36 of copending Application No. 16/276,260. Claim 1 of the instant application is generic to claims 2, 3, 5-8, 10-26, and 32-36 of copending Application No. 16/276,260.

This is a provisional nonstatutory double patenting rejection.

Claim1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2-28 and 30-32 of copending Application No. 16/276,235. Claim 1 of the instant application is generic to claims 2-28 and 30-32 of copending Application No. 16/276,235.

This is a provisional nonstatutory double patenting rejection.

Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 9,371,598. Claim 1 of the instant application is generic to claims 1-46 of U.S. Patent No. 9,371,598.

Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-43 of U.S. Patent No. 10,208,982. Claim 1 of the instant application is generic to claims 1-43 of U.S. Patent No. 10,208,982.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES MARTINELL whose telephone number is (571) 272-0719.

The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be e-mailed to james.martinell@uspto.gov. Since e-mail communications may not be secure, it is suggested that information in such requests be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen, can be reached on (571) 272-0731.

OFFICIAL FAX NUMBER

The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Any Official Communication to the USPTO should be faxed to this number.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/JAMES MARTINELL/
Primary Examiner, Art Unit 1634

Notice of References Cited	Application/Control No. 16/414,213	Applicant(s)/Patent Under Reexamination CHEE, Mark S.	
	Examiner JAMES MARTINELL	Art Unit 1634	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-10308982-B2	06-2019	Chee; Mark S.	C12Q1/6837	1/1
	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
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/414,213	CHEE, Mark S.
	Examiner	Art Unit
	JAMES MARTINELL	1634

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

CLAIMS

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

CLAIM		DATE								
Final	Original	06/04/2019								
	1	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/414,213	CHEE, Mark S.
	Examiner	Art Unit
	JAMES MARTINELL	1634

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
Parent SN 13/080,616 (PN 9,371,598)	06/04/2019	JM
Parent SN 15/187,661 (PN 10,308,982)	06/04/2019	JM
Parent SN 16/276,235 (Pending)	06/04/2019	JM
Parent SN 16/402,098 (Pending)	06/04/2019	JM
Inventor search (PALM)	06/04/2019	JM
EAST text search (printout attached)	06/04/2019	JM
STN search (2 sets of printouts dated 4/12/19 attached)	06/04/2019	JM

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/JAMES MARTINELL/ Primary Examiner, Art Unit 1634	

Curio EX1056-p. 175
Curio v Prognosys

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/414,213	CHEE, Mark S.
	Examiner	Art Unit
	JAMES MARTINELL	1634

/JAMES MARTINELL/ Primary Examiner, Art Unit 1634	

Curio EX1056-p. 176
Curio v Prognosys

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 NEWS  2  JAN  4  DWPI Manual Code revision in 2019
 NEWS  3  JAN 17  First 2019 Emtree(R) update now available in Embase(TM)
 NEWS  4  JAN 29  The 2019 Version of MEDLINE Now Available on STN(TM)
 NEWS  5  FEB  4  INPADOC/INPAFAM: Major enhancements for PCT
 NEWS  6  FEB 26  FRFULL and GBFULL reloaded
 NEWS  7  MAR  7  Search Limits Significantly Expanded Exclusively in STNext(R)
 NEWS  8  MAR  7  New Key Terms field supports efficient full-text searching
                  and results evaluation in Patent Full-text Databases
 NEWS  9  MAR  8  CPC Combination Sets Now Fully Available in Derwent
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 NEWS 10  MAR 25  Derwent World Patent Index Coverage Expanded to Include
                  Eight Former Soviet Republics and the Eurasian Patent
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FILE 'HOME' ENTERED AT 13:36:30 ON 12 APR 2019

=> file biosis caplus medline
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                          ENTRY    SESSION
FULL ESTIMATED COST                          0.40       0.40

FILE 'BIOSIS' ENTERED AT 13:36:48 ON 12 APR 2019
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FILE 'MEDLINE' ENTERED AT 13:36:48 ON 12 APR 2019

=> s ((locat? or address? or spac?)(20a)(bead? or micorbead? or sphere? or microsphere?) and (cod? or barcod? or tag?))/bi,ab
L1          392 ((LOCAT? OR ADDRESS? OR SPAC?)(20A)(BEAD? OR MICORBEAD? OR SPHER
                E? OR MICROSPHERE?) AND (COD? OR BARCOD? OR TAG?))/BI,AB
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=> dup rem l1
PROCESSING COMPLETED FOR L1
L2          326 DUP REM L1 (66 DUPLICATES REMOVED)

=> s ((locat? or address or spac?)(20a)(bead? or microbead? or sphere? or microsphere?) and target? and (cod? or barcod? or
tag?))/bi,ab
L3          85 ((LOCAT? OR ADDRESS OR SPAC?)(20A)(BEAD? OR MICROBEAD? OR SPHERE
              ? OR MICROSPHERE?) AND TARGET? AND (COD? OR BARCOD? OR TAG?))/BI
              ,AB

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L4          252 L2 NOT L3

=> s l4 not 2019/py
L5          245 L4 NOT 2019/PY

=> s l5 not 2018/py
L6          232 L5 NOT 2018/PY

=> s l6 not 2017/py
L7          224 L6 NOT 2017/PY

=> s l7 not 2016/py
L8          210 L7 NOT 2016/PY

=> s l8 not 2015/py
L9          205 L8 NOT 2015/PY

=> s l9 not 2014/py
L10         193 L9 NOT 2014/PY

=> s l10 not 2013/py
L11         174 L10 NOT 2013/PY

=> s l11 not 2012/py
L12         163 L11 NOT 2012/PY

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L2          326 DUP REM L1 (66 DUPLICATES REMOVED)
L3           85 S ((LOCAT? OR ADDRESS OR SPAC?)(20A)(BEAD? OR MICROBEAD? OR SPH
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L5          245 S L4 NOT 2019/PY
L6          232 S L5 NOT 2018/PY
L7          224 S L6 NOT 2017/PY
L8          210 S L7 NOT 2016/PY
L9          205 S L8 NOT 2015/PY
L10         193 S L9 NOT 2014/PY
L11         174 S L10 NOT 2013/PY
L12         163 S L11 NOT 2012/PY

=> s l12 and (aptamer# or oligonucleotide# or nucleotide# or probe# or protein# or peptide# or antibod?)/bi,ab
L13          43 L12 AND (APTAMER# OR OLIGONUCLEOTIDE# OR NUCLEOTIDE# OR PROBE#
              OR PROTEIN# OR PEPTIDE# OR ANTIBOD?)/BI,AB

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L2          326 DUP REM L1 (66 DUPLICATES REMOVED)
L3           85 S ((LOCAT? OR ADDRESS OR SPAC?)(20A)(BEAD? OR MICROBEAD? OR SPH
L4          252 S L2 NOT L3
L5          245 S L4 NOT 2019/PY
L6          232 S L5 NOT 2018/PY
L7          224 S L6 NOT 2017/PY
L8          210 S L7 NOT 2016/PY
L9          205 S L8 NOT 2015/PY
L10         193 S L9 NOT 2014/PY
L11         174 S L10 NOT 2013/PY
L12         163 S L11 NOT 2012/PY
L13          43 S L12 AND (APTAMER#  OR OLIGONUCLEOTIDE#  OR NUCLEOTIDE#  OR PROBE

=> d l13 bib ab
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L13 ANSWER 1 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2012:107054 BIOSIS Full-text
DN PREV201200107054
TI An exonic insertion within Tex14 gene causes spermatogenic arrest in pigs.
AU Sironen, Anu [Reprint Author]; Uimari, Pekka; Venhoranta, Heli; Andersson, Magnus; Vilkki, Johanna
CS Agrifood Res Finland, MTT, Biotechnol and Food Res, Genom, FI-36100 Jokioinen, Finland
anu.sironen@mtt.fi
SO BMC Genomics, (DEC 2 2011) Vol. 12, pp. Article No.: 591.
http://www.biomedcentral.com/bmcgenomics.
ISSN: 1471-2164. E-ISSN: 1471-2164.
DOI 10.1186/1471-2164-12-591
DT Article
LA English
ED Entered STN: 25 Jan 2012
Last Updated on STN: 4 Jul 2018
AB Background: Male infertility is an increasing problem in all domestic species including man. Localization and identification of genes involved in defects causing male infertility provide valuable information of specific events in sperm development. Sperm development is a complex process, where diploid spermatogonia develop into haploid, highly specialized spermatozoa. Correct expression and function of various genes and their protein products are required for production of fertile sperm. We have identified an infertility defect in Finnish Yorkshire boars caused by spermatogenic arrest. The aim of this study was to locate the disease associated region using genome wide screen with the PorcineSNP60 Beadchip and identify the causal mutation by candidate gene approach.Results: In the Finnish Yorkshire pig population the spermatogenic arrest (SA) defect appears to be of genetic origin and causes severe degeneration of germ cells and total absence of spermatozoa. Genome wide scan with the PorcineSNP60 Beadchip localized the SA defect to porcine chromosome 12 in a 2 Mbp region. Sequencing of a candidate gene Tex14 revealed a 51 bp insertion within exon 27, which caused differential splicing of the exon and created a premature translation stop codon. The expression of Tex14 was markedly down regulated in the testis of a SA affected boar compared to control boars and no protein product was identified by Western blotting. The SA insertion sequence was also found within intron 27 in all analyzed animals, thus the insertion appears to be a possible duplication event.Conclusion: In this study we report the identification of a causal mutation for infertility caused by spermatogenic arrest at an early meiotic phase. Our results highlight the role of TEX14 specifically in spermatogenesis and the importance of specific genomic remodeling events as causes for inherited defects.

=> d l13 2-43 bib ab

L13 ANSWER 2 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2011:692038 BIOSIS Full-text
DN PREV201100692038
TI A Study of the Spatial Protein Organization of the Postsynaptic Density Isolated from Porcine Cerebral Cortex and Cerebellum.
AU Yun-Hong, Yen; Chih-Fan, Chuang; Chia-Wei, Chang; Yen-Chung, Chang [Reprint Author]
CS Natl Tsing Hua Univ, Inst Mol Med, 101 Sec 2,Kung Fu Rd, Hsinchu 30013, Taiwan
ycchang@life.nthu.edu.tw
SO Molecular & Cellular Proteomics, (OCT 2011) Vol. 10, No. 10, pp. Article No.: M110.007138. http://www.mcponline.org/.
ISSN: 1535-9476. E-ISSN: 1535-9484.
DOI 10.1074/mcp.M110.007138
DT Article
LA English
ED Entered STN: 2 Nov 2011
Last Updated on STN: 31 Aug 2016
AB Postsynaptic density (PSD) is a protein supramolecule lying underneath the postsynaptic membrane of excitatory synapses and has been implicated to play important roles in synaptic structure and function in mammalian central nervous system. Here, PSDs were isolated from two distinct regions of porcine brain, cerebral cortex and cerebellum. SDS-PAGE and Western blotting analyses indicated that cerebral and cerebellar PSDs consisted of a similar set of proteins with noticeable differences in the abundance of various proteins between these samples. Subsequently, protein localization in these PSDs was analyzed by using the Nano-Depth-Tagging method. This method involved the use of three synthetic reagents, as agarose beads whose surface was covalently linked with a fluorescent, photoactivable, and cleavable chemical crosslinker by spacers of varied lengths. After its application was verified by using a synthetic complex consisting of four layers of different proteins, the Nano-Depth-Tagging method was used here to yield information concerning the depth distribution of various proteins in the PSD. The results indicated that in both cerebral and cerebellar PSDs, glutamate receptors, actin, and actin binding proteins resided in the peripheral regions within similar to 10 nm deep from the surface and that scaffold proteins, tubulin subunits, microtubule-binding proteins, and membrane cytoskeleton proteins found in mammalian erythrocytes resided in the interiors deeper than 10 nm from the surface in the PSD. Finally, by using the immunoabsorption method, binding partner proteins of two proteins residing in the interiors, PSD-95 and alpha-tubulin, and those of two proteins residing in the peripheral regions, elongation factor-1 alpha and calcium, calmodulin-dependent protein kinase II alpha subunit, of cerebral and cerebellar PSDs were identified. Overall, the results indicate a striking similarity in protein organization between the PSDs isolated from porcine cerebral cortex and cerebellum. A model of the molecular structure of the PSD has also been proposed here. Molecular & Cellular Proteomics 10: 10.1074/mcp.M110.007138, 1-20, 2011.

L13 ANSWER 3 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2011:622500 BIOSIS Full-text
DN PREV201100622500
TI Modulation of the distribution of small proteins within porous matrixes by smart-control of the immobilization rate.
AU Bolivar, Juan M.; Hidalgo, Aurelio; Sanchez-Ruiloba, Lucia; Berenguer, Jose; Guisan, Jose M. [Reprint Author]; Lopez-Gallego, Fernando
CS Inst Catalisis and Petroleoquim CSIC, Dept Biocatalisis, Campus UAM, Madrid 28049, Spain
jmguisan@icp.csic.es; flopez@icp.csic.es
SO Journal of Biotechnology, (OCT 10 2011) Vol. 155, No. 4, pp. 412-420.
CODEN: JBITD4. ISSN: 0168-1656. E-ISSN: 1873-4863.
DOI 10.1016/j.jbiotec.2011.07.039
DT Article
LA English
ED Entered STN: 28 Sep 2011
Last Updated on STN: 23 Nov 2011
AB The distribution of enzymes attached to porous solid supports is a major concern in multienzymatic bioreactors. Herein, as proof of the concept that protein localization on porous surfaces can be controlled by tuning the protein immobilization rate. We study the distribution of two poly-histidine-tagged fluorescent proteins (His-GFP and His-mCherryFP) immobilized on different 4% crosslinked agarose-type carriers by confocal laser scanning microscopy. In this context, immobilization rate is easily modulated by controlling the (i) nature of physico-chemical interaction between protein and surface (reactive groups on surface), (ii) by controlling the reactive group density and (iii) by adding competitors to the immobilization process. His-GFP is 350-fold more rapid immobilized on agarose surfaces activated with either glyoxyl groups or chelates than the same matrix activated with primary amine groups instead. A similar effect is seen with agarose matrixes activated with lower glyoxyl densities that immobilize His-GFP roughly 350-fold slower than the corresponding highly activated matrix. When His-GFP is immobilized on agarose activated with chelates groups in presence of imidazol which competes with the protein for the reactive groups on the support, the immobilization rate is again 400-fold slower than when the same protein was immobilized on the same support but with no imidazol during the immobilization process. In all cases, it was observed that rapid immobilizations (quantitative immobilization in less than 10 min) located 100% of the loaded protein at the crown of the carrier beads, meaning that only the 10% of the bead radius was colonized by the protein. On the contrary, when immobilization is much slower, a homogeneous distribution is obtained, resulting in beads whose whole radius is occupied by the protein. Therefore, we set that the more rapid immobilization, the more heterogeneous distribution. All the knowledge gained in protein distribution by immobilization rate alteration of a single protein is applied to the co-immobilization of the two fluorescent proteins in order to develop four different co-immobilization patterns with an enormous applied potential to other multi-protein systems. (C) 2011 Elsevier B.V. All rights reserved.

L13 ANSWER 4 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2011:292049 BIOSIS Full-text
DN PREV201100292049
TI Fluorescent semiconductor nanocrystals (quantum dots) in protein biochips.
AU Oleinikov, V. A. [Reprint Author]
CS Russian Acad Sci, Shemyakin Ovchinnikov Inst Bioorgan Chem, Ul Miklukho Maklaya 16-10, Moscow 117997, Russia
voleinik@mail.ru
SO Russian Journal of Bioorganic Chemistry, (MAR 2011) Vol. 37, No. 2, pp. 151-167. http://www.springerlink.com/content/1068-1620/.
ISSN: 1068-1620. E-ISSN: 1068-330X.
DOI 10.1134/S1068162011020117
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 4 May 2011
Last Updated on STN: 13 Jun 2012
AB Understanding the biological processes in cells, tissues, and organisms requires the identification and analysis of multiple biological objects and the mechanisms of their functioning and regulation. The biological chip (biochip) technique is one of the most efficient tools for these tasks. Biochips are highly efficient and can quantitatively register multiple molecules simultaneously in samples of microscopic volume. Biochips allow the parallel genomic or proteomic analysis of normal or pathologically modified cells and tissues and a comparative analysis to elucidate disease-related changes. Fluorescent dyes used for signal readout from biochips have the following disadvantages: low photostability, low brightness, and the presence of a fluorescent background. It was recently shown that these limitations can be removed if fluorescent semiconductor nanocrystals (quantum dots) are used. Individual quantum dots in the form of colloid nanocrystals (QDs) are easily registered by conventional microscopic equipment due to their high brightness; they are extremely resistant to photobleaching and provide unique opportunities for multiplexing. QDs are ideal fluorophores for information readout from biochips and allow for the detection of single molecules.The present work is aimed at developing approaches for the use of QDs in biochip-based detection systems. The possibilities of using QDs in both planar (or matrix) biochips and suspension (or liquid) biochips, which are undergoing intensive development, are demonstrated. The use of the latter in analytical systems for the simultaneous identification of multiple objects in proteomics, genomics, drug testing, and clinical diagnostics is currently increasing. These systems are based on spectrally coded elements (usually polymer microspheres). An advantage of liquid biochips over matrix planar solid biochips is the possibility of the free movement of microspheres in three-dimensional space. Organic fluorophores allow the realization of a limited number of codes, i.e., objects analyzed simultaneously (multiplexing), while semiconductor QDs make possible a significant increase in both biochip multiplexing and the photostability and sensitivity of the biochips. In addition, the use of FRET (Foerster resonance energy transfer) in liquid biochips makes possible an increase in the detection specificity. The absence of a background signal from the fluorescent labels not bound to the microparticles increases the sensitivity of the analysis and provides additional opportunities for multiplex analysis and diagnostics.Thus, a combination of the biochip technique and semiconductor QDs makes it possible to increase the method's sensitivity and the number of objects detected (the degree of multiplexing). This combination is likely to enable a significant breakthrough in proteomics, particularly in the development of new drugs, clinical diagnostics, identification of molecular markers, and elucidation of the intracellular processes.

L13 ANSWER 5 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2011:187957 BIOSIS Full-text
DN PREV201100187957
TI Light transmitted assay beads.
AU Ho, Winston Z. [Inventor]; Anonymous
CS Hacienda Heights, CA USA
ASSIGNEE: Maxwell Sensors Inc
PI US 07871770 20110118
SO Official Gazette of the United States Patent and Trademark Office Patents, (JAN 18 2011)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 30 Mar 2011
Last Updated on STN: 30 Mar 2011
AB A micro bead having a digitally coded structure that is partially transmissive and opaque to light. The pattern of transmitted light is determined by to decode the bead. The coded bead may be structured a series of alternating light transmissive and opaque sections, with relative positions, widths and spacing resembling a 1D or 2D bar code image. To decode the image, the alternating transmissive and opaque sections of the body are scanned in analogous fashion to bar code scanning. The coded bead may be coated or immobilized with a capture or probe to effect a desired bioassay. The coded bead may include a paramagnetic material. A bioanalysis system conducts high throughput bioanalysis using the coded bead, including a reaction detection zone and a decoding zone.

L13 ANSWER 6 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2011:64576 BIOSIS Full-text
DN PREV201100064576
TI Light transmitted assay beads.
AU Ho, Winston Z. [Inventor]; Anonymous
CS Hacienda Heights, CA USA
ASSIGNEE: Maxwell Sensors Inc
PI US 07858307 20101228
SO Official Gazette of the United States Patent and Trademark Office Patents, (DEC 28 2010)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 19 Jan 2011
Last Updated on STN: 19 Jan 2011
AB A micro bead having a digitally coded structure that is partially transmissive and opaque to light. The pattern of transmitted light is determined by to decode the bead. The coded bead may be structured a series of alternating light transmissive and opaque sections, with relative positions, widths and spacing resembling a 1D or 2D bar code image. To decode the image, the alternating transmissive and opaque sections of the body are scanned in analogous fashion to bar code scanning. The coded bead may be coated or immobilized with a capture or probe to effect a desired bioassay. The coded bead may include a paramagnetic material. A bioanalysis system conducts high throughput bioanalysis using the coded bead, including a reaction detection zone and a decoding zone.

L13 ANSWER 7 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2008:247801 BIOSIS Full-text
DN PREV200800240201
TI On-chip oligonucleotide ligation assay using one-dimensional microfluidic beads array for the detection of low-abundant DNA point mutations.
AU Zhang, He; Yang, Xiaohai; Wang, Kemin [Reprint Author]; Tan, Weihong; Li, Huimin; Zuo, Xinbing; Wen, Hanhui
CS Hunan Univ, Coll Chem and Chem Engn,Biomed Engn Ctr, State Key Lab Chemo Biosensing and Chemomet, Key Lab Bio Nanotechnol and Mol Engn Hunan Prov, Changsha 410082, Peoples R China
kmwang@hnu.cn
SO Biosensors & Bioelectronics, (FEB 28 2008) Vol. 23, No. 7, pp. 945-951.
CODEN: BBIOE4. ISSN: 0956-5663.
DOI 10.1016/j.bios.2007.09.012
DT Article
LA English
ED Entered STN: 2 Apr 2008
Last Updated on STN: 12 May 2008
AB The detection of low-abundant DNA point mutations is very important for the early prediction of cancer, diagnostics of disease and clinical prognosis. In this paper, an on-chip oligonucleotide ligation approach that arrayed a series of functionalized beads in a single microfluidic channel was described for detection of low-abundant point mutations in p53 gene. This gene carried the point mutation with high diagnostic value for assessment of tumor progression and resectional borders. This work extended our prior efforts using one-dimensional (1-D) microfluidic beads array for protein and nucleic acid molecular profiling, and displayed high discrimination sensitivity to mutations detection due to the enhanced mass transport capability caused by microfluidic addressing format of beads array. As a demonstration, it was found that the on-chip beads ligation held high mutation discrimination sensitivity in 1 pM quantities at a SNR (signal-to-noise ratio) >2 using synthesized DNA oligonucleotides in accordance with target fragment. The RT-PCR products of tumor cell line A549, CNE2 and SKBr-3 were further examined to distinguish the point mutation at codon 175 of p53 gene. This approach was capable of detecting a point mutation in a p53 oncogene at a level of I mutant in 1000 wild-type sequences using PCR products without the need of LDR amplification. Additionally, this on-chip beads ligation approach also displayed other microfluidic-based advantages of simple handling (one sample injection per test), little reagent quantities, and low potential of contaminations. (C) 2007 Elsevier B.V. All rights reserved.

L13 ANSWER 8 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2008:155703 BIOSIS Full-text
DN PREV200800144871
TI Spatially addressable bead-based biosensor for simple and rapid DNA detection.
AU Ng, Johnson K.; Selamat, Ezrein S.; Lin, Wen-Tso [Reprint Author]
CS Natl Univ Singapore, Div Environm Sci and Engn, 21 Lower Kent Ridge Rd, Singapore 119077, Singapore
eseliuwt@nus.edu.sg
SO Biosensors & Bioelectronics, (JAN 18 2008) Vol. 23, No. 6, pp. 803-810.
CODEN: BBIOE4. ISSN: 0956-5663.
DT Article
LA English
ED Entered STN: 27 Feb 2008
Last Updated on STN: 27 Feb 2008
AB A simple glass-polymer-based biosensor that allows arrays of beads to be immobilized, separated and identified without any prior encoding is developed. To do so, distinct bead types that are conjugated with different oligonucleotide probes are sequentially spotted onto a polymeric matrix (or gel pad) on the surface of the device. The spotted beads are firmly immobilized to the gel pad, acquiring spatial codes that allow them to be identified. Throughput is enhanced by spotting different bead types onto hundreds of different gel pads. The bead-based biosensor was applied for the DNA-based detection of 10 model bacterial species and two single-nucleotide polymorphisms, and based on passive hybridization the final signals are obtained with single-mismatch specificity within 10 min. (C) 2007 Elsevier B.V. All rights reserved.

L13 ANSWER 9 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2007:542069 BIOSIS Full-text
DN PREV200700532507
TI Complex microparticles for delivery of low-molecular weight, water-soluble nutrients and pharmaceuticals to marine fish larvae.
AU Langdon, Chris; Clack, Brendan; Onal, Urnur [Reprint Author]
CS Canakkale Onsekiz Univ, Fac Fisheries, Dept Aquaculture, Terzioglu Campus, TR-17100 Canakkale, Turkey
chris.langdon@oregonstate.edu; umuronal@yahoo.com
SO Aquaculture, (AUG 22 2007) Vol. 268, No. 1-4, Sp. Iss. SI, pp. 143-148.
CODEN: AQCLAL. ISSN: 0044-8486.
DT Article
LA English
ED Entered STN: 17 Oct 2007
Last Updated on STN: 17 Oct 2007
AB Most currently available microparticulate artificial diets for rearing marine suspension feeders, including larval fish, are not effective in retaining low-molecular weight, water-soluble (LMWS) nutrients and other materials [Lopez-Alvarado, J., Langdon, C.J., Teshima, S., Kanazawa, A., 1994. Effects of coating and encapsulation of crystalline amino acids on leaching in larval feeds. Aquaculture 122, 335-346; Baskerville-Bridges, B., Kling, L.J., 2000. Development and evaluation of microparticulate diets for early weaning of Atlantic cod, Gadus morhua, larvae. Aquae. Nutr. 6, 171-182]. Rapid leaching losses occur as a result of high surface-to-volume ratios and the porosity of the matrix or walls of the particles [Langdon, C.J., 2003. Microparticle types for delivery nutrients to marine fish larvae. Aquaculture 227, 259-275]. In order to address this problem of high leakage losses, a novel complex particle type was developed consisting of LMWS incorporated in lipid beads that are then bound, with other nutrients, in a matrix of the water-insoluble protein zein.A spray method for preparing lipid beads was developed to increase the concentration of incorporated core material as well as to reduce losses due to leakage from beads suspended in water. It was possible to prepare lipid spray beads (LSB) that delivered 8.5% of their dry weight as glycine after 1-h suspension in water, resulting in free amino acid concentrations similar to those of commonly used live feeds for fish larvae, such as rotifers and Artemia; however, this delivery efficiency was reduced to 1.2% glycine for complex particles made up of 30% w/w glycine-containing LSB and other dietary nutrients. Further experiments are required to determine if complex particles can replace living feeds for the early larval stages of marine fish species. (C) 2007 Published by Elsevier B.V.

L13 ANSWER 10 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2007:331117 BIOSIS Full-text
DN PREV200700335080
TI Defining the role of "second sphere" residues in the activity of glyoxasomal malate dehydrogenase.
AU Jean, Sophonie [Reprint Author]; Bell, Ellis
CS Univ Richmond, Lab Struct Biol Biophys and Bioinformat, Gottwald Sci Ctr, Richmond, VA 23173 USA
SO FASEB Journal, (APR 2007) Vol. 21, No. 5, pp. A643.
Meeting Info.: Experimental Biology 2007 Annual Meeting. Washington, DC, USA. April 28 -May 02, 2007. Amer Assoc Anatomists; Amer Physiol Soc; Amer Soc Biochem & Mol biol; Amer Soc Investigat Pathol; Amer Soc Nutr; Amer Soc Pharmacol & Expt Therapeut.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 30 May 2007
Last Updated on STN: 30 May 2007
AB Malate Dehydrogenase catalyses the interconversion of Malate and Oxaloacetate using NAD(H). Although the 3-D structure has long been known and a catalytic mechanism proposed involving a histidine-aspartate pair in the active site, little is known about the roles that residues further from the active site may play in either hydride transfer or proton abstraction. Analysis of the active site cavity, both visually and by QM-MM approaches, led to the construction of "second sphere" mutants involving residues located 5- [OA from the site of catalysis using quickchange mutagenesis, and the resultant proteins purified using Ni-NTA affinity chromatography making use of the histidine tag introduced in the pQE 60 vector. While H220 and D193 play well characterized roles in proton abstraction, other residues, N124, T152, T186, A183, G180,V164,N165, S166 and H90 have been mutated and appear to play various roles in the overall reaction. Several mutants appear to be affecting the pH dependence and substrate inhibition. For example, while the N 165D mutant showed similar Vmax values at PH 7 & 8 there is a marked increase in the effects of substrate inhibition at PH 7 and a reversal of the pH effects on K-m for oxaloacetate relative to the native protein or the S166A mutant. The N165D and the S166A mutants have been selected for crystal screening. It is clear that a number of residues within this second sphere contribute to protein stability and aid in the fine tuning of the regulatory effects of substrate inhibition and PH dependence.

L13 ANSWER 11 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2006:499024 BIOSIS Full-text
DN PREV200600505344
TI Novel interaction between XIAP-Associated Factor 1 (XAF1) and nuclear coactivator clip in colon cancer.
AU Sun, Yunwei; Xia, Harry. H. X.; Zhu, Senlin; Zou, Bing; Lin, Marie Cm; Kung, Hsiang Fu; Wong, Benjamin C.
SO Gastroenterology, (APR 2006) Vol. 130, No. 4, Suppl. 2, pp. A680.
Meeting Info.: Digestive Disease Week Meeting/107th Annual Meeting of the American-Gastroenterological-Association. Los Angeles, CA, USA. May 19 -24, 2006. Amer Gastroenterol Assoc Inst.
CODEN: GASTAB. ISSN: 0016-5085.
DT Conference; (Meeting)
Conference; (Meeting Poster)
LA English
ED Entered STN: 4 Oct 2006
Last Updated on STN: 4 Oct 2006
AB Background: XAF1 (XIAP-Associated Factor 1) is a nuclear protein that directly interacts with endogenous XIAP and results in XIAP sequestration in nuclear inclusions. cAMP response element binding protein (CREB)-binding protein (CBP) play an important role as multifunctional transcriptional coactivators. In this study, we examined the association between XAF1 and CBP in colon cancer cell. Methods: Expressions of XAF1 and CBP were detected by Western blot in colon cancer cells. The association of XAF1 with CBP was confirmed in vitro by glutathione S-transferase (GST) pull-down assay and in vivo by coimmumoprecipitation. Co-localization of XAF1 and CBP was demonstrated by immunofluorescence microscopy. An AP1 reporter assay was used to determine the functional interaction between XAF1 and CBP in the presence or absence of PMA. Results: Low level of XAF1 and CBP was detected in SW1116 cells. Using GST-CBP (1-1099,1098-1758,1098-1858 and 1620-1877) bound to sepharose beads and in vitro expressed 35S-labeled XAF1, we found the XAF1 binding sites on CBP are located in the cysteine-histidine-rich C/H1 domains (residues 1-1098). Plasmids encoding XAF1 and HA-tagged CBP were transfected into SW1116 cells alone or in combination. Immunoprecipitation of over-expressed CBP protein with anti-CBP polyclonal antibody co-precipitated XAF I was mainly located in the nucleus. CBP was located exclusively in the nucleus. XAF1-RFP and CBP-HA co-localization were seen in the nucleus after immunofluorescence staining. Reporter assays demonstrated that co-transfection with pCDNA3-XAF1 and pRc/RSV-CBP led to one fold reduction of AP1 luciferase activity stimulated by PMA, which was further enhanced by co-transfection of CBP's homolog pCMV-P300. Conclusions: Our results identified CBP as a novel binding partner for XAF1 and indicated that CBP, as a coactivator, cooperated with XAF1-mediated inhibition of AP 1 transcription.

L13 ANSWER 12 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2006:418747 BIOSIS Full-text
DN PREV200600411198
TI Synthetic modification of silica beads that allows for sequential attachment of two different oligonucleotides.
AU Steinberg-Tatman, Gali; Huynh, Michael; Barker, David; Zhao, Chanfeng [Reprint Author]
CS Illunina Inc, 9885 Towne Ctr Dr, San Diego, CA 92121 USA chanfeng@illumina.com
SO Bioconjugate Chemistry, (MAY 17 2006) Vol. 17, No. 3, pp. 841-848. CODEN: BCCHES. ISSN: 1043-1802.
DT Article
LA English
ED Entered STN: 23 Aug 2006
Last Updated on STN: 23 Aug 2006
AB We developed a simple and elegant synthesis strategy that enables us to attach controlled (equimolar) amounts of two different oligonucleotides onto one silica bead. The method involves addition of orthogonally protected lysine followed by activation and derivatization of each amino group with a different moiety. This sequential oligonucleotide attachment enables the use of a combinatorial scheme to generate millions of bead types, each characterized by its two oligo tags. (In our randomly assembled arrays each bead type can then be identified by a series of hybridizations of fluorescently labeled decoder oligos to the address tags.) To demonstrate feasibility of such a scheme we created over 1000 bead types, which were characterized by their two oligo tags. The method enables genotyping or gene expression assays at multiplex levels of hundreds of thousands to millions.

L13 ANSWER 13 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2006:343605 BIOSIS Full-text
DN PREV200600342737
TI Defining the role of "second sphere" residues in the activity of glyoxasomal malate dehydrogenase.
AU Jean, Sophonie [Reprint Author]; Bell, Ellis
CS Univ Richmond, Gottwald Sci Ctr, Richmond, VA 23173 USA
SO FASEB Journal, (MAR 6 2006) Vol. 20, No. 4, Part 1, pp. A45.
Meeting Info.: Experimental Biology 2006 Meeting. San Francisco, CA, USA. April 01 -05, 2006. Amer Assoc Anatomists; Amer Physiol Soc; Amer Soc Biochem & Mol Biol; Amer Soc Investigat Pathol; Amer Soc Nutr; Amer Soc Pharmacol & Expt Therapeut.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 12 Jul 2006
Last Updated on STN: 12 Jul 2006
AB Malate Dehydrogenase catalyses the interconversion of Malate and Oxaloacetate with the concommitant oxidation and reduction of the cofactor NAD(H). Although the 3 dimensional structure has been known for many years and a catalytic mechanism proposed involving a histidine-aspartate pair in the active site little is known about the roles that residues furthjer from the active site may play in either the hydride transfer or proton abstraction steps of catalysis. Analysis of the active site cavity of the enzyme led to the design of a number of "second sphere" mutants involving various hydrophilic residues located 5-10A from the site of catalysis. Mutants were constructed using quikchange mutagenesis and the resultant proteins purified using NiNTA affinity chromatography making use of the histidine tag introduced in the pQE 60 vector used for expression.The activity of various mutants has been characterized using initial rate kinetic studies and Kin and Vmax values determined. Activation energies have been calculated from the temperature dependence of Vmax and the stabilities of the protein determined using both heat inactivation and guanidine hydrochloride denaturation. It is clear that a number of residues within this second sphere contribute to both protein stability and activity.

L13 ANSWER 14 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2006:206354 BIOSIS Full-text
DN PREV200600197577
TI Fractionation of chromosome 15 with an affinity-based approach using magnetic beads.
AU Vitharana, Samadhi N.; Wilson, George S. [Reprint Author]
CS Univ Kansas, Dept Chem, 1251 Wescoe Hall Dr, Lawrence, KS 66045 USA
gwilson@ku.edu
SO Genomics, (JAN 2006) Vol. 87, No. 1, pp. 158-164.
CODEN: GNMCEP. ISSN: 0888-7543.
DT Article
LA English
ED Entered STN: 22 Mar 2006
Last Updated on STN: 22 Mar 2006
AB The two main shortcomings of the state-of-the-art method of sorting chromosomes, specificity and the efficiency of fractionating a significant amount of chromosomes, are addressed by this work in the design of a massively parallel approach using magnetic beads binding to a chromosome-specific DNA probe. In an attempt to isolate human chromosome 15 from a lymphoblastoid cell line, a chromosome 15 centromere-specific DNA probe with a fluorescent tag attached was reacted with the chromosomes. Magnetic beads bound to anti-FITC antibody were reacted with the labeled pool of chromosomes and separated by exposure to a magnetic field. The specificity of the fractionated pool was verified by performing fluorescence in situ hybridization on the isolated pool. The chromosome of interest could be enriched to about 75% within a maximum of 3-4 days, regardless of the amount of material. (c) 2005 Elsevier Inc. All rights reserved.

L13 ANSWER 15 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2005:196329 BIOSIS Full-text
DN PREV200500197698
TI Latex bead immobilisation in PDMS matrix for the detection of p53 gene point mutation and anti-HIV-1 capsid protein antibodies.
AU Marquette, Christophe A. [Reprint Author]; Degiuli, Agnes; Imbert-Laurenceau, Emmanuelle; Mallet, Francois; Chaix, Carole; Mandrand, Bernard; Blum, Loic J.
CS CNRSLab Genie Enzymat and BiomolUMR 5013,EMB2, Univ Lyon 1, Batiment CPE-43,Bd 11 Novembre 1918, F-69622, Villeurbanne, France Christophe.marquette@univ-lyon1.fr
SO Analytical and Bioanalytical Chemistry, (March 2005) Vol. 381, No. 5, pp. 1019-1024. print.
ISSN: 1618-2642 (ISSN print).
DT Article
LA English
ED Entered STN: 25 May 2005
Last Updated on STN: 25 May 2005
AB Two diagnostic chemiluminescent biochips were developed for either the detection of p53 gene point mutation or the serological detection of anti-HIV-1 p24 capsid protein. Both biochips were composed of 24 microarrays of latex beads spots (4x4) (150 mum in diameter, 800 mum spacing) entrapped in a poly(dimethylsiloxane) elastomer (PDMS). The latex beads, bearing oligonucleotide sequences or capsid protein, were spotted with a conventional piezoelectric spotter and subsequently transferred at the PDMS interface. The electron microscopy observation of the biochips showed how homogeneous and well distributed the spots could be. Point mutation detection on the codon 273 of the p53 gene was performed on the basis of the melting temperature difference between the perfect match sequence and the one base pair mismatch sequence. The hybridisation of a 20-mer oligonucleotide form the codon 273 including a one base pair mutation in its sequence on a biochip arrayed with non-muted and the muted complementary sequences, enabled a clear discrimination at 56degreeC between muted and wild sequences. Moreover, the quantitative measurement of the amount of muted sequence in a sample was possible in the range 0.4-4 pmol. Serological measurement of anti-HIV-1 p24 capsid protein on the biochip, prepared with 1-mum-diameter latex beads, enabled the detection of monoclonal antibodies in the range 1.55-775 ng mL-1. Such a range could be lowered to 0.775 ng mL-1 when using 50-nm-diameter beads, which generated a higher specific surface. The validation of the biochip for the detection of anti-HIV-1 capsid protein antibodies was performed in human sera from seropositive and seronegative patients. The positivity of the sera was easily discriminated at serum dilutions below 1:1,000.

L13 ANSWER 16 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 1996:152033 BIOSIS Full-text
DN PREV199698724168
TI Filensin and phakinin form a novel type of beaded intermediate filaments and coassemble de novo in cultured cells.
AU Goulielmos, George; Gounari, Fotini; Remington, Susann; Mueller, Shirley; Haener, Markus; Aebi, Ueli; Georgatos, Spyros D. [Reprint author]
CS Dep. Basis Sci., Univ. Crete Sch. Med., 711 10 Heraklion, Crete, Greece
SO Journal of Cell Biology, (1996) Vol. 132, No. 4, pp. 643-655.
CODEN: JCLBA3. ISSN: 0021-9525.
DT Article
LA English
ED Entered STN: 11 Apr 1996
Last Updated on STN: 11 Apr 1996
AB The fiber cells of the eye lens possess a unique cytoskeletal system known as the "beaded-chain filaments" (BFs). BFs consist of filensin and phakinin, two recently characterized intermediate filament (IF) proteins. To examine the organization and the assembly of these heteropolymeric IFs, we have performed a series of in vitro polymerization studies and transfection experiments. Filaments assembled from purified filensin and phakinin exhibit the characteristic 19-21-nm periodicity seen in many types of IFs upon low angle rotary shadowing. However, quantitative mass-per-length (MPL) measurements indicate that filensin/phakinin filaments comprise two distinct and dissociable components: a core filament and a peripheral filament moiety. Consistent with a nonuniform organization, visualization of unfixed and unstained specimens by scanning transmission electron microscopy (STEM) reveals the existence of a central filament which is decorated by regularly spaced 12-15-nm-diam beads. Our data suggest that the filamentous core is composed of phakinin, which exhibits a tendency to self-assemble into filament bundles, whereas the beads contain filensin/phakinin hetero-oligomers. Filensin and phakinin copolymerize and form filamentous structures when expressed transiently in cultured cells. Experiments in IF-free SW13 cells reveal that coassembly of the lens-specific proteins in vivo does not require a preexisting IF system. In epithelial MCF-7 cells de novo forming filaments appear to grow from distinct foci and organize as thick, fibrous laminae which line the plasma membrane and the nuclear envelope. However, filament assembly in CHO and SV40-transformed lens-epithelial cells (both of which are fibroblast-like) yields radial networks which codistribute with the endogenous vimentin IFs. These observations document that the filaments formed by lens-specific IF proteins are structurally distinct from ordinary cytoplasmic IFs. Furthermore, the results suggest that the spatial arrangement of filensin/phakinin filaments in vivo is subject to regulation by host-specific factors. These factors may involve cytoskeletal networks (e.g., vimentin IFs) and/or specific sites associated with the cellular membranes.

L13 ANSWER 17 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 1995:386857 BIOSIS Full-text
DN PREV199598401157
TI RNA transcription from immobilized DNA templates.
AU Marble, H. Anthony; Davis, Robert H. [Reprint author]
CS Dep. Chem. Eng. Chem. Biochem., Univ. Colorado, Boulder, CO 80309-0424, USA
SO Biotechnology Progress, (1995) Vol. 11, No. 4, pp. 393-396.
CODEN: BIPRET. ISSN: 8756-7938.
DT Article
LA English
ED Entered STN: 13 Sep 1995
Last Updated on STN: 13 Sep 1995
AB We describe an RNA transcription protocol based on the multiple reuse of solid-phase synthetic DNA templates. The templates are assembled onto streptavidin-coated agarose beads via a single 5'-terminal biotin located on the noncoding template strand. Transcription occurs in an aqueous buffered suspension containing solid-phase DNA, dissolved enzyme (T7 RNA polymerase), and nucleoside triphosphate substrates (NTPs). A direct comparison of solution and solid-phase templates under standard transcription conditions reveals similar initial reaction rates and overall yields. Immobilized templates store stably for periods of several months and are easily recovered by mild centrifugation. We demonstrate the successive reuse of these templates throughout 15 rounds of transcription. The templates remained active, although an incremental decay in transcription was observed beyond five rounds. Template activity was partially restored by supplementing the support-bound oligonucleotide with fresh coding-strand DNA. These findings indicate that multiple reuse of template is a viable strategy for reducing the amount of DNA template required in RNA transcription.

L13 ANSWER 18 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 1994:131613 BIOSIS Full-text
DN PREV199497144613
TI The origin of serotoninergic afferents to the cat's cerebellar nuclei.
AU Kitzman, Patrick H.; Bishop, Georgia A. [Reprint author]
CS Ohio State Univ., Dep. Cell Biol. Neurobiol. Anatomy, 333 W. 10th Ave., Columbus, OH 43210, USA
SO Journal of Comparative Neurology, (1994) Vol. 340, No. 4, pp. 541-550.
CODEN: JCNEAM. ISSN: 0021-9967.
DT Article
LA English
ED Entered STN: 24 Mar 1994
Last Updated on STN: 25 Mar 1994
AB In the cat, serotoninergic (5HT) axons and terminals form a dense plexus that is present throughout the granule cell and Purkinje cell layers of the cerebellar cortex and all of the cerebellar nuclei. The intent of the present study was to identify the source of 5HT fibers in the cerebellar nuclei. The medial, interposed, and lateral cerebellar nuclei were selectively injected with either rhodamine or fluorescein-labeled latex microspheres that were retrogradely transported to brainstem neurons. Transverse sections of the brainstem were processed with a primary antibody to 5HT and secondary antibody tagged with either rhodamine or fluorescein. The location of neurons containing both serotonin-like immunoreactivity and retrogradely transported microspheres was plotted. All three of the cerebellar nuclei receive 5HT afferents from the nucleus locus coeruleus, the dorsal raphe nucleus, and the dorsal tegmental nucleus. In addition, the medial nucleus receives projections from the superior central nucleus, the nucleus raphe obscurus, the nucleus raphe magnus, and the periolivary reticular formation. The interposed nuclei receive additional projections from the nucleus raphe magnus, whereas the lateral nucleus receives additional projections from the superior central nucleus. In conclusion, the 5HT projections to the cerebellar nuclei do not appear to be collaterals of those projecting to the cortex (Kerr and Bishop, J Comp Neurol 304:502-515, 1991). These findings suggest that, although the cortex and nuclei are anatomically and physiologically related, they do not process all information in parallel.

L13 ANSWER 19 OF 43 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 1978:237422 BIOSIS Full-text
DN PREV197866049919; BA66:49919
TI HYDRODYNAMIC PROPERTIES OF MACRO MOLECULAR COMPLEXES PART 4 INTRINSIC VISCOSITY THEORY WITH APPLICATIONS TO ONCE BROKEN RODS AND MULTI SUBUNIT PROTEINS.
AU GARCIA DE LA TORRE J [Reprint author]; BLOOMFIELD V A
CS DEP QUIM FIS, UNIV EXTREMADURA, BADAJOZ, SPAIN
SO Biopolymers, (1978) Vol. 17, No. 7, pp. 1605-1628.
CODEN: BIPMAA. ISSN: 0006-3525.
DT Article
FS BA
LA ENGLISH
AB Previous theories of the translational and rotational frictional properties of multisubunit complexes were extended to calculate the intrinsic viscosity of such structures. This theory is similar to those recently constructed by McCammon and Deutch and by Nakajima and Wada, in that it uses a modified hydrodynamic interaction tensor and solves the system of simultaneous interaction equations by digital computation rather than by successive approximations. There are some differences in the formulation and averaging of these equations. Extensive numerical comparison is made between this theory and others that are available associated with the names of Hearst and Tagami, Abdel-Khalik and Bird, and Tsuda, using as a basis exact results for prolate ellipsoids of revolution. For large axial ratios, only this theory asymptotically approaches the correct limit; but for small axial ratios, only the Tsuda shell-model theory is adequate, because the other theories neglect the preponderant influence of the sphere located at the center of rotation. Intrinsic viscosities, translational frictional coefficients and Scheraga- Mandelkern β parameters, are tabulated for a large number of polygonal and polyhedral subunit structures, with up to 8 elements, using both this theory and Tsuda's. Particular application is made to hemerythrin and aspartate transcarbamylase. Finally, the viscosities and friction coefficients of once-broken rods are calculated and compared with an approximate theory by Wilenski.

L13 ANSWER 20 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2012:98207 CAPLUS Full-text
DN 159:255937
TI An exonic insertion within Tex14 gene causes spermatogenic arrest in pigs
AU Sironen, Anu; Uimari, Pekka; Venhoranta, Heli; Andersson, Magnus; Vilkki, Johanna
CS Biotechnology and Food Research, Genomics, Agrifood Research Finland, MTT, Jokioinen, FI-36100, Finland
SO BMC Genomics (2011), 12, 591
CODEN: BGMEET; ISSN: 1471-2164
DOI 10.1186/1471-2164-12-591
PB BioMed Central Ltd.
DT Journal; (online computer file)
LA English
AB Background: Male infertility is an increasing problem in all domestic species including man. Localization and identification of genes involved in defects causing male infertility provide valuable information of specific events in sperm development. Sperm development is a complex process, where diploid spermatogonia develop into haploid, highly specialized spermatozoa. Correct expression and function of various genes and their protein products are required for production of fertile sperm. We have identified an infertility defect in Finnish Yorkshire boars caused by spermatogenic arrest. The aim of this study was to locate the disease associated region using genome wide screen with the PorcineSNP60 Beadchip and identify the causal mutation by candidate gene approach. Results: In the Finnish Yorkshire pig population the spermatogenic arrest (SA) defect appears to be of genetic origin and causes severe degeneration of germ cells and total absence of spermatozoa. Genome wide scan with the PorcineSNP60 Beadchip localized the SA defect to porcine chromosome 12 in a 2 Mbp region. Sequencing of a candidate gene Tex14 revealed a 51 bp insertion within exon 27, which caused differential splicing of the exon and created a premature translation stop codon. The expression of Tex14 was markedly down regulated in the testis of a SA affected boar compared to control boars and no protein product was identified by Western blotting. The SA insertion sequence was also found within intron 27 in all analyzed animals, thus the insertion appears to be a possible duplication event. Conclusion: In this study we report the identification of a causal mutation for infertility caused by spermatogenic arrest at an early meiotic phase. Our results highlight the role of TEX14 specifically in spermatogenesis and the importance of specific genomic remodeling events as causes for inherited defects.
OSC.G 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 21 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2011:1355454 CAPLUS Full-text
DN 157:543534
TI A study of the spatial protein organization of the postsynaptic density isolated from porcine cerebral cortex and cerebellum
AU Yen, Yun-Hong; Chuang, Chih-Fan; Chang, Chia-Wei; Chang, Yen-Chung
CS Institute of Molecular Medicine, National Tsing Hua University, Hsinchu, Taiwan
SO Molecular and Cellular Proteomics (2011), 10(10), M110.007138, 20 pp.
CODEN: MCPOBS; ISSN: 1535-9484
URL: http://www.mcponline.org/content/10/10/M110.007138.full.pdf+html
DOI 10.1074/mcp.M110.007138
PB American Society for Biochemistry and Molecular Biology
DT Journal; (online computer file)
LA English
AB Postsynaptic d. (PSD) is a protein supramol. lying underneath the postsynaptic membrane of excitatory synapses and has been implicated to play important roles in synaptic structure and function in mammalian central nervous system. Here, PSDs were isolated from two distinct regions of porcine brain, cerebral cortex and cerebellum. SDS-PAGE and Western blotting analyses indicated that cerebral and cerebellar PSDs consisted of a similar set of proteins with noticeable differences in the abundance of various proteins between these samples. Subsequently, protein localization in these PSDs was analyzed by using the Nano-Depth-Tagging method. This method involved the use of three synthetic reagents, as agarose beads whose surface was covalently linked with a fluorescent, photoactivable, and cleavable chemical crosslinker by spacers of varied lengths. After its application was verified by using a synthetic complex consisting of four layers of different proteins, the Nano-Depth-Tagging method was used here to yield information concerning the depth distribution of various proteins in the PSD. The results indicated that in both cerebral and cerebellar PSDs, glutamate receptors, actin, and actin binding proteins resided in the peripheral regions within .apprx.10 nm deep from the surface and that scaffold proteins, tubulin subunits, microtubule-binding proteins, and membrane cytoskeleton proteins found in mammalian erythrocytes resided in the interiors deeper than 10 nm from the surface in the PSD. Finally, by using the immunoabsorption method, binding partner proteins of two proteins residing in the interiors, PSD-95 and α-tubulin, and those of two proteins residing in the peripheral regions, elongation factor-1α and calcium, calmodulin-dependent protein kinase II α subunit, of cerebral and cerebellar PSDs were identified. Overall, the results indicate a striking similarity in protein organization between the PSDs isolated from porcine cerebral cortex and cerebellum. A model of the mol. structure of the PSD has also been proposed here.
OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
RE.CNT 96 THERE ARE 96 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 22 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2010:1226916 CAPLUS Full-text
DN 153:422367
TI Microsphere having hot spots and method for identifying chemicals through surface enhanced Raman scattering using the same
IN Park, Se Jin; Chung, Taek Dong; Piao, Lilin; Boo, Han Kil
PA Cubiq, Inc., S. Korea
SO U.S. Pat. Appl. Publ., 11pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20100245817	A1	20100930	US 2010-750648	20100330
KR 2010109264	A	20101008	KR 2009-27800	20090331
WO 2010114297	A2	20101007	WO 2010-KR1958	20100331
WO 2010114297	A3	20110120		

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRAI KR 2009-27800 A 20090331
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The present invention relates to the microsphere whose surface is covered with hot spots and the method for identifying chems. through Surface Enhanced Raman Scattering (SERS) using the same. The microsphere having hot spots, according to the present invention, includes a microsphere and metal networks as a shell which covers the surface of the microsphere, and nano-sized pores are distributed randomly on the surface or in the interstitial space of the metal networks. The microsphere having hot spots, according to the present invention, can be individually manipulated under a conventional optical microscope. SERS spectra of the monolayer of mols. on Pt or Au can be measured using single microsphere having hot spots mentioned as a sensitive probe. The microsphere having hot spots can be applied for decoding the microspheres with Raman tags flowing in a microfluidic system.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L13 ANSWER 23 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2009:178294 CAPLUS Full-text
DN 151:269252
TI Air velocity characteristics within vented pallets loaded in a refrigerated vehicle with and without air ducts
AU Moureh, J.; Tapsoba, S.; Derens, E.; Flick, D.
CS UMR Genie Industriel Alimentaire, Genie des Procedes AN/Refrigerating Process Engineering Research Unit, Cemagref, AgroParisTech, Cemagref, INRA, Antony, 92163, Fr.
SO International Journal of Refrigeration (2008), Volume Date 2009, 32(2), 220-234
CODEN: IJRFDI; ISSN: 0140-7007
DOI 10.1016/j.ijrefrig.2008.06.006
PB Elsevier Ltd.
DT Journal
LA English
AB During transport using refrigerated vehicles, this being a vital link in the cold chain, the maintaining of even temperature throughout the cargo is essential in order to preserve the quality, safety and shelf life of perishable food. Within the refrigerated container, the temperature level and its homogeneity are directly governed by airflow patterns. The design of the air-distribution system should allow these airflows to compensate heat fluxes exchanged through the insulated walls or generated by the products. In this paper, a reduced-scale model and CFD predictions were used to investigate exptl. and numerically the airflow patterns within a typical refrigerated truck configuration loaded with vented pallets filled with spherical objects. The expts. were carried out using a laser Doppler velocimetry and thermal sphere-shaped probes located inside the pallets. The aim was to investigate air velocity characteristics above and within pallets. The performance of ventilation was characterized with and without supply air duct systems. Both configurations are extensively used in refrigerated transport. Full-scale measurements were also performed within a load of fruit during transport in a refrigerated truck in order to evaluate the temperature distribution under given operating conditions. The numerical modeling of airflow was performed using the computational fluid dynamics (CFD) fluent code and the Reynolds Stress Model (RSM) turbulence model. Numerical and exptl. data make it possible to evaluate the air ventilation levels and their heterogeneity between the pallets. The numerical predictions show reasonable agreement with exptl. data. The studied supply air duct system improves significantly the homogeneity of ventilation in the vehicle.
OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 24 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2009:139767 CAPLUS Full-text
DN 150:186302
TI Measurement of multiple analytes using flow cytometry utilizing antibodies attached to microspheres
IN Thornthwaite, Jerry T.
PA NED, LLC, USA
SO PCT Int. Appl., 14pp.; Chemical Indexing Equivalent to 150:186301 (US)
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009018210	A1	20090205	WO 2008-US71343	20080728
US 20090029347	A1	20090129	US 2007-829877	20070727

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI US 2007-829877 A 20070727
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The present invention relates generally to laboratory diagnostics as related to the use of microspheres in flow cytometry. The present invention is directed to a method of using antibodies attached to different types of microspheres against different antigens located within a biol. sample. Optical and electronic particle detection may be used to sep. the microspheres via flow cytometry, allowing the subsequent measurement of multiple analytes in a single sample of body fluid by separating and gating such analytes based on the type of microsphere to which the analyte is coupled. According to the present invention, various biol. components may be attached to microspheres of different vols., shapes, conductivity, densities, and/or colors to detect biol. components by gating on the type of microsphere and analyzing the biol. component attached thereto.
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 25 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2009:116595 CAPLUS Full-text
DN 150:186301
TI Measurement of multiple analytes using flow cytometry utilizing antibodies attached to microspheres
IN Thornthwaite, Jerry T.
PA Ned, LLC, USA
SO U.S. Pat. Appl. Publ., 6 pp., Chemical Indexing Equivalent to 150:186302 (WO)
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20090029347	A1	20090129	US 2007-829877	20070727
WO 2009018210	A1	20090205	WO 2008-US71343	20080728

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI US 2007-829877 A 20070727
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The present invention relates generally to laboratory diagnostics as related to the use of microspheres in flow cytometry. The present invention is directed to a method of using antibodies attached to different types of microspheres against different antigens located within a biol. sample. Optical and electronic particle detection may be used to sep. the microspheres via flow cytometry, allowing the subsequent measurement of multiple analytes in a single sample of body fluid by separating and gating such analytes based on the type of microsphere to which the analyte is coupled. According to the present invention, various biol. components may be attached to microspheres of different vols., shapes, conductivity, densities, and/or colors to detect biol. components by gating on the type of microsphere and analyzing the biol. component attached thereto.

L13 ANSWER 26 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2007:1381649 CAPLUS Full-text
DN 148:460869
TI Ion-collecting sphere in a stationary, weakly magnetized plasma with finite shielding length
AU Patacchini, Leonardo; Hutchinson, Ian H.
CS Plasma Science and Fusion Center, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SO Plasma Physics and Controlled Fusion (2007), 49(10), 1719-1733
CODEN: PPCFET; ISSN: 0741-3335
DOI 10.1088/0741-3335/49/10/009
PB Institute of Physics Publishing
DT Journal
LA English
AB Collisionless ion collection by a neg. biased stationary spherical probe in a finite shielding length plasma is investigated using the Particle in Cell code SCEPTIC, in the presence of a weak magnetic field B. The overall effect of the magnetic field is to reduce the ion current, linearly in |B| for weak enough fields, with a slope steepness increasing with the electron Debye length. The angular current distribution and space-charge buildup strongly depend on the focusing properties of the probe, hence on its potential and the plasma shielding length. In particular, it is found that the concavity of the ion collection flux distribution can reverse sign when the electron Debye length is comparable to or larger than the probe radius (λDe .gtorsim. rp), provided the ion temperature is much lower than the probe bias (Ti « -ZeVp).
OSC.G 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 27 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2007:574237 CAPLUS Full-text
DN 147:136723
TI Proteome analysis technologies based on mass spectrometry for quantitation, phosphoproteomics, and drug discovery
AU Oda, Yoshiya
CS Laboratory of Seeds Finding Technology, Eisai Co., Ltd., Tsukuba, Ibaraki, Japan
SO Journal of the Mass Spectrometry Society of Japan (2007), 55(2), 63-75
CODEN: JMSJEY; ISSN: 1340-8097
DOI 10.5702/massspec.55.63
PB Nippon Shitsuryo Bunseki Gakkai
DT Journal; General Review
LA Japanese
AB A review. Protein concentration is one of the most basic and important parameters in functional anal. because the kinetics/dynamics of cellular mols. is described by changes in the concns. of proteins in particular compartments. Mass spectrometry (MS) plays a central role in proteome studies and allows protein identification and quantitation at the same time. An MS-based method allows simultaneous identification and quantitation of individual proteins and determination of changes in the levels of modifications at specific sites on individual proteins. Accurate quantitation is achieved through the use of whole cell stable isotope labeling, and the seminal work on differential metabolic labeling of proteins by Oda et al. has led to many strategies for quant. proteomics including quant. tissue proteome anal. based on culture-derived isotope tag (CDIT). This is a generalized approach and affords a quant. description of cellular differences at the level of protein expression and modification, thus providing information that is critical to the understanding of complex biol. phenomena. In addition to this relative quant. proteomics, MS-based absolute quantitation is also possible by adding a known amount of standard peptides (e.g. isotope dilution), or reverse isotope dilution (CDIT). Although it has become feasible to rapidly identify proteins from crude cell exts. using mass spectrometry, it can be difficult to elucidate protein kinase substrates in the presence of a large excess of relatively abundant non-phosphoproteins. Therefore, for effective proteome anal. it becomes critical to enrich the sample of phosphorylated proteins. Although enrichment of phosphotyrosine-containing proteins has been achieved through the use of high-affinity anti-phosphotyrosine antibodies, we developed a method for enriching phosphoserine/threonine-containing proteins from crude cell exts. after chemical replacement of the phosphate moieties by affinity tags. Although this is an interesting method, the procedure is complicated and of low efficiency. Therefore, we developed a simple, highly specific enrichment procedure for phosphopeptides, by increasing the specificity of an immobilized metal affinity column (IMAC) without using any chemical reaction. The increase in selectivity was achieved by (a) using a strong acid to discriminate phosphates from carboxyl groups of peptides, (b) using a high concentration of acetonitrile to remove hydrophobic non-phosphopeptides, and (c) desalting the phosphate buffer used for competitive elution from the IMAC. By applying this efficient approach, we were able to identify more than one thousand phosphopeptides. Chemical proteomics is an effective approach to focused proteomics, having the potential to find specific interactors in moderate-scale comprehensive anal. Unlike chemical genetics, chemical proteomics directly and comprehensively identifies proteins that bind specifically to candidate compds. by means of affinity chromatog. purification using the immobilized candidate, combined with mass spectrometric identification of interacting proteins. This is an effective approach for discovering unknown protein functions, identifying the mol. mechanisms of drug action, and obtaining information for optimization of lead compds. However, immobilized-small mol. affinity chromatog. always suffers from the problem of nonspecific binders. Although several approaches have been reported to reduce nonspecific binding proteins, these are mainly focused on the use of low-binding-affinity beads or insertion of a spacer between the bead and the compound Stable isotope labeling strategies have proven particularly advantageous for the discrimination of true interactors from many nonspecific binders, including carrier proteins such as serum albumin, and are expected to be valuable for drug discovery.

L13 ANSWER 28 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2006:408793 CAPLUS Full-text
DN 144:428416
TI Device and method for analytical cell imaging
IN Trainer, Michael Norman
PA Immunivest Corporation, USA
SO U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060094109	A1	20060504	US 2004-979388	20041102

PRAI US 2004-979388 20041102

AB In patients with carcinomas tumor cells are shed into the blood, enumeration and characterization of these cells offers the opportunity to obtain a "real time" biopsy of the tumor and may improve the management of the disease. The frequency of circulating tumor cells is rare (<1 cell/mL) and technol. is needed that has sufficient sensitivity and specificity to enumerate and characterize these cells. The present system was developed to provide an immunophenotype, fluorescence wave forms as well as images of immunomagnetically enriched cells. Blood vols. ranging from 7.5-30 mL are immunomagnetically enriched for epithelial cells. The sample volume is reduced to 320 μl and inserted into an anal. chamber. Upon introduction of the chamber in a magnetic field, the immunomagnetically tagged cells rise out of the sample and align between nickel lines (period 30 μm, space 15 μm) that are present on the viewing surface of the chamber. A multi laser system is used to detect the fluorescence emitted by DAPI, Phycoerythrin and Allophycocyan labeled and magnetically aligned cells. Compact disk optics are used to maintain alignment and focus of the laser beams onto nickel lines while moving the chamber. The chamber is scanned with a speed of 10 mm/s and the entire chamber is analyzed in approx. 5 min. The fluorescent signals obtained from the events provide an immunophenotype similar to that of a flow cytometer. The fluorescence waveforms improve the characterization of the events and add to the classification as background, cellular debris and cells. Since the cell locations are preserved, objects that immunophenotypically classify as epithelial cells can be revisited for further anal. Bright field and fluorescent images of the selected objects are captured to confirm that the identified objects are tumor cells.

OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L13 ANSWER 29 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2006:180045 CAPLUS Full-text
DN 144:428318
TI Cleavable Hydrophilic Linker for One-Bead-One-Compound Sequencing of Oligomer Libraries by Tandem Mass Spectrometry
AU Paulick, Margot G.; Hart, Kathryn M.; Brinner, Kristin M.; Tjandra, Meiliana; Charych, Deborah H.; Zuckermann, Ronald N.
CS Chiron Corporation, Emeryville, CA, 94608, USA
SO Journal of Combinatorial Chemistry (2006), 8(3), 417-426
CODEN: JCCHFF; ISSN: 1520-4766
DOI 10.1021/cc0501460
PB American Chemical Society
DT Journal
LA English
OS CASREACT 144:428318
AB The authors have developed a method for the rapid and unambiguous identification of sequences of hit compds. from one-bead-one-compound combinatorial libraries of peptide and peptoid ligands. The approach uses a cleavable linker that is hydrophilic to help reduce nonspecific binding to biol. samples and allows for the attachment of a halogen tag, which greatly facilitates post-screening sequencing by tandem mass spectrometry (MS/MS). The linker is based on a tartaric acid unit, which, upon cleavage from resin, generates a C-terminal aldehyde. This aldehyde can then be derivatized with a bromine-containing amino-oxy compound that serves as an isotope tag for subsequent MS/MS anal. of y-ion fragments. The authors have applied this linker and method to the syntheses of a number of peptoids that vary in sequence and length and have also demonstrated single-bead sequencing of a peptoid pentamer. The linker is also shown to have very low levels of nonspecific binding to proteins.
OSC.G 52 THERE ARE 52 CAPLUS RECORDS THAT CITE THIS RECORD (52 CITINGS)
RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 30 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2006:81815 CAPLUS Full-text
DN 144:288658
TI Microsphere sedimentation arrays for multiplexed bioanalytics
AU Moser, Christoph; Mayr, Torsten; Klimant, Ingo
CS Institute of Analytical Chemistry and Radiochemistry, Graz University of Technology, Graz, 8010, Austria
SO Analytica Chimica Acta (2006), 558(1-2), 102-109
CODEN: ACACAM; ISSN: 0003-2670
DOI 10.1016/j.aca.2005.11.066
PB Elsevier B.V.
DT Journal
LA English
AB A new measurement platform to analyze multiple assays in parallel in a single well of a standard microplate is presented. The approach is based on optically addressable encoded microbeads as carriers for a series of bioassays, a fluorescence microscope equipped with a LED as excitation source, a fast-gateable CCD-camera and automated image anal. Bead arrays are suspended in the analyte solution and targets are bound to receptors immobilized at the bead surface. Gravitational or magnetical sedimentation of the beads to the transparent bottom of the microplate leads to in situ formation of randomly ordered arrays. Beads are encoded by three features: size, luminescence intensity and luminescence decay time. Luminescence lifetime imaging in the microsecond range is introduced as a new technique for bead identification. Twenty-seven distinguishable bead classes were produced and characterized. The coeffs. of variation were 5.4% for size, 9% intensity and 1.3% for decay time. Based on these results, the number of potential codes is calculated to be about 140. Multiplexed DNA assays at detection limits of 2 nM were carried out to demonstrate the feasibility of the concept presented here.
OSC.G 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 31 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2005:696494 CAPLUS Full-text
DN 143:169179
TI Method for identifying bead location information
IN Sato, Keiichi
PA Hitachi Software Engineering Co., Ltd., Japan
SO U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050170400	A1	20050804	US 2005-41263	20050125
JP 2005214940	A	20050811	JP 2004-25890	20040202
JP 4344624	B2	20091014		

PRAI JP 2004-25890 A 20040202
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Location information of carriers such as beads arranged inside a capillary represented by a probe array is detected accurately, and an identification method for various materials is developed substituting conventional bar codes for the beads. The arrangement order of a plurality of beads is identified on the basis of stain color information and location information concerning the plurality of stained beads.

L13 ANSWER 32 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2004:634179 CAPLUS Full-text
DN 141:159053
TI Hybrid random bead/chip based microarray
IN Moon, John; Kersey, Alan D.; Putnam, Martin A.; Li, Tuo
PA Cyvera Corporation, USA
SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 26
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004066210	A1	20040805	WO 2004-US1685	20040122
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ				
US 20040233485	A1	20041125	US 2003-661234	20030912
US 7106513	B2	20060912		
US 7349158	B2	20080325	US 2003-661031	20030912
US 7399643	B2	20080715	US 2003-661836	20030912
US 20040132205	A1	20040708		
WO 2005079545	A2	20050901	WO 2005-US5745	20050222
WO 2005079545	A3	20061116		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20090034078	A1	20090205	US 2008-144209	20080623
US 7791802	B2	20100907		

PRAI US 2003-60441678 P 20030122
US 2003-661031 A 20030912
US 2003-661234 A 20030912
US 2003-661836 A 20030912
US 2003-60519932 P 20031114
US 2002-60410541 P 20020912
US 2003-645686 A2 20030820
US 2003-645689 A2 20030820
US 2004-60546445 P 20040219
US 2004-60547013 P 20040219
US 2005-63660 A1 20050222
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB A hybrid random bead/chip based microarray includes multiple loose optical identification elements (or beads) comprising a substrate having ≥1 identifiable code. The elements are randomly placed on a substrate, e.g., tray, plate, slide, or chip, in an identifiable position on the slide (but not necessarily immobilized). E.g., the beads are randomly distributed (but oriented) in one dimension along grooves in the slide. Then, each bead code is read and its location determined, i.e., the bead code and location are mapped to its location on the chip. The beads on the chip may then be read/examined by a conventional chip reader. The beads may be functionalized with a desired probe and/or reacted with a desired analyte in the loose state and/or on the chip. After reading the chip, the beads may be removed from the chip for further or alternative processing.
OSC.G 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

Curio EX1056-p. 212
Curio v Prognosys

L13 ANSWER 33 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2004:451556 CAPLUS Full-text
DN 141:3772
TI Simplified detection process for colored bead random microarrays
IN Kocher, Thomas E.
PA Eastman Kodak Company, USA
SO U.S. Pat. Appl. Publ., 6 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040106114	A1	20040603	US 2002-307664	20021202

PRAI US 2002-307664 20021202
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This article discloses a method of manufacturing a colored microsphere mol. biol./chemical random microarray system, comprising: randomly dispersing on a support a composition including a first set of microspheres modified with a biol./chemical probe and containing an optical bar code generated from at least one colorant associated with the microspheres to produce a biol./chemical active region on the support; scanning the biol./chemical active region with a high-resolution color scanner to produce a color map of the locations of the randomly dispersed first set of microspheres; creating a digital file of the color map; and linking the digital file of the color map with the support.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L13 ANSWER 34 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2002:444423 CAPLUS Full-text
DN 137:16488
TI Analysis of sequence tags with hairpin primers to amplify DNA and add an address sequence to the amplification product
IN Lizardi, Paul M.; Latimer, Darin R.
PA Yale University, USA
SO U.S., 42 pp., Cont.-in-part of U.S. 6,261,782.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 5
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403319	B1	20020611	US 2000-637384	20000811
US 6261782	B1	20010717	US 2000-544713	20000406
AT 318932	T	20060315	AT 2000-954029	20000811
US 20020106649	A1	20020808	US 2001-855793	20010515
US 6677121	B2	20040113		

PRAI US 1999-60148870 P 19990813
US 2000-544713 A2 20000406
US 1999-60127932 P 19990406
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Disclosed is a method for the comprehensive anal. of nucleic acid samples and a detector composition for use in the method. The method involves amplifying nucleic acid fragments of interest using a primer that can form a hairpin structure; sequence-based coupling of the amplified fragments to detector probes; and detection of the coupled fragments. The amplified fragments are coupled by hybridization and coupling, preferably by ligation, to detector probes. A hairpin structure formed at the end of the amplified fragments facilitates coupling of the fragments to the probes. The hairpin sequence can be unique to drive the extension product to a specific probe on a microarray. The method allows detection of the fragments where detection provides some sequence information for the fragments. The method allows a complex sample of nucleic acid to be quickly and easily cataloged in a reproducible and sequence-specific manner. The method can also be used to detect amplified fragments having a known sequence.
OSC.G 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)
RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 35 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2002:368747 CAPLUS Full-text
DN 136:352271
TI Fluorescence and FRET based assays for biomolecules on beads
IN Buranda, Tione; Huang, Jinman; Perez-Luna, Victor H.; Lopez, Gabriel P.; Simons, Peter; Sklar, Larry A.
PA Science & Technology Corporation UNM, USA
SO PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002039083	A2	20020516	WO 2001-US42983	20011106
WO 2002039083	A3	20020711		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002030419	A	20020521	AU 2002-30419	20011106
US 20020081617	A1	20020627	US 2001-985873	20011106

PRAI US 2000-60246564 P 20001108
WO 2001-US42983 W 20011106
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The invention concerns a sensing device comprising: a vessel; a plurality of sensor beads located within the vessel to form interstitial spaces therethrough; and a plurality of biomols. bound to at least at portion of the plurality of beads, each of the biomols. having a fluorescent tag. The invention also provides a method for detecting the binding of two biomols. comprising the following steps: providing a plurality of first biomols., each of the first biomols. having a first fluorescent tag, each of the first biomols. being bound to a resp. substrate of a plurality of substrate; providing a plurality of second biomols., each of the second biomols. having a second fluorescent tag, binding at least portion of the second biomols. to at least a portion of the first biomols. to form complexes, wherein the plurality of first biomols. and the plurality of second biomols. prior to the binding step have a pre-complexing total fluorescence and wherein the complexes and free second biomols. after the binding step have a post-complexing total fluorescence; and detecting any difference between the pre-complexing total fluorescence and the post-complexing total fluorescence. A sensing device comprising a suspension of a plurality of sensor beads; and a plurality of biomols. bound to at least a portion of the plurality of beads, each of the biomols. having a fluorescent tag is also provided. Diagrams describing the apparatus assembly and operation are given.
OSC.G 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 36 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2002:291694 CAPLUS Full-text
DN 136:291315
TI Method and device for the integrated synthesis of probes and their usage for analysis on a carrier chip
IN Staehler, Cord F.; Gueimil, Ramon; Scheffler, Matthias; Staehler, Peer F.; Heidbrede, Anke
PA Febit Ferrarius Biotechnology G.m.b.H., Germany
SO Ger. Offen., 20 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10051396	A1	20020418	DE 2000-10051396	20001017
WO 2002032567	A1	20020425	WO 2001-EP12027	20011017
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002010552	A	20020429	AU 2002-10552	20011017
EP 1330307	A1	20030730	EP 2001-978431	20011017
EP 1330307	B1	20050907		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
AT 303863	T	20050915	AT 2001-978431	20011017
US 20040043509	A1	20040304	US 2003-399450	20030801
US 7470540	B2	20081230		
US 20090156423	A1	20090618	US 2008-333417	20081212

PRAI DE 2000-10051396 A 20001017
US 2000-60240793 P 20001017
WO 2001-EP12027 W 20011017
US 2003-399450 A1 20030801
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The invention concerns a method and a device for the synthesis of probes, especially nucleic acids on microspheres that are immobilized onto a carrier chip; the probes on the microspheres are used for anal. in combination with the detection capabilities of the carrier chip. After anal. the beads are discarded and the more valuable carrier chip is reused. The chip can be thermostated, it is usually transparent for spectroscopic detection, and can be involved in the non-permanent immobilization of the microspheres using elec. or electromagnetic field effects. As a first step the microspheres are immobilized onto the carrier chip either permanently or non-permanently. The second step is the synthesis of the probes on the beads; different probes can be formed on predetd. locations of the chip; the procedure involves the microflow of monomers and other reagents to the beads. The final step is the usage of the prepared array for anal., e.g. nucleic acid hybridization and fluorometric detection.
OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 37 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2001:904602 CAPLUS Full-text
DN 136:32666
TI Address/capture oligonucleotide tags on microspheres for flow-cytometry based minisequencing
IN White, P. Scott; Torney, David C.
PA The Regents of the University of California, USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001094639	A1	20011213	WO 2001-US18590	20010607
WO 2001094639	A9	20021010		
AU 2001068269	A	20011217	AU 2001-68269	20010607
US 20030190609	A1	20031009	US 2001-877819	20010607
US 20050147998	A1	20050707	US 2004-992971	20041118

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-60210759 P 20000608
US 2001-877819 B1 20010607
WO 2001-US18590 W 20010607
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB A method for generating address/capture tags for use in a sensitive and rapid flow-cytometry based assay for the multiplexed anal. of SNPs based on polymerase-mediated primer extension using microspheres as solid supports is described. Single-nucleotide polymorphisms (SNPs) are the most abundant type of human genetic variation. These variable sites are present at high d. in the genome, making them powerful tools for mapping and diagnosing disease-related alleles. Subnanomolar concns. of sample in small vols. (10 mL) can be analyzed at rates greater than one sample per min, without a wash step. Genomic anal. using multiplexing microsphere arrays, enables the simultaneous anal. of dozens, and potentially hundreds of SNPs per sample. The method has been tested by genotyping the Glu69 variant from the HLA DPB1 locus, an SNP associated with chronic beryllium disease, as well as HLA DPA1 alleles.
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 38 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2000:402289 CAPLUS Full-text
DN 133:174117
TI Capillary Electrochromatography of Proteins on an Anion-Exchanger Column
AU Zhang, Jian; Huang, Xian; Zhang, Shuhong; Horvath, Csaba
CS Department of Chemical Engineering, Yale University, New Haven, CT, 06520, USA
SO Analytical Chemistry (2000), 72(14), 3022-3029
CODEN: ANCHAM; ISSN: 0003-2700
DOI 10.1021/ac000114t
PB American Chemical Society
DT Journal
LA English
AB Capillary electrochromatog. (CEC) of proteins was carried out using 50-μm-i.d. fused-silica capillaries packed with 5-μm silica beads having strong anion-exchanger functions attached to hydrophilic spacers at the chromatog. surface. The siliceous microspheres and the capillary inner wall were treated first with a heterobifunctional silanizing agent and reacted subsequently with a vinyl monomer containing quaternary ammonium groups to form a "tentacular" anion exchanger. A mixture of bovine carbonic anhydrase, α-lactalbumin, soybean trypsin inhibitor, and ovalbumin was separated using CEC by isocratic elution in the codirectional mode with aqueous phosphate buffer, pH 7.0, containing sodium chloride. The retention mechanism of isocratic CEC for proteins on the anion-exchanger column was illustrated by the results of a study on the effect of salt concentration on the separation The potential of CEC for protein separation with high resolution was also demonstrated by electrochromatograms of conalbumin and Hb variants. The results shed light on the mechanism of protein separation by isocratic CEC, which is believed to be a combination of chromatog. retention by electrostatic interactions and electrophoretic migration. Assuming that the contributions of the two mechanisms to the overall migration velocity are additive, an electrochromatog. resolution equation was derived and compared to the resolution equation in HPLC to reveal the constituents responsible for the enhancement of resolution by CEC with respect to that in HPLC. The advantage of CEC was also examined by comparing peak capacities in CEC on an isocratic platform with peak capacities obtained with isocratic and gradient elution HPLC.
OSC.G 59 THERE ARE 59 CAPLUS RECORDS THAT CITE THIS RECORD (59 CITINGS)
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 39 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2000:351749 CAPLUS Full-text
DN 132:345123
TI Device and method for analyzing a biologic sample
IN Lea, Peter
PA Biophys Inc., Can.
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000029847	A2	20000525	WO 1999-CA1079	19991112
WO 2000029847	A3	20000908		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6403384	B1	20020611	US 1999-335732	19990618
CA 2350789	A1	20000525	CA 1999-2350789	19991112
AU 2000011440	A	20000605	AU 2000-11440	19991112
BR 9915406	A	20010724	BR 1999-15406	19991112
EP 1131632	A2	20010912	EP 1999-972308	19991112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002530648	T	20020917	JP 2000-582799	19991112
JP 4544498	B2	20100915		
CA 2289416	C	20050215	CA 1999-2289416	19991112
TW 468046	B	20011211	TW 1999-120038	19991117
WO 2000078917	A1	20001228	WO 2000-US13056	20000512
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2000047126	A	20010109	AU 2000-47126	20000512

PRAI CA 1998-2254223 A 19981116
US 1999-335732 A 19990618
WO 1999-CA1079 W 19991112
WO 2000-US13056 W 20000512
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB A device for separating fluid from a biol. sample when the sample has a fluid and non-fluid component. The device is a point-of-care device through which data may be electronically collected and electronically transmitted for further evaluation. A method for separating fluid from a biol. sample is provided wherein the method comprises the step of bringing the fluid sample in fluid contact with the microspheres such that the fluid component moves by capillary action between the microspheres along capillary channels formed by the spaces between the spheres and leaving, for example, a cellular fraction behind. In the device of the present invention, the step of separating the fluid may be combined with other assay techniques for detecting and/or measuring one or more analytes which may be present in the fluid sample such as immunoassays and chromatog. assays. These may be further combined with groups of microspheres for use in the analyte detection step as well as the separation step whereby the microspheres act as labels for the analyte or as a source of label for the analyte.
OSC.G 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 40 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 1998:119468 CAPLUS Full-text
DN 128:146375
OREF 128:28697a,28700a
TI Reconstruction of spherical torus (low-aspect ratio tokamak) equilibria in absence of magnetic measurements in the central cavity
AU Alladio, F.; Micozzi, P.
CS Centro Ricerche Frascati, Associazione Euratom-ENEA Fusione, Frascati, Italy
SO Nuclear Fusion (1997), 37(12), 1759-1774
CODEN: NUFUAU; ISSN: 0029-5515
DOI 10.1088/0029-5515/37/12/I08
PB International Atomic Energy Agency
DT Journal
LA English
AB Magnetic measurements alone on spherical tori should allow a very good separation of the poloidal beta βP from the internal self-inductance li/2 and should even permit an accurate estimate of the c.d. jΦ profile. However, the reduced space allowed for magnetic sensors near the central conductor in a spherical tokamak, and the possibility of producing flux core spheromak configurations without a central conductor, could imply that magnetic probes are not present in the cavity of the spherical torus. The fluxes and fields of a variety of calculated spherical torus configurations, all endowed with a single or double null separatrix, are analyzed in terms of spherical multipolar moments obtained from simulated magnetic measurements located only upon a sphere surrounding the spherical plasma. The solution to the problem of the absence of magnetic measurements in the cavity of the spherical torus is to fix from non-magnetic measurements (e.g., spectroscopy) the plasma inboard boundary rin on the equatorial plane. This constraint is added to the constraints of matching the spherical multipolar expansion in an iterative solution of the Grad-Shafranov equation, on the basis of a spherical geometry. The convergence of the spherical reconstructive equilibrium code is extremely fast and gives an error on the total plasma current IP of less than 1% at an aspect ratio A = 1.2, an error on the position of the plasma boundary of less than 2% of the radius of the plasma sphere, an error on βP of at most 15% and, finally, the jΦ profile is extremely well reconstructed in peaked, flat and even hollow cases. The effect of an uncertainty ±δrin upon the spectroscopic identification of the plasma inboard boundary on the equatorial plane rin is assessed.
OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L13 ANSWER 41 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 1994:503633 CAPLUS Full-text
DN 121:103633
OREF 121:18554h,18555a
TI Complex combinatorial chemical libraries encoded with tags
IN Still, W. Clark; OHL-Meyer, Michael H. J.; Wigler, Michael; Dillard, Lawrence; Reader, John
PA Columbia University, USA; Cold Spring Harbor Lab.
SO PCT Int. Appl., 147 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9408051	A1	19940414	WO 1993-US9345	19931001
W: AT, AU, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KR, LU, NL, NO, NZ, PL, RO, RU, SE, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, PT, SE				
AU 9455369	A	19940426	AU 1994-55369	19931001
AU 686579	B2	19980212		
EP 665897	A1	19950809	EP 1994-900350	19931001
EP 665897	B1	20030709		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
HU 72495	A2	19960528	HU 1995-952	19931001
JP 08506175	T	19960702	JP 1994-509330	19931001
IL 107166	A	20001031	IL 1993-107166	19931001
AT 244769	T	20030715	AT 1994-900350	19931001
PT 665897	E	20031128	PT 1994-900350	19931001
ES 2204910	T3	20040501	ES 1994-900350	19931001
CA 2143848	C	20070911	CA 1993-2143848	19931001
NO 9501230	A	19950330	NO 1995-1230	19950330
US 6001579	A	19991214	US 1995-485018	19950607
AU 9745258	A	19980212	AU 1997-45258	19971117
AU 716621	B2	20000302		

PRAI US 1992-955371 A 19921001
US 1993-13948 A 19930204
US 1993-130271 B2 19931001
WO 1993-US9345 W 19931001
US 1993-159861 B2 19931130
US 1994-227007 A3 19940413
OS MARPAT 121:103633
AB Methods and compns. are provided for encoded combinatorial chemical, whereby at each stage of the synthesis, a support such as a particle upon which a compound is being synthesized is uniquely tagged to define a particular event, usually chemical, associated with the synthesis of the compound on the support. The tagging is accomplished using identifier mols. which record the sequential events to which the supporting particle is exposed during synthesis, thus providing a reaction history for the compound produced on the support. Various products can be produced in the multi-stage synthesis, such as oligomers and synthetic nonrepetitive organic mols. Conveniently, nested families of compds. can be employed as identifiers, where number and/or position of a substituent define the choice. Alternatively, detectable functionalities may be employed, such as radioisotopes, fluorescers, halogens, and the like, where presence and ratios of two different groups can be used to define stage or choice. Particularly, pluralities of identifiers may be used to provide a binary or higher code, so as to define a plurality of choices with only a few detachable tags. The particles may be screened for a characteristic of interest, particularly binding affinity, where the products may be detached from the particle or retained on the particle. The reaction history of the particles which are pos. for the characteristic can be determined by the release of the tags and anal. to define the reaction history of the particle. An encoded combinatorial library of 2401 peptides was prepared (by solid phase synthesis) having the sequence (X4)EEDLGGGG (X = Asp, Glu, Ile, Lys, Leu, Gln, or Ser). The 4 Gly served as a spacer between the encoded amino acid sequence and the bead. The library included the sequence KLISEEDL, part of the epitope bound by monoclonal antibody 9E10 to the human C-myc gene product. The identifiers used were 2-nitro-4-carboxybenzyl O-aryl-substituted ω-hydroxyalkyl carbonates (aryl = pentachlorophenyl, 2,4,6-trichlorophenyl, or 2,6-dichloro-4-fluorophenyl) and were attached via their carboxylic acids to tag free amino groups

on each bead. The tags were released from each selected bead by photolysis, silylated, and analyzed by electron capture gas chromatog. The binary synthesis code of the bead was directly determined from the chromatogram of the tags.

OSC.G 75 THERE ARE 75 CAPLUS RECORDS THAT CITE THIS RECORD (82 CITINGS)

L13 ANSWER 42 OF 43 CAPLUS COPYRIGHT 2019 ACS on STN
AN 1986:1614 CAPLUS Full-text
DN 104:1614
OREF 104:299a,302a
TI Exon-intron structure of eukaryote genes can be due to the chromatin nucleosome organization and to the features of the gene expression regulation connected with it
AU Solov'ev, V. V.; Kolchanov, N. A.
CS Inst. Tsitol. Genet., Novosibirsk, USSR
SO Doklady Akademii Nauk SSSR (1985), 284(1), 232-7 [Biochem.]
CODEN: DANKAS; ISSN: 0002-3264
DT Journal
LA Russian
AB A model for chromatin nucleosome formation is proposed wherein coding DNA (exons), which is located in the nucleosome, is split, and noncoding DNA (introns) is inserted to ensure proper bead-on-string organization. In support of the model, contextual anal. of the sequences of several eukaryotic genes showed histone-binding AA, TT, AT, and TA pairs, which are near sites of nucleosome formation initiation, to occur at a 1.5-3-fold greater concentration in introns than in exons. Polytracts (A or T), which packed poorly into nucleosome structures, are found at the 5' end of genes and may insure proper nucleosome distribution along the DNA. Enhancer-like sequences, which are capable of Z-DNA formation, are also detected in intron segments. This specific chromatin structure, dictated by intron-exon organization, ensures the accessibility of regulatory regions to proteins which participate in transcription.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L13 ANSWER 43 OF 43 MEDLINE ® on STN
AN 2011894924 MEDLINE Full-text
DN PubMed ID: 21715321
TI A study of the spatial protein organization of the postsynaptic density isolated from porcine cerebral cortex and cerebellum.
AU Yun-Hong Yen
CS Institute of Molecular Medicine, National Tsing Hua University, Hsinchu, Taiwan.
AU Chih-Fan Chuang; Chia-Wei Chang; Yen-Chung Chang
SO Molecular & cellular proteomics : MCP, (2011 Oct) Vol. 10, No. 10, pp. M110.007138. Electronic Publication Date: 28 Jun 2011
Journal code: 101125647. E-ISSN: 1535-9484. L-ISSN: 1535-9476.
Report No.: PMC-PMC3205859.
DOI http://dx.doi.org/10.1074/mcp.M110.007138
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201202
ED Entered STN: 11 Oct 2011
Last Updated on STN: 4 Feb 2012
Entered Medline: 3 Feb 2012
OSC.G 5 There are 5 MEDLINE records that cite this record
REM.CNT 92 There are 92 cited references available in MEDLINE for this document.
AB Postsynaptic density (PSD) is a protein supramolecule lying underneath the postsynaptic membrane of excitatory synapses and has been implicated to play important roles in synaptic structure and function in mammalian central nervous system. Here, PSDs were isolated from two distinct regions of porcine brain, cerebral cortex and cerebellum. SDS-PAGE and Western blotting analyses indicated that cerebral and cerebellar PSDs consisted of a similar set of proteins with noticeable differences in the abundance of various proteins between these samples. Subsequently, protein localization in these PSDs was analyzed by using the Nano-Depth-Tagging method. This method involved the use of three synthetic reagents, as agarose beads whose surface was covalently linked with a fluorescent, photoactivable, and cleavable chemical crosslinker by spacers of varied lengths. After its application was verified by using a synthetic complex consisting of four layers of different proteins, the Nano-Depth-Tagging method was used here to yield information concerning the depth distribution of various proteins in the PSD. The results indicated that in both cerebral and cerebellar PSDs, glutamate receptors, actin, and actin binding proteins resided in the peripheral regions within .apprx. 10 nm deep from the surface and that scaffold proteins, tubulin subunits, microtubule-binding proteins, and membrane cytoskeleton proteins found in mammalian erythrocytes resided in the interiors deeper than 10 nm from the surface in the PSD. Finally, by using the immunoabsorption method, binding partner proteins of two proteins residing in the interiors, PSD-95 and α-tubulin, and those of two proteins residing in the peripheral regions, elongation factor-1α and calcium, calmodulin-dependent protein kinase II α subunit, of cerebral and cerebellar PSDs were identified. Overall, the results indicate a striking similarity in protein organization between the PSDs isolated from porcine cerebral cortex and cerebellum. A model of the molecular structure of the PSD has also been proposed here.

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FILE 'BIOSIS, CAPLUS, MEDLINE' ENTERED AT 13:36:48 ON 12 APR 2019
L1 392 S ((LOCAT? OR ADDRESS? OR SPAC?)(20A)(BEAD? OR MICORBEAD? OR SP
L2 326 DUP REM L1 (66 DUPLICATES REMOVED)
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L4 252 S L2 NOT L3
L5 245 S L4 NOT 2019/PY
L6 232 S L5 NOT 2018/PY
L7 224 S L6 NOT 2017/PY
L8 210 S L7 NOT 2016/PY
L9 205 S L8 NOT 2015/PY

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L10         193 S L9 NOT 2014/PY
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 NEWS  2  JAN  4  DWPI Manual Code revision in 2019
 NEWS  3  JAN 17  First 2019 Emtree(R) update now available in Embase(TM)
 NEWS  4  JAN 29  The 2019 Version of MEDLINE Now Available on STN(TM)
 NEWS  5  FEB  4  INPADOC/INPAFAM: Major enhancements for PCT
 NEWS  6  FEB 26  FRFULL and GBFULL reloaded
 NEWS  7  MAR  7  Search Limits Significantly Expanded Exclusively in STNext(R)
 NEWS  8  MAR  7  New Key Terms field supports efficient full-text searching
                  and results evaluation in Patent Full-text Databases
 NEWS  9  MAR  8  CPC Combination Sets Now Fully Available in Derwent
                  World Patents Index
 NEWS 10  MAR 25  Derwent World Patent Index Coverage Expanded to Include
                  Eight Former Soviet Republics and the Eurasian Patent
                  Organization (EAPO)
 NEWS 11  APR  3  Derwent World Patents Index and Derwent Markush
                  Resource (DWPIM) Now Updated Twice Weekly
 NEWS 12  APR 11  Updates in database World Surface Coatings Abstracts
                  (file WSCA) have resumed

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FULL ESTIMATED COST                                    0.40        0.40

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FILE 'MEDLINE' ENTERED AT 13:24:25 ON 12 APR 2019

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tag?))/bi,ab
L1            85 ((LOCAT? OR ADDRESS OR SPAC?)(20A)(BEAD? OR MICROBEAD? OR SPHERE
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L2            81 L1 NOT 2019/PY

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L3            78 L2 NOT 2018/PY

=> s l3 not 2017/py
L4            76 L3 NOT 2017/PY

=> s l4 not 2016/py
L5            70 L4 NOT 2016/PY

=> s l5 not 2015/py
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=> s l6 not 2014/py
L7            38 L6 NOT 2014/PY

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L9            24 L8 NOT 2012/PY

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L2            81 S L1 NOT 2019/PY
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L4            76 S L3 NOT 2017/PY
L5            70 S L4 NOT 2016/PY
L6            62 S L5 NOT 2015/PY
L7            38 S L6 NOT 2014/PY
L8            27 S L7 NOT 2013/PY
L9            24 S L8 NOT 2012/PY
L10           20 DUP REM L9 (4 DUPLICATES REMOVED)

=> d l10 1-20 bib ab
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L10 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2011:246257 CAPLUS Full-text
DN 155:164894
TI SearchFill: A stochastic optimization code for detecting atomic vacancies in crystalline and non-crystalline systems
AU Davis, Sergio M.; Belonoshko, Anatoly B.; Johansson, Boerje
CS Applied Materials Physics, Department of Materials Science and Engineering, KTH, Stockholm, SE-100 44, Swed.
SO Computer Physics Communications (2011), 182(5), 1105-1110
CODEN: CPHCBZ; ISSN: 0010-4655
DOI 10.1016/j.cpc.2010.12.009
PB Elsevier B.V.
DT Journal
LA English
AB We present an implementation of a stochastic optimization algorithm applied to location of atomic vacancies. Our method labels an empty point in space as a vacancy site, if the total spatial overlap of a "virtual sphere", centered around the point, with the surrounding atoms (and other vacancies) falls below a tolerance parameter. A Metropolis-like algorithm displaces the vacancies randomly, using an "overlap temperature" parameter to allow for acceptance of moves into regions with higher overlap, thus avoiding local min. Once the algorithm has targeted a point with low overlap, the overlap temperature is decreased, and the method works as a steepest descent optimization. Our method, with only two free parameters, is able to detect the correct number and coordinates of vacancies in a wide spectrum of condensed-matter systems, from crystals to amorphous solids, in fact in any given set of atomic coordinates, without any need of comparison with a reference initial structure.
OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2011:1346525 CAPLUS Full-text
DN 156:526034
TI Development of DNA point mutation detection methods using probe DNA-immobilized microbeads
AU Hashimoto, Masahiko; Tamai, Yusuke; Tsukagoshi, Kazuhiko
CS Department of Chemical Engineering and Materials Science, Doshisha University, Kyoto, Japan
SO Science and Engineering Review of Doshisha University (2011), 52(2), 93-98
CODEN: DDRKAZ; ISSN: 0036-8172
PB Doshisha University, Science and Engineering Research Institute
DT Journal
LA Japanese
AB One technique that can distinguish low-abundant mutant DNA from wild-type DNA is the ligase detection reaction (LDR) coupled to a primary polymerase chain reaction (PCR). The LDR products as a target obtained by the sequential PCR/LDR reactions can be analyzed in a variety of fashions such as microarray and slab gel electrophoresis. In the present work, we employed probe DNA-immobilized magnetic microbeads to selectively capture the fluorescently labeled-LDR products via the target hybridization with the probe. After the hybridization, the microbeads were rinsed and introduced into a capillary tube and packed in one space in the tube with a magnet. Photoluminescence from the beads aggregates in the tube was successfully obtained with fluorescence or chemiluminescence detection system, showing that the present method can be amenable to mutation detection.

L10 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN DUPLICATE 1
AN 2011:1147644 CAPLUS Full-text
DN 156:142398
TI Profiling and quantitative evaluation of three nickel-coated magnetic matrices for purification of recombinant proteins: helpful hints for the optimized nanomagnetisable matrix preparation
AU Nejadmoghaddam, Mohammad Reza; Chamankhah, Mahmood; Zarei, Saeed; Zarnani, Amir Hassan
CS Nanobiotechnology Research Center (NBRC), Avicenna Research Institute, ACECR, Tehran, Iran
SO Journal of Nanobiotechnology (2011), 9, 31
CODEN: JNOAAO; ISSN: 1477-3155
URL: http://www.jnanobiotechnology.com/content/pdf/1477-3155-9-31.pdf
DOI 10.1186/1477-3155-9-31
PB BioMed Central Ltd.
DT Journal; (online computer file)
LA English
AB Background: Several materials are available in the market that work on the principle of protein magnetic fishing by their histidine (His) tags. Little information is available on their performance and it is often quoted that greatly improved purification of histidine-tagged proteins from crude exts. could be achieved. While some com. magnetic matrixes could be used successfully for purification of several His-tagged proteins, there are some which have been proved to operate just for a few extent of His-tagged proteins. Here, we address quant. evaluation of three com. available Nickel nanomagnetic beads for purification of two His-tagged proteins expressed in Escherichia coli and present helpful hints for optimized purification of such proteins and preparation of nanomagnetisable matrixes. Results: Marked differences in the performance of nanomagnetic matrixes, principally on the basis of their specific binding capacity, recovery profile, the amount of imidazole needed for protein elution and the extent of target protein loss and purity were obtained. Based on the aforesaid criteria, one of these materials featured the best purification results (SiMAG/N-NTA/Nickel) for both proteins at the concentration of 4 mg/mL, while the other two (SiMAC-Nickel and SiMAG/CS-NTA/Nickel) did not work well with respect to specific binding capacity and recovery profile. Conclusions: Taken together, functionality of different types of nanomagnetic matrixes vary considerably. This variability may not only be dependent upon the structure and surface chemical of the matrix which in turn determine the affinity of interaction, but, is also influenced to a lesser extent by the phys. properties of the protein itself. Although the results of the present study may not be fully applied for all nanomagnetic matrixes, but provide a framework which could be used to profiling and quant. evaluation of other magnetisable matrixes and also provide helpful hints for those researchers facing same challenge.
OSC.G 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 20 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2011:624137 BIOSIS Full-text
DN PREV201100624137
TI Profiling and quantitative evaluation of three Nickel-Coated magnetic matrices for purification of recombinant proteins: helpful hints for the optimized nanomagnetisable matrix preparation.
AU Nejadmoghaddam, Mohammad Reza; Chamankhah, Mahmood; Zarei, Saeed; Zarnani, Amir Hassan [Reprint Author]
CS ACECR, Avicenna Res Inst, Nanobiotechnol Res Ctr NBRC, Tehran, Iran
zarnani25@yahoo.com
SO Journal of Nanobiotechnology, (AUG 8 2011) Vol. 9, pp. Article No.: 31.
http://www.jnanobiotechnology.com/.
ISSN: 1477-3155.
DOI 10.1186/1477-3155-9-31
DT Article
LA English
ED Entered STN: 28 Sep 2011
Last Updated on STN: 13 Jan 2016
AB Background: Several materials are available in the market that work on the principle of protein magnetic fishing by their histidine (His) tags. Little information is available on their performance and it is often quoted that greatly improved purification of histidine-tagged proteins from crude extracts could be achieved. While some commercial magnetic matrices could be used successfully for purification of several His-tagged proteins, there are some which have been proved to operate just for a few extent of His-tagged proteins. Here, we address quantitative evaluation of three commercially available Nickel nanomagnetic beads for purification of two His-tagged proteins expressed in Escherichia coli and present helpful hints for optimized purification of such proteins and preparation of nanomagnetisable matrices.Results: Marked differences in the performance of nanomagnetic matrices, principally on the basis of their specific binding capacity, recovery profile, the amount of imidazole needed for protein elution and the extent of target protein loss and purity were obtained. Based on the aforesaid criteria, one of these materials featured the best purification results (SiMAG/N-NTA/Nickel) for both proteins at the concentration of 4 mg/ml, while the other two (SiMAC-Nickel and SiMAG/CS-NTA/Nickel) did not work well with respect to specific binding capacity and recovery profile.Conclusions: Taken together, functionality of different types of nanomagnetic matrices vary considerably. This variability may not only be dependent upon the structure and surface chemistry of the matrix which in turn determine the affinity of interaction, but, is also influenced to a lesser extent by the physical properties of the protein itself. Although the results of the present study may not be fully applied for all nanomagnetic matrices, but provide a framework which could be used to profiling and quantitative evaluation of other magnetisable matrices and also provide helpful hints for those researchers facing same challenge.

L10 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2009:901702 CAPLUS Full-text
DN 151:261208
TI Liquid phase chip for detecting CYP2C9 and CYP2C19 gene mutation
IN Xu, Jiasen; He, Jiaying; Guo, Yuanjie
PA Guangzhou Surexam Bio-Tech Co., Ltd., Peop. Rep. China
SO Faming Zhuanli Shenqing, 30pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 101487052	A	20090722	CN 2009-10037358	20090224
CN 101487052	B	20111228		

PRAI CN 2009-10037358 20090224

AB A liquid-phase chip comprises: (1) microspheres coated with specific anti-tag sequences and having different colors, (2) wild-type and mutant ASPE primers for each mutation, wherein the primers are composed of 3'-terminal specific sequences and 5'-terminal tag sequences complementary with the anti-tag sequences, and (3) primers for amplifying the target sequences having CYP2C9 and/or CYP2C19 gene mutations. Spacing arms are arranged between the anti-tag sequences and the microspheres. The above 3'-terminal specific sequences of wild-type and mutant ASPE primers are disclosed. The detection with the liquid-phase chip has largely increased fluorescent signal value, sensitivity, signal-to-noise ratio, accuracy and reliability.

L10 ANSWER 6 OF 20 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 2010:443399 BIOSIS Full-text
DN PREV201000443399
TI Transcolonic NOTES Peritoneoscopy for the Detection of Peritoneal Metastases.
AU Voermans, Rogier P.; Faigel, Douglas O.; Henegouwen, Mark I. van Berge; Conlon, Sean; Spivey, James T.; Rowe, Renee L.; Sheppard, Brett C.; Fockens, Paul
SO Gastroenterology, (MAY 2009) Vol. 136, No. 5, Suppl. 1, pp. A648.
Meeting Info.: Digestive Disease Week/110th Annual Meeting of the American-Gastroenterological-Association. Chicago, IL, USA. May 30 -June 04, 2009. Amer Gastroenterol Assoc.
CODEN: GASTAB. ISSN: 0016-5085.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 4 Aug 2010
Last Updated on STN: 4 Aug 2010
AB Background: Natural Orifice Transluminal Endoscopic Surgery (NOTES) peritoneoscopy could replace laparoscopic peritoneoscopy (LAP) for staging of gastrointestinal malignancies. In previously performed porcine experiments we successfully created a model for peritoneal metastases and established a benchmark for LAP detection. In this model the NOTES transgastric peritoneoscopy (TGP) appeared to be inferior to LAP, mainly due to limited visualization of the liver. Visualisation of the liver could be improved by approaching through the colon. Aim: To compare the transcolonic peritoneoscopy (TCP) with previously set LAP standard in detecting peritoneal metastases. Methods: This investigator-initiated protocol was performed in a live acute porcine model. 2.5 mm color-coded beads were stapled via LAP in the peritoneum to simulate metastases. In the same model we previously established the benchmark for LAP detection: yield 95% of beads (90% CI: 91-100%). Using a non-inferiority design a sample size of 31 beads was determined. Three to 7 beads were placed in each of 6 animals. Randomization was performed for number and location of beads. Locations were based on the most likely targets for metastases and included: abdominal peritoneum (4 beads), diaphragm (8), surface of liver and hepatoduodenal ligament (18), and miscellaneous sites (1). TCP was then performed with a 2 channel therapeutic endoscope using either standard accessories (forceps, cap; TCP-s) or with a specially designed toolkit (bendable overtube, articulating retractors and graspers; TCP-t) in randomized order by one of 2 endoscopists, blinded to bead placement. Results: A total of 31 beads were placed into 6 pigs. TCP-s found 23 beads (yield 74%, 90% CI: 67-88%, non-inferior to LAP minus the margin of equivalence). TCP-t found 17 beads (yield 55%; 90% CI: 39-70%, inferior to LAP minus the margin of equivalence). TCP-s was superior for detecting beads in comparison with TCP-t (p=0.034). TCP-s was, using a transparent cap, superior in detecting beads on the inferior liver surface. Exclusion of these liver beads resulted in non significant difference between TCP-s and TCP-t (p=0.317). Conclusions: In this prospective, blinded, comparative trial, TCP was non inferior in comparison with the predetermined standard. The use of a transparent cap improved visualization of the inferior liver surface and should be integrated in the bendable overtube to achieve optimal results. TCP seems to result in improved visualization of the liver in comparison with TGP.

L10 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2008:1051430 CAPLUS Full-text
DN 149:371618
TI Method and liquid-phase chip for detecting and typing human papilloma virus
IN Xu, Jiasen; Lin, Yiqun; Yang, Huiyi
PA Guangzhou Surexam Biotech Co., Ltd., Peop. Rep. China
SO Faming Zhuanli Shenqing, 29pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 101250593	A	20080827	CN 2008-10026275	20080203
CN 101250593	B	20110126		

PRAI CN 2008-10026275 20080203

AB The title liquid-phase chip comprises: microspheres coated with specific anti-tag sequences, specific ASPE primers designed according to each human papilloma virus (HPV) subtypes, and primers for amplifying the target sequence containing mutation site. The anti-tag sequences are immobilized on the microspheres via spacing arm sequence of 7-10 T bases. The anti-tag sequences are selected from two or more of SEQ ID Number 25-SEQ ID Number 47. The ASPE primers are selected from two or more of SEQ ID Number 1-SEQ ID Number 23. Each ASPE primer comprises mutation-specific sequence at 3'-end, and a tag sequence at 5'-end. The tag sequence is complementary with the anti-tag sequence. The liquid-phase chip has the advantages of wide application range, high sensitivity, high signal/noise ratio, and accurate results.

L10 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2008:918964 CAPLUS Full-text
DN 150:162515
TI Use of stagnation point flows for DNA trapping, manipulation, and target sequence detection
AU Dylla-Spears, Rebecca; Sohn, Lydia L.; Muller, Susan J.
CS Department of Chemical Engineering, University of California, Berkeley, CA, 94720, USA
SO AIP Conference Proceedings (2008), 1027(Pt. 2, 15th International Congress on Rheology, 2008), 959-961
CODEN: APCPCS; ISSN: 0094-243X
PB American Institute of Physics
DT Journal
LA English
AB We use a stagnation point flow to manipulate single mols. of double-stranded genomic DNA for applications requiring detection of specific sequences along the DNA backbone. Fluorescent polystyrene beads are surface-functionalized with site-specific probes and incubated with fluorescently labeled double-stranded γ-DNA. The solution is introduced into a microfluidic cross slot where the tagged DNA mols. are trapped and elongated at the stagnation point of the planar extensional flow. Beads bound along the stretched DNA may be directly observed, and their locations along the backbone determined, using fluorescence microscopy. We have demonstrated the feasibility of this method for detection of specific sequences. (c) 2008 American Institute of Physics.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 20 MEDLINE® on STN
AN 2008717598 MEDLINE Full-text
DN PubMed ID: 18982660
TI Fast marker based C-Arm pose estimation.
AU Kainz Bernhard
CS Institute for Computer Graphics and Vision, Graz University of Technology, Austria. kainz@icg.tugraz.at
AU Grabner Markus; Ruther Matthias
SO Medical image computing and computer-assisted intervention : MICCAI ... International Conference on Medical Image Computing and Computer-Assisted Intervention, (2008) Vol. 11, No. Pt 2, pp. 652-9.
Journal code: 101249582.
CY Germany: Germany, Federal Republic of
DT (EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print
EM 200812
ED Entered STN: 6 Nov 2008
Last Updated on STN: 2 Jan 2009
Entered Medline: 30 Dec 2008
OSC.G 3 There are 3 MEDLINE records that cite this record
AB To estimate the pose of a C-Arm during interventions therapy we have developed a small sized X-Ray Target including a special set of beads with known locations in 3D space. Since the patient needs to remain in the X-Ray path for all feasible poses of the C-Arm during the intervention, we cannot construct a single marker which is entirely visible in all images. Therefore finding 2D-3D point correspondences is a non-trivial task. The marker pattern has to be chosen in a way such that its projection onto the image plane is unique in a minimal-sized window for all relevant poses of the C-Arm. We use a two dimensional adaption of a linear feedback shift register (LFSR) to generate a two-dimensional pattern with unique sub-patterns in a certain window range. Thereby uniqueness is not achieved by placing unique 2D sub patterns side by side but by the code property itself. The code is designed in a way that any sub window of a minimal size guarantees uniqueness and that even occlusions from medical instruments can be handled. Experiments showed that we were able to estimate the C-Arm's pose from a single image within one second with a precision below one millimeter and one degree.

L10 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2009:178700 CAPLUS Full-text
DN 150:253112
TI First application of PCR-Luminex system for molecular diagnosis of fungicide resistance and species identification of fungal pathogens
AU Ishii, Hideo; Tanoue, Junko; Oshima, Michiyo; Chung, Wen-Hsin; Nishimura, Kumiko; Yamaguchi, Junichiro; Nemoto, Fumihiro; So, Kazuhiro; Iwama, Toshitaka; Yoshimatsu, Hideaki; Shimizu, Motoshige; Kozawa, Toru
CS National Institute for Agro-Environmental Sciences, Kannondai 3-1-3, Tsukuba, Ibaraki, 305-8604, Japan
SO Journal of General Plant Pathology (2008), 74(6), 409-416
CODEN: JGPPBQ; ISSN: 1345-2630
DOI 10.1007/s10327-008-0119-z
PB Springer Japan
DT Journal
LA English
AB Fungicide resistance in plant pathogens is often caused by a single point mutation in a gene encoding fungicide target proteins. Such is the case for resistance to MBI-D (inhibitors of scytalone dehydratase in melanin biosynthesis) fungicides in rice blast fungus (Magnaporthe oryzae), which is caused by a mutation in the scytalone dehydratase gene that results in a replacement of valine with methionine at codon 75 of the fungicide target protein. PCR-Luminex, a novel system developed for high-throughput anal. of single nucleotide polymorphisms (SNPs) was successfully introduced to diagnose MBI-D resistance using specific oligonucleotide probes coupled with fluorescent beads. The PCR-Luminex system was further tested for its potential in identifying species causing Fusarium head blight on wheat. Four major pathogens, Fusarium graminearum (=F. asiaticum), F. culmorum, F. avenaceum, and Microdochium nivale, known to cause the disease, were tested, and the species were identified using the PCR-Luminex method. So far, this report is the first on the application of the DNA-based PCR-Luminex system in the area of crop protection and/or agricultural sciences.
OSC.G 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2007:359116 CAPLUS Full-text
DN 146:352601
TI Purifying nucleic acids using oligonucleotide attached to solid support
IN Slepnev, Vladimir I.
PA Primera Biosystems, Inc., USA
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007035685	A2	20070329	WO 2006-US36382	20060918
WO 2007035685	A3	20080124		

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

CA 2622712	A1	20070329	CA 2006-2622712	20060918
US 20070072223	A1	20070329	US 2006-523255	20060918
EP 1924591	A2	20080528	EP 2006-814900	20060918

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PRAI US 2005-60717593 P 20050916
WO 2006-US36382 W 20060918
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Described herein are compns. and methods for enriching a nucleic acid sample for target sequence(s). The compns. comprise an oligonucleotide attached to a solid support, directly or indirectly, wherein the oligonucleotide does not serve as a primer for a polymerase enzyme. Also provided is a method of performing a polymerase reaction using the compns. provided herein. The composition of the present invention can further comprise a second oligonucleotide. The second oligonucleotide comprises a tag binding sequence is substantially complementary to and hybridizes to a tag sequence within the first oligonucleotide. In one embodiment, the second oligonucleotide further comprises a target binding sequence, which is covalently linked to the tag binding sequence. Two examples of one oligonucleotide composition are single oligonucleotide attached at its 3' end to a magnetic bead, and attached at an internal location to a silica bead; the 3' terminal nucleotide being a substituted dideoxy nucleotide which prevents the oligonucleotide from serving as a primer for a polymerase enzyme.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L10 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN DUPLICATE 2
AN 2008:615762 CAPLUS Full-text
DN 149:4179
TI Neutron spectrometry in a pet cyclotron with a Bonner sphere system
AU Fernandez, F.; Amgarou, K.; Domingo, C.; Garcia, M. J.; Quincoces, G.; Marti-Climent, J. M.; Mendez, R.; Barquero, R.
CS Group de Fisica de les Radiations, Departament de Fisica, Universitat Autonoma de Barcelona, Bellaterra, E-08193, Spain
SO Radiation Protection Dosimetry (2007), 126(1-4), 371-375
CODEN: RPDODE; ISSN: 0144-8420
DOI 10.1093/rpd/ncm077
PB Oxford University Press
DT Journal
LA English
AB Positron emission tomog. (PET) is a non-invasive medical imaging technique normally used for diagnostic purposes to determine the location and concentration of physiol. active compds. in a human body. An unshielded cyclotron is used for PET at the Clinica Universitaria de Navarra to produce short-lived positron emitting radionuclides (15O, 13N, 11C and 18F) by bombarding appropriate target material with proton or deuteron beams with energies up to 18 and 9 MeV, resp. Subsequent nuclear reactions may generate undesirable neutrons that should be evaluated and controlled. In this study, the neutron measurements performed with an active and a passive Bonner sphere systems at different locations outside and inside the cyclotron vault during operation have been presented. The neutron spectrum at each location was determined with an unfolding code developed by the authors.
OSC.G 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2006:294061 CAPLUS Full-text
DN 145:391545
TI Injection and manipulation of silicon microbeads in a customized microfluidic platform
AU Hoffmann, Daniel; Brennan, Des; Loughran, Michael
CS Biophotonics and Microfluidics Research, Tyndall National Institute, Univ. College Cork, Cork, Ire.
SO Proceedings of SPIE-The International Society for Optical Engineering (2006), 6112(Microfluidics, BioMEMS, and Medical Microsystems IV), 61120E/1-61120E/8
CODEN: PSISDG; ISSN: 0277-786X
DOI 10.1117/12.660342
PB SPIE-The International Society for Optical Engineering
DT Journal
LA English
AB The first on-chip injection and manipulation of optically encoded, silicon microbeads in a microfluidic platform is reported. Encoded microbeads of different shapes and sizes were fabricated in silicon via standard microfabrication techniques. The optical signature consisted of a series of lithog. defined bar-codes, which can be identified by a laser detection system. In-situ identification of encoded microbeads was possible at microbead velocities ≤ 50 cm per s. The microbeads can also be transported within a channel network in accordance with the encoded optical signature of each bead. The microbead transport is controlled by the laminar flow of a liquid in pressure driven microchannels. Hydrodynamic pulsing facilitated single and multiple injection of microbeads from a reservoir into the laminar fluid stream of a branched microfluidic network. Careful control of the fluid velocity and alteration of the microchannel geometry also enabled manipulation of microbead velocity. The incorporation of five pillars to retain microbeads at a specific location within the microchannel network formed the basis of a reaction chamber for on chip functionalization of microbeads. The principle of hydrodynamic switching was utilized to re-direct the transport of microbeads at a branched microfluidic network. In the final part of this research the authors verify that this microbead technol. is suitable for detection of specific target DNA.
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2005:371399 CAPLUS Full-text
DN 142:405531
TI Mutation typing method by identification tag ligation and sequencing
IN Koyama, Nobuto; Mineno, Junichi; Yamashita, Shusaku; Yamanaka, Nao; Sato, Masahiro; Izu, Hiroyuki; Takayama, Masanori; Asada, Kiyozo; Kato, Ikunoshin
PA Takara Bio Inc., Japan
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005038026	A1	20050428	WO 2004-JP15214	20041015

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI JP 2003-356850 A 20031016
AB A method of typing a mutation characterized by comprising the step of preparing target DNA containing a mutation site to be typed, the step of attaching a sample identification code to the target DNA, and the step of determining the base sequence of a region containing the sample identification code and the mutation site in the target DNA having the sample identification code attached thereto. A variation of the method comprises (a) ligation of ID code and the mutation site-containing region to a tag vector to construct a tag library, (b) preparing tag-ligated DNA from the library, (c) ligating to microbeads, (d) ligating initiation adaptor to the end of labeled DNA on microbeads, (e) spreading microbeads two dimensionally on flow cell and recording the location of each beads, (f) cleaving DNA on microbeads with restriction enzyme to obtain sticky ends, (g) ligating complementary encoded adaptor to the target DNA on microbeads, (h) hybridizing microbeads with decoder probe to analyze encoded adaptor, (i) removing decoder probe from microbeads to use microbeads in steps after (f).
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2003:856135 CAPLUS Full-text
DN 139:347728
TI Method for detecting ligands and targets in a mixture
IN Hammond, David J.; Lathrop, Julia Tait
PA American National Red Cross, USA
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 6
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003089922	A1	20031030	WO 2003-US11799	20030414
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2482529	A1	20031030	CA 2003-2482529	20030414
AU 2003231731	A1	20031103	AU 2003-231731	20030414
US 20030212253	A1	20031113	US 2003-414524	20030414
US 7223734	B2	20070529		
EP 1495318	A1	20050112	EP 2003-747009	20030414
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005522712	T	20050728	JP 2003-586604	20030414
JP 4585766	B2	20101124		
CN 1659432	A	20050824	CN 2003-813727	20030414
CN 100525829	C	20090812		
HK 1082040	A1	20100423	HK 2006-102446	20060223
US 20080160501	A1	20080703	US 2007-797318	20070502
US 20090258834	A1	20091015	US 2007-802730	20070524
PRAI US 2002-60372091	P	20020415		
US 2003-414524	A1	20030414		
WO 2003-US11799	W	20030414		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention provides a method of characterizing a target that binds to a ligand. The method comprises providing ligands, optionally attached to a support, and contacting the ligands with targets to allow at least one target to bind to at least one ligand. The method further comprises immobilizing the resulting complexes in a first matrix, such that each complex has a different position within the first matrix, and transferring the target of the complex to a second matrix. The position of the target within the second matrix corresponds to the position of the ligand-support complex within the first matrix. The target on the second matrix is then detected. Ligand-support complexes displaying a library of peptide hexamers were incubated with diluted blood plasma. The beads were washed, suspended in buffer, combined with low m.p. agarose and spread across an agarose base. The resin-agarose mixture was allowed to harden to form a gel system before target protein was transfered onto a second matrix membrane and detected. Resin beads aligning with locations of target protein on the membrane were selected, washed, and reincubated with plasma. Transfer and detection of target protein on the membrane was repeated. Several peptides were identified that bound to both von Willebrand factor and to Factor VIII.

OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2002:664468 CAPLUS Full-text
DN 137:334742
TI Detection of DNA hybridization via fluorescent polymer superquenching
AU Kushon, Stuart A.; Ley, Kevin D.; Bradford, Kirsten; Jones, Robert M.; McBranch, Duncan; Whitten, David
CS QTL Biosystems LLC, Santa Fe, NM, 87507, USA
SO Langmuir (2002), 18(20), 7245-7249
CODEN: LANGD5; ISSN: 0743-7463
DOI 10.1021/la026211u
PB American Chemical Society
DT Journal
LA English
AB An assay for a target single strand 20-base sequence of DNA coding for the anthrax lethal factor, based on conjugated polymer fluorescence superquenching, is reported. The assay employs a platform in which the receptor (a biotinylated complementary sequence "capture strand") and polymer (two components: an anionic poly(phenylene ethynylene) (PPE) and a biotinylated -PPE) are co-located on streptavidin-derivatized polystyrene microspheres. A conjugate of the target strand with the energy transfer quencher QSY-7 (DNA-QTL) is used to construct competition assays for the target. A direct competition assay between the target-DNA and DNA-QTL for the microsphere-bound capture is only marginally successful due evidently to greater kinetic affinity of the polymer-capture ensemble for the conjugate. However a sequential addition of target, followed by DNA-QTL affords a quant. assay for the target by attenuation of PPE fluorescence quenching by the DNA-QTL. Likewise a direct competition in solution between the target and DNA-QTL for the biotinylated capture strand followed by addition of microspheres provides a sensitive and quant. assay for the target single strand DNA.
OSC.G 121 THERE ARE 121 CAPLUS RECORDS THAT CITE THIS RECORD (121 CITINGS)
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 2000:191259 CAPLUS Full-text
DN 132:232708
TI Method for identification in Drosophila of dominant suppressor genes useful for gene therapy
IN Rorth, Pernille; Cohen, Stephen M.
PA European Molecular Biology Laboratory, Germany
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000015843	A1	20000323	WO 1999-IB1548	19990907
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9955283	A	20000403	AU 1999-55283	19990907
PRAI GB 1998-19914	A	19980911		
WO 1999-IB1548	W	19990907		

AB The invention relates to a method for the identification of a dominant suppressor gene useful in gene therapy and the use of the identified gene for diagnosis or treatment of a disease caused by a genetic mutation in a mammal. The genes are identified in Drosophila by a screening technique that utilizes a modular misexpression system that allows conditional expression of genes tagged by insertion of a P-element carrying a GAL4 regulatable Enhancer and a basal promoter oriented to direct expression of adjacent genes. A Drosophila strain carrying a mutant gene is crossed with a library of target strain to form a crossed strain, and the gene that alters the level or effects of expression of the mutant gene is identified. The gene therapy consists of introducing the dominant suppressor gene cloned in a vector under the control of regulatory sequences to block the abnormal mutant gene activity in a mammal. In particular, gene therapy for cancer, neurodegenerative disease, or T cell acute lymphocytic lymphoma, using LDB1 dominant suppressor gene is proposed. Two EP element insertions on the Drosophila X chromosome producing phenotypes suggesting a role in dorsal-ventral axis formation when expressed in the developing wing, were independently isolated. These elements, EP1306 and EP1394, were mapped to cytol. position 17C1-4 on polytene chromosome corresponding to Beadex gene location, and the sequence adjacent to the insertion sites were overexpressed in Beadex1 mutant wing disks, suggesting that the EP elements direct the expression of the Beadex gene. Genetic interactions between Beadex and apterous or chip genes were observed Studies suggested that the protein encoded by the Beadex gene, dLMO protein, competes with Apterous for binding to Chip and thus interferes with Apterous-Chip complex formation.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 18 OF 20 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
DUPLICATE 3
AN 1996:361748 BIOSIS Full-text
DN PREV199699084104
TI Selection of chymotrypsin inhibitors from a conformationally-constrained combinatorial peptide library.
AU McBride, Jeffrey D.; Freeman, Neil; Domingo, Gonzalo J.; Leatherbarrow, Robin J. [Reprint author]
CS Dep. Chemistry, Imperial Coll. Sci. Technol. Med., South Kensington, London SW7 2AY, UK
SO Journal of Molecular Biology, (1996) Vol. 259, No. 4, pp. 819-827.
CODEN: JMOBAK. ISSN: 0022-2836.
DT Article
LA English
ED Entered STN: 14 Aug 1996
Last Updated on STN: 14 Aug 1996
AB A synthetic library of cyclic peptides was constructed utilizing the anti-tryptic loop region of the Bowman-Birk inhibitor, D4 from Macrotyloma axillare, as a template. The loop region of this proteinase inhibitor was reproduced by an 11 residue sequence, conformationally constrained by the presence of a disulfide bridge, to act as a mimetic of the functional reactive site region of this protein. This sequence, plus a pentaglycine spacer arm, was used to create a "one bead, one peptide" combinatorial library after on-resin deprotection and cyclization. Randomization at three positions considered to be important for proteinase specificity (P-2, P-1 and P-2) with the genetically coded amino acids (minus cysteine) plus norleucine generated 8000 permutations. Screening this library with biotinylated alpha-chymotrypsin under appropriate conditions revealed a small number (lt 0.05%) of beads that selectively bound the labeled proteinase. The sequences present on these active beads were determined, and found to have a well-defined consensus. Analysis of chymotrypsin inhibition in solution using re-synthesized peptides reveals that the sequences identified are potent inhibitors with K-i values in the nanomolar range. These results show that directed randomization of the canonical loop is a powerful way of generating proteinase inhibitors with targeted specificities. Incorporation of selective random changes within a defined structural framework is found to be an effective means of generating variation in large synthetic systems. The functional basis for inhibition by the identified sequences is discussed.

L10 ANSWER 19 OF 20 BIOSIS COPYRIGHT (c) 2019 Clarivate Analytics on STN
AN 1993:79987 BIOSIS Full-text
DN PREV199395044487
TI Quantitative single photon emission tomography: Verification for sources in an elliptical water phantom.
AU Ljungberg, Michael H. [Reprint author]; King, Michael A.; Strand, Sven-Erik
CS Radiation Physics Dep, Univ. Lund, Lasarettet, S-22185 Lund, Sweden
SO European Journal of Nuclear Medicine, (1992) Vol. 19, No. 10, pp. 838-844. CODEN: EJNMD9. ISSN: 0340-6997.
DT Article
LA English
ED Entered STN: 26 Jan 1993
Last Updated on STN: 26 Jan 1993
AB Accurate absorbed dose calculations are important for a proper dose planning in internal radionuclide therapy. The activity distribution must be measured and the target volume defined. This can be done with single photon emission tomography (SPET) if proper attenuation and scatter correction are employed. This study investigated the calculation of the activity and the volume of different spherical sources. These two parameters are essential for a proper dose calculation. The scatter and attenuation correction method is based on spatially variant scatter functions and density maps. The volume calculation method is based on obtaining a threshold from a grey-level histogram. Both point sources and spheres of different diameters containing technetium-99m were placed in different locations in an elliptical water phantom and imaged by SPET. The activity and the volume of the spheres were calculated from the SPET images and compared with known activities. Results show a quantification of activity within 10% for most of the sources. Important influences on the quantification are (a) the presence of artefacts due to improper reconstruction and (b) the finite spatial resolution which affects the total number of counts within the determined volume.

L10 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2019 ACS on STN
AN 1976:23528 CAPLUS Full-text
DN 84:23528
OREF 84:3831a,3834a
TI Neutron spectrum from an oralloy sphere
AU Ragan, C. E.; Auchampaugh, G. F.; Hemmendinger, A.; Silbert, M. G.
CS Los Alamos Sci. Lab., Los Alamos, NM, USA
SO Report (1975), LA-5949-MS, 15 pp. Avail.: NTIS
From: Nucl. Sci. Abstr. 1975, 32(7), Abstr. No. 18502
DT Report
LA English
AB The neutron [12586-31-1] spectrum from a 38-kg fully enriched U (orally) sphere, pulsed by a centrally located 14-MeV n source, was measured by using time-of-flight (TOF) techniques. The nearly isotropic source of 14-MeV n was produced by bombarding a T gas target with low-energy d. Neutrons of 0.180-15.0 MeV were detected at the end of a partially evacuated, 39-m flight path by a NE-213 liquid scintillator that used pulse-shape discrimination to distinguish n events from γ-ray events. Detector thresholds of 0.15 and 0.85 MeV were used to cover the energy range, and the detector efficiency was measured over this range by using monoenergetic n from T(p,n), T(d,n), and D(d,n) reactions. Several measurements of the TOF spectrum were used to determine the n flux at the detector, and a comparison of this flux with the results of Monte-Carlo calcns. is presented. These calcns. were performed with the code MCN using 2 cross-section sets, those from Lawrence Livermore Laboratory and those from ENDF/B-IV library. The results calculated by using ENDF/B-IV cross sections are in excellent agreement with measurements, especially at 1-6 MeV, where the uncertainties in both the calculated and exptl. results are smallest.

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FILE 'BIOSIS, CAPLUS, MEDLINE' ENTERED AT 13:24:25 ON 12 APR 2019
L1 85 S ((LOCAT? OR ADDRESS OR SPAC?)(20A)(BEAD? OR MICROBEAD? OR SPH
L2 81 S L1 NOT 2019/PY
L3 78 S L2 NOT 2018/PY
L4 76 S L3 NOT 2017/PY
L5 70 S L4 NOT 2016/PY
L6 62 S L5 NOT 2015/PY
L7 38 S L6 NOT 2014/PY
L8 27 S L7 NOT 2013/PY
L9 24 S L8 NOT 2012/PY
L10 20 DUP REM L9 (4 DUPLICATES REMOVED)

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	261.79	262.19

STN INTERNATIONAL LOGOFF AT 13:27:36 ON 12 APR 2019

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 47706-0004006	Application No. 16/414,213
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	1.	4,683,195	7/28/1987	Mullis			
	2.	4,883,867	11/28/1989	Lee			
	3.	5,002,882	3/26/1991	Lunnen			
	4.	5,308,751	5/3/1994	Ohkawa			
	5.	5,455,166	10/3/1995	Walker			
	6.	5,512,439	4/30/1996	Hornes			
	7.	5,512,462	4/30/1996	Cheng			
	8.	5,599,675	2/4/1997	Brenner			
	9.	5,641,658	6/24/1997	Adams			
	10.	5,750,341	5/12/1998	Macevicz			
	11.	5,763,175	6/1/1998	Brenner			
	12.	5,912,148	6/15/1999	Eggerding			
	13.	6,013,440	1/11/2000	Lipshutz			
	14.	6,130,073	10/10/2000	Eggerding			
	15.	6,143,496	11/7/2000	Brown			
	16.	6,153,389	11/28/2000	Haarer			
	17.	6,210,891	4/3/2001	Nyren			
	18.	6,210,894	4/3/2001	Brennan			
	19.	6,214,587	4/10/2001	Dattagupta			
	20.	6,258,558	7/10/2001	Szostak			
	21.	6,258,568	7/10/2001	Nyren			
	22.	6,266,459	7/24/2001	Walt			
	23.	6,281,804	8/28/2001	Haller			
	24.	6,309,824	10/30/2001	Drmanac			
	25.	6,344,316	2/5/2002	Lockhart			
	26.	6,355,431	3/12/2002	Chee			

Examiner Signature	/JAMES MARTINELL/	Date Considered	06/03/2019

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.M./

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 47706-0004006	Application No. 16/414,213
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	27.	6,401,267	6/11/2002	Drmanac			
	28.	6,404,907	6/11/2002	Gilchrist			
	29.	6,416,950	7/9/2002	Lohse			
	30.	6,485,982	11/26/2002	Charlton			
	31.	6,579,695	6/17/2003	Lambalot			
	32.	6,632,641	10/14/2003	Brennan			
	33.	6,770,441	8/3/2004	Dickinson			
	34.	6,773,886	8/10/2004	Kaufman			
	35.	6,787,308	9/7/2004	Balasubramanian			
	36.	6,800,453	10/5/2004	Labaer			
	37.	6,828,100	12/7/2004	Ronaghi			
	38.	6,833,246	12/21/2004	Balasubramanian			
	39.	6,878,515	4/12/2005	Landegren			
	40.	6,897,023	5/24/2005	Fu			
	41.	6,911,345	6/28/2005	Quake			
	42.	6,969,488	11/29/2005	Bridgham			
	43.	6,969,589	11/29/2005	Patil			
	44.	6,977,033	12/20/2005	Becker			
	45.	7,052,244	5/30/2006	Fouillet			
	46.	7,057,026	6/6/2006	Barnes			
	47.	7,115,400	10/3/2006	Adessi			
	48.	7,118,883	10/10/2006	Inoue			
	49.	7,163,612	1/16/2007	Sterling			
	50.	7,211,414	5/1/2007	Hardin			
	51.	7,229,769	6/12/2007	Kozlov			
	52.	7,264,929	9/4/2007	Rothberg			

Examiner Signature	Date Considered
/JAMES MARTINELL/	06/03/2019

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.M/

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 47706-0004006	Application No. 16/414,213
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	53.	7,297,518	11/20/2007	Quake			
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Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
	475.	PCT International Search Report and Written Opinion issued in International Appln. No. PCT/US2011/031163, dated 5/23/2011, 8 pages
	476.	PCT International Search Report and Written Opinion issued in International Appln. No. PCT/US2011/031308, dated 6/7/2011, 8 pages
	477.	PCT International Search Report and Written Opinion issued in International Appln. No. PCT/US2012/032759, dated 9/28/2012, 14 pages
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	479.	Perler et al., "Intervening sequences in an Archaea DNA polymerase gene," PNAS USA, June 1992, 89(12): 5577-5581
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	485.	Ronaghi et al., "A sequencing method based on real-time pyrophosphate," Science, July 1998, 281(5375): 363-365
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	489.	ROUNTENBERG et al., "Microfluidic probe: a new tool for integrating microfluidic environments and electronic wafer-orobina," Lab Chip, October 2009, 10: 123-127
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	494.	Schlapak et al., "Glass surfaces grafted with high-density poly (ethylene glycol) as substrates for DNA oligonucleotide microarrays," Langinuir, January 2006, 22: 277-285
	495.	Schmitt et al., "Detection of ultra-rare mutations by next-generation sequencing," PNAS (2012) 109:14508-14523

Examiner Signature	Date Considered
/JAMES MARTINELL/	06/03/2019

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form

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Other Documents (include Author, Title, Date, and Place of Publication)		
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	496.	SERGEEVA et al., "Display technologies: Application for the discovery of drug and gene delivery aaents," Advanced Drua Delivery Reviews (2006) 58(15):1622-1654
	497.	Seurynck-Servoss et al., "Evaluation of Surface Chemistries for Antibody Microarrays", Anal Biochem., 371(1): 105–115, 2007
	498.	Shelbourne et al., "Fast copper-free click DNA ligation by the ring-strain promoted alkyne-azide cycloaddition reaction.", Chem. Commun., 47: 6257-6259, 2011
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	500.	Shi et al., "The MicroArray Quality Control (MAQC) project shows inter- and intraplatform reproducibility of gene expression measurements," Nature Biotechnology, 2006, 24(9):1151-61
	501.	Shirai et al., "Novel Tools for Analyzing Gene Expressions in Single Cells," The 5th International Workshop on Approaches to Single-Cell Analysis, The University of Tokyo, March 3-4th 2011, 1 page
	502.	SHOEMAKER et al., "Quantitative phenotypic analysis of yeast deletion mutants using a highly parallel molecular bar-coding strategy," Nature genetics (1996) 14:450-456
	503.	SHULTS et al., "A multiplexed protein kinase assay," Chem Bio Chem (2007) 8:933-942
	504.	Sievertzon et al., "Transcriptome analysis in primary neural stem cells using a tag cDNA amplification method," BMC Neuroscience, December 2005, 6: 28
	505.	Slonim and Yanai, "Getting started in gene expression microarray analysis," Plos Computational Biology, 2009, 5(10):e1000543
	506.	Soni and Meller, "Progress toward ultrafast DNA sequencing using solid-state nanopores," Clin Chem., 2007, 53: 1996-2001
	507.	Spitale et al., "Structural imprints in vivo decode RNA regulatory mechanisms", Nature, 519(7544): 486-90, 2015
	508.	Spurgeon et al., "High Throughput Gene Expression Measurement with Real Time PCR in a Microfluidic Dynamic Array," PlosONE, 2008, 3(2):e1662
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	510.	Sun et al., "Direct immobilization of DNA probes on non-modified plastics by UV irradiation and integration in microfluidic devices for rapid bioassay," Anal. Bio. Chem., 402: 741-748, 2012
	511.	TAKAHASHI et al., "In Vitro Selection of Protein and Peptide Libraries Using mRNA Display," Nucleic Acid and Peptide Aptamers: Methods and Protocols (2009) 535:293-314 (Ch.17).
	512.	Tang et al., "RNA-Seq analysis to capture the transcriptome landscape of a single cell.," Nat Protoc., 5: 516-35, 2010
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	514.	Taylor et al., "Mitochondrial DNA mutations in human disease." Nature Reviews Genetics. May 2005, 6(5):389-402
	515.	Thornton, "High rate thick film growth." Annual review of materials science, August 1977, 7(1):239-60

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	516.	Tian et al., "Antigen peptide-based immunosensors for rapid detection of antibodies and antigens," Anal Chem May 26, 2009, 81 (13):5218-5225
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	533.	Woo et al., "A Comparison of cDNA, Oligonucleotide, and Affymetrix GeneChip Gene Expression Microarray Platforms," Journal of Biomolecular Techniques, 2004, 15(4), 276-284
	534.	WORTHINGTON et al., "Cloning of random oligonucleotides to create single-insert plasmid libraries," Analyt. Biochem, 2001, 294:169-175
	535.	XIAO et al., "Direct determination of haplotypes from single DNA molecules," Nature Methods, 2009, 6(3):199-01

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		Applicant: Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date: May 16, 2019	Group Art Unit

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	536.	YIN et al., "Genetically encoded short peptide tag for versatile protein labeling by Sfp phosphopantetheinyl transferase," PNAS, 2005, 102(44):15815-20
	537.	YONEZAWA et al., "DNA display for in vitro selection of diverse peptide libraries," Nucleic Acids Research , 2003, 31 (19):e118
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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	133	((array$4 or microarray$4 or support$4 or surface) near5 (dna or (nucleic adj acid) or protein or antibod$4)) same (probe near5 pool$6) same (probe near5 sequenc$6)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/04 10:22
L2	7502	(((high adj density) or (high adj resolution)) near5 (array$4 or microarray$4)) near10 (dna or (nucleic adj acid) or protein or antibod$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/04 10:22
L3	7600	L1 or L2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/04 10:22
L4	3332819	@rlad<"20110405"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/04 10:22
L5	5157	L3 and L4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/04 10:22
L6	1706	L5 and @pd>"20101231"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/04 10:22
L7	1479	L5 and @pd<"20050101"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/04 10:22
L8	1972	L5 not (L6 or L7)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/04 10:22
L9	1972	l5 not (l6 or l7)	US-PGPUB; USPAT;	OR	ON	2019/06/04 10:27

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Curio v Prognosys

			USOCR; FPRS; EPO; JPO; DERWENT			
L10	20	l5 and @pd>"20190414"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/04 10:28
S1	133	((array$4 or microarray$4 or support$4 or surface) near5 (dna or (nucleic adj acid) or protein or antibod$4)) same (probe near5 pool$6) same (probe near5 sequenc$6)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/03 16:53
S2	6388	(((high adj density) or (high adj resolution)) near5 (array$4 or microaray$4)) near10 (dna or (nucleic adj acid) or protein or antibod$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/03 16:55
S3	7499	(((high adj density) or (high adj resolution)) near5 (array$4 or microarray$4)) near10 (dna or (nucleic adj acid) or protein or antibod$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/03 16:56
S4	7597	S1 or S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/03 16:57
S5	3332297	@rlad<"20110405"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/03 16:57
S6	5156	S4 and S5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/03 16:57
S7	1705	S6 and @pd>"20101231"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/03 16:58
S8	1479	S6 and @pd<"20050101"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/03 16:58
S9	19	S6 and @pd>"20190414"	US-PGPUB; USPAT;	OR	ON	2019/06/03 16:59

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Curio v Prognosys

			USOCR; FPRS; EPO; JPO; DERWENT			
S10	1972	S6 not (S7 or S8)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2019/06/03 17:00

6/ 4/ 2019 10:30:01 AM
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Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	16414213
Filing Date	16-May-2019
First Named Inventor	Mark CHEE
Attorney Docket Number	47706-0004006
Title of Invention	Spatially Encoded Biological Assays

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Prognosys Biosciences, Inc.	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

16430109 filed on 06/03/2019

16430015 filed on 06/03/2019

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
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 is of record in this application Registration Number 58674 ○ 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 request

Signature	/Cameron Mark Luitjens/
Name	Cameron Mark Luitjens

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16414213
Filing Date:	16-May-2019
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Attorney Docket Number:	47706-0004006

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16414213

Filing Date: 16-May-2019

Applicant/Patent under Reexamination: CHEE

Electronic Terminal Disclaimer filed on June 20, 2019

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This patent is subject to a terminal disclaimer

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Electronic Acknowledgement Receipt

EFS ID:	36361795
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	20-JUN-2019
Filing Date:	16-MAY-2019
Time Stamp:	15:18:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	062119INTEFSW00001848061050
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	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	34690 bbd6e5dc9910b26d4e01556f24307a99b53bdf9c	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30472 72e3c0bc0f9fa41c3b5bc2b402e116283aba2509	no	2
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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.

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Prognosys Biosciences, Inc.	100%

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16435176 filed on 06/07/2019

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
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 is of record in this application Registration Number 58674 ○ 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 request

Signature	/Cameron Mark Luitjens/
Name	Cameron Mark Luitjens

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16414213
Filing Date:	16-May-2019
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Attorney Docket Number:	47706-0004006

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16414213

Filing Date: 16-May-2019

Applicant/Patent under Reexamination: CHEE

Electronic Terminal Disclaimer filed on June 25, 2019

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	36397902
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	25-JUN-2019
Filing Date:	16-MAY-2019
Time Stamp:	11:51:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	062519INTEFSW00012779061050
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	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	33895 02f2d8f64968422bdffdfb5a8d4d0acfea3a080f	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30472 dad6086f45aec5ccc8323cea54e2efe2a7cdec33	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	64367		

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.

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	16414213
Filing Date	16-May-2019
First Named Inventor	Mark CHEE
Attorney Docket Number	47706-0004006
Title of Invention	Spatially Encoded Biological Assays

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Prognosys Biosciences, Inc.	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

16437726 filed on 06/11/2019

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
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 is of record in this application Registration Number 58674 ○ 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 request

Signature	/Cameron Mark Luitjens/
Name	Cameron Mark Luitjens

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16414213
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First Named Inventor/Applicant Name:	Mark S. CHEE
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Attorney Docket Number:	47706-0004006

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16414213

Filing Date: 16-May-2019

Applicant/Patent under Reexamination: CHEE

Electronic Terminal Disclaimer filed on June 27, 2019

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	36425974
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	27-JUN-2019
Filing Date:	16-MAY-2019
Time Stamp:	12:27:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	062719INTEFSW00013803061050
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	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	33895 41365a9d0c37643c5ae0873d3f0ae8439445e75a	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30471 d363b9867d284a66e6b56f20040325e66f2978c3	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	64366		

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

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New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/414,213	Filing Date 05/16/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	07/01/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 28	Minus	** 20	= 8		x $100 =	800
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	800

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

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

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	1636
Application No.	:	16/414,213	Examiner	:	Unknown
Filed	:	May 16, 2019	Conf. No.	:	8760
Title	:	SPATIALLY ENCODED BIOLOGICAL ASSAYS			

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

REPLY TO ACTION OF JUNE 7, 2019

Please consider the following reply.

Amendments to the Specification:

Replace paragraph [00114] with the following amended paragraph:

[00114] ~~Fig. 1~~ Fig. 4 illustrates such a target-specific assay system for identification of nucleic acid sequences in a sample. In this system ~~101~~ 401, two reagents ~~120~~ 420, ~~122~~ 422 that specifically bind to a biological molecule of interest are associated with coding identifiers ~~106~~ 406, ~~108~~ 408 that encode for a spatial location in the sample. These coding identifiers ~~106~~ 406, ~~108~~ 408 are optionally associated with sites that assist in their identification in the assay format, *e.g.,* universal priming sites ~~104~~ 404, ~~110~~ 410 for amplification of the assay products or adapters to enable identification of the coding identifiers and the binding agents using sequencing technologies. The sample that is tested, here shown as a tissue section ~~116~~ 416 is encoded using the combination of the patterns ~~112~~ 412, ~~114~~ 414 created using the separate coding identifiers ~~106~~ 406, ~~108~~ 408 which provide a two dimensional code ~~118~~ 418 that shows the location of any positive detection of the biological molecule ~~102~~ 402 as well as quantifying the biological molecule ~~102~~ 402 at each location assayed in the tissue.

Replace paragraph [00122] with the following amended paragraph:

[00122] In ~~Figure 2~~ Figure 3, two target-specific assay oligonucleotides are ligated together ~~202~~ 302 following *in situ* hybridization to target sequences. At the same time, encoding oligonucleotides containing tag sequence sets X and Y are ligated ~~204~~ 304 to the target specific oligonucleotides. Oligonucleotides containing X ligate specifically to one side of the targeting construct and oligonucleotides containing Y ligate to the other. The oligonucleotides contain

universal primer sites Pl and P2. Following ligation, the constructs are eluted and, optionally, sequencing adapters can be attached ~~206~~ 306, *e.g.,* via PCR.

Amendments to the Drawings:

The attached replacement sheet of drawings includes changes to Fig. 4 and replaces the original sheet including Figs. 4A-C.

In Figure 4, Figures 4A, 4B, and 4C are clearly indicated.

Attachments following last page of this Amendment:

Replacement Sheet (1 page)

Amendments to Claims:

1. (**Currently Amended**) An assay system to determine spatial patterns of presence or abundance ~~abundance or activity~~ or both of multiple biological targets at multiple sites in a sample, wherein the assay system performs the following steps:

providing a sample affixed to a support;

delivering encoded probes for the multiple biological targets to the multiple sites in the sample in a known spatial pattern, wherein each encoded probe comprises a probe region that interacts ~~may interact~~ with the biological targets and a coding tag that identifies a location of the site to which the encoded probe was delivered;

~~allowing the encoded probes to interact with the biological targets;~~

separating encoded probes that interact with the biological targets from encoded probes that do not interact with the biological targets;

determining all or a portion of a sequence of the encoded probes; and

associating the presence or abundance ~~abundance or activity~~ or both of the multiple biological targets to the location of the sites in the sample.

2. (**New**) The assay system of claim 1, wherein the encoded probes bind to unique biological targets in the sample.

3. (**New**) The assay system of claim 1, wherein the biological target comprises a nucleic acid.

4. (**New**) The assay system of claim 1, wherein the biological target comprises a protein.

5. (**New**) The assay system of claim 1, wherein the biological target is present in a subcellular target.

6. (**New**) The assay system of claim 5, wherein the subcellular target comprises a mitochondrion or a nucleus.

7. (**New**) The assay system of claim 1, wherein the sequence of the encoded probes are determined in parallel.

8. (**New**) The assay system of claim 2, wherein the sequence of the encoded probes are used to associate the abundance of greater than 75 unique biological targets to the location of the sites in the sample.

9. (**New**) The assay system of claim 1, wherein the multiple sites are determined by histological features of the sample.

10. (**New**) The assay system of claim 1, wherein the separating step comprises washing.

11. (**New**) The assay system of claim 1, wherein the sample is a tissue sample.

12. (**New**) The assay system of claim 11, wherein the tissue sample comprises a fresh-frozen or formalin fixed paraffin embedded (FFPE) tissue sample.

13. (**New**) The assay system of claim 1, wherein the determined sequence is used to associate abundance of the biological targets to the location of the sites in the sample.

14. (**New**) The assay system of claim 1, wherein the assay system further performs a step of detecting differential expression of the biological targets at the location of the sites in the sample.

15. (**New**) The assay system of claim 14, wherein the differential expression of the biological targets is associated with a biological structure or cell type at the location of the sites in the sample.

16. (**New**) The assay system of claim 1, wherein the assay system further performs a step of identifying a location of the biological targets in one or more serial sections of the sample.

17. (**New**) The assay system of claim 16, wherein the assay system further performs a step of generating a 3-dimensional map of the biological targets in the sample.

18. (**New**) The assay system of claim 1, wherein the determined sequence is used to associate the presence of the biological targets to the location of the sites in the sample.

19. (**New**) The assay system of claim 1, wherein the assay system further performs a step of determining activity of the biological targets at the location of the sites in the sample.

20. (**New**) The assay system of claim 1, wherein the determined sequence is used to associate the presence and abundance of the biological targets to the location of the sites in the sample.

21. (**New**) The assay system of claim 2, wherein the determined sequences of the encoded probes are used to associate the presence or abundance or both, of the unique biological targets to the location of the sites in the sample.

22. (**New**) The assay system of claim 24, wherein the unique biological targets comprise at least one protein and at least one nucleic acid.

23. (**New**) The assay system of claim 1, wherein the encoded probes comprises an antibody that interacts with a biological target in the sample.

24. (**New**) The assay system of claim 2, wherein the determined sequences of the encoded probes are used to associate the presence or abundance or both, of the unique biological targets to the location of the sites in the sample in parallel.

25. (**New**) The assay system of claim 2, wherein sequences of the encoded probes are determined sequentially.

26. (**New**) The assay system of claim 2, wherein determined sequences of the encoded probes are used to associate the presence of greater than 100 unique biological targets to the location of the sites in the sample.

27. (**New**) The assay system of claim 2, wherein determined sequences of the encoded probes are used to associate the presence of greater than 150 unique biological targets to the location of the sites in the sample.

28. (**New**) The assay system of claim 2, wherein determined sequences of the encoded probes are used to associate the presence of greater than 500 unique biological targets to the location of the sites in the sample.

REMARKS

Examiner Interview

Applicant thanks Examiner Martinell for the courtesy of the telephonic interview conducted on June 27, 2019 with the undersigned and Tiffany Reiter, Ph.D., J.D., USPTO Registration Number 61,359. The various claim amendments and additions that were discussed are reflected in the above listing of the claims.

Amendments to the Claims

Claim 1 has been amended to recite determining spatial patterns of presence or abundance or both of multiple biological targets. Support for this amendment can be found, e.g., in paragraph [0008] of the specification as filed. Claim 1 has also been amended to recite that a probe region that interacts with the biological targets. In light of this amendment, claim 1 has been amended to delete the superfluous feature of allowing the encoded probes to interact with the biological targets.

New claims 2-28 have been added. Applicant's specification fully supports these new claims. See, e.g.:

Claim	Exemplary Support (specification as filed)
2	[0008]
3-4	[0009]
5-6	[0053]
7-8, 24-28	[0011]
9	[0012]
10	[0013]
11-12	[0052]
13	[0008]
14-15	[0067]
16-17	[0089]
18-21	[0040]
22	[0053]
23	[0009]

No new matter has been added. Applicant reserves the right to pursue any subject matter canceled as a result of the present amendments in future prosecution, either in this application or in one or more continuing applications.

In light the present amendments, remarks, and submissions, Applicant respectfully requests reconsideration and allowance of claim 1, and consideration and allowance of newly added claims 2-28.

Drawings

The drawings were objected to because they do not include various reference characters mentioned in the description. As shown in the Amendments to the Specification section above, the specification has been amended to delete the reference characters noted by the Examiner. The specification now reflects the Figure numbers and reference characters numbers in Figures 3 and 4, as originally filed. As such, this objection is rendered moot.

Additionally, a replacement drawing sheet that includes changes to Fig. 4 and clearly indicates Figures 4A, 4B, and 4C is submitted with this response.

No new matter has been added.

Rejections Under 35 USC § 112, Second Paragraph

Claim 1 was rejected under 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Without conceding the merits of this rejection and solely to advance prosecution of the present application, claim 1 has been amended to recite a probe region that interacts with the biological targets. As such this rejection is moot, and Applicant respectfully requests its withdrawal.

Non-Statutory Double Patenting Rejection

Claim 1 was provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2, 3, 5-8, 10-26, and 32-36 of copending Application No. 16/276,260. Without conceding the merits of this rejection and solely to advance prosecution of

the present application, Applicant submitted a terminal disclaimer over the '260 application on June 6, 2019, which was approved on June 6, 2019. As such, Applicant respectfully requests withdrawal of this provisional rejection.

Claim 1 was provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2-28 and 30-32 of copending Application No. 16/276,235. Without conceding the merits of this rejection and solely to advance prosecution of the present application, Applicant submitted a terminal disclaimer over the '235 application on June 6, 2019, which was approved on June 6, 2019. As such, Applicant respectfully requests withdrawal of this provisional rejection.

Claim 1 was rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 9,371,598. Without conceding the merits of this rejection and solely to advance prosecution of the present application, Applicant submitted a terminal disclaimer over the '598 patent on June 6, 2019, which was approved on June 6, 2019. As such, Applicant respectfully requests withdrawal of this rejection.

Claim 1 was rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-43 of U.S. Patent No. 10,208,982. Without conceding the merits of this rejection and solely to advance prosecution of the present application, Applicant submitted a terminal disclaimer over the '982 patent on June 6, 2019, which was approved on June 6, 2019. As such, Applicant respectfully requests withdrawal of this rejection.

CONCLUSION

Applicant respectfully submits claims 1-28 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned at the telephone number below if such will advance prosecution of this application.

Please apply any necessary charges or credit any overpayments to Deposit Account 06-1050, referencing Attorney Docket No. 47706-0004006.

Respectfully submitted,

Date: July 1, 2019

/Cameron Luitjens/

Cameron M. Luitjens, Ph.D., J.D.
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61959164.doc

FIG. 4A

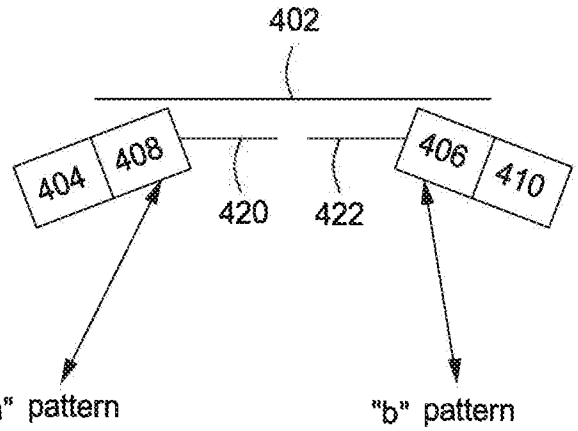


FIG. 4B

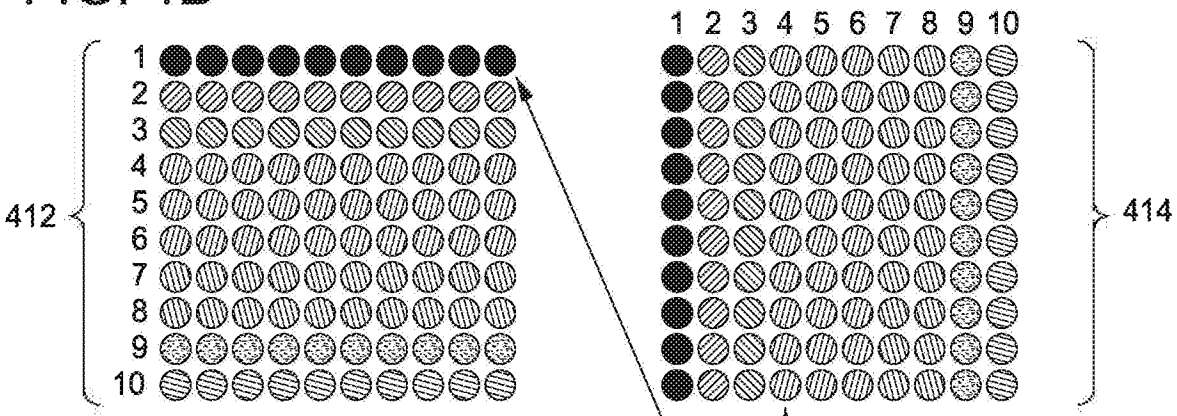
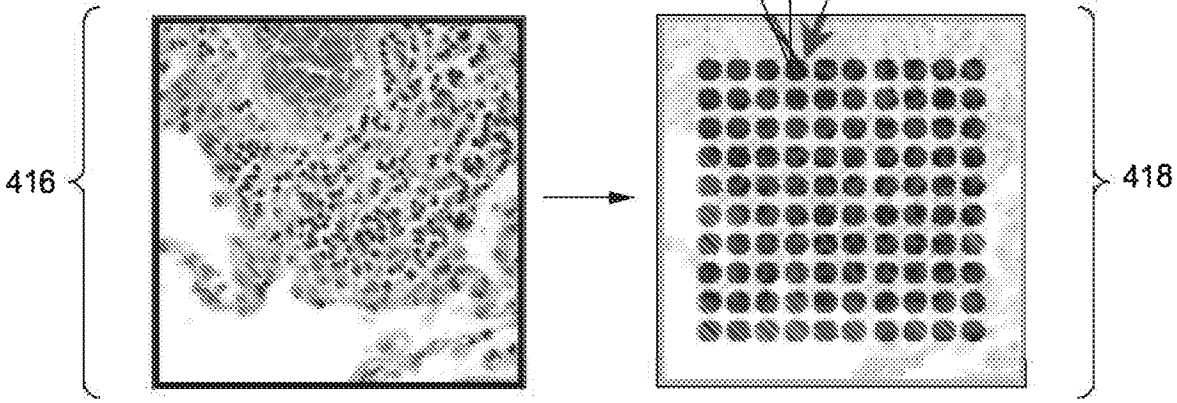


FIG. 4C



Electronic Patent Application Fee Transmittal

Application Number:	16414213
Filing Date:	16-May-2019
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Attorney Docket Number:	47706-0004006

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:				
CLAIMS IN EXCESS OF 20	1202	8	100	800
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**800**

Electronic Acknowledgement Receipt

EFS ID:	36463310
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	01-JUL-2019
Filing Date:	16-MAY-2019
Time Stamp:	14:36:36
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$800
RAM confirmation Number	070219INTEFSW00000976061050
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		RESPONSE.pdf	136602 a896644fb2af5884c9239192fb5332de30013696	yes	12

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Specification	2	3
Drawings-only black and white line drawings	4	4
Claims	5	8
Applicant Arguments/Remarks Made in an Amendment	9	12

Warnings:

Information:

2	Drawings-only black and white line drawings	DRAWING_.pdf	1608392 99decf5099f7a378e4e67f6ea1e4adadf7f3705e	no	1

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	30239 d8a38b4e520bd0e3084f7ada3337cd3b04b40868	no	2

Warnings:

Information:

Total Files Size (in bytes):	1775233

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.

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	16414213
Filing Date	16-May-2019
First Named Inventor	Mark CHEE
Attorney Docket Number	47706-0004006
Title of Invention	Spatially Encoded Biological Assays

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Prognosys Biosciences, Inc.	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

16435295 filed on 06/07/2019

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
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 is of record in this application Registration Number 58674 ○ 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 request

Signature	/Cameron Mark Luitjens/
Name	Cameron Mark Luitjens

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16414213
Filing Date:	16-May-2019
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Attorney Docket Number:	47706-0004006

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16414213

Filing Date: 16-May-2019

Applicant/Patent under Reexamination: CHEE

Electronic Terminal Disclaimer filed on July 2, 2019

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	36464730
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	02-JUL-2019
Filing Date:	16-MAY-2019
Time Stamp:	13:25:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	070219INTEFSW00012120061050
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	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	33897 13688f6db70fbc0284ffc310a13dbd97f881c48c	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30472 d3b6df7623aebfc19b6961be312354acfd415a32	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	64369		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/414,213	05/16/2019	Mark S. CHEE	47706-0004006	8760

159367 7590 07/03/2019

FISH & RICHARDSON P.C.
10x Genomics
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
MARTINELL, JAMES	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
07/03/2019	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):

PATDOCTC@fr.com
ipadmin@10xgenomics.com

Applicant-Initiated Interview Summary	**Application No.** 16/414,213	**Applicant(s)** CHEE, Mark S.	
	Examiner JAMES MARTINELL	**Art Unit** 1634	**AIA (FITF) Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) JAMES MARTINELL.

(2) Dr. Reiter.

(3) Dr. Luitjens.

(4) _____.

Date of Interview: 27 June 2019.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☑ Yes ☐ No.
If Yes, brief description: See the attached Draft Amended Claim Set.

Issues Discussed ☐101 ☑112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1 and the attached Draft Claim Set.

Identification of prior art discussed: None.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant has submitted Terminal Disclaimers. Applicant intends to respond to Office action mailed 6/7/19 and to amend the specification to correspond to the Drawings, amend claim 1 to overcome the 112(b) rejection [Examiner agrees that proposed amendment to claim 1 is sufficient to overcome 112(b) rejection]; point to basis in the application as filed for proposed new claims 2-28. It was noted that the Office action mailed 6/7/19 misidentified U.S. Patent No. 10,,308,982 as 10,208,392. Applicant noted that proposed claims 27 and 28 are identical and intends to file a new claim 28 that differs from the proposed claim 28 in the attachment to this summary..

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

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

☑ Attachment

/JAMES MARTINELL/ Primary Examiner, Art Unit 1634	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	1634
Serial No.	:	16/414,213	Examiner	:	James Martinell
Filed	:	May 16, 2019	Conf. No.	:	8760
Title	:	SPATIALLY ENCODED BIOLOGICAL ASSAYS			

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

DRAFT AMENDED CLAIM SET FOR DISCUSSION WITH EXAMINER

1. (Currently Amended) An assay system to determine spatial patterns of presence or abundance ~~abundance or activity~~ or both of multiple biological targets at multiple sites in a sample, wherein the assay system performs the following steps:

providing a sample affixed to a support;

delivering encoded probes for the multiple biological targets to the multiple sites in the sample in a known spatial pattern, wherein each encoded probe comprises a probe region that interacts ~~may interact~~ with the biological targets and a coding tag that identifies a location of the site to which the encoded probe was delivered;

~~allowing the encoded probes to interact with the biological targets;~~

separating encoded probes that interact with the biological targets from encoded probes that do not interact with the biological targets;

determining all or a portion of a sequence of the encoded probes; and

associating the presence or abundance ~~abundance or activity~~ or both of the multiple biological targets to the location of the sites in the sample.

2. (New) The assay system of claim 1, wherein the encoded probes bind to unique biological targets in the sample.

3. (New) The assay system of claim 1, wherein the biological target comprises a nucleic acid.

4. (New) The assay system of claim 1, wherein the biological target comprises a protein.

5. (New) The assay system of claim 1, wherein the biological target is present in a subcellular target.

6. (New) The assay system of claim 5, wherein the subcellular target comprises a mitochondrion or a nucleus.

7. (New) The assay system of claim 1, wherein the sequence of the encoded probes are determined in parallel.

8. (New) The assay system of claim 2, wherein the sequence of the encoded probes are used to associate the abundance of greater than 75 unique biological targets to the location of the sites in the sample.

9. (New) The assay system of claim 1, wherein the multiple sites are determined by histological features of the sample.

10. (New) The assay system of claim 1, wherein the separating step comprises washing.

11. (New) The assay system of claim 1, wherein the sample is a tissue sample.

12. (New) The assay system of claim 11, wherein the tissue sample comprises a fresh-frozen or formalin fixed paraffin embedded (FFPE) tissue sample.

13. (New) The assay system of claim 1, wherein the determined sequence is used to associate abundance of the biological targets to the location of the sites in the sample.

14. (New) The assay system of claim 1, wherein the assay system further performs a step of detecting differential expression of the biological targets at the location of the sites in the sample.

15. (New) The assay system of claim 14, wherein the differential expression of the biological targets is associated with a biological structure or cell type at the location of the sites in the sample.

16. (New) The assay system of claim 1, wherein the assay system further performs a step of identifying a location of the biological targets in one or more serial sections of the sample.

17. (New) The assay system of claim 16, wherein the assay system further performs a step of generating a 3-dimensional map of the biological targets in the sample.

18. (New) The assay system of claim 1, wherein the determined sequence is used to associate the presence of the biological targets to the location of the sites in the sample.

19. (New) The assay system of claim 1, wherein the assay system further performs a step of determining activity of the biological targets at the location of the sites in the sample.

20. (New) The assay system of claim 1, wherein the determined sequence is used to associate the presence and abundance of the biological targets to the location of the sites in the sample.

21. (New) The assay system of claim 2, wherein the determined sequences of the encoded probes are used to associate the presence or abundance or both, of the unique biological targets to the location of the sites in the sample.

22. (New) The assay system of claim 24, wherein the unique biological targets comprise at least one protein and at least one nucleic acid.

23. (New) The assay system of claim 1, wherein the encoded probes comprises an antibody that interacts with a biological target in the sample.

24. (New) The assay system of claim 2, wherein the determined sequences of the encoded probes are used to associate the presence or abundance or both, of the unique biological targets to the location of the sites in the sample. in parallel.

25. (New) The assay system of claim 2, wherein sequences of the encoded probes are determined sequentially.

26. (New) The assay system of claim 2, wherein determined sequences of the encoded probes are used to associate the presence of greater than 100 unique biological targets to the location of the sites in the sample.

27. (New) The assay system of claim 2, wherein determined sequences of the encoded probes are used to associate the presence of greater than 150 unique biological targets to the location of the sites in the sample.

28. (New) The assay system of claim 2, wherein determined sequences of the encoded probes are used to associate the presence of greater than 150 unique biological targets to the location of the sites in the sample.

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	16414213
Filing Date	16-May-2019
First Named Inventor	Mark CHEE
Attorney Docket Number	47706-0004006
Title of Invention	Spatially Encoded Biological Assays

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Prognosys Biosciences, Inc.	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

16437637 filed on 06/11/2019

16443771 filed on 06/17/2019

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
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 is of record in this application Registration Number 58674 ○ 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 request

Signature	/Cameron Mark Luitjens/
Name	Cameron Mark Luitjens

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16414213
Filing Date:	16-May-2019
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Attorney Docket Number:	47706-0004006

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16414213

Filing Date: 16-May-2019

Applicant/Patent under Reexamination: CHEE

Electronic Terminal Disclaimer filed on July 9, 2019

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	36516032
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Shannon Stadnick
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	09-JUL-2019
Filing Date:	16-MAY-2019
Time Stamp:	09:28:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	070919INTEFSW00010025061050
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	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	34692 730b55ab30d97818c68c39d91a1d12f0d379f401	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30471 ecead6efdc07d93eae1323541f7a07456fbbd865	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	65163		

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	1636
Application No.	:	16/414,213	Examiner	:	Unknown
Filed	:	May 16, 2019	Conf. No.	:	8760
Title	:	SPATIALLY ENCODED BIOLOGICAL ASSAYS			

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

INFORMATION DISCLOSURE STATEMENT

Please consider the documents listed on the disclosure form submitted with this statement. Copies of the documents are being submitted with this statement to the extent required under 37 C.F.R. § 1.98(a)(2).

This statement is being filed within three months of the filing date of the application or before the receipt of a first action on the merits.

Apply any necessary charges or credits applicable under 37 C.F.R. § 1.17(p) to deposit account 06-1050, referencing the above attorney docket number.

Please contact the undersigned if there are any questions regarding this statement.

Respectfully submitted,

Date: August 12, 2019

/Cameron Luitjens/
Cameron M. Luitjens, Ph.D., J.D.
Reg. No. 58,674

Customer Number 159367
Fish & Richardson P.C.
Telephone: (612) 335-5070
Facsimile: (877) 769-7945

62054341.doc

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No.	Application No.
Information Disclosure Statement by Applicant (Use several sheets if necessary)		47706-0004006	16/414,213
		Applicant: Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date: May 16, 2019	Group Art Unit: 1636

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	1.	6,673,620	1/6/2004	Loeffler			
	2.	20020040275	4/4/2002	Cravatt			
	3.	20110275077	11/10/2011	James			

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document

Examiner Signature	Date Considered

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form

Electronic Acknowledgement Receipt

EFS ID:	36853377
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Peter Wolff
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	12-AUG-2019
Filing Date:	16-MAY-2019
Time Stamp:	21:31:39
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)	InformationDisclosureStatment.pdf	126220 90204223c857d9b549e3bdd99dc27ac464428ae2	no	2

Warnings:

Information:	
This is not an USPTO supplied IDS fillable form	
Total Files Size (in bytes):	126220

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New International Application Filed with the USPTO as a Receiving Office

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Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 47706-0004006	Application No. 16/414,213
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Prognosys Biosciences, Inc.	
(37 CFR §1.98(b))		Filing Date May 16, 2019	Group Art Unit 1636

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	1.	5,559,032	9/1/1996	Pomeroy			
	2.	6,699,710	3/1/2004	Kononen			

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document

Examiner Signature	Date Considered
EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Substitute Disclosure Form

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	1636
Application No.	:	16/414,213	Examiner	:	Unknown
Filed	:	May 16, 2019	Conf. No.	:	8760
Title	:	SPATIALLY ENCODED BIOLOGICAL ASSAYS			

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

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Apply any necessary charges or credits applicable under 37 C.F.R. § 1.17(p) to deposit account 06-1050, referencing the above attorney docket number.

Please contact the undersigned if there are any questions regarding this statement.

Respectfully submitted,

Date: August 15, 2019

/Cameron Luitjens/

Cameron M. Luitjens, Ph.D., J.D.
Reg. No. 58,674

Customer Number 159367
Fish & Richardson P.C.
Telephone: (612) 335-5070
Facsimile: (877) 769-7945

62059478.doc

Electronic Acknowledgement Receipt

EFS ID:	36892372
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Cameron Mark Luitjens/Lindsey Ericson
Filer Authorized By:	Cameron Mark Luitjens
Attorney Docket Number:	47706-0004006
Receipt Date:	15-AUG-2019
Filing Date:	16-MAY-2019
Time Stamp:	22:05:16
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)	IDS.pdf	429976 351f94d646b21e25d8397761c0409aa117c6ddfe	no	2

Warnings:

Information:	
This is not an USPTO supplied IDS fillable form	
Total Files Size (in bytes):	429976

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New Applications Under 35 U.S.C. 111

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UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/414,213	05/16/2019	Mark S. CHEE	47706-0004006

CONFIRMATION NO. 8760

159367
FISH & RICHARDSON P.C.
10x Genomics
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

PUBLICATION NOTICE

OC000000110895182

Title: Spatially Encoded Biological Assays

Publication No.US-2019-0271031-A1
Publication Date:09/05/2019

NOTICE OF PUBLICATION OF APPLICATION

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

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

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

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

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	1636
Application No.	:	16/414,213	Examiner	:	James Martinell
Filed	:	May 16, 2019	Conf. No.	:	8760
Title	:	SPATIALLY ENCODED BIOLOGICAL ASSAYS			

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

SUPPLEMENTAL RESPONSE TO AMENDMENTS FILED ON JULY 1, 2019

Further to the response to non-final Office Action filed July 1, 2019, Applicant submits the following amendments and remarks. Applicant treats the claim amendments made on July 1, 2019 as entered and the amendments made to the specification on July 1, 2019 as entered.

Amendments to Claims

Listing of Claims.

1. (**Currently Amended**) An assay system to determine the ~~spatial patterns of~~ presence or abundance or both of ~~multiple~~ biological targets at multiple sites in a sample, wherein the assay system performs the following steps:

providing a sample affixed to a support;

delivering ~~encoded~~ probes for the ~~multiple~~ biological targets to the multiple sites in the sample ~~in a known spatial pattern~~, wherein each ~~encoded~~ probe comprises a probe region that interacts with ~~the~~ biological target(s) ~~targets~~ and a coding tag that identifies ~~a location of~~ the site to which the ~~encoded~~ probe was delivered;

separating ~~encoded~~ probes that interact with the biological targets from ~~encoded~~ probes that do not interact with the biological targets;

determining all or a portion of a sequence of the ~~encoded~~ probes that interact with the biological targets[[;]], and using the determined sequence of the probes to associate ~~associating~~ the presence or abundance or both of the ~~multiple~~ biological targets to the ~~location of the~~ sites in the sample.

2. (**Currently Amended**) The assay system of claim 1, wherein the ~~encoded~~ probes bind to unique biological targets in the sample.

3. (**Currently Amended**) The assay system of claim 1, wherein the biological targets comprise ~~target comprises~~ a nucleic acid.

4. (**Currently Amended**) The assay system of claim 1, wherein the biological targets comprise ~~target comprises~~ a protein.

5. (**Currently Amended**) The assay system of claim 1, wherein the biological targets are ~~target is~~ present in a subcellular target.

6. (**Previously Presented**) The assay system of claim 5, wherein the subcellular target comprises a mitochondrion or a nucleus.

7. (**Currently Amended**) The assay system of claim 1, wherein the sequence of the ~~encoded~~ probes are determined in parallel.

8. (**Currently Amended**) The assay system of claim 2, wherein the sequence of the ~~encoded~~ probes are used to associate the abundance of greater than 75 unique biological targets to the multiple ~~location of the~~ sites in the sample.

9. (**Previously Presented**) The assay system of claim 1, wherein the multiple sites are determined by histological features of the sample.

10. (**Previously Presented**) The assay system of claim 1, wherein the separating step comprises washing.

11. (**Previously Presented**) The assay system of claim 1, wherein the sample is a tissue sample.

12. (**Previously Presented**) The assay system of claim 11, wherein the tissue sample comprises a fresh-frozen or formalin fixed paraffin embedded (FFPE) tissue sample.

13. (**Currently Amended**) The assay system of claim 1, wherein the determined sequence is used to associate abundance of the biological targets to the multiple ~~location of the~~ sites in the sample.

14. (**Currently Amended**) The assay system of claim 1, wherein the assay system further performs a step of detecting differential expression of the biological targets at the multiple ~~location of the~~ sites in the sample.

15. (**Currently Amended**) The assay system of claim 14, wherein the differential expression of the biological targets is associated with a biological structure or cell type at the multiple ~~location of the~~ sites in the sample.

16. (**Currently Amended**) The assay system of claim 1, wherein the assay system further performs a step of identifying multiple sites ~~a location~~ of the biological targets in one or more serial sections of the sample.

17. (**Previously Presented**) The assay system of claim 16, wherein the assay system further performs a step of generating a 3-dimensional map of the biological targets in the sample.

18. (**Currently Amended**) The assay system of claim 1, wherein the determined sequence is used to associate the presence of the biological targets to the multiple ~~location of the~~ sites in the sample.

19. (**Currently Amended**) The assay system of claim 1, wherein the assay system further performs a step of determining activity of the biological targets at the multiple ~~location of the~~ sites in the sample.

20. (**Currently Amended**) The assay system of claim 1, wherein the determined sequence is used to associate the presence and abundance of the biological targets to the multiple ~~location of the~~ sites in the sample.

21. (**Cancelled**)

22. (**Currently Amended**) The assay system of claim 2[[24]], wherein the unique biological targets comprise at least one protein and at least one nucleic acid.

23. (**Currently Amended**) The assay system of claim 1, wherein the ~~encoded~~ probes comprise ~~comprises~~ an antibody that interacts with a biological target in the sample.

24. (**Currently Amended**) The assay system of claim 2, wherein the determined sequences of the ~~encoded~~ probes are used to associate the presence or abundance or both, of the unique biological targets to the multiple ~~location of the~~ sites in the sample in parallel.

25. (**Currently Amended**) The assay system of claim 2, wherein the sequences of the ~~encoded~~ probes are determined sequentially.

26. (**Currently Amended**) The assay system of claim 2, wherein the determined sequences of the ~~encoded~~ probes are used to associate the presence of greater than 100 unique biological targets to the multiple ~~location of the~~ sites in the sample.

27. (**Currently Amended**) The assay system of claim 2, wherein the determined sequences of the ~~encoded~~ probes are used to associate the presence of greater than 150 unique biological targets to the multiple ~~location of the~~ sites in the sample.

28. (**Currently Amended**) The assay system of claim 2, wherein the determined sequences of the ~~encoded~~ probes are used to associate the presence of greater than 500 unique biological targets to the multiple ~~location of the~~ sites in the sample.

29. **(New)** The assay system of claim 1, wherein the sample is at least one tissue section.

REMARKS

Upon entry of the present amendments, claims 1-20 and 22-29 will be pending.

Applicant has amended claims 1-5, 7, 8, 13-16, 18-20, and 22-28, and has cancelled claim 21, without prejudice or disclaimer. New claim 29 has been added. Support for the amendments to claim 1 is found in the previous version of this claim and in the specification, e.g., in paragraph [0049]. Support for the amendments to claims 2-5, 7, 23, and 25 is found, e.g., in the original version of each claim, respectively. Support for the amendments to claim 8 is found, e.g., in previous claims 1 and 8. Support for the amendments to claim 13 is found, e.g., in previous claims 1 and 13. Support for the amendments to claim 14 is found, e.g., in previous claims 1 and 14. Support for the amendments to claim 15 is found, e.g., in previous claims 1 and 15. Support for the amendments to claim 16 is found, e.g., in previous claims 1 and 16. Support for the amendments to claim 18 is found, e.g., in previous claims 1 and 18. Support for the amendments to claim 19 is found, e.g., in previous claims 1 and 19. Support for the amendments to claim 20 is found, e.g., in previous claims 1 and 20. Support for the amendments to claim 22 is found, e.g., in previous claims 2 and 22. Support for the amendments to claim 24 is found, e.g., in previous claims 1 and 24. Support for the amendments to claim 26 is found, e.g., in previous claims 1 and 26. Support for the amendments to claim 27 is found, e.g., in previous claims 1 and 27. Support for the amendments to claim 28 is found, e.g., in previous claims 1 and 28. Support for new claim 29 is found in the specification, e.g., in paragraph [0040].

No new matter has been added by these amendments to the claims. Applicant reserves the right to pursue any cancelled subject matter in this or a continuation application.

No fees are believed to be due. Apply any necessary charges or credits to Deposit Account 06-1050, referencing Attorney Docket No. 47706-0004006.

Respectfully submitted,

Date: September 9, 2019

/Tiffany A. Reiter/
Tiffany A. Reiter, Ph.D.
Reg. No. 61,359

Customer Number 159367
Fish & Richardson P.C.
Telephone: +1 (617) 956-5937
Facsimile: (877) 769-7945

Electronic Acknowledgement Receipt

EFS ID:	37110770
Application Number:	16414213
International Application Number:	
Confirmation Number:	8760
Title of Invention:	Spatially Encoded Biological Assays
First Named Inventor/Applicant Name:	Mark S. CHEE
Customer Number:	159367
Filer:	Tiffany A. Reiter/Lisa Gray
Filer Authorized By:	Tiffany A. Reiter
Attorney Docket Number:	47706-0004006
Receipt Date:	09-SEP-2019
Filing Date:	16-MAY-2019
Time Stamp:	19:48:29
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		47706-0004006suppresponse.pdf	91402 02a47e91618ad2e163e9e58f01c4d5e2acab66cb	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6
Warnings:			
Information:			
	Total Files Size (in bytes):	91402	

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